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Mathematical modeling and simulation in animal health – Part II: principles, methods, applications, and value of physiologically based pharmacokinetic modeling in veterinary medicine and food safety assessment

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This review provides a tutorial for individuals interested in quantitative veterinary pharmacology and toxicology and offers a basis for establishing guidelines for physiologically based pharmacokinetic (PBPK) model development and application in veterinary medicine. This is important as the application of PBPK modeling in veterinary medicine has evolved over the past two decades. PBPK models can be used to predict drug tissue residues and withdrawal times in food-producing animals, to estimate chemical concentrations at the site of action and target organ toxicity to aid risk assessment of environmental contaminants and/or drugs in both domestic animals and wildlife, as well as to help design therapeutic regimens for veterinary drugs. This review provides a comprehensive summary of PBPK modeling principles, model development methodology, and the current applications in veterinary medicine, with a focus on predictions of drug tissue residues and withdrawal times in food-producing animals. The advantages and disadvantages of PBPK modeling compared to other pharmacokinetic modeling approaches (i.e., classical compartmental/noncompartmental modeling, nonlinear mixed-effects modeling, and interspecies allometric scaling) are further presented. The review finally discusses contemporary challenges and our perspectives on model documentation, evaluation criteria, quality improvement, and offers solutions to increase model acceptance and applications in veterinary pharmacology and toxicology.

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INTRODUCTION

Physiologically based pharmacokinetic (PBPK) modeling is a computational simulation process that describes the absorption, distribution, metabolism, and elimination (ADME) of environmental chemicals, drugs, or nanomaterials in an organism based on interrelationships among key physiological, biochemical, and physicochemical determinants using mathematical equations (WHO, 2010). It is generally recognized that the concept of PBPK modeling dates back to 1937, when Teorell realized that the body regulates drug disposition as an integrative system, that is, pharmacokinetic processes that take place in one organ affect, and are in turn influenced by, processes occurring in other tissues through a central connective circuitry, the vascular system (Teorell, 1937). However, due to the mathematical and computational complexities of PBPK models and the lack of relevant physiological data at the time, the field of PBPK modeling did not advance substantially until the 1960s, when the necessary computational capabilities became available (Rowland *et al.*, 2004).

In the last several decades, PBPK models have been extensively applied in numerous fields, ranging from risk assessment

of environmental chemicals on human health and drug pharmacokinetic predictions to aid drug development, to nanomaterial pharmacokinetic simulations and nanotechnology-based drug delivery assessment. The increasing application of PBPK modeling is illustrated by a growing number of scientific publications with the keywords 'PBPK model', especially during the last 5 years (Fig. 1).

To be more specific, PBPK models have become an important and indispensable tool in the risk assessment of toxicants by regulatory agencies [e.g., US EPA (Environmental Protection Agency) and EFSA (European Food Safety Authority)] because they offer the only ethical yet scientifically sound method of predicting the systemic exposure to toxic xenobiotics in humans through animal-to-human extrapolation or based on human biomonitoring data (Reddy *et al.*, 2005; EPA, 2006; McLanahan *et al.*, 2012; EFSA, 2015). In the pharmaceutical arena, PBPK models have become an integral part of human drug discovery and development (EMA, 2014; Jones *et al.*, 2015) and are frequently included in the preclinical submission package to regulatory agencies [e.g., US FDA (Food and Drug Administration) and EMA (European Medicines Agency)] for evaluating investigational drugs, particularly predicting drug–drug interactions, dose selection, and in scenarios that have not been evaluated or are not easy to investigate in dedicated clinical trials (Wagner *et al.*, 2015, 2016). PBPK models have not been commonly used in veterinary drug development, but the US FDA's Center for Veterinary Medicine has started to collaborate with the industry and academia to develop PBPK models in dogs that aim to streamline veterinary drug product development and evaluation; several posters have been published from this collaboration (Mistry *et al.*, 2013; Pade, 2015; Pade *et al.*, 2015). Due to the importance of PBPK modeling, multiple excellent review articles and textbooks summarizing its applications in risk assessment (Andersen, 2003; Reddy *et al.*, 2005; Lipscomb *et al.*, 2012; McLanahan *et al.*, 2012), drug development (Lave *et al.*, 2007; Rowland *et al.*, 2011; Zhao *et al.*, 2011; Peters, 2012; Jones & Rowland-Yeo, 2013; Heikkinen *et al.*, 2015; Jones *et al.*, 2015), and nanomedicine (Li *et al.*, 2010; Yang *et al.*, 2010; Moss & Siccardi, 2014; Lin *et al.*, 2015b) have been published.

In recent years, PBPK models have found new applications in the field of veterinary medicine, especially in the predictions of veterinary drug tissue residue depletion and withdrawal times in food-producing animals, because they allow for predictions of drug concentrations in the target tissues monitored by veterinary regulatory authorities (Craigmill, 2003; Riviere, 2009). PBPK models have been shown to be a promising tool to provide more scientifically sound withdrawal time estimates than statistical or empirical methods that were established several decades ago (Owen, 1968; FDA, 2006; Baynes & Riviere, 2014). This is particularly important as violations of drug residues have recently been reported despite food animals slaughtered following the withdrawal times calculated using these established methods (USDA, 2015). In addition, PBPK models can be applied to assess the risk of environmental contaminants in domestic animals and wildlife by predicting chemical concentrations and toxicity in the target organ (MacLachlan, 2010; Dietz *et al.*, 2015) and to help design drug dosage regimens in companion animals (Lin *et al.*, 2015a). However, these new applications have not been reviewed.

The objective of this manuscript was to introduce the principles, methodology, and applications of PBPK modeling in the field of veterinary medicine, with a focus on the safety assessment of animal-derived food. This article is part of a series of manuscripts that are devoted to introducing applications of mathematical modeling approaches to veterinary medicine (Riviere *et al.*, 2016). The advantages and disadvantages of PBPK modeling are also compared to other mathematical modeling approaches.

PRINCIPLES OF PBPK MODELING

The aim of physiological modeling is to integrate available knowledge on physiological processes with physicochemical attributes of an investigated xenobiotic in order to predict and/or simulate concentrations in various tissues and body fluids under complex biological scenarios. In essence, PBPK models of cells, tissues, organs, and organisms as a whole aid in increasing the mechanistic understanding of how xenobiotics interact

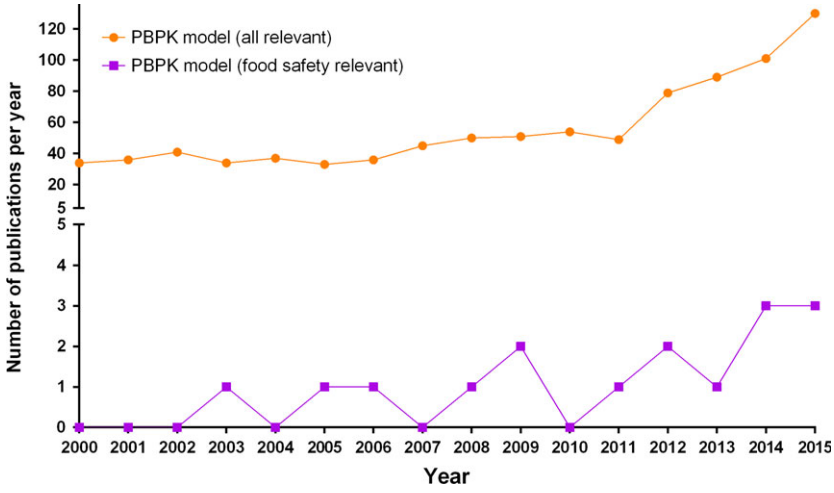

Fig. 1. The annual number of scientific publications related to 'PBPK model'. Data for the yellow circle symbols were collected from the PubMed using the keyword 'PBPK model' on October 14, 2015. Data for the purple square symbols representing the PBPK publications related to tissue residue, and withdrawal time predictions in food-producing animals were counted manually (these studies are listed in Table 1). PBPK, physiologically based pharmacokinetic.

with biological systems (Peters, 2012). Such models are composed of three major parts: species-specific physiological parameters, chemical-specific parameters, and the structural model. All components can be described mathematically, *obtained* experimentally, and estimated by computation algorithms. Physiological parameters include body weight, cardiac output, organ mass or volume, blood flow, vascular space of each organ, tissue composition, metabolizing enzyme phenotype, and abundance. Chemical-specific parameters constitute partition and permeability coefficients, metabolic rate constants, protein binding affinity, and enzyme/transporter activity among others. Incorporation of chemical-specific parameters allows the model to assess the impact of changes due to drug-specific properties on the whole-body pharmacokinetics, making PBPK models mechanistic in nature.

The structural model comprises the exposure routes [e.g., intravenous (i.v.), intramuscular (i.m.), subcutaneous (s.c.), and oral] and anatomically correct network of tissues and organs that comprise the whole body (Fig. 2). The capability of including various exposure routes provides PBPK models the power to conduct extrapolation across routes. Each tissue/organ (termed 'a model compartment') is perfused by and connected through the circulatory system. The physiological organ-based model feature empowers PBPK models to predict the concentration of a substance in a particular organ of interest at a specific time under a certain exposure scenario. It should be noted that the structural model for a drug is the same across species within a given class of animals (mammals, avian, reptiles, etc.), making it possible to conduct interspecies pharmacokinetic extrapolation by adjusting species-specific physiological parameters (Thiel *et al.*, 2015). This is particularly important in veterinary medicine because pharmacokinetic data for most drugs are available in common species (e.g., cattle and swine), but very limited in minor species (e.g., rabbits, pheasants, quail, and domestic game animals). In theory, PBPK model extrapolation across species/breeds within the same class of animals using species- or breed-specific model parameters enables simulation of drug pharmacokinetics from one species/breed to another in which experimental pharmacokinetic data may not be available. Overall, the mechanistic nature, the ability to predict target organ concentrations, and the great extrapolation power across species and dosing scenarios are the main reasons for the extensive applications of PBPK models in various areas.

METHODOLOGY

The development and application of a PBPK model generally include the following steps: (i) literature search for experimental pharmacokinetic data, relevant physiological (e.g., blood flows), physicochemical (e.g., partition coefficients), and biochemical (e.g., liver metabolic rates) parameter values (or conduct new experiments if needed), and identification of target organs, (ii) specification of the model structure, (iii) equation building and model coding, (iv) model parameterization (including estimation of unknown values of some of the model parameters) and calibration, (v) model evaluation that includes

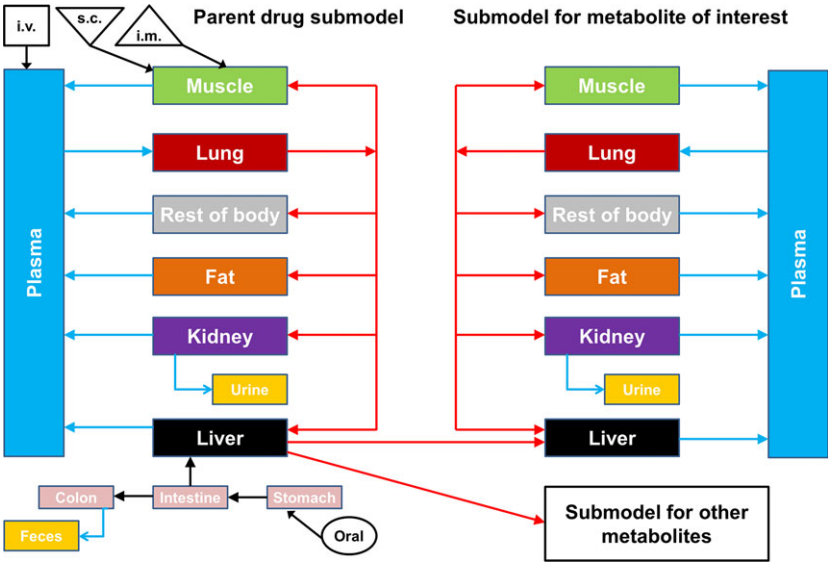

Fig. 2. A schematic of a general physiologically based pharmacokinetic (PBPK) model for veterinary drugs in food-producing animals. i.v., i.m., s.c., and oral represent drug administration through intravenous, intramuscular, subcutaneous, and oral routes, respectively. Metabolism is assumed to occur only in the liver, and elimination is depicted as through only the hepatic and renal pathways; other metabolic and excretory pathways can also be included. The rest-of-body compartment can be divided into slowly and richly perfused compartments depending on the similarity of kinetics of the modeled substance in the rest of tissues. Other target organs of interest (e.g., milk and eggs for applicable species) can be added as a single compartment. The submodel for the metabolite of interest is usually for the predominant metabolite. The model can be extended to include additional submodels for other metabolites of interest.

model validation and extrapolation, parameter sensitivity, uncertainty and variability analyses, as well as model completeness and portability assessment (whether the description of the model code is complete and whether the model code can be translated to and from other programming language) (McLanahan *et al.*, 2012), and (vi) model applications. A flowchart for PBPK model development, evaluation, and application processes is provided in Fig. 3. Note that in some research areas where funding is sufficient and new animal experiments are allowed, PBPK model development can begin by determining the essential model structure, followed by literature search and conducting new experiments to collect additional necessary data. However, in some cases if funding is limited or animal studies are not allowed such as developing a PBPK model in protected wildlife, PBPK model development has to start with a literature search and design the model structure based on available literature information. In addition, during step (v), iterative model adjustments may be needed based on model evaluation results.

Model structure

The criteria of the model structure are based on the intended application that may dictate specific tissues/compartments to be modeled, the availability of experimental/literature data, the design of the studies used to generate the experimental data, and the distribution properties of the substances (small molecules vs. nanoparticles). Typically, liver and kidney are selected as individual compartments because they are, respectively, the main metabolic and excretory organs for most drugs. From the food safety perspective, the edible tissues (i.e., muscle, liver, kidney, fat, milk, and/or eggs) are usually chosen as separate compartments so that specific inferences can be *made* due to their central role in establishing tissue tolerances for regulatory inspection (MacLachlan, 2010; Leavens *et al.*, 2014; Huang *et al.*, 2015a). For therapeutic purposes, the target organ of an initiated treatment, such as the lungs for respiratory diseases, should be included in the models (Baneyx *et al.*, 2014). Regarding risk assessment application, the target organ of toxicity, such as the brain for neurotoxicants, needs to be included in the model (Lin *et al.*, 2011, 2013). The fat should also be selected as a single compartment for highly lipophilic compounds (Evans & Andersen, 2000). In the field of nanomaterial PBPK modeling, the liver, spleen, kidneys, and lungs are designated as individual compartments because they are major phagocytic organs where nanomaterials primarily accumulate (Bachler *et al.*, 2015; Lin *et al.*, 2016a,b).

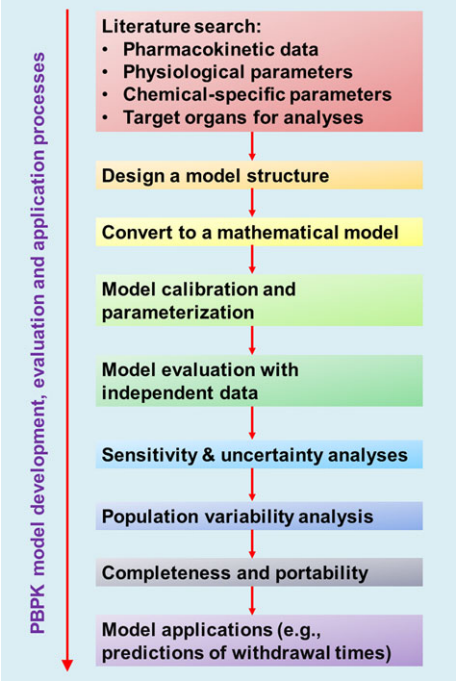

Fig. 3. A basic flowchart for physiologically based pharmacokinetic (PBPK) model development, evaluation, and application. Note that PBPK model development can also begin by determining the essential model structure, followed by literature search (please refer to the text for additional explanation). Additionally, during model evaluations, iterative model adjustments may be needed based on model evaluation results.

The remainder of the organs, unless therapeutically, toxicologically, or pharmacokinetically important can be lumped together as a 'rest-of-body' compartment (also called 'carcass' or 'others') or classified into slowly perfused tissue compartment and richly perfused tissue compartment depending on the similarity of kinetics of the modeled substance in these other tissues. Notably, the compartment lumping strategies have recently been applied to develop minimal PBPK models for antibody drugs in various species (e.g., humans, sheep, dogs, cats); these models make the bridge between compartmental and full PBPK models and provide meaningful predictions of drug disposition in the plasma and the lumped tissues with less complexity than a full PBPK model (Cao *et al.*, 2013; Li *et al.*, 2014a; Zhao *et al.*, 2015).

Mathematical descriptions of the ADME processes

Once the model structure is established, the complex physiological, biochemical, physicochemical, and pharmacokinetic processes can be translated into computer code using appropriate mathematical equations and software platforms. i.v. dosing is usually described with a single rate of administration directly into the venous blood, which is equal to the dose (mg/kg) multiplied by the body weight and then divided by the duration of the injection/infusion period (Martin *et al.*, 2012). Intramuscular or subcutaneous injection can be simulated using a one- or two-compartment injection site model. The former approach assumes that the injected drug is instantaneously and homogeneously mixed and absorbed directly into the venous compartment. The latter assumes that the injected amount is distributed between two compartments (i.e., site 1 and site 2) with absorption occurring from site 1 (Leavens *et al.*, 2012). A schematic depicting these two simulation approaches is shown in Fig. 4. The two-compartment model can be modified to simulate the intramuscular or subcutaneous injection of

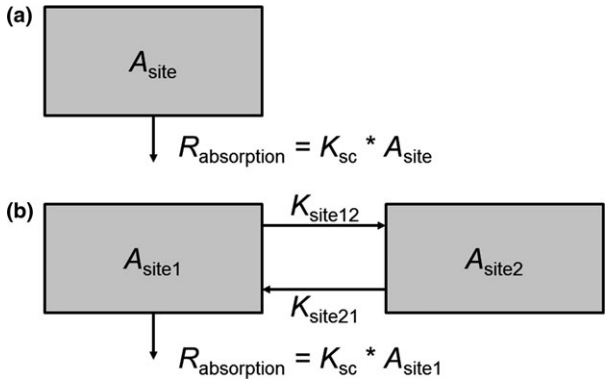

Fig. 4. A schematic of one- (a) and two-compartment (b) injection site model for describing intramuscular or subcutaneous injection. (a) A_{site}, K_{sc}, and $R_{absorption}$ represent the amount of the drug in the injection site (mg or μg), the absorption rate constant (per hour), and the absorption rate (mg/h or μg/h), respectively. (b) A_{site1}, A_{site2}, K_{sc}, K_{site12}, K_{site21}, and $R_{absorption}$ represent the amount of the drug in the injection site 1 (mg or μg), the amount of the drug in the injection site 2 (mg or μg), the absorption rate constant (per hour), the distribution rate constant from site 1 to site 2 (per hour), the distribution rate constant from site 2 to site 1 (per hour), and the absorption rate (mg/h or μg/h), respectively. This schematic was adapted from Leavens *et al.* (2012).

long-acting drug by dividing the drug into instantaneously mixed fraction and slowly released fraction (Lin *et al.*, 2015a). If *in vitro* dissolution profiles are available, these could be incorporated into the model.

Oral or dietary exposure is usually modeled using a simple two-tissue compartment assuming that (i) the drug is immediately available in the stomach following oral administration; (ii) distribution into the intestine is regulated by the rate of gastric emptying ($K_{emptying}$); and (iii) drug absorption is controlled by intestinal absorption rate ($K_{absorption}$) (Buur *et al.*, 2006; Yuan *et al.*, 2011). However, as PBPK modeling is a mechanistic approach and drug oral absorption depends on numerous factors, including *in vivo* drug solubility and lipophilicity, small intestinal length and diameter, intestinal villus morphology, gastric emptying time, small and large intestine transit times, fecal moisture content, intestinal flora, as well as intestinal permeability (Oswald *et al.*, 2015), oral absorption of drugs can also be simulated using a more complex mathematical description incorporating these various factors (e.g., advanced compartmental absorption and transit model) (Agoram *et al.*, 2001; Huang *et al.*, 2009; Sjodin *et al.*, 2011). These complex oral absorption simulations require more *in vitro* and *in silico* input data, such as drug disintegration and solubility, particle size, intestinal permeability, partition coefficient (logP), and ionization constant (p*K*a).

Because many factors can affect drug oral absorption, marked differences in drug oral bioavailability between humans and veterinary species, and between ruminants and nonruminants, are not unusual. In this regard, the principles of the Biopharmaceutics Classification System (BCS) initially developed to assess human drug oral bioavailability have been suggested as an important prognostic tool to be extrapolated to aid oral drug evaluation and development in canine species (Papich & Martinez, 2015). Readers are directed to these review articles (Martinez *et al.*, 2002a,b) regarding the physiological, biopharmaceutical, and formulation considerations when applying the BCS criteria to evaluate drug oral bioavailability in canine species. Unfortunately, such data are not available for other veterinary species.

Distribution of small molecular drugs or chemicals across biological membranes (the blood capillary membrane or cell membrane) may occur through passive diffusion, carrier-mediated transport, facilitated transport, or a combination of these processes. In practice, there are two mathematical representations describing the distribution of xenobiotics across membranes: flow-limited vs. membrane-limited models (Shen, 2013). A flow-limited distribution (also termed blood flow-limited or perfusion-limited) can be used if the cell membrane permeability for a particular drug is much greater than the blood flow rate to the tissue, meaning that the drug uptake rate to the tissue subcompartment is limited by the flow rate at which the blood carrying the drug arrives at the tissue, not by the rate at which the drug crosses the membrane. A membrane-limited model is used when uptake into the tissue subcompartment is limited by the cell membrane permeability and the total membrane surface, in which case the movement of the drug across cell membranes is slower than what is delivered by blood flow to the tissue. Usually, a flow-limited model is suitable for molecules that are very small and lipophilic (molecular weight < 300 Da), while a membrane-limited model is applicable for large and polar molecules (Shen, 2013). Compared to flow-limited models, membrane-limited models require more complex mathematical descriptions and additional parameters (i.e., permeability coefficients), which are usually estimated by fitting to experimental blood and tissue exposure data. This ultimately results in greater uncertainty for membrane-limited compared to flow-limited models. The type of model used in published PBPK models in the field of veterinary medicine is summarized in Tables 1 and 2.

In PBPK models, blood concentrations of bound and free compound can be described separately, and only free compound is generally considered to be available to participate in processes such as diffusion, metabolism, tissue activity, and intercompartmental transfer. Protein binding of xenobiotics (veterinary drugs and environmental contaminants) could be described using binding–unbinding homeostasis equations (related parameters include association/dissociation rate constants and maximum binding capacity scalar) or a first-order linear equation (percentages of bound and unbound). The former approach is usually used for PBPK modeling of environmental contaminants (Crowell *et al.*, 2011; Lin *et al.*, 2013), and the latter is commonly used in PBPK models of veterinary drugs (Leavens *et al.*, 2014; Huang *et al.*, 2015a). Note that both approaches can be used for environmental chemicals or drugs; and the selection of using which approach is mainly dependent on the available data. As in the case of tissue binding, the relationship of free to bound concentrations in the blood is

Table 1. Published PBPK models for drugs in food animal species

Drug	Species	Route	Model type	Validation	WT	Sens.	Uncert.	Varia.	Code	Software	Reference
Oxytetracycline	Salmonids	Oral	Mixed	Yes	NA	NA	NA	NA	NA	ACSL	Law (1992)
Oxytetracycline	Salmon	Oral	Mixed	Yes	Yes	NA	NA	NA	NA	ACSL	Brocklebank *et al.* (1997)
Oxytetracycline	Salmon	Oral	Mixed	Yes	Yes	Yes	NA	Yes	NA	ACSL	Law (1999)
Oxytetracycline*	Cattle	i.m., s.c.	Flow-limited	Yes	NA	Yes	NA	NA	NA	Excel	Achenbach (2000)
Oxytetracycline	Sheep	i.m.	Flow-limited	Yes	NA	Yes	NA	NA	Yes	ACSL	Craigmill (2003)
Sulfamethazine	Swine	i.v.	Flow-limited	Yes	Yes	Yes	NA	NA	NA	ACSLXtreme	Buur *et al.* (2005)
Sulfamethazine	Swine	i.v., oral	Flow-limited	Yes	Yes	Yes	NA	Yes	NA	ACSLXtreme	Buur *et al.* (2006)
Melamine	Rat, swine	i.v., oral	Flow-limited	Yes	Yes	Yes	NA	NA	NA	ACSLXtreme	Buur *et al.* (2008)
Sulfamethazine	Swine	i.v.	Flow-limited	Yes	NA	NA	NA	NA	NA	ACSLXtreme	Buur *et al.* (2009)
Midazolam	Chicken, turkey, pheasant, quail	i.v.	Flow-limited	Yes	NA	Yes	NA	NA	Yes	ACSLXtreme	Cortright *et al.* (2009)
Valnemulin	Rat, swine	Oral	Flow-limited	Yes	Yes	NA	NA	NA	NA	ACSLXtreme	Yuan *et al.* (2011)
Tulathromycin	Goat	s.c.	Membrane-limited	Yes	NA	Yes	NA	NA	NA	AcslX	Leavens *et al.* (2012)
Doxycycline	Swine	i.m., i.v.	Flow-limited	Yes	Yes	NA	NA	Yes	NA	ACSLXtreme	Yang *et al.* (2012)
Florfenicol	Crucian carp	i.m., oral	Flow-limited	Yes	NA	NA	NA	NA	NA	ACSLXtreme	Yang *et al.* (2013)
Flunixin	Cattle	i.v., i.m., s.c.	Flow-limited	NA	Yes	Yes	NA	Yes	NA	AcslX	Leavens *et al.* (2014)
Marbofloxacin	Chicken	Oral	Flow-limited	Yes	Yes	NA	NA	Yes	NA	ACSLXtreme	Yang *et al.* (2014b)
Olaquindox	Swine	Oral	Flow-limited	Yes	NA	Yes	NA	Yes	NA	ACSLXtreme	Yang *et al.* (2014a)
Cyadox	Swine	Oral	Flow-limited	Yes	NA	Yes	NA	Yes	NA	AcslX	Huang *et al.* (2015a)
Cyadox	Rat, swine	Oral	Flow-limited	Yes	Yes	Yes	NA	NA	NA	AcslX	Yang *et al.* (2015b)
Danofloxacin	Chicken	Oral	Flow-limited	Yes	Yes	Yes	NA	Yes	NA	ACSLXtreme	Yang *et al.* (2015a)

i.m., i.v., and s.c. represent intramuscular, intravascular, and subcutaneous injections, respectively. Mixed means that some compartments of the PBPK model are flow-limited and others are membrane-limited. WT means withdrawal time predictions. Sens. Uncert. and Varia. represent sensitivity, uncertainty, and variability analyses, respectively. Code means availability of the complete model code. Yes indicates that data are available. NA indicates that information is not available. ACSL and ACSLXtreme are former names of acslX. *This study was described in a Master Thesis and has not been published in peer-reviewed journal.

generally calculated by knowledge of dissociation binding constants and maximum concentrations of binding proteins (Buur *et al.*, 2009). Alternatively, plasma protein binding fraction of compounds can be determined using an equilibrium dialysis method (Huang *et al.*, 2015a).

The tissue–plasma partition coefficient (PC) is another important drug-specific input parameter that regulates drug distribution in PBPK models. PC represents the ratio of the concentrations of compounds between the tissue and the plasma at steady-state conditions. Thermodynamically, tissue–plasma partitioning is mainly the result of two processes: molecular diffusion due to thermal motion and intermolecular interactions (e.g., nonspecific van der Waals interactions, specific H-bond interactions, and ionic interactions) between two phases (Praetorius *et al.*, 2014). Depending on these interactions, once the system reaches thermodynamic equilibrium, the number of molecules moving back and forth between the two phases is the same.

The values of PC depend on many physicochemical and physiological factors, including solubility and unbound fraction in tissues and plasma, *n*-octanol–water partition coefficient ($K_{o:w}$), ionization constant (p*K*a), and tissue/plasma composition (e.g., fractions of neutral lipids, neutral phospholipids, acidic phospholipids, water, and proteins). PC values can be determined or calculated using *in vivo*, *in vitro*, empirical quantitative structure–activity relationships (QSAR), or mechanistic mathematical equations. Specifically, PC values can be calculated based on the ratio of the area under the concentration curves between the tissue and the plasma ($AUC_{tissue}/AUC_{plasma}$) or the ratio of tissue vs. plasma concentrations (C_{tissue}/C_{plasma}) at steady-state conditions (Lin *et al.*, 2011; Huang *et al.*, 2015a). PC values can also be determined using *in vitro* vial-equilibration methods (Tremblay *et al.*, 2012). Several empirical QSAR equations have been published to predict PC of drugs used in PBPK models (Lombardo *et al.*, 1996; Lanevskij *et al.*, 2011). Of note, these *in vivo*, *in vitro*, and empirical QSAR methods are generally time and cost intensive. In this regard, several mechanistic mathematical equations have been developed for predicting *a priori* PC for both drugs and environmental

Table 2. Published PBPK models for environmental contaminants in food animals and wildlife

Drug	Species	Route	Model type	Validation	WT	Sensitivity	Uncertainty	Variability	Code	Software	Reference
Lipophilic xenobiotics	Cattle, goat, swine, sheep	Oral	Mixed	NA	NA	NA	NA	NA	NA	lcc C compiler	MacLachlan (2009)
Organohalogen contaminants	East Greenland polar bear	Oral	NA	Yes	NA	NA	NA	NA	NA	NA	Sonne *et al.* (2009)
Cadmium	Trout, carp	Oral	Flow-limited	NA	NA	NA	NA	NA	NA	NA	Franco-Uria *et al.* (2010)
Lipophilic pesticides	Hen, chicken	Oral	Mixed	NA	NA	NA	NA	NA	NA	lcc C compiler	MacLachlan (2010)
PCB 153	Harbor porpoises	Oral	Flow-limited	Yes	NA	Yes	NA	NA	NA	Berkeley Madonna	Weijs *et al.* (2010)
Six PCB congeners	Harbor porpoises	Oral	Flow-limited	Yes	NA	NA	NA	NA	NA	Berkeley Madonna	Weijs *et al.* (2011)
PBDEs	Harbor porpoises	Oral	Flow-limited	Yes	NA	Yes	NA	NA	NA	Berkeley Madonna	Weijs *et al.* (2012)
PFOS	Cattle	Oral	Flow-limited	Yes	NA	NA	NA	NA	NA	ACSL	van Asselt *et al.* (2013)
DDT, DDE, DDD	Harbor porpoises	Oral	Flow-limited	Yes	NA	Yes	NA	Yes	Yes	Berkeley Madonna	Weijs *et al.* (2013)
PCB 153	Pilot whale	Oral	Flow-limited	NA	NA	Yes	NA	Yes	Yes	AcslX	Weijs *et al.* (2014)
Organohalogen contaminants	Polar bear	Oral, inhalation	Flow-limited	Yes	NA	Yes	NA	Yes	NA	Excel	Dietz *et al.* (2015)

Mixed means that some compartments of the PBPK model are flow-limited and others are membrane-limited. WT means withdrawal time predictions. Code means availability of the complete model code. Yes indicates that data are available. NA indicates that information is not available. ACSL is a former name of acslX. PBDE, polybrominated diphenyl ether; PCB, polychlorinated biphenyl; PFOS, perfluorooctanesulfonic acid; DDD, dichlorodiphenyldichloroethane; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane.

chemicals (Poulin & Krishnan, 1995; Poulin & Theil, 2000; Peyret *et al.*, 2010). These mathematical algorithms are based on drug-specific physicochemical and tissue-specific physiological parameters (e.g., tissue composition, $K_{o:w}$, pKa) that are usually known in early stages of drug development. PC values estimated using published mathematical algorithms have been shown to correlate well with those measured *in vivo* or *in vitro* (Poulin & Krishnan, 1995; Poulin & Theil, 2000; Peyret *et al.*, 2010). Therefore, mathematical algorithms for predicting PC have greatly facilitated PBPK model development for both drugs and environmental chemicals.

Most drugs are primarily metabolized in the liver. Metabolism of a compound can be described using a first-order linear equation or a Michaelis–Menten type of model (for describing nonlinearity in pharmacokinetics). For most environmental chemicals, the measured maximum metabolic rate (V_{max}) and/or Michaelis constant (K_m) using *in vitro* human or rodent hepatic microsomes, hepatocytes, or individual cytochrome P450s in human-expressed recombinant systems are usually available. Exposure doses to environmental toxicants could be very high (i.e., in animal toxicity studies), allowing their metabolism to reach saturation in the body, and hence, their metabolism is usually described with the Michaelis–Menten equation to simulate saturable metabolism (Crowell *et al.*, 2011; Lin *et al.*, 2011; Yang *et al.*, 2014c). As for veterinary drugs, metabolic rate parameters derived from hepatocytes and liver microsomal preparations are also available in preclinical species (i.e., rodents and dogs) and target food animal species, including pigs, chickens, cattle, and goats (Dalvi *et al.*, 1987; van 't Klooster *et al.*, 1993; Nebbia *et al.*, 2001; Szotakova *et al.*, 2004). Species-specific differences in drug metabolism (both qualitative and quantitative) are major drivers of pharmacokinetics of many therapeutic agents in individual animal species and contribute largely to variability in pharmacokinetic parameters (changes with age, gender, breed, feeding regimen, and disease). Note that the therapeutic dose window of veterinary drugs is narrow and their metabolism is generally not saturated at therapeutic doses, so a linear equation is often sufficient and commonly used to simulate their metabolism in food animals (Leavens *et al.*, 2014; Huang *et al.*, 2015a).

Elimination of veterinary drugs and their metabolites, similar to environmental chemicals, is mainly through urinary and biliary pathways. Urinary and biliary excretion can be described using a first-order linear equation (Lin *et al.*, 2015a) or a saturable nonlinear transport model (Clewell *et al.*, 2008; Emond *et al.*, 2013).

Representative equations describing key pharmacokinetic processes can be found from the references cited above. Complete model codes are also available for several recently published models (Yoon *et al.*, 2009; Loccisano *et al.*, 2012; Weijs *et al.*, 2014; Yang *et al.*, 2014c; Lin *et al.*, 2015a, 2016b). Readers are encouraged to refer to these references for further explanations of model equations and codes.

Modeling software

Availability of appropriate software tools is critical for model development, simulations, and applications. They determine how difficult it is to develop and apply the model. A comprehensive summary of available PBPK modeling software has recently been published by Rowland *et al.* (2011). These tools can be divided into custom and general-purpose software.

Custom software represents proprietary software systems that are custom designed for use by pharmaceutical companies in drug discovery and development, and include products such as Simcyp® Simulator (Certara, Princeton, NJ, USA), GastroPlus™ (Simulations Plus, Inc., Lancaster, CA, USA), and PK-Sim® (Bayer Technology Services, Leverkusen, Germany). These software systems generally have a user-friendly graphical interface, require minimal programming knowledge and are relatively easy to use, but are very limited to user-defined models and specific applications. For example, Simcyp® has included well-validated PBPK models for humans, dogs and rats, but not yet for food-producing animals, such as cattle and swine. Thus, Simcyp® is helpful in canine drug development (Mistry *et al.*, 2013; Pade, 2015; Pade *et al.*, 2015), but it cannot be used to predict drug tissue residues and withdrawal times in cattle or swine at this stage. In theory, however, the cattle or swine model can also be added to the Simcyp® platform, which requires proper validation before applications.

Another relevant custom software is the Phoenix® software (Certara), which is extensively used in veterinary medicine by drug companies to analyze pharmacokinetic, pharmacodynamic, and toxicokinetic data. However, recent studies have shown that it is also possible to use Phoenix® to develop PBPK models for drugs (Cao *et al.*, 2013; Hao *et al.*, 2014).

General-purpose software includes scientific computing or biomathematical modeling software, such as acslX™ (AEgis Technologies Group, Huntsville, AL, USA), Berkeley Madonna™ (University of California at Berkeley, CA, USA), and MATLAB® (The MathWorks, Inc., Natick, MA, USA). These software tools are more versatile and flexible, and in theory, could be used to simulate all possible drug administration scenarios, but they typically require medium- to high-level programming expertise, making the derived PBPK model relatively difficult to be applied by experimental and regulatory scientists with minimal modeling experience. In the field of risk assessment, acslX™ and Berkeley Madonna™ are two of the most commonly used software platforms, while for the purpose of predicting veterinary drug tissue residues and withdrawal times, all published models have been developed using acslX™ (Table 1). Unfortunately, the AEgis Technologies Group has officially sunsetted acslX™ since November 24, 2015, and thus, future PBPK models for veterinary drugs are recommended to be developed using alternative software platforms, such as Berkeley Madonna™ and MATLAB®. However, acslX™ models can be easily recoded into these other software platforms, underlying the importance of specifying all mathematical equations (or providing the complete model code in the supplementary materials) in any published model.

Model parameters and data sources

Model parameter values and data sources for model calibration/evaluation are usually *obtained* from the literature or, if not available, can be determined from a dedicated study. PBPK-related physiological parameter values are now available in many species, including humans, mice, rats, dogs, rabbits, monkeys (Davies & Morris, 1993; Brown *et al.*, 1997), swine (Upton, 2008), sheep (Craigmill, 2003), goats (Leavens *et al.*, 2012), cattle (Leavens *et al.*, 2014), chickens (Cortright *et al.*, 2009; Yang *et al.*, 2015a), turkeys, pheasants, quail (Cortright *et al.*, 2009), crucian carp (Yang *et al.*, 2013), as well as even pilot whales, polar bears, and harbor porpoises (Weijs *et al.*, 2013, 2014; Dietz *et al.*, 2015). Physiological parameters relevant to PBPK models for veterinary drugs in common food-producing animal species are summarized in Table 3. Chemical-specific parameters, besides those *obtained* from the literature, can be measured using *in vivo* or *in vitro* assays (Buur *et al.*, 2009; Tremblay *et al.*, 2012; Huang *et al.*, 2015a), estimated using *in silico* methods (Poulin & Theil, 2000), or optimized by fitting the model to experimental data using mathematical

Table 3. Physiological parameters for PBPK modeling in common food-producing animal species

Parameter	Cattle*,†	Chicken‡,§	Carp¶	Goat** (juvenile)	Goat** (market age)	Swine††,‡‡	Sheep‡‡,§§
Body weight (kg)	50–500	0.35–1.95	0.26	8.4	19.9	25	45
Cardiac output (L/h/kg)	5.67	11.3–17.6	5.151	4.5	4.5	4.944	6.9
Tissue volume (fraction of body weight, unitless)							
Blood	0.04	0.047–0.07	0.0411	0.026	0.06	0.06	0.045–0.057
Liver	0.013–0.03	0.0224–0.024	0.0116	0.034	0.019	0.02–0.0294	0.015–0.016
Kidney	0.0026–0.0035	0.0058–0.0064	0.008	0.0079	0.0035	0.004	0.003–0.0046
Muscle	0.27–0.45	0.4–0.4015	0.465	0.23	0.38	0.4	0.277
Fat	0.15–0.20	0.05	NA	0.041	0.085	0.3–0.34	0.168
Lung	0.008–0.0093	0.0054–0.0059	NA	0.0053	0.012	0.01	0.01
Blood flow (fraction of cardiac output, unitless)							
Liver	0.35–0.53	0.15–0.23	0.1814	0.18	0.18	0.24–0.305	0.183–0.474
Kidney	0.09–0.11	0.10–0.15	0.1023	0.064	0.064	0.1–0.14	0.064–0.1673
Muscle	0.18–0.45	0.35	0.3977	0.22	0.22	0.25–0.252	0.1374–0.224
Fat	0.02–0.08	0.015	NA	0.11	0.11	0.08–0.175	0.06–0.15

Data represent the average value or the range of reported values. NA, not available. *Achenbach (2000); †Leavens *et al.* (2014); ‡Cortright *et al.* (2009); §Yang *et al.* (2014b); ¶Yang *et al.* (2013); **Leavens *et al.* (2012); ††Buur *et al.* (2005); ‡‡Upton (2008); §§Craigmill (2003).

algorithms (Smith *et al.*, 2014). For example, as introduced before, hepatic metabolic rates can be determined using *in vitro* hepatic microsomes or hepatocytes (van 't Klooster *et al.*, 1993; Nebbia *et al.*, 2001). Partition coefficients can be measured using *in vitro* negligible depletion solid-phase microextraction and ultrafiltration methods (Tremblay *et al.*, 2012), estimated using tissue composition mathematical models (Poulin & Theil, 2000), or calculated based on the $AUC_{tissue}/AUC_{plasma}$ ratio (Leavens *et al.*, 2012). Partition and permeability coefficients can also be estimated/optimized through mathematical algorithms based on experimental blood and tissue concentration profiles (Craigmill, 2003; Leavens *et al.*, 2012).

CURRENT APPLICATIONS IN VETERINARY MEDICINE

Estimation of drug tissue residues and withdrawal times in food-producing animals

In the field of veterinary medicine, the most common application of PBPK modeling relates to the prediction of drug tissue or milk residue depletion and withdrawal times in food-producing animals. This is key because the noncentral *t* distribution statistical tolerance limit methodology (Owen, 1968) commonly used by US FDA [in the Europe the Stange method is used (EMEA/CVMP, 1996)] to derive withdrawal times makes inferences on a limited number of healthy animals, while the real-life use of drugs relates to the treatment of a quite diverse population of diseased animals often using different routes of administration. Violations of drug residues have occurred in the National Residue Program quarterly report, even though animals were slaughtered following the FDA withdrawal time guidelines (USDA, 2015). It goes without saying that drug residue violations are a global public health issue (Baynes & Riviere, 2014), such that more appropriate methods are needed to properly estimate the withdrawal time of drugs intended for use in food-producing animals.

PBPK modeling has been shown to be a scientifically sound approach to estimate withdrawal times because mechanistic physiological information (e.g., mode of action of the drug, exposures in organs of interest, and effect of the disease on drug disposition) can be incorporated in the model predictions. This is particularly true in milk withdrawal time estimation because milk composition can be very different among different mammalian species (Iyengar, 1982; Potočnik *et al.*, 2011). A few PBPK models with a milk compartment for drugs or environmental contaminants have been reported (MacLachlan, 2009; van Asselt *et al.*, 2013; Leavens *et al.*, 2014). A sensitivity analysis could be useful to anticipate withdrawal time violations and the main factors that should be taken into account could be identified in the sensitivity analysis of individual parameters. Typically, for a drug that is metabolized in the body, metabolic rate and partition coefficient parameters should be considered.

Early studies. PBPK models for predicting drug residue depletion and withdrawal times have been reported for a dozen drugs in several common food animal species, including fish, sheep, goat, cattle, swine, and chickens (Table 1). To the authors' knowledge, Law's group from Canada was the first to apply PBPK modeling to food safety studies. In 1992, Law realized that the legislation on the withdrawal periods of oxytetracycline- (OTC)-treated fish did not take into consideration the various doses, dosing schedules, fish weights, and several additional factors, which would significantly affect OTC distribution and residues in fish tissues (Law, 1992). He therefore developed a nine-compartment (flow-limited: blood, gills, liver, gut, kidney, and carcass; membrane-limited: bone, muscle, and skin) PBPK model for OTC disposition in trout and chinook salmon that successfully predicted the measured concentrations of OTC in fish tissues after single or multiple oral dosing (Law, 1992). This model predicted a withdrawal period of 100 days postdosing in a 14-day 100 mg/kg oral exposure paradigm, which was much shorter than the 145 days recommended withdrawal time calculated using a classical pharmacokinetic approach (Brocklebank *et al.*, 1997). This earlier model was used as a basis for subsequent modeling efforts. Although it proved extremely valuable, this initial model did not consider population variability. In fish, body (water) temperature is a major covariate for withdrawal times. To address this drawback, the model was further optimized using Monte Carlo sampling techniques to account for the interindividual variability across the population (Law, 1999). The population model-predicted withdrawal periods were 60 days in a 21-day 75 mg/kg oral exposure at 9 °C seawater and 49 days at 15 °C seawater for the 99th percentile population with 95% confidence, which were very close to those determined using an empirical statistical method (62 and 49 days, respectively). The authors concluded that the population PBPK model was a more useful tool than the statistical method for withdrawal time determination because treatment specific information, such as fish weight, bioavailability, dose regimen, and water temperature could be incorporated in the simulation. Law's OTC PBPK model was also extrapolated to simulate the kinetics and determine tissue residues of OTC in the cattle after i.m. and s.c. injections, but the cattle model has not yet been published in a peer-reviewed journal (Achenbach, 2000).

Based upon Law's work, Craigmill further expanded PBPK applications to domestic food animals. He developed a flow-limited PBPK model for OTC in sheep that well predicted OTC tissue residues after i.m. injection with a long-acting formulation (Craigmill, 2003). This model suggests the applicability of PBPK modeling to the prediction of tissue residues and establishment of withdrawal times in ruminants, and provides a rationale for extrapolation to other food animals. Craigmill, Cortright and their co-workers also developed a PBPK model for midazolam in the chicken, which was successfully extrapolated to the turkey, pheasant and quail (Cortright *et al.*, 2009).

Recent studies. Since early 2000s, Riviere, Baynes, and co-workers have been applying PBPK modeling to address drug residue and withdrawal time-related issues within the framework of the Food Animal Residue Avoidance Databank (FARAD) program. Buur *et al.* (2005) first developed and validated a flow-limited 6-compartment PBPK model for sulfamethazine in swine that accurately predicted sulfamethazine concentrations in edible tissues after i.v. injection. The model-predicted withdrawal interval was 120 h compared to 100 h previously estimated by FARAD based on a FARAD-recommended approach (i.e., using 10 times of the plasma half-life). This PBPK model built from i.v. exposure was then adapted to include an oral dosing route, with a Monte Carlo sampling technique finally used to predict the withdrawal time of sulfamethazine in swine after a FDA-labeled oral exposure paradigm (Buur *et al.*, 2006). The population model-predicted withdrawal time was 21 days for the 99th percentile of the population with 95% confidence based on the amounts of residues in the kidney, compared to the FDA-labeled withdrawal time of 15 days and a calculated withdrawal time of 12 days using FDA's tolerance limit algorithm. Based on these results, the authors concluded that the withdrawal time of 15 days may be inadequate to cover the upper limit of the 95% confidence interval for the 99th percentile of the swine population and should be re-evaluated in light of public health concerns over the presence of sulfamethazine residues.

Another important milestone in the PBPK modeling of sulfamethazine in veterinary species relates to the inclusion of drug interactions with flunixin. This was motivated by the common concurrent administration of the two drugs, which could potentially lead to increased tissue residues of sulfamethazine and/or flunixin (Buur *et al.*, 2009). The model successfully linked plasma protein binding interactions to drug disposition for sulfamethazine and flunixin in swine and predicted a sustained decrease in total sulfamethazine and a temporary increase in free drug concentration, which was confirmed by an *in vivo* experiment. This case study illustrates an additional application of PBPK modeling in veterinary medicine. The model could be a useful tool to aid in the determination of dosage regimens for labeling veterinary drugs and in the protection of the food supply chain through predictions of withdrawal times.

Besides the sulfamethazine model, Riviere and co-workers have also developed PBPK models for disposition kinetics of melamine in swine (Buur *et al.*, 2008), tulathromycin in goats (Leavens *et al.*, 2012), flunixin in cattle (Leavens *et al.*, 2014), and cyadox in swine (Huang *et al.*, 2015a). The melamine model was initially built in rats and then extrapolated to pigs to predict withdrawal intervals after single and multiple oral administrations. This was done because both plasma and tissue data were available in rats, but only plasma data were available in pigs, such that PCs for rats were used in the pig model. This strategy makes it possible to develop PBPK models in species for which pharmacokinetic data are relatively limited. This modeling approach was applied in a few subsequent models by other scientists (Yuan *et al.*, 2011; Yang *et al.*, 2015b). The tulathromycin model used both flow-limited and membrane-limited approaches to simulate the pharmacokinetics of tulathromycin after s.c. injection and it was reported that the latter provided better predictions. This may be in part because tulathromycin has a relatively high molecular weight (806 Da) for a small molecule. In addition, this model was initially developed in market age goats and then successfully validated in juvenile goats using age-related physiological parameters. This study demonstrated that PBPK models for veterinary drugs in food animals can be extrapolated across ages and production classes.

The flunixin cattle model was used to simulate up to 14 pharmacokinetic studies in both healthy and diseased cattle from different production classes after i.v., i.m., or s.c. exposure (Leavens *et al.*, 2014). The simulation results suggest that it was necessary to consider variability due to disease and age in establishing withdrawal intervals and that extravascular routes of administration prolonged flunixin depletion in milk, which may result in violative milk residues in treated cattle. All the above mentioned veterinary drug models focused on simulating the pharmacokinetics of parent drugs, without considering their metabolites. In this regard, the cyadox PBPK model by Huang *et al.* (2015a) was used to simultaneously predict the depletion of cyadox and its main metabolite, the marker residue 1,4-bisdesoxycyadox, in both plasma and tissues of swine. This model provides a basis for developing PBPK models to estimate tissue residues and withdrawal times of both parent drugs and their metabolites in food animals.

Since 2010, many scientists in China have started to apply PBPK modeling in food safety research. Liu, Zeng, Fang and their colleagues have developed PBPK models for valnemulin in swine (Yuan *et al.*, 2011), doxycycline in swine (Yang *et al.*, 2012), florfenicol in fish (Yang *et al.*, 2013), marbofloxacin in chickens (Yang *et al.*, 2014b), cyadox in swine (Yang *et al.*, 2015b), and danofloxacin in chickens (Yang *et al.*, 2015a). In addition, Yuan's laboratory has recently developed PBPK models for olaquindox and cyadox in swine (Yang *et al.*, 2014a; Huang *et al.*, 2015a). These models further demonstrate the great applicability of PBPK modeling in the determination of drug tissue residues and withdrawal times. Simulation results from this work have the potential to guide regulatory agencies in their overall assessment of the validity of studies focusing on residue and withdrawal time determination.

Risk assessment of environmental contaminants in food animals and in wildlife

Food animals and wildlife may be exposed to environmental contaminants, including lipophilic pesticides, through the contamination of their food supply and/or water. This could result in residues in plasma, tissues, milk, or eggs, requiring an appropriate assessment and management of the risks associated with it. A list of published PBPK models for environmental contaminants in food animals and wildlife is provided in Table 2. For food animals, MacLachlan developed a PBPK

model to simulate the transfer of lipophilic xenobiotics from the feed to lactating dairy cows, and this model was extrapolated to beef cattle, goats, sheep, and pigs (MacLachlan, 2009). A similar model was developed in laying hens and extrapolated to broilers (MacLachlan, 2010). These studies demonstrated that PBPK modeling can be used to assess the risks of environmental contaminants in the feed supply of food animals by extrapolating within and between species to maximize the use of available experimental data.

In the environment, fish can be exposed to various water contaminants, including the heavy metal cadmium. Franco-Uria *et al.* (2010) developed a PBPK model using a set of generic parameters (only the absorption rate was condition-specific) to predict cadmium concentrations in the tissues of diverse fish species under different environmental conditions. The model predicted 27 experimental datasets for cadmium concentrations in fish tissues relatively well. This study suggests that a general PBPK model could be established using a generic global input parameter set to predict environmental contaminant concentrations in various fish species in different exposure scenarios to aid risk assessment.

Polar bears consume a large amount of seal blubber and other high tropic marine mammals, and consequently, have high tissue concentrations of persistent organic pollutants, such as organohalogen contaminants. It is extremely difficult to assess the potential toxic effect in wildlife as a result of exposure to organohalogen contaminants because the exposure history of individual animals is unknown and usually only a 'snapshot' of plasma or tissue concentrations of organohalogen contaminants at a given time in the individual's life is available. PBPK modeling was applied to conduct a risk quotient evaluation to more quantitatively evaluate the risk of organohalogen contaminants, including polychlorinated biphenyl (PCB), dichlorodiphenyldichloroethylene (DDE), dieldrin, oxychlordane, polybrominated diphenyl ether (PBDE), and perfluorooctanesulfonic acid (PFOS) on reproduction, immunotoxicity, and carcinogenicity in polar bears across the Arctic based on known pharmacokinetics and dynamics of organohalogen contaminants in laboratory rats (Sonne *et al.*, 2009; Dietz *et al.*, 2015). The simulation results suggest that environmental exposure to PCB, PFOS, or dieldrin is associated with adverse health effects on reproduction in polar bears in East Greenland, but environmental exposure to oxychlordane, dichlorodiphenyltrichloroethane (DDT), hexachlorobenzene, and hexachlorocyclohexane appears less likely to be linked to reproductive effects. These studies indicate that PBPK models may be a supportive tool in the evaluation of possible adverse health effects associated with environmental exposure to persistent organic pollutants in wildlife.

PBPK models have been developed to simulate the bioaccumulation of persistent organic pollutants, including PCB, DDE, DDT, and PBDE, during the entire life span of marine mammals, such as harbor porpoises and long-finned pilot whales (Weijs *et al.*, 2010, 2011, 2012, 2013, 2014). These models are important in the risk assessment of environmental pollution on the health of marine mammals because exposure experiments to environmental contaminants are not feasible or ethical in marine mammals and they are highly sensitive to pollution due to their limited metabolic capacities, long life span, and top position in marine food chains. These models provide a new, nondestructive tool that enables the integration of biomonitoring activities, *in vitro* studies, and *in vivo* data on laboratory animals for risk assessment purposes in these protected marine mammals. It should be noted that PBPK modeling in marine mammals is a challenge due to the lack of species-specific physiological and chemical-specific parameter information and the ban on exposure experiments. Nevertheless, recent studies have shown that parameters for these PBPK models could be estimated using the Bayesian approach executed with Markov chain Monte Carlo simulations using 'prior' information of the parameters, either from the literature or from previous model runs, to calculate probability distributions for determining 'posterior' values that best explain the field observations (Weijs *et al.*, 2013, 2014). This PBPK modeling approach could be well extended to other protected marine mammals.

Design of therapeutic regimens in veterinary medicine

Similar to applications in human medicine, PBPK models can also be used in the design of optimal therapeutic regimens for veterinary drugs. Recently, we developed a multiroute PBPK model for OTC in dogs after i.v., i.m., and oral administration with traditional or long-acting formulation (Lin *et al.*, 2015a). This dog model was then validated using multiple independent datasets and successfully extrapolated to humans. The dog model was applied to predict the 24-h area under the curve of OTC concentrations in the plasma, liver, kidney and muscle under three different therapeutic regimens. These simulations can guide the design of optimal therapeutic plans with OTC in veterinary, and potentially, human medicine. The latter is especially important when human exposure to potentially toxic therapeutics or drug trials to treat lethal human pathogens (e.g., Ebola, certain bacteria) are not possible, requiring animal studies as a substitute.

ADVANTAGES AND DISADVANTAGES OF PBPK MODELING COMPARED TO OTHER PHARMACOKINETIC MODELING APPROACHES

As recently described by Riviere *et al.* (2016), other mathematical pharmacokinetic modeling and simulation techniques besides PBPK can be applied to problems in animal health. These include traditional compartmental/noncompartmental pharmacokinetic modeling, population pharmacokinetic modeling, and interspecies allometric scaling (Riviere *et al.*, 2016). All these methods have been shown to be useful in human and veterinary medicine, but each method has inherent advantages and shortcomings.

PBPK modeling vs. traditional compartmental/noncompartmental pharmacokinetic modeling

Traditional pharmacokinetic models simulate the ADME processes of a particular compound in a one matrix (plasma or individual tissues) for a small sample of animals (Riviere, 2009, 2011). These usually include compartmental (one-, two-, or three-compartment models) and noncompartmental analyses, also referred to as the statistical moments approach. Compartmental model parameters include volume of distribution (V_d), clearance (Cl), half-life ($T_{1/2}$), bioavailability (F), absorption rate constant (K_a or K_{01}), elimination rate constant (K_{el} or K_{10}), and intercompartmental distribution rate constants (e.g., K_{12} and K_{21}). Noncompartmental model parameters include mean residence time, maximum or peak concentration (C_{max}), and area under the concentration curve (AUC). Note that common compartmental pharmacokinetic parameters can be calculated using noncompartmental analyses (listed in Table 9.3 in Riviere, 2011).

Compared to noncompartmental analysis, the strength of compartmental models is that they can be used to predict plasma time–concentration profiles for different dosage regimens. The limitation is that the parameter values are specific to the sample of the population from which data were collected and this may vary widely between different studies. As a result, it is often difficult to integrate disparate compartmental pharmacokinetic parameters for in-depth analysis to obtain general conclusions (unless population-based approaches are used) and to extrapolate across studies. Additionally, depending on the sensitivity of the assay, classical pharmacokinetic studies often pay little attention to the terminal kinetic phase where the plasma concentrations are relatively low and have no therapeutic significance, especially when the concentrations are close to detection limits. However, when it comes to animal-derived food safety assessment, this slowly depleting phase is related to possible violative residue levels and is thus critical for the determination of withdrawal times. Also, PBPK modeling could be very useful for doping control because it could simulate the low concentration terminal phase of the kinetic profile of illicitly used drugs.

PBPK modeling vs. population pharmacokinetic modeling

Nonlinear mixed-effects pharmacokinetic (NLME-PK) modeling is the most commonly used population pharmacokinetic approach. NLME-PK modeling is a single-stage modeling approach for integrated analysis of diverse pharmacokinetic datasets that considers the population rather than the individual as the unit of analysis for estimating the distribution of pharmacokinetic parameters and their relationship with covariates within the population (Beal & Sheiner, 1982; Martin-Jimenez & Riviere, 1998; Kiang *et al.*, 2012; Li *et al.*, 2015). NLME-PK models are typically composed of three components: the structural, statistical, and covariate (if data are available) models. NLME-PK modeling is essentially the same approach as compartmental (curve-fitting) pharmacokinetic modeling, except that a statistical model of parameter variability is overlaid on the structural pharmacokinetic model. As a result, NLME-PK modeling can be used to describe the intersubject and intrasubject variability in pharmacokinetic parameters and explore how this variability can be explained by covariates of the population.

In veterinary medicine, NLME-PK modeling technique has been used to integrate the results from numerous studies to determine withdrawal times that ensure drug residue concentrations below violative levels in 99% of the population (Wu *et al.*, 2013a,b; Li *et al.*, 2014b). The advantage of using NLME-PK approach to estimate withdrawal times is that it pools all available data from different studies, making it possible to provide a range of withdrawal times in both diseased and heathy animals. This is in contrast to typical residue studies that are carried out in a relatively small sample of animals from the target population (Li *et al.*, 2015). In this regard, both NLME-PK and PBPK modeling approaches are, even though different in theory, excellent tools for drug withdrawal time estimations in food animals (especially diseased) and for dosage regimen selection in veterinary medicine. However, as NLME-PK modeling is not a physiologically based mechanistic approach, it is limited in usefulness to extrapolate beyond the inference range of the experimental data, although that range is considerably wider because data from many sources and studies can be combined. Additionally, it is not optimal for assessing the risk of environmental toxicants in wildlife.

PBPK modeling vs. interspecies allometry

Allometry is the study of the relationship between the size of an organism and the properties of the organism (Boxenbaum, 1982; Huang & Riviere, 2014). The assumption of interspecies allometric scaling is that there are anatomic, physiological and biochemical similarities among animal species and simple mathematical models can be used to describe these interrelationships. The simple allometric scaling equation is $Y = a \times W^b$, where Y is the parameter of interest, W represents the average body weight of the species, a and b are the allometric coefficient and exponent for a given drug, respectively. The strength of using interspecies allometric scaling to predict pharmacokinetic parameters is that the analysis is rather simple and fast with a relatively high success rate (~80%) (Riviere *et al.*, 1997; Mahmood *et al.*, 2006; Martinez *et al.*, 2006; Huang & Riviere, 2014; Huang *et al.*, 2015b).

Allometric approaches have been used with some success for compounds for which pharmacokinetics is driven by passive processes (e.g., ampicillin and OTC) (Huang *et al.*, 2015b). For example, allometric scaling of animal renal clearance has been relatively successful when renal clearance is driven by glomerular filtration rate which is also scaling allometrically. However, attempts to apply allometric scaling techniques to compounds metabolized, biliary excreted, highly protein bound, or actively transported (e.g., antipyrine, diazepam, doxycycline, and warfarin) have resulted in poor predictions (Riond *et al.*, 1990; Huang *et al.*, 2015b). These failures are due to the

inability of these approaches to account for species differences in the transport rate, protein isoform and abundance. There is a growing momentum to use *in vitro* methods, nestled within PBPK models as the primary source of prediction of human pharmacokinetics. This represents a shift in the paradigm for predictions in humans, which has been traditionally based on *in vivo* empirical approaches involving allometric scaling.

Allometric interspecies scaling has proven to be a useful tool for the extrapolation of pharmacokinetic parameters from animals to humans and it is often used for estimating the dose in first-time-in-human studies. This approach also plays a pivotal role in zoo animal and wildlife medicine because there are very few (<15) therapeutic drugs approved for zoo and wildlife species and relevant pharmacokinetic data are rather limited (Riviere, 1997). Interspecies allometric scaling provides a powerful tool in this scenario to extrapolate the drug pharmacokinetic characteristics from domestic species to nondomestic species.

Interspecies allometric scaling has several limitations. First, as mentioned before, drugs that are highly protein bound, have significant biliary excretion, extensive active renal secretion, active metabolism and other transport processes, or have species-specific binding, distribution or metabolism characteristics that may not be suitable for allometric scaling extrapolation (Huang & Riviere, 2014). Nanomaterial pharmacokinetic interspecies allometric predictions may also not be applicable because of extensive nanomaterial–protein bioconora formation (Sahneh *et al.*, 2015). Also, this approach cannot be applied to extrapolate from ectothermic to endothermic animals as the rate of metabolism of ectothermic animals is variable and dependent on environmental factors, such as temperature (at higher temperatures, ectothermic animals may have higher rates of metabolism) (Brischoux *et al.*, 2008). Most importantly, although interspecies allometry can be used to predict pharmacokinetic parameters across species, it is not the optimal approach to predict the time course of plasma or tissue concentrations of drugs in another species. Therefore, interspecies allometric scaling is useful in veterinary medicine in terms of dose selection and predictions of pharmacokinetic parameters, to identify individual species that are outliers compared to others (e.g., vertical allometry), and has limited application in drug withdrawal time determination in food animals or risk assessment of environmental pollutants in wildlife.

Overall comparisons of pharmacokinetic modeling techniques

Compared to classical compartmental/noncompartmental, NLME-PK, and allometry modeling approaches, the advantages of PBPK models in veterinary medicine are (Shen, 2013): (i) They can simulate the time course and predict the concentration of drugs in any organ or tissue of interest, (ii) they allow for the evaluation of the effects of changing physiological parameters on tissue drug concentrations, (iii) they constitute a powerful tool for extrapolation across species, exposure routes, doses and duration, (iv) they have the ability to integrate concurrent ADME mechanisms with a variety of compound properties in a physiological context, and (v) these models are best-suited to directly incorporate *in vitro* data. The disadvantages are (Shen, 2013): (i) mathematical modeling per se can be difficult for many veterinarians, pharmacologists, or toxicologists because it is usually performed using biomathematical software that requires medium- to high-level programming expertise due to lack of 'plug-and-play' custom software for the majority of veterinary species (except dogs that are available in Simcyp®), and (ii) model parameters may not be available for nondomestic species, especially in pathophysiological states, which would increase model parameter uncertainty. The advantages and disadvantages of NLME-PK modeling compared to other pharmacokinetic modeling approaches will be discussed in details in a subsequent review from this series of manuscripts that aim to foster the application of mathematical modeling in veterinary medicine (Riviere *et al.*, 2016). Overall, we contend that PBPK modeling is a conceptually sound approach with a variety of applications in veterinary medicine.

FUTURE PERSPECTIVES

In future PBPK modeling studies, model parameter uncertainty and variability should be addressed or discussed. PBPK models for veterinary species, especially for wild animals such as marine mammals, typically have a high degree of parameter uncertainty and variability due to the scarcity of information and the embryonic nature of this field. Physiological parameter values used in veterinary species models are sometimes taken from the average estimate of laboratory animal species (e.g., rats and mice), which might not be appropriate. While compiled databases for PBPK-related physiological parameters exist in the literature for laboratory animals and humans (Brown *et al.*, 1997), these data have not been compiled for food animals or wildlife. Therefore, to reduce model uncertainty, it is important to conduct a comprehensive review on comparative anatomic/vascular structure and physiological parameters in veterinary species, including cattle, swine, goats, sheep, chickens, turkeys, ducks, geese, cats, dogs, horse, marine mammals, reptiles, amphibians and various species of fish, similar to what have been done in laboratory animals and humans (Brown *et al.*, 1997). As a first step, PBPK-related physiological parameters for several common food animal species are summarized in Table 3. Uncertainty in drug-specific parameters can be resolved by experimental determination using appropriate methods. Monte Carlo technique should be used to address the question of parameter variability (Buur *et al.*, 2006). This is particularly important for food safety applications because the withdrawal time derived from a simple deterministic PBPK model only represents the average of a group of animals. Monte Carlo simulations can consider the variability of physiological parameters (e.g., organ weight and blood flow) due to disease, genetic polymorphism, or other factors to simulate population variability of drug pharmacokinetics and to estimate withdrawal times for a large and diverse population within a PBPK model.

A publicly available comprehensive veterinary pharmacokinetic database needs to be developed. Unlike human medicine for which drug pharmacokinetic data are abundant, veterinary pharmacokinetic data are relatively limited, scattered, and some are old and difficult to find; it is therefore often difficult to collect sufficient data to develop a reliable model in veterinary species.

Thorough and consistent documentation of model development and quality assessment is needed to increase user confidence and to have more widespread applications of published models. The guidelines for publications and peer review of PBPK models in human risk assessment (WHO, 2010; McLanahan *et al.*, 2012) and drug development (Sager *et al.*, 2015) have recently been published. Specific guidance for model applications in veterinary medicine is not yet available and needs to be established in the future. The present manuscript provides a first basis for establishing guidelines of PBPK model development and application in veterinary medicine.

PBPK model codes should be published or made readily available along with the manuscripts. Although publishing a PBPK model in a peer-reviewed journal is a mark of good science, the supporting computer code is necessary for subsequent model applications. It has been shown that the availability of model codes is a key factor in determining whether a published PBPK model may be applicable in human risk assessment for environmental toxicants (McLanahan *et al.*, 2012). Among the three dozen published PBPK models in veterinary species, only a few model codes are published (Craigmill, 2003; Cortright *et al.*, 2009; Weijs *et al.*, 2013, 2014; Lin *et al.*, 2015a). The availability of such materials should be one of the key criteria highlighted in the guideline of PBPK model documentation and evaluation in veterinary medicine. Note that nowadays most journals accept model codes and other types of raw data as supplementary materials published online and some journals exist to publish only raw data, including model codes. Therefore, it is highly recommended that future PBPK model manuscripts publish the associated model codes.

Further to this, user-friendly affordable PBPK software packages for veterinary species should be developed. One reason for the great advancement of PBPK modeling in human drug development lies in the availability of user-friendly PBPK software tools. These tools would enable scientists to develop and apply PBPK models without the need of special mathematical or computer programming skills. These software systems are mostly custom designed, proprietary, and specifically for humans and laboratory animal species. We suggest that these software tools be extended to veterinary species to increase the application of this technique in veterinary medicine.

The establishment of graduate education programs focusing on PBPK modeling training in academic institutions is highly encouraged, because unlike the biomedical job market in which the supply greatly exceeds the demand (Alberts *et al.*, 2014), the PBPK modeling field is very narrow, specialized, and the supply does not meet the demand due to lack of graduate education programs.

To conclude, the current application of PBPK modeling in veterinary medicine is not as widespread, nor accepted by regulatory agencies, as it is in the human drug discovery and development. However, in light of its promising applications, we expect that this efficient and versatile tool will be utilized increasingly in both human and veterinary medicine. Future PBPK modeling research, education, and applications in veterinary medicine should consider the aforementioned suggestions on model development and documentation, physiological parameter databases for minor species, veterinary pharmacokinetic databanks, as well as availability of model codes, user-friendly software tools, and graduate education programs.

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CONFLICT OF INTEREST STATEMENT

The authors report no conflict of interests.

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