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Review

Physiologically based kinetic models for farm animals: Critical review of published models and future perspectives for their use in chemical risk assessment

L.S. Lautz[a,*], R. Oldenkamp[a], J.L. Dorne[b], A.M.J. Ragas[a,c]

[a] Department of Environmental Science, Institute for Water and Wetland Research, Radboud University Nijmegen, Houtlaan 4, 6525 XP Nijmegen, The Netherlands
[b] European Food Safety Authority, Via Carlo Magno, 1A, 43126 Parma, Italy
[c] Department of Science, Faculty of Management, Science & Technology, Open University, 6419 AT Heerlen, The Netherlands

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ABSTRACT

Physiologically based kinetic (PBK) models in the 10 most common species of farm animals were identified through an extensive literature search. This resulted in 39 PBK models, mostly for pharmaceuticals. The models were critically assessed using the WHO criteria for model evaluation, i.e. 1) purpose, 2) structure and mathematical representation, 3) computer implementation, 4) parameterisation, 5) performance, and 6) documentation. Overall, most models were calibrated and validated with published data (92% and 67% respectively) but only a fraction of model codes were published along with the manuscript (28%) and local sensitivity analysis was performed without considering global sensitivity analysis. Hence, the reliability of these PBK models is hard to assess and their potential for use in chemical risk assessment is limited. In a risk assessment context, future PBK models for farm animals should include a more generic and flexible model structure, use input parameters independent on calibration and include assessment tools to assess model performance. Development and application of PBK models for farm animal species would furthermore benefit from the setup of structured databases providing data on physiological and chemical-specific parameters as well as enzyme expression and activities to support the development of species-specific QIVIVE models.

1. Introduction

Chemical risk assessment in food and feed safety aims to set safe levels of regulated compounds and contaminants to protect farm animals after exposure through feed, and to protect humans against carry over and residues in animal products (e.g. meat, milk, eggs). Currently, hazard and exposure metrics used in risk assessment for farm animal species and humans are typically based on external exposure. Basing such metrics on internal exposure provides opportunities to better account for interindividual and interspecies differences in physiology, toxicokinetics and toxicity (Dorne and Fink-Gremmels, 2013).

PBK models integrate mathematical relationships that link key physiological and anatomical parameters (e.g. blood flow, organ volumes) and biochemical parameters (e.g. partition coefficients, protein binding), to dynamically predict absorption, distribution, metabolism and excretion (ADME) processes of a chemical using differential mass balance equations (WHO, 2010). Typically, PBK models consist of a variable number of compartments representing different organs and tissues (e.g. liver, kidney, gut, lung, and blood) and provide means to simulate concentration-time profiles of chemicals and corresponding metabolite(s) in these compartments (Bois et al., 2010; Chiu et al., 2007) (Fig. 1). For this reason, PBK models are extensively applied in the pharmaceutical industry in drug discovery and development (EMA, 2018; Jones and Rowland-Yeo, 2013). PBK models vary in complexity, ranging from full PBK models where all of the distribution organs and tissues are represented as separate perfused compartments to more simplified PBK models in which tissues with similar kinetics are lumped (Bois et al., 2010). While the simultaneous modelling of ADME processes provides several advantages, complex PBK models have the disadvantage of requiring many physiological and chemical-specific data (Sager et al., 2015).

In literature, the term “physiologically based pharmacokinetic” (PBPK) model is widely used. In the context of general chemical risk assessment this term is not entirely correct (Clewell et al., 2008; Paini et al., 2019). A more general term, such as PBK, covering the field of pharmacokinetics (PK) as well toxicokinetics (TK), might be more

* Corresponding author.
E-mail address: l.lautz@science.ru.nl (L.S. Lautz).

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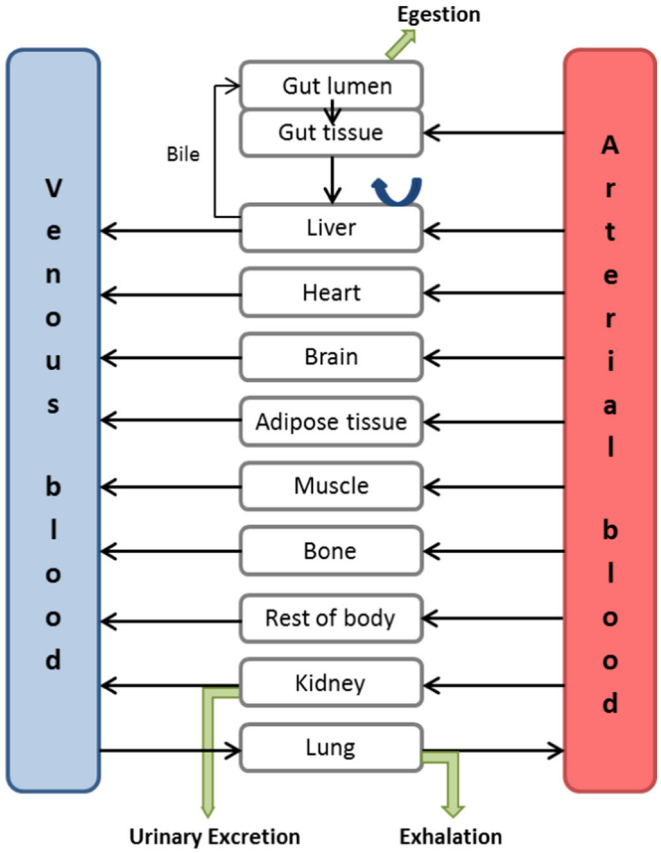

Fig. 1. Scheme of a generic PBK model. Chemical uptake routes can be oral, intravenous, inhalation, intramuscular, or subcutaneous. In this example, metabolism is assumed to occur in the liver only (blue arrow). Elimination of the chemical takes place via urinary excretion (kidney), egestion (gut lumen) and exhalation (lung). Muscle, adipose tissue, and bone are included as storage organs. The "Rest of body" compartment account for anatomically missing organs. Other organs such as skin and spleen can be added as additional compartments. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

appropriate. However, PBPK, PBTK, and PBK can be considered synonyms of each other. Throughout this document, we will use the more general term PBK model.

A recent survey across academia, industry and regulatory agencies such as the European Food Safety Authority (EFSA), the European Medicine Agency (EMA), the US Environmental Protection Agency (US EPA), the US Food and Drug Administration (US FDA), and the Organisation for Economic Co-operation and Development (OECD) highlighted the importance of PBK models for regulatory risk assessment (EFSA, 2014a; EFSA, 2014b; Paini et al., 2017). While the use of PBK models in risk assessment is encouraged, there are also challenges, such as the need for well-trained persons capable of model development and to ensure model quality (Barton et al., 2007; Chiu et al., 2007; Tan et al., 2018). The increasing use of PBK modelling in regulatory human health risk assessment (HRA) has led to several guidance documents facilitating good modelling practice and standardising their review, acceptance and implementation (EMA, 2018; EPA, 2006; FDA, 2018; WHO, 2010).

In the European Union, the chemical risk assessment for animal health, including farm as well as companion animals, follows the same principles as human health risk assessment (Alexander et al., 2012). Main differences towards human health risk assessment are related to species-specific and interspecies differences in kinetics, dose-dependent toxicity and methodologies to estimate exposure to characterise the chemical risk in each species (Dorne and Fink-Gremmels, 2013). Furthermore, animal health risk assessment accounts for animal health due to chemical exposure, as well as possible impacts on human health due to transfer of chemicals into the food-chain (Alexander et al., 2012). In the animal health and veterinary medicine area, several PBK models have been developed in recent years, mostly for the prediction of tissue residues and withdrawal intervals in farm animals (Henri et al., 2017; Li et al., 2017; Zeng et al., 2017). While PBK models are relevant for regulatory agencies that monitor chemical concentrations in animal target tissues and animal products, e.g. meat, milk and eggs (Craigmill, 2003), as well as for the veterinary pharmaceutical industry, a specific guidance document on their use in animal health risk assessment is currently lacking.

A previous review on PBPK models for farm animal species focused on their application in veterinary medicine (Lin et al., 2016a). However, several models specific for farm animals were not included and the review did not assess the application potential of the PBK models for risk assessment purposes. Therefore, the aim of the current paper is to critically review existing PBK models for farm animals in order to develop recommendations for their use in animal and human health risk assessment. Existing models were identified through an extensive literature review and these models were characterised and assessed using criteria set by WHO for practice in human PBK modelling (WHO, 2010). Recommendations are proposed for the future development and application of PBK models in farm animals in chemical risk assessment.

2. Materials and methods

2.1. Species selection

There are more than 40 domestic animal species, whereof 13 species contribute to most of the world's food production or are of veterinary relevance (Toutain et al., 2010). In Europe, cattle, sheep, swine, chicken and salmonids are classified as major food-producing animals. In contrast, other animals such as goat, horse, rabbit, deer/reindeer, turkey, duck, goose, and non-salmonid fin fish species are classified as minor food-producing animals (EMEA/CVMP, 2003). Based on this list of food-producing animals in Europe, 10 species were selected for inclusion in this review, namely chicken, cattle, swine, sheep, goat, horse, deer/reindeer, turkey, duck, and goose (Fig. 2). Fish species were excluded, since a review on PBK models in fish is available elsewhere (Grech et al., 2017). Since the focus of this review is on farm animals, test species used in human risk assessment, such as rabbit, mouse, rats and companion animals (cat, dog) were excluded.

2.2. Search strategy

An extensive literature search (up to February 2019) was performed in PubMed and Scopus to identify available PBK models for farm animals. Table 1 summarises the keywords applied. Peer reviewed publications in English were selected, with a focus on PBK modelling of chemicals in the 10 species selected. Individual publications were then assessed based on title and abstract, followed by further cross-referencing of publications from the reference lists. In a second step, a grey literature search was conducted by consulting websites of EFSA, US EPA and the Dutch National Institute for Public Health and the Environment. Publications with a primary focus on preclinical studies for human health were excluded.

2.3. Model description and assessment

The selected PBK models for farm animals were characterised and assessed using the model features listed in guidance documents for the evaluation and application of PBK models in HRA (EPA, 2006; WHO, 2010). We grouped these features in six categories: (1) purpose, (2) structure and mathematical representation, (3) computer implementation, (4) parameterisation, (5) performance, and (6) documentation

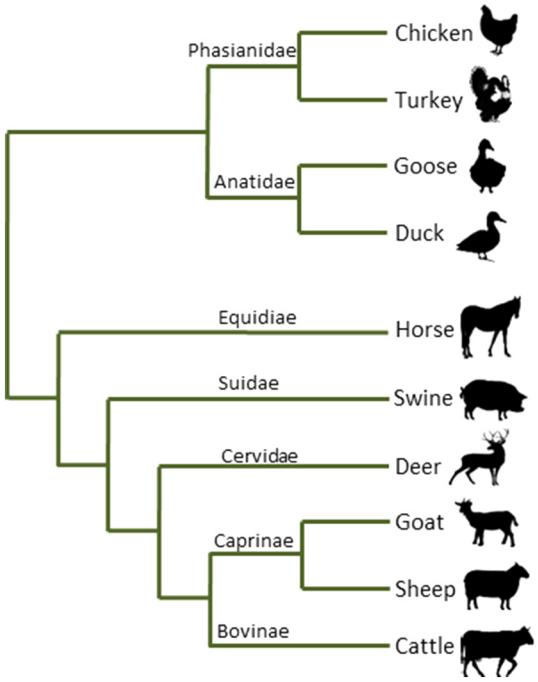

Fig. 2. Major food producing animals: cattle (milk, meat), sheep (meat, milk), swine (meat), and chicken (meat, eggs). Minor food-producing animals: goat (milk, meat), deer (meat), horse (meat), avian species (meat, eggs).

Table 1
Keywords identified for extensive literature search.

Category	Keywords
General keywords	< chicken > < cattle > < pig OR swine > < sheep > < goat > < horse > < deer OR reindeer > < turkey > < goose > < duck >
More complex tools and methods and full biologically-based models	< pbpk OR pbtk > < physiologically based kinetic model > < physiologically based pharmacokinetic model >

(Table 2).

3. Model description

3.1. Purpose

Thirty-nine PBK models were identified through extensive literature search, covering nine of the farm animal species included (Table 3). Specifically, PBK models were available for cattle (n = 10), swine (n = 17), chicken (n = 6), sheep (n = 1), goat (n = 1), horse (n = 1), and turkey (n = 1) while two models included multiple poultry species, i.e., chicken, goose, turkey and duck (Cortright et al., 2009; MacLachlan, 2010). For deer and reindeer, no PBK models were found. Most PBK models were developed for either juvenile or adult life stage, with the exception of five models that included growth rates to simulate lifetime exposure for cattle, swine and poultry (Henri et al., 2017; Hoogenboom et al., 2007; MacLachlan, 2010; van Eijkeren et al., 1998; Zeng et al., 2019) (Table 3). The vast majority of models were chemical-specific and mostly developed for antibiotics and contaminants (e.g., melamine, PFOS) with the exception of four generic models developed for lipophilic chemicals (Freijer et al., 1999; MacLachlan, 2009; MacLachlan, 2010; van Eijkeren et al., 1998). The models were developed for specific scientific purposes, such as concentrations predictions of a specific chemical in certain target tissues (e.g. liver, muscle) (Appendix S1).

3.2. Structure and mathematical description

All available publications provided a graphical representation of the model structure, and 28 out of 37 articles provided mass balance equations. The conceptual structures of the models ranged from two compartments to ten compartments, showing a lack of harmonisation across the published models. Model structures were mostly based on the model purpose rather than on physiological differences between species (Li et al., 2017; Lin et al., 2016b). PBK models with a focus on distribution of the metabolite had at least as many compartments for the metabolite as for the parent compound (Huang et al., 2015; Yang et al., 2014a). Furthermore, differences between model structures resulted from a reduction in model complexity through “lumping” tissues with similar blood flows (Buur et al., 2009), and from species-specific differences such as the inclusion of a milk compartment for dairy cattle (Leavens et al., 2014; Li et al., 2018) and an egg compartment for chicken (Hekman and Schefferlie, 2011; MacLachlan, 2010; Schefferlie and Hekman, 2016).

In cattle, the simplest model was structured into two compartments (carcass and serum) (van Asselt et al., 2013) and more complex models split liver, adipose tissue, and blood into separate compartments lumping the remaining tissue as richly and poorly perfused (Derks et al., 1994; Freijer et al., 1999; Hoogenboom et al., 2010; van Eijkeren et al., 1998). In addition to the compartments cited above, Leavens et al. (2014) published a comprehensive PBK model with separate compartments for blood, liver, adipose tissue, kidney, muscle, lung, and richly and poorly perfused tissue. Three models included all compartments listed above, while all remaining tissues were aggregated in a “rest of the body” lumped compartment, including richly and poorly perfused tissues (Achenbach, 2000; Li et al., 2017; Lin et al., 2016b; MacLachlan, 2009). Another model included the gastrointestinal tract as a single compartment (Lin et al., 2016b), and four models included milk/mammary tissue compartments to take into account secretion from plasma into milk for dairy lactating cattle (Derks et al., 1994; Leavens et al., 2014; Li et al., 2018; MacLachlan, 2009). Finally, two models accounted for metabolite formation through the inclusion of metabolism rates (Leavens et al., 2014; Lin et al., 2016b).

For swine, 17 PBK models were available, with one model structured into two compartments (carcass, fat) (Hoogenboom et al., 2007) and four models consisting of three compartments (liver, blood, rest of the body) or as a lumped distinction between richly and poorly perfused tissues (Buur et al., 2009; Yang et al., 2014a; Yang et al., 2015b; Zeng et al., 2017). Other models included liver, blood, and kidney (Buur et al., 2008), and a compartment for the rest of the body, or compartments for muscle and adipose tissue (Buur et al., 2005; Buur et al., 2006; Huang et al., 2015; Qian et al., 2017; Yang et al., 2012; Zhu et al., 2017). Four models included the lung as an additional compartment (Chen and Seng, 2012; Li et al., 2017; Lin et al., 2016b; Yuan et al., 2011), whereas Qian et al. (2017) divided the lung in three sub-compartments. The anatomical most detailed models contained 8–10 compartments (Chen and Seng, 2012; Sjögren et al., 2012; Yuan et al., 2011). In terms of exposure route, nine PBK models integrated oral dosing modules consisting of either stomach and intestine or intestine only (Buur et al., 2008; Buur et al., 2006; Huang et al., 2015; Lin et al., 2016b; Yang et al., 2014a; Yang et al., 2012; Yang et al., 2015b; Zeng et al., 2017; Zhu et al., 2017). In contrast, Yang et al. (2012) and Qian et al. (2017) included a separate compartment for intramuscular injection. With regards to metabolism, nine models integrated metabolite

Table 2
Model features used to characterize and assess PBK models.

Category	Model feature
Purpose	- What is the model purpose? - What is the included species? - What are the included chemicals? - What age(s), life stage(s), sex, exposure window(s) is included? - What exposure route(s), and dose metric(s) is/are modelled? - What target organs or whole body?
Structure and mathematical representation	- Is a graphical representation of the model available? - What is the complexity in terms of number of compartments? - Are steady-state or differential calculations used? - Are the mass balance (ADME-) equations given?
Computer implementation	- What software (package) is used for the implementation?
Parameterisation	- Are physiological parameter values derived from experiments, literature, or predicted? - Are physicochemical parameter values derived from experiments, literature, or predicted? - Are biochemical parameter values derived from experiments, literature, or predicted? - Has the model been calibrated with a dataset? - Are the calibration data adequately reported?
Model evaluation of predictive ability	- Has the model been validated against external data (i.e., not those used for calibration)? - Are the validation data adequately reported? - Is a variability analysis performed? - Is a sensitivity analysis performed? - Is a visual inspection of the adequacy of the model predictions possible (e.g., via concentration-time plots?)
Model documentation	- Has the model been peer-reviewed? - Are model codes and syntax available? - Is the model publicly available?

formation through implementing metabolism rates. The number of compartments for the major metabolite was similar to the parent compound ranging from three to seven compartments. In two models, the metabolite was modelled using a more complex PBK model than that for the parent compound (Yang et al., 2014a; Yang et al., 2015b).

For chicken, most PBK models had similar compartment numbers, albeit with some variations. Exception to this, are two models with two compartments (blood, fat/egg) (Hekman and Schefferlie, 2011; van Eijkeren et al., 2006). In four models liver, blood, (leg) muscle and kidney was included (Cortright et al., 2009; Yang et al., 2015a; Yang et al., 2014b; Zeng et al., 2019), a lung compartment in two models (Yang et al., 2015a; Yang et al., 2014b), and a compartment for adipose tissue in four models (Cortright et al., 2009; Henri et al., 2017; MacLachlan, 2010; Zeng et al., 2019). Oral dosing modules consisting mainly of intestine, and sometimes including crop, were only implemented in four models (Henri et al., 2017; Yang et al., 2015a; Yang et al., 2014b; Zeng et al., 2019). MacLachlan (2010) incorporated egg formation in a PBK model to account for partitioning from plasma into eggs, while Hekman and Schefferlie (2011) split the egg into yolk and white compartment. Metabolite formation was included in a model describing the metabolism of monensin via Michaelis-Menten kinetics (Henri et al., 2017). Metabolite formation for T-2 toxins was described by a metabolism rate (Zeng et al., 2019). For other avian species (turkey, duck, goose), two PBK models were identified (Cortright et al., 2009; MacLachlan, 2010) with identical structures to those described for chicken. One model was specifically developed for turkey, consisting of four compartments, i.e. blood, liver, gastrointestinal tract, and a compartment to lump the rest of the body (Pollet et al., 1985).

For sheep, goat, and horse, only one model per species was available. The PBK model for sheep consisted of six compartments, i.e., adipose tissue, muscle, kidney, liver, blood and a compartment to lump the rest of the body. An intramuscular injection site was included as a specific absorption compartment (Craigmill, 2003). In contrast, the goat PBK model contained eight compartments, i.e., lung, adipose tissue, muscle, liver, kidney, blood, richly perfused tissue, and poorly perfused tissue (Leavens et al., 2012). The PBK model for horse included four compartments, i.e., liver, blood, gastro intestinal circulatory system, and a compartment lumping the rest of the body (Abbiati et al., 2017). This model also included metabolite formation and elimination of tramadol through hepatic clearance.

3.3. Computer implementation

Most PBK models were written in the Advanced Continuous Simulation Language (ACSL, 76%), a computer language designed for modelling and evaluating the performance of continuous systems described by time-dependent, nonlinear differential equations (Mitchell and Gauthier Associates, 1981). 26% used other software (Berkley Madonna, Excel). For 18% of models, information on computer implementation was lacking.

3.4. Parameterisation

Parameters incorporated in PBK models can be divided into physiological parameter (species-specific, e.g. body weight), chemical parameters (chemical-specific, e.g. molecular weight), and biochemical parameters (species- and chemical-specific, e.g. blood-tissue partitioning, protein binding, clearance, absorption). Physiological parameters are dependent on the organisms modelled, e.g. small- or large-sized animals, and are typically obtained from literature or the experiment that is being simulated. Data on interindividual variation in physiological parameters are needed to parameterise a typical individual for deterministic analyses (e.g., worst-case) or to perform probabilistic analyses describing the variation in the population.

For most models, physiological and biochemical parameter values were either derived for the species of interest from the literature or using in vivo experiments conducted and described in the same paper (Appendix S1). From the 29 PBK models available, 90% determined some of the biochemical parameters, e.g. clearance and absorption, by means of calibration, i.e. fitting model predictions to experimental data. van Eijkeren et al. (1998) provided a quantitative structure activity relationship (QSAR) to derive blood-tissue partition coefficient, and Buur et al. (2008) and Yuan et al. (2011) extrapolated biochemical parameter values form rats to pigs.

3.5. Performance

From the 39 PBK models available, 67% were validated against an external dataset independent from the calibration dataset. 31% of the PBK model applications included interindividual variability in biochemical parameter values (blood-tissue partition coefficients,

Table 3
Published PBK models for various farm animals. Detailed information on all model features are provided in the supporting information (Appendix S1).

Reference	Species	Life stage	Chemicals	Exposure route(s)	Number of compartments[a]	Mass balance equations	Software	Model code available	Calibration[c]	Validation[c]	Variability analysis performed	Sensitivity analysis performed	Peer-reviewed
Derks et al. (1994)	Cattle	Mature	2,3,7,8-TCDD	oral	6	No	N/A[b]	No	Literature	Literature	No	No	No
van Eijkeren et al. (1998)	Cattle	Lifetime	Lipophilic contaminates	oral	5	No	ACSL	Yes	N/A[b]	N/A[b]	No	No	No
Freijer et al. (1999)	Cattle	Mature	2,3,7,8-TCDD, Lindane, PCB-169	oral	5	Yes	ResAnA	No	Literature	Literature	No	No	No
Achenbach (2000)	Cattle	N/A[b]	Oxytetracycline	im (steers); sc (calves)	8	No	Microsoft Excel	No	Experiment	Experiment	No	Yes	No
MacLachlan (2009)	Cattle, Swine, Sheep	Mature	Lipophilic xenobiotics	oral	7	Yes	lcc C compiler	No	N/A[b]	N/A[b]	No	No	Yes
Hoogenboom et al. (2010)	Cattle	Mature	Dioxin	oral	5	No	N/A[b]	No	Literature	N/A[b]	No	No	Yes
van Asselt et al. (2013)	Cattle	Mature	PFOS	oral	2	Yes	ACSL	No	Literature	Literature	No	No	Yes
Leavens et al. (2014)	Cattle	Mature	Flunixin	iv; im	9	Yes	acsIX	No	Literature	N/A[b]	No	Yes	Yes
Lin et al. (2016b)	Cattle, Swine	Mature,Juvenile	Ceftiofur, Enrofloxacin, Flunixin, Sulfamethazine	iv, sc, im, oral	8; 7	No	acslX	Yes	Literature	Literature	No	Yes	Yes
Li et al. (2017)[d]	Cattle, Swine	Mature,Juvenile	Penicillin G	im, sc	7	Yes	Berkeley Madonna	Yes	Literature	Literature	Yes	Yes	Yes
Leavens et al. (2012)	Goat	Juvenile, market age	Tulathromycin	sc	8	Yes	acslX	No	Experiment	N/A[b]	No	Yes	Yes
Abbiati et al. (2017)	Horse	Mature	Tramadol	iv	4	Yes	N/A[b]	No	Literature	N/A[b]	No	No	Yes
van Eijkeren et al. (2006)	Chicken	Mature	Dioxin, PCBs	oral	2	Yes	N/A[b]	No	Literature	Literature	No	No	Yes
Cortright et al. (2009)	Chicken, Turkey	Mature	Midazolam	iv	6	Yes	ACSLXtreme	Yes	Experiment	Experiment	No	Yes	Yes
MacLachlan (2010)	Chicken, Duck, Goose, Turkey	Lifetime	Lipophilic pesticides	oral	6	Yes	lcc C compiler	No	N/A[b]	N/A[b]	No	No	Yes
Hekman and Schefferlie (2011)[e]	Chicken	Mature	Sulphanilamide, pyrimethamine, sulphaquinoxaline	oral	3	Yes	Multisim	No	Literature	N/A[b]	No	No	Yes
Yang et al. (2014b)	Chicken	Juvenile	Marbofloxacin	oral	7	Yes	ACSLXtreme	No	Literature	Literature	Yes	Yes	Yes
Yang et al. (2015a)	Chicken	Mature	Danofloxacin	oral	7	Yes	ACSLXtreme	No	Literature	Literature	Yes	No	Yes
Henri et al. (2016)	Chicken	Lifetime	Monensin	oral	6	Yes	ACSLXtreme	Yes	Experiment	Experiment	Yes	Yes	Yes
Zeng et al. (2019)	Chicken	Lifetime	T-2	oral, iv	6; 6	No	Berkeley Madonna	Yes	Experiment	Literature	Yes	Yes	Yes
Pollet et al. (1985)	Turkey	N/A[b]	Chlortetracycline	oral	4	Yes	N/A[b]	No	Experiment	N/A[b]	No	No	Yes
Buur et al. (2005)	Swine	Market age	Sulfamethazine	iv	6; 3	Yes	ACSLXtreme	No	Literature	Literature	No	Yes	Yes
Buur et al. (2006)[f]	Swine	Market age	Sulfamethazine	iv, oral	8; 3	Yes	ACSLXtreme	No	Literature	Experiment; Literature	Yes	Yes	Yes
Hoogenboom et al. (2007)	Swine	Lifetime	Dioxins	oral	2	No	N/A[b]	No	Literature	N/A[b]	No	No	Yes
Buur et al. (2008)	Swine	Market age	Melamine	iv, oral	6	Yes	ACSLXtreme	No	Literature	Literature	No	Yes	Yes
Buur et al. (2009)	Swine	Market age	Sulfamethazine, flunixin	iv	4; 3	Yes	ACSLXtreme	No	Literature	Literature	No	No	Yes

(*continued on next page*)

Table 3 (*continued*)

Reference	Species	Life stage	Chemicals	Exposure route(s)	Number of compartments[a]	Mass balance equations	Software	Model code available	Calibration[c]	Validation[c]	Variability analysis performed	Sensitivity analysis performed	Peer-reviewed
Yuan et al. (2011)	Swine	N/A[b]	Valnemulin	oral	8	No	ACSLXtreme	No	Experiment	N/A[b]	No	No	Yes
Chen and Seng (2012)	Swine	N/A[b]	Soman	Iv	10	No	N/A[b]	No	Experiment	Experiment	No	No	Yes
Sjögren et al. (2012)[g]	Swine	N/A[b]	Repaglinide	iv	9	Yes	Berkeley Madonna	No	Experiment	Experiment	No	Yes	Yes
Yang et al. (2012)	Swine	Market age	Doxycycline	im, iv	7	Yes	ACSLXtreme	No	Literature	Literature	Yes	No	Yes
Yang et al. (2014a)	Swine	Juvenile	Olaquindox	oral	5; 6	Yes	ACSLXtreme	No	Experiment; Literature	Literature	Yes	Yes	Yes
Yang et al. (2015b)	Swine	Juvenile	Cyadox	oral	4; 6	Yes	ACSLX	No	Literature	Literature	No	Yes	Yes
Huang et al. (2015)	Swine	Juvenile	Cyadox	oral	7; 7	Yes	ACSLX	No	Literature	Experiment	Yes	Yes	Yes
Zhu et al. (2017)	Swine	N/A[b]	Quinocetone, Mequindox	oral	8; 7	Yes	acslX	No	Experiment	Experiment	Yes	Yes	Yes
Zeng et al. (2017)	Swine	Juvenile	Mequindox	oral, im	5; 6	Yes	Berkeley Madonna	Yes	Experiment	Experiment	Yes	Yes	Yes
Qian et al. (2017)	Swine	N/A	Florfenicol	im	7	Yes	ACSLXtreme	Yes	Experiment	Literature	No	No	Yes
Craigmill (2003)	Sheep	Mature	Oxytetracycline	im	7	Yes	ACSL	Yes	Experiment	Experiment (from calibration)	No	Yes	Yes

im: intramuscular, sc: subcutaneous; iv: intravenous;

[a] First value indicates the number of the compartments parent compound, the second value when available indicates the number of compartments metabolite.

[b] N/A: not available.

[c] Experiment means that data is based on experiments described in the article itself. Literature means that experimental data is based on other articles.

[d] Extended with udder compartment (Li et al., 2018).

[e] Extended by detailed egg compartment (Schefferlie and Hekman, 2016).

[f] Validated by Mason et al. (2008).

[g] Extended with fexofenadine (Sjogren et al., 2014)

clearance, absorption rate), while some also included interindividual variability in physiological parameters (Henri et al., 2017; Li et al., 2017; Zeng et al., 2017; Zeng et al., 2019). Local sensitivity analysis was performed for 54% of the models to assess the impact of variations in a single input parameter on the model output. A global sensitivity analysis investigating the interactions and the impact of simultaneous variations in input parameters is lacking for all models.

3.6. Documentation

Most models were published in peer-reviewed literature (90%), while others were available in reports only. Model codes were published for 28% of the models.

4. Model assessment

In the previous section, an overview of the 39 PBK models for farm animals identified in from the extensive literature was presented (Table 3). In total, four PBK models were fully described and characterised according to the WHO guidance document (Henri et al., 2017; Li et al., 2017; Zeng et al., 2017), whereas all other models were missing information. The aim of the present section is to assess their potential usefulness for application in chemical risk assessment based on the model features presented in Tables 2 and 3.

4.1. Scope and purpose of the model

None of the reviewed farm animal models were developed and applied to a risk assessment context for either animal or human health purposes. Instead, most models were developed for a specific scientific purpose, such as the predicting the concentrations of a specific chemical in certain target tissues (e.g. liver or muscle). Consequently, these models were unique, each tailored for a specific purpose, often focusing on one particular substance in one particular species. These models can be useful for substance- and species-specific risk assessments, but risk assessors in practice have to deal with a diversity of substances and species. Within this context, the development and application of separate PBK models for each unique substance-species combination is inefficient and practically unfeasible (Punt et al., 2011). Risk assessors need more generic PBK models that can simulate ADME processes for multiple substances, and ideally also for multiple farm animal species. The four models developed for lipophilic substances (Freijer et al., 1999; MacLachlan, 2009; MacLachlan, 2010; van Eijkeren et al., 1998) constitute a first step in the right direction since these models can simulate multiple substances in one species. Grech et al. (2019) went one step further by publishing an open source generic PBK model for four fish species (rainbow trout, fathead minnow, zebra fish and European stickleback) together with an anatomical and physiological database and nine case studies to validate the models.

4.2. Model structure and mathematical description of ADME

Although the PBK models reviewed have many commonalities, each model has its own specific structure, often reflecting the uniqueness of the substance-species combination under study. The simplest model has two compartments (van Asselt et al., 2013), whereas the most extensive model has ten (Chen and Seng, 2012). As noted in the previous section, risk assessors require generic PBK models which can be applied to multiple substances and species. This triggers the question how these generic models should be structured. A generic PBK model should be sufficiently detailed to capture the diversity of processes relevant to a multitude of chemicals and the diversity of organs that may potentially be of interest to risk assessors. Liver, intestine and kidney should be included as compartments because of their metabolic and excretory functions. Muscle, adipose tissue, bone, milk and/or eggs should be included because of their role as storage organs, which is important for analysing tissue residues in food and feed safety. In addition, organs critical to the oral route or inhalation should also be included, i.e. gastrointestinal tract and lung respectively (EPA, 2006).

In terms of structure, some compartments are only relevant to specific species because of specific traits including crop and egg compartment for birds and multiple stomachs for ruminants. In addition, compartments can also be substance-specific including the subdivision of the lung compartment into bronchioles, alveolae and mucosa to simulate the so-called washin–washout principle for polar chemicals after inhalation (Johanson, 1991). Overall, these species- and substance-specific adaptations provide a challenge for generic PBK models and an option would be to develop a flexible modelling structure that can be adjusted based on the species and substances of interest. The basic structure would then include compartments common to all species, e.g. lungs, stomach, intestines, liver, kidney, bone and muscle, while specific compartments could be implemented as optional, i.e. switched on or off to accommodate species- or substance-specific requirements.

4.3. Computer implementation

Application of PBK models in a risk assessment context for either regulatory products of contaminants requires transparency and reproducibility. These criteria can partially be met through implementation of the model in an open source environment. However, none of the reviewed models were implemented as such. The most widely used computer language ACSL is of commercial nature and is no longer available. Another type of software is Berkeley-Madonna, which is non-commercial proprietary shareware but is not open source, since a license is necessary for full access. A more promising trend is the development of PBK models in R (Wambaugh et al., 2015). The R language and environment was originally developed for statistical computing and graphics, but is increasingly being used for dynamic modelling. This language is freely available under the terms of the GNU General Public License in source code form (Free Software Foundation, 2007). It compiles and runs on a variety of platforms, including UNIX, Windows and MacOS. Recently, a methodology was published for converting existing PBK models that were initially developed in acslX, Berkeley Madonna to R (Lin et al., 2017).

4.4. Parametrisation

PBK models applied in chemical risk assessment must be parameterised transparently since the selection of input values have an important impact on the results. The selected physiological parameters should reflect the population of interest. This is highly relevant for farm animals, since the variation in their physiology can be much larger compared with humans. For example, the bodyweight of pigs can vary between 100 kg and 300 kg depending on the breed. It is therefore important that risk assessment includes a detailed and motivated description of the population of interest, and considers how variation in physiology will be dealt with. For human physiology, a reference dataset has been compiled to parameterise PBK models (Brown et al., 1997). Such datasets are largely lacking for farm animal species. Ad-hoc parameterisation is inefficient and can potentially lead to inconsistencies between specific risk assessments. Hence, it is recommended to develop peer reviewed reference datasets reporting physiologically parameters for farm animal species.

In a risk assessment context, calibration of parameters such as clearance and absorption will rarely be feasible because experimental data on the species of interest are generally lacking, particularly for new substances. In such cases, extrapolation across chemicals and species may be an option, e.g. using QSAR-based approaches and allometric scaling (Peyret and Krishnan, 2011; Sharma and McNeill, 2009). Although these methods can provide valuable input in data-poor situations, uncertainty in prediction of kinetic parameters may be high due to potential interspecies differences in metabolic and transporter

activities. An alternative is to use in vitro data, e.g. for the prediction of metabolism. Unfortunately, specific in vitro systems for farm animal species are rarely available and the quantitative extrapolation of in vitro results to in vivo conditions (QIVIVE) remains a challenge. Therefore, data collection on abundance and expression of CYP enzymes and transporters in a variety of farm animal species can support QIVIVE and the parameterisation of ADME processes in PBK models. Insight in the quantitative differences in metabolism for key farm animal species will allow to include relative expression and activity of phase I (cytochrome P-450 isoforms, esterases, alcohol dehydrogenase etc.), phase II (UDP-glucuronyltransferases, glutathione-s-transferases, glycine conjugation, methyl-transferases etc.) and transporters (P-glycoprotein, organic anion transporter proteins etc.) (Dorne and Fink-Gremmels, 2013; Fink-Gremmels, 2008; Giantin et al., 2008; Gusson et al., 2006; Martinez et al., 2018). This will help to address three major challenges in animal risk assessment: 1. Moving away from default test species (rat, rabbit, mice, dog) by enabling species-specific assessments for farm animals and other animal species (e.g., companion animals such as cats and dogs), 2. Reducing and replacing animal testing, and (3) future development of quantitative in vitro in vivo extrapolation models.

4.5. Model performance

Before PBK models can be applied in a risk assessment context, it is essential to assess their performance (EFSA, 2014b). Model predictions should be sufficiently accurate to support risk assessment or regulatory decision to be taken. The most obvious way to assess model performance is by comparing predicted internal concentrations with measured ones under the same exposure scenario. Unfortunately, measured data are rarely available for the substance and scenario under assessment since this would make model application redundant. Model performance should therefore be assessed based on other criteria, such as the performance for other substances and scenarios, biological plausibility, and a review of the model code. Variability, sensitivity and uncertainty analysis can further support the assessment of model performance. Uncertainty analysis should not only focus on the propagation of input uncertainties, but also on uncertainties underlying model equations and assumptions, e.g. the homogeneous distribution of substances within compartments and the estimation of absorption or partitioning coefficients based on Kow (Ragas et al., 1999).

In the context of the review, it is difficult to assess the performance of the reviewed models since: 1) only local sensitivity analysis was performed, 2) model validation was not performed systematically, and 3) codes for computer implementation were rarely published (Leavens et al., 2014; MacLachlan, 2009; van Eijkeren et al., 1998). Local sensitivity analysis does not allow to investigate interactions and simultaneous variations in input parameters and may give misleading results (Hsieh et al., 2018). In terms of good modelling practice, global sensitivity analysis has been demonstrated to be much more robust than local sensitivity analysis, providing means to assess the variation of all parameters simultaneously, their interactions and quantifying the relative contribution of each parameter to the overall sensitivity of the model (Hsieh et al., 2018; McNally et al., 2011; McNally et al., 2018).

4.6. Model documentation

Only a small part of the reviewed PBK models were appropriately documented, i.e. published in peer-reviewed literature and publicly available (model and underlying code). Appropriate documentation contributes to transparency and reproducibility; two essential criteria for application of PBK models in a regulatory context. It is a prerequisite for well-informed use of the models (McLanahan et al., 2012).

5. Conclusions and recommendations

The available PBK models for farm animal species have generally been developed for specific purposes, often focusing on one particular substance in a specific species. This approach of developing unique models for each substance and each species is less suitable for a risk assessment context because a risk assessor has to deal with multiple regulated substances and a diversity of species. Most models also do not meet the criteria for application in risk assessment, such as (1) implementation in an open source environment, (2) parameterisation in the absence of calibration data, (3) assessment of model performance in the absence of validation data (e.g. uncertainty analysis), and (4) appropriate model documentation. Future PBK models for farm animals to be applied in a risk assessment context should therefore:

1) Have a generic and flexible model structure covering all relevant target organs;
2) Be published in peer-reviewed literature, implemented in an open source environment and publicly available (model & code);
3) Use input data that are not dependent on calibration, preferably empirical data, or otherwise data estimated using techniques such as allometric scaling, QSAR approaches and QVIVIVE, provided the limitations of these techniques are accounted for;
4) Include tools to assess model performance, e.g. variability and uncertainty analyses.

Development and application of PBK models for farm animal species would furthermore benefit from the setup of structured databases providing data on physiological parameters (e.g., body weight, organ weights, and organ blood flow), ADME and chemical-specific parameters as well as data on enzyme expression and activities in farm animal species to support the development of species-specific QIVIVE models.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tiv.2019.05.002.

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