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An open source physiologically based kinetic model for the chicken (*Gallus gallus domesticus*): Calibration and validation for the prediction residues in tissues and eggs

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ABSTRACT

Xenobiotics from anthropogenic and natural origin enter animal feed and human food as regulated compounds, environmental contaminants or as part of components of the diet. After dietary exposure, a chemical is absorbed and distributed systematically to a range of organs and tissues, metabolised, and excreted. Physiologically based kinetic (PBK) models have been developed to estimate internal concentrations from external doses. In this study, a generic multi-compartment PBK model was developed for chicken. The PBK model was implemented for seven compounds (with log K_{ow} range −1.37–6.2) to quantitatively link external dose and internal dose for risk assessment of chemicals. Global sensitivity analysis was performed for a hydrophilic and a lipophilic compound to identify the most sensitive parameters in the PBK model. Model predictions were compared to measured data according to dataset-specific exposure scenarios. Globally, 71% of the model predictions were within a 3-fold change of the measured data for chicken and only 7% of the PBK predictions were outside a 10-fold change. While most model input parameters still rely on *in vivo* experiments, *in vitro* data were also used as model input to predict internal concentration of the coccidiostat monensin. Future developments of generic PBK models in chicken and other species of relevance to animal health risk assessment are discussed.

1. Introduction

Xenobiotics from anthropogenic and natural origins enter animal feed and human food as regulated compounds, dietary components or environmental contaminants. Risk assessment associated with exposure to such xenobiotics in food and feed is a priority of the European Union (Silano and Silano, 2017) because of the impact they may have on (1) the feed chain potentially affecting productivity and health of farm and companion animals, and (2) the food chain potentially affecting human health via transfer of residues in farm animal products (i.e. meat, milk, eggs) (EFSA, 2018a; Verstraete, 2013). In the European Union and worldwide, regulated chemicals of high relevance to the food and feed safety area include substances added to raw commodities as feed additives, pesticides/biocides or veterinary medicinal products (e.g. antibiotics, coccidiostats, histomonostats) as well as nutrients including amino acids or oligo-elements (e.g. zinc, copper). Environmental contaminants as undesirable substances include anthropogenic substances such as persistent organic pollutants (i.e., dioxins, polychlorinated biphenyls, brominated flame retardants, perfluoroalkyls, phthalates) and natural toxins such as mycotoxins, plant alkaloids and marine biotoxins to cite but a few (Dorne and Fink-Gremmels, 2013).

Chemicals present in the diet are absorbed (A), distributed (D) over a range of organs and tissues, metabolised (M) to a range of more polar metabolites or bioactivated to a toxic moiety, and finally excreted (E) (ADME). Understanding such ADME properties in a quantitative fashion can provide means to determine internal concentrations, predict target organ concentrations and adverse effects in farm animals and humans. Physiologically based kinetic (PBK) models integrate anatomical and physiological characteristics of an organism into algorithms and provide practical means to quantify internal dose metrics and ultimately refine human and animal health risk assessment in food and feed (Andersen et al., 2006; Bois and Brochot, 2016; Cortright et al., 2009).

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Moving towards internal dose metrics using PBK models has major two major advantages over the use of external dose metrics 1. quantify target organ concentrations in humans and animals on a species-specific basis to set safe levels of exposure for chemicals or therapeutic doses for drugs, 2. determine residue levels and transfer of chemicals in animal products (e.g. meat, milk, eggs) for animal health or as occurrence inputs combined with human consumption patterns for human exposure assessment (Lautz et al., 2019). Human PBK models for specific compounds including pharmaceuticals, cosmetics, pesticides and contaminants as well as generic models are readily available. In addition, a range of New Approach Methods (NAMS) have been developed to reduce animal testing and these include quantitative *in vitro in vivo* extrapolation (QIVIVE) models which can be incorporate PBK models as well as other *in silico* tools such as quantitative structure activity (QSAR) relationship models (Paini et al., 2019).

For farm animals, availability of PBK models is much more limited compared to human PBK models and is mostly restricted to specific compounds. A recent literature search and review identified 39 available PBK models for farm animals which were mostly focused on veterinary drugs (Lautz et al., 2019). In addition, the review critically assessed whether the model evaluation was performed using the WHO criteria namely purpose, structure, mathematical representation, computer implementation, parameter estimation and analysis, model performance and documentation. For most compound-specific PBK models available in farm animals, model evaluation was found to be rarely performed using the WHO criteria (WHO, 2010). Development and application of PBK models for farm animals would furthermore benefit from publication of open source model codes and databases, use of global sensitivity analysis and data collection on enzyme expression and activities to support the development of species-specific QIVIVE models (Lautz et al., 2019). Recently, PBK models have been developed as generic open source tools in the R free software environment for four fish species (zebrafish, trout, fathead minnow, and European stickleback) and three farm animal species (cattle, swine and sheep) and validated for a range of chemicals (Grech et al., 2019; Lautz et al., 2020b).

With regards to avian species, compound-specific models have been developed for a limited number of compounds such as marbofloxacin, danofloxacin, midazolam, and monensin, residues of lipophilic pesticides and T-2 Toxin. All these available compound-specific models mostly focused on body distribution and target tissue concentrations of the parent compound without considering generic models (Cortright et al., 2009; Henri et al., 2017; MacLachlan, 2010; Yang et al., 2015; Yang et al., 2014; Zeng et al., 2019). However, developing PBK models for every single chemical separately requires a large amount of information regarding their parametrisation including physiological, anatomical, biochemical entities (e.g. organ volume, cardiac output, biotransformation enzymes, and drug transporter expression) and kinetic parameters. Since such kinetic parameters are often sparse for a large number of chemicals, the development of generic PBK models provides means to predict kinetic properties (persistence, clearance, half-life, etc) of known chemicals and emerging chemical hazards for which limited information and data are available (EFSA, 2014). The present paper describes the development of an open source PBK model for the chicken (*Gallus gallus domesticus*) and its implementation in the R freeware environment. The open source chicken PBK model aims to predict kinetic properties of orally administered chemicals with a particular focus on tissue and egg concentrations. The model has been evaluated using all WHO criteria including structure, anatomical and physiological parameters, mathematical representation, results from global sensitivity analysis, calibration and validation of its performance for a range of regulated compounds and contaminants. A summary table is also provided to transparently report the model evaluation against each WHO criteria. Finally, conclusions and recommendations for future work are formulated to refine PBK models in chicken and other species of relevance to animal health risk assessment.

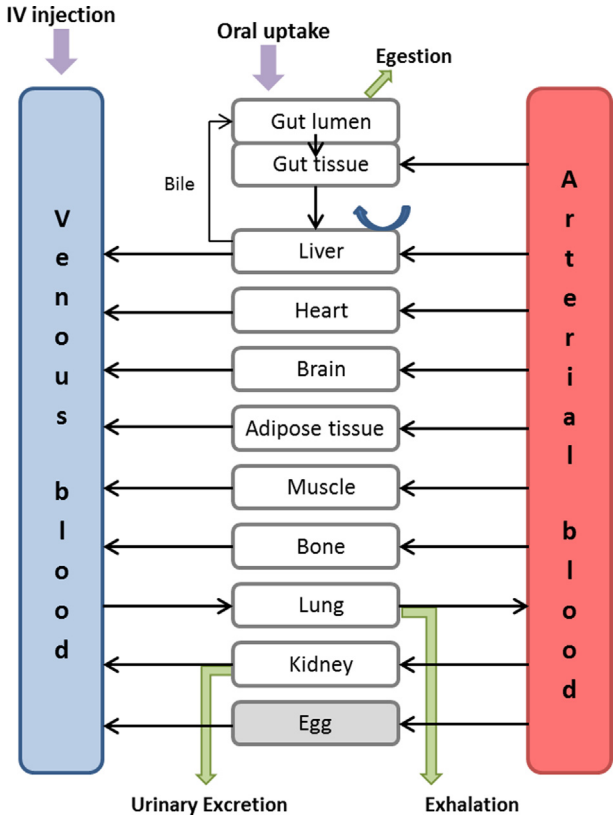


Fig. 1. Structure of the generic PBK model for chicken. Uptake, excretion and metabolism sites are illustrated in the purple, green, and blue, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2. Materials and methods

2.1. Generic model structure, mathematical representation and computer implementation

The generic chicken PBK **model structure** consists of eleven compartments, as previously described by Lautz et al. (2020b) for cattle, swine and sheep, with the addition of a twelfth compartment for eggs. All organs and tissues are modelled as well-mixed compartments with a blood-flow limited distribution considering the gastrointestinal tract (GIT) as two compartments: gut lumen and tissue collecting venous blood from the portal vein into the liver. Absorption from the gut lumen into the gut tissue is modelled as a first order process and distribution is modelled throughout the body by systematic circulation. Elimination processes can be included in the model through implementation of data reporting hepatic metabolism or renal excretion, as well as transfer to eggs. Structure and Mathematical representation of the model are provided in Fig. 1 and Table 2 of the result section respectively (3.1). Mathematical equations were the same as described previously (Lautz et al., 2020b), except for the egg compartment. **Computer implementation** of all differential equations was performed in the R software (version 3.3.3) to provide model codes and syntax (R Core Development Team, 2014). The model implementation is available as an open source model code in the R freeware on EFSA knowledge junction under the **DOI** [https://doi.org/10.5281/zenodo.1414332] with a Creative Commons Attribution 4.0 license.

2.2. Parameter estimation and analysis

2.2.1. Data collection of anatomical and physiological parameters

An extensive literature search was performed in PubMed and

Table 1
Keywords for the extensive literature search for the data collection of anatomical and physiological parameters in chicken.

Type	Keywords
Species	⟨chicken/fowl/poultry⟩ OR
Anatomical and physiological parameters	⟨organ weight⟩ OR ⟨cardiac (output)⟩ OR ⟨blood (flow)⟩ OR ⟨adipose/body fat⟩ OR ⟨liver/hepatic⟩ OR ⟨intestine⟩ OR ⟨heart⟩ OR ⟨kidney/renal⟩ OR ⟨lung⟩ OR ⟨brain⟩ OR ⟨bone/carcass⟩ OR ⟨muscle⟩ OR ⟨reproductive tissue⟩

Google Scholar to identify experimental data providing quantitative anatomical and physiological parameters for the parameterisation of the generic PBK model (e.g. relative organ volumes, relative blood flows). A list of relevant keywords for the extensive literature search is provided below in Table 1.

Each individual reference was screened for anatomical and physiological data which were then computed in an Excel database. Each physiological parameter was assumed to follow a normal distribution with a given arithmetic mean and standard deviation. Meta-analyses for the parameters were performed as described previously (Lautz et al., 2020a) to estimate summary statistics such as arithmetic means and interspecies variability expressed as the coefficient of variation (CV) in male and female adult chicken. The complete dataset with references is available as structured, open source excel databases with a Creative Commons Attribution 4.0 license on EFSA knowledge junction [DOI: https://doi.org/10.5281/zenodo.1414332]. Data gaps were identified for blood flow parameters in different organs and were filled using allometric scaling allocating a default variability of 30% (Clewell and Clewell, 2008; Lindstedt and Schaeffer, 2002). Tissue composition parameters were expressed as fractions of neutral lipids, polar lipids, proteins and water using available values in humans (Schmitt, 2008) and assuming similarity in chicken.

2.2.2. Case studies

Chemicals were selected from the literature using specific criteria: 1. relevance to food and feed safety, e.g. veterinary drugs, feed additives and environmental contaminants, 2. covering a broad range of physico-chemical properties (solubility, vapour pressure, Log P, K_{ow}, pKa) including polar and lipophilic structures, 3. availability of *in vivo* kinetic data in chicken (constant of absorption (k_{abs}), hepatic and renal clearances ($Cl_{hepatic}$, Cl_{renal}), concentrations in whole body, blood, individual organs, tissues, and eggs) as well as exposure scenarios (single and multiple oral dosing). For each chemical, physico-chemical parameters such as tissue:blood partition coefficients and blood:air partition coefficients were calculated using an available QSAR (Hendriks et al., 2005). This allowed us to determine chemical affinity for all tissues based on the octanol/water partition coefficient and tissue composition by considering the tissues constituents' lipids (both neutral and polar), proteins and water (Hendriks et al., 2005). Biochemical parameters were collected for each chemical from the literature when available.

2.3. Model evaluation

2.3.1. Global sensitivity analysis

Global sensitivity analysis aims to identify the main parameters of the PBK model that contribute to the variation in the model outcome while ordering the inputs by relative importance and was performed using the variance-based Sobol method. The Sobol method is based on variance decomposition allowing to quantify the relative variance contribution of each parameter to the unconditional variance of the model output expressed as tissue, blood or whole body concentration and can handle nonlinear and non-monotonic functions (Saltelli et al., 2008; Sobol' et al., 2007). Model output variances were computed using the Monte Carlo method with two independent input sample n × p matrices (the "sample" matrix M1 and the "resample" matrix M2 as individual rows), where n is the sample size and p the number of parameters. M1 and M2 represents a possible parameter combination for the model and the first order sensitivity index (Si) reflects the relative contribution of one parameter to the total model variance. Finally, total Sobol sensitivity indices (STi) reflect the relative contribution of the parameter and its inter-relations with the other individual parameters (up to the p^{th} order). In order to generalise the applicability of the global sensitivity analysis to a broad range of polar and lipophilic chemicals, two sensitivity analyses were run for a polar and a lipophilic compound (melamine, deltamethrin) for three time points: (1) uptake phase (0.75 h), (2) initial elimination phase (5.5 h), and (3) delayed elimination phase (19.5 h) after a single oral dose. For each sensitivity analysis, since CVs differ between physiological parameters, uniform distributions were assigned for each parameter as U (min = 0.9 × median; max = 1.1 × median) and the median value was fixed by the calibration step. The function "soboljansen" in the "sensitivity" package was used to carry out the global sensitivity analysis (Pujol et al., 2017).

2.3.2. Model calibration and validation

For each compound, **model calibration** was performed using partition coefficients estimated with an available QSAR model (Hendriks et al., 2005). The QSAR model allows the calculation of the chemical affinity for all tissues based on the K_{ow} and tissue composition as given below:

$$PC_{tissue} = f_{nl,t} * b_{nl,t} * K_{ow}^{a,nl} + f_{pl,t} * b_{pl,t} * K_{ow}^{a,pl} + f_{pr,t} * b_{pr,t} * K_{ow}^{a,pr} + f_{H_2O,t}$$

where PC_{tissue} is the tissue:water partition coefficient, K_{ow} is the octanol-water partition coefficient, $f_{nl,t}$, $f_{pl,t}$, $f_{pr,t}$, and $f_{H2O,t}$ are the fractions of neutral lipids, polar lipids, protein and water in tissue, $b_{nl,t}$, $b_{pl,t}$, and $b_{pr,t}$ are the intercepts for neutral lipids, polar lipids, and proteins, a_{nl}, a_{pl}, and a_{pr} are the affinity exponents for neutral lipids, polar lipids and proteins.

where PC_{tissue} is the tissue:water partition coefficient, K_{ow} is the octanol–water partition coefficient, $f_{nl,t}$, $f_{pl,t}$, $f_{pr,t}$, and $f_{H2O,t}$ are the fractions of neutral lipids, polar lipids, protein and water in tissue, $b_{nl,t}$, $b_{pl,t}$, and $b_{pr,t}$ are the intercepts for neutral lipids, polar lipids, and proteins, a_{nl}, a_{pl}, and a_{pr} are the affinity exponents for neutral lipids, polar lipids and proteins.

In vivo kinetic data included constant of absorption (k_{abs}), hepatic and renal clearances, concentrations in whole body, blood, individual organs, tissues, and eggs as well as exposure scenarios (single and multiple oral dosing). One set of experimental data was used to estimate absorption rate constant or elimination rates by visual fitting. This dataset was subsequently excluded from model validation, which was performed on the remaining experimental studies. **Model validation** of the generic chicken PBK model was assessed through comparison of fold changes (FC) between model predictions of organ, tissue and egg concentrations and experimental data from the literature.

3. Results and discussion

3.1. Generic model structure, mathematical representation and computer implementation

The **purpose** of this generic PBK model for the adult chicken is to

Table 2
Mathematical representation of the differential equations describing mass balance in each anatomical and physiological compartment for the generic PBK model in chicken.

Tissue compartment	Equation
Gut lumen	$\frac{dM_{lumen}}{dt} = Q_{food} * (C_{food} - C_{faeces})$
Gut tissue	$\frac{dM_{gut}}{dt} = Q_{gut} * \left(C_{art} - \frac{C_{gut}}{P_{gut}}\right) + k_a * M_{lumen}$
Liver	$\frac{dM_{liver}}{dt} = Q_{liver} * \left(C_{art} - \frac{C_{liver}}{P_{liver}}\right) - \frac{V_{max} * C_{liver}}{K_m + C_{liver}} * V_{liver} + Q_{gut} * \left(\frac{C_{gut}}{P_{gut}}\right) - Q_{gut} * \left(\frac{C_{liver}}{P_{liver}}\right)$
Metabolism	$\frac{dM_{liver}}{dt} = Q_{liver} * \left(C_{art} - \frac{C_{liver}}{P_{liver}}\right) - Q_{gut} * \left(\frac{C_{liver}}{P_{liver}}\right)$
Clearance	$\frac{dM_{liver}}{dt} = Q_{liver} * \left(C_{art} - \frac{C_{liver}}{P_{liver}}\right) - (C_{liver} * Cl_{hepatic}) + Q_{gut} * \left(\frac{C_{gut}}{P_{gut}}\right) - Q_{gut} * \left(\frac{C_{liver}}{P_{liver}}\right)$
Heart, Brain, Bone, Adipose tissue, Muscle, Lung	$\frac{dM_{tissue}}{dt} = Q_t * \left(C_{art} - \frac{C_t}{P_t}\right)$
Kidney	$\frac{dM_{kidney}}{dt} = Q_{kidney} * \left(C_{art} - \frac{C_{kidney}}{P_{kidney}}\right) - (C_{kidney} * Cl_{renal})$
Venous blood	$\frac{dM_{ven}}{dt} = \sum_T^{notliver+gut} Q_t * \left(\frac{C_t}{P_t}\right) + (Q_{gut} + Q_{liver}) * \left(\frac{C_{liver}}{P_{liver}}\right) - Q_{tot} * C_{ven}$
Arterial blood	$\frac{dM_{art}}{dt} = Q_{tot} * C_{ven} * \left(\frac{Q_{tot}}{Q_{tot} + Q_{exhale} * P_{air}}\right) - Q_{tot} * C_{art}$
Egg	$\frac{dM_{ingland}}{dt} = Q_{reprod} * \left(C_{art} - \frac{C_{reprod}}{P_{egg}}\right) - Q_{egg} * C_{reprod}$

V_i: Tissue volume (L); Q_t: Tissue blood flow (L/min); Q_{tot}: Cardiac output (L/min); Q_{egg} Egg production (L/min); Q_{exhale}:Exhalation (L/min); C_i: concentration in tissue (mg/kg); M_i: mass in tissue (mmol); P_i: tissue:blood partition coefficient; k_a: absorption rate constant (h^{-1}); $Cl_{hepatic}$: hepatic clearance (L/min); Cl_{renal}: renal clearance (L/min); Vmax: maximal metabolic velocity (mg/min/L liver); Km: Miachelis constant (mg/L); Mathematical equations were the same as described previously (Lautz et al., 2020b), except for the egg compartment.

predict quantities such as area under the curve (AUC) or residues in edible tissues (muscle, liver, kidney) and eggs after oral acute or chronic exposure. In practice, these predictions can be applied to derive either reference points or points of departure on an internal dose basis or carry over and residues as an input for basis for human exposure assessment. The **structure** of the generic PBK model is illustrated in Fig. 1 and Table 2 provides its **mathematical representation** for mass balance in each anatomical and physiological compartment with associated abbreviations for physiological and chemical specific parameters.

3.2. Parameter estimation and analysis

3.2.1. Data collection of anatomical and physiological parameters

Individual anatomical and physiological data from 102 scientific publications in adult male and female chicken (*Gallus gallus domesticus*) were collected from the literature through an extensive literature search (see Section 2.2) for a wide range of chicken male and female chicken breed, cross-breed and un-named breeds (50% of the dataset). The chicken breeds included were as follows: Arbor Acres, Anak, Anak 2000, Araucana, Archer Arbor, Avian 43, Brahma, Brown Hyssex, Cobb, Cobb 315, Cornish cross, Creeper, Crossbreed, Hy-line Brown chicken, Japanese Bantam, Naked neck, New Hampshire, Novo Brown, Ovambo, Ross, Ross 308, Ross PM3, Shamo, Silky, Starbro, Venda, White Crested Polish, White Leghorn, White Leghorn hybrid. Meta-analyses on data for individual tissue weights and blood flows were performed and normalised as a percentage of body weight and percentage of cardiac output respectively to characterise means and CVs for each compartment of the PBK model in males, females and mixed chicken population as aggregated values (Table 3).

Overall, physiological parameters did not show significant differences (means and CVs) between male and female chicken, with the exception of variability in intestinal weight which was higher in males (Table 3). Blood flow values could only be described for the whole chicken population, since these literature values were very limited available and mostly reported as combined value. For the aggregated *meta*-analysis, large intra-species variation between studies were observed for brain weight, spleen weight and brain blood flow (> 50%). Blood flows for the carcass, lung and muscle were estimated using allometric scaling. A default value for the CV of 30% was allocated to the population variability (Clewell and Clewell, 2008). Intestinal weight showed large intra-species variation across studies (CV = 57%) which mostly reflected differences between chicken breeds while influencing tissue-to-body ratio. Blood flow parameters were only available from few studies and these were measured with different experimental design, however variability was below 20 and 33% with the exception of intestine (39%) and liver blood flow (43%).

3.2.2. Case studies

Seven compounds (melamine, florfenicol, monensin, salinomycin, fipronil, deltamethrin, and sanguinarine) were identified from the literature as relevant to food and feed safety, covering a range of molecular weights and physico-chemical properties and with available *in vivo* kinetic data in chicken (kinetic parameters in body fluids, tissues, and eggs). Key features are given in Table 4 including chemical name, classification and use, molecular weight, physico-chemical properties (log K_{ow}, pKa) and structure. Melamine is an environmental contaminant that can be present in animal feed and is eliminated by renal excretion (Dorne et al., 2013a). Deltamethrin is a broad-spectrum pyrethroid insecticide which is mainly oxidised into 3-phenoxybenzoic acid in chickens by CYP enzymes. Such metabolism is consistent with oxidative metabolism in humans (Abass et al., 2012; Akhtar et al., 1994; Huyuk and Eraslan, 2017). Fipronil is a hydrophobic chiral insecticide (phenylpyrazole) commonly used in agriculture which is metabolised by a range of cytochrome *P*-450 isoforms (CYP) in different species. In chicken, fipronil sulfone is the main detected metabolite

Table 3
Mean organ weights, tissue weights and blood flows and associated coefficient of variations in males and female chicken breeds (*Gallus gallus domesticus*).

Anatomical parameters	Female (Ref. 1–44)			Male (Ref. 1–44)			Mixed chicken population (Ref. 1–44)				Blood flows[a] (Ref. 45–60)		
	N	BW (%)	CV (%)	N	BW (%)	CV (%)	N	BW (%)	CV	ρ(BW, OW)	N	CO (%)[d]	CV
Adipose tissue	100	12.1	17	100	10.4	19	228	10.7	24	0[a]	1	1.5	30[b]
Blood	69	7.5	22	59	6.8	17	201	7.1	18	0.47	NA	NA	NA
Brain	59	0.2	49	NA	NA	NA	207	0.3	39	0[a]	13	0.4	20
Carcass	NA	NA	NA	27	22.9	NA	45	20.3	36	0[a]	0[c]	12.4	30[b]
Heart	561	0.6	21	572	0.7	19	2624	0.6	20	0.48	35	5.5	33
Intestine	12	5.8	16	80	3.1	51	193	3.9	57	0.36	13	17.7	39
Kidney	83	0.7	30	68	0.7	21	182	0.8	33	0[a]	48	11.4	29
Liver	669	2.6	17	614	2.6	19	2833	2.4	17	0.6	116	6.6	43
Lung	562	0.8	27	538	0.8	21	1167	0.8	27	0.17	0[c]	3.0	30[b]
Muscle	67	39.8	12	67	40.9	11	152	40.8	13	0[a]	1	19.8	30[b]
Rep. tissue	25	2.8	4	NA	NA	NA	25	2.8	4	0[a]	72	14.3	26

Body weight (kg) and CV (2.11, 10); Cardiac output (L/min/kg) and CV (0.34, 30); Abbreviations: N: sample size (number of individuals); NA: not applicable; BW (%): Organ or tissue normalised as a percentage of body weight, CO (%): blood flow normalised as percentage of cardiac output, CV: Coefficient of variation; rho: ρ(BW,OW), Pearson's correlation coefficient between organ weight/blood flow and body weight/cardiac output, Rep. tissue: reproductive tissue (lumped); Organ and tissue weights (1–44): (Adil et al., 2010; Agnvall et al., 2017; Alikwe et al., 2014; Becker et al., 1979; Bochno et al., 1999; Bond and Gilbert, 1958; Bowes and Julian, 1988; Chikumba and Chimonyo, 2014; Cortright et al., 2009; Dairo et al., 2010; Diarra et al., 2014; Dominguez-Romero et al., 2016; Fernandez et al., 1994; Frahm and Rehkamper, 1998; Hanif et al., 2008; Harris and Koike, 1977; Hassan et al., 2010; Koike et al., 1983; Kosarachukwu et al., 2010; Landers et al., 2008; Lee et al., 2015; Mabelebele et al., 2015; Manafi et al., 2015; Mavromichalis et al., 2000; Medway and Kare, 1959; Mirsalimi and Julian, 1993; Mirsalimi et al., 1993; Moura et al., 2016; Park and Kim, 2015; Ryu et al., 2016; Shahzad et al., 2012; Sieo et al., 2005; Stoev et al., 2004; Szabo et al., 2014; Tickle et al., 2014; Togun et al., 2006; Venturini et al., 2014; Viscor et al., 1985; Wels et al., 1967; Williams and Rodbard, 1960; Wolfenson et al., 1978; Wolfenson et al., 1981; Yahav et al., 1997; Yokhana et al., 2016); Cardiac output and blood flows (45–60): (Boelkins et al., 1973; Cortright et al., 2009; Merrill et al., 1981; Moynihan and Edwards, 1975; Nightingale, 1976; Sapirstein and Hartman, 1959; Stebel and Wideman, 2008; Sturkie and Abati, 1975; Sturkie and Vogel, 1959; Vogel and Sturkie, 1963; Whittow et al., 1964; Wideman, 1999; Wideman et al., 1998; Wideman and Tackett, 2000; Wolfenson et al., 1978; Wolfenson et al., 1981).

[a] No correlation between body weight and organ weights or cardiac output and blood flow assumed.
[b] ± 30% variability.
[c] fCO based on allometric scaling.
[d] No correlation assumed between cardiac output and blood flow.

mediated via CYP3A and CYP2C oxidation (JMPR, 2001; Wang et al., 2016). Florfenicol is a veterinary medicine (i.e., broad-spectrum antibiotic) and monensin and salinomycin are ionophoric (poly-ethers) coccidiostatics used in poultry (Anadon et al., 2008). Monensin and florfenicol are extensively metabolised by CYP3A in chicken and salinomycin is nearly completely metabolised by individual CYP isoforms which have not been characterised to date in chicken (Dorne et al., 2013b; EFSA FEEDAP Panel, 2017; Nebbia, 2001; Wang et al., 2018). Sanguinarine is an alkaloid applied as a feed additive which is widely distributed in the plant families *Papaveraceae, Fumariaceae,* and *Rutaceae*. Sanguinarine metabolism involves oxidation into dihydro-metabolites which are generated by CYP1A oxidation in humans and rats (Deroussent et al., 2010; Hu et al., 2018; Xie et al., 2015).

3.3. Model evaluation

3.3.1. Global sensitivity analysis

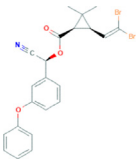
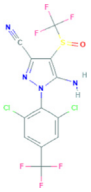
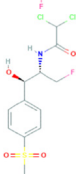
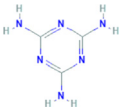
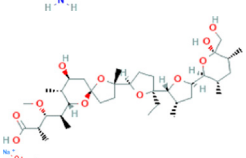
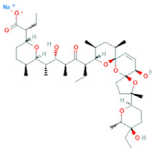
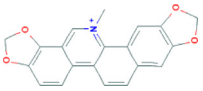
Melamine and deltamethrin were selected for the global sensitivity analysis as polar and lipophilic compounds. Global sensitivity analysis using variance-based Sobol method was performed for each PBK input parameter for concentrations in the whole animal, blood, liver and kidney. Parameter values and exposure scenarios are described in Table 5. Results of the global sensitivity analysis for both compounds are presented in Fig. 2 for three time points (0.75, 5.5, and 19.5 h); parameters are ordered by relative importance. Overall, body weight (BW) and the cardiac output (CO) were parameters of the PBK model that contributed the most to the variation in the model outcome (Fig. 2). Since the global sensitivity analysis was run for the oral route of exposure, intestinal blood flow (fCO_intestine) represents an important source of variance, particularly during the absorption phase. For melamine, renal blood flow (fCO_kidney) was the most sensitive parameter in the elimination phase since its elimination is driven by renal clearance. In contrast, for deltamethrin, the neutral fraction of the tissue (nl), the adipose tissues relative volume (fBW_adipose), blood flow to the adipose tissue (fCO_adipose) and the lipid content of the tissues contributed the most to the overall variance and predictions of internal concentrations. These results are consistent with deltamethrin's lipophilicity (MacLachlan, 2010). Other organ blood flows did not contribute significantly to the overall variance of concentration predictions. Overall, results of the sensitivity analysis for model outputs in the whole animal and kidney concentrations were similar compared to those for melamine blood concentrations, but were more variable for deltamethrin.

3.3.2. Model calibration and validation

Model calibration has been conducted on a compound-specific basis depending on data availability. For melamine, pharmacokinetic parameters were estimated for renal clearance using allometric scaling, and the model was calibrated with an independent dataset (Lautz et al., 2020b; Poapolathep et al., 2015). Monensin intrinsic clearance was determined based on *in vitro* parameters (Vmax (646 pmol/mg/min) and Km (28.6 μM) (Henri et al., 2008)) and these were scaled to total liver weight using liver weight and milligrams of microsomal protein per gram liver (value of 9.31) (Henri et al., 2017). Hepatic clearances of salinomycin, florfenicol, deltamethrin and fipronil were estimated by visual fitting (Henri et al., 2012; Huyuk and Eraslan, 2017; MacLachlan, 2008; Shen et al., 2003). Finally, an absorption rate constant for sanguinarine was not available in literature and was therefore estimated by visual fitting (Xie et al., 2015). Compound-specific kinetic parameters including absorption rate constant (k_{abs}), hepatic clearances ($Cl_{hepatic}$) and renal clearance (Cl_{renal}) are reported in Table 6.

Model validation for each compound was performed using the comparison between *in vivo* kinetic data reported from peer-reviewed experimental studies (n = 13) providing concentrations in blood, tissues including mostly adipose, muscle, liver and kidney and eggs and their PBK prediction counterparts. Availability of residue changes in blood and tissues over time were limited to salinomycin and florfenicol in various tissues (Fig. 3), showing model performance for the

Table 4
Chemical characteristics and classification of the compounds selected for the case studies.[a]

Chemical name (CAS number)	Classification	MW (g/mol)	Log K_{ow}	Solubility (mg/L)	Vapour Pressure (Pa)	pKa	Structure
Deltamethrin (52918-63-5)	Pesticide	505.2	6.20	0.002	1.20E-08	NA	
Fipronil (120068-37-3)	Pesticide	437.1	4.00	2.1	1.29E-22	NA	
Florfenicol (73231-34-2)	Drug	358.2	−0.12[b]	1320	3.70E-07	9.03[b]	
Melamine (108-78-1)	Contaminant	126.1	−1.37	3230	4.37E-08	5.0	
Monensin (17090-79-8)	Drug	670.9	5.43	0.1	6.93E-21	6.6	
Salinomycin sodium (55721-31-8)	Drug	773.0	5.12[b]	622.3	8.30E-23	6.4[b]	
Sanguinarine (2447-54-3)	Botanical	332.3	−0.9[c]	0.001	1.33E-22	NA	

[a] Data was retrieved from PubChem unless stated otherwise.
[b] Zhao and Ball (2009; EFSA, 2018a).
[c] Estimated; NA: not available, MW: molecular weight.

Table 5
Exposure scenario characteristics for melamine and deltamethrin analysis.

Chemical	Reference	Characteristics	Study design	Organ
Melamine	Bai et al. (2010)	Species: Chicken Age: 55 weeks Sex: Female Weight: NA N: 12	Dose: 8.6 mg/kg Route: food Multiple doses Duration: 34 days	Plasma
Deltamethrin	Huyuk and Eraslan (2017)	Species: Chicken Age: 5 weeks Sex: Male Weight: 1.75 N: 10	Dose: 0.75 mg/kg Route: oralSingle dose	Plasma

prediction of blood, adipose tissue, kidney and muscle after single and multiple oral doses. Overall, for salinomycin and florfenicol 63% and 51% of the predictions were within a 3-FC. However, slight overestimations were noted for the prediction of internal concentrations (absorption phase) and concentrations in adipose tissue for salinomycin and blood and muscle concentrations (absorption phase) for florfenicol. Model discrepancies might be due to variability in feeding patterns or overestimation of tissue:blood partition coefficients. However, based on the available K_{ow} for salinomycin sodium, higher concentrations in adipose tissue would be expected.

Model validation is provided for the seven compounds in Fig. 4 and Fig. 5 comparing experimental and PBK predicted concentrations in blood, tissues and the egg compartment. Globally, 71% of the model predictions were within a 3-fold change of the measured data for chicken and only 7% of the PBK predictions were outside a 10-fold change. Accuracy of the model predictions between compounds was variable but similar between water soluble and lipophilic chemicals. For water soluble compounds (melamine, florfenicol, and sanguinarine), over 70% of the predictions were within 3-fold of the experimental data with only 9% of predictions over- or underestimating by more than a 10-fold. For lipophilic compounds (fipronil, salinomycin, monensin and deltamethrin), 72% of the predictions were within a 3-fold of the experimental data. Only 5% of concentrations were over- or underestimated by more than a 10-fold factor particularly for florfenicol concentration predictions in the brain and the bone compartments (Afifi and Abo el-Sooud, 1997). Florfenicol has low bioavailability, high clearance rates, and is subject to efflux transport (P-glycoprotein (P-gp) and ABCG2) limiting enteric absorption and blood brain barrier transfer and ultimately influencing internal concentrations (Afifi and Abo el-

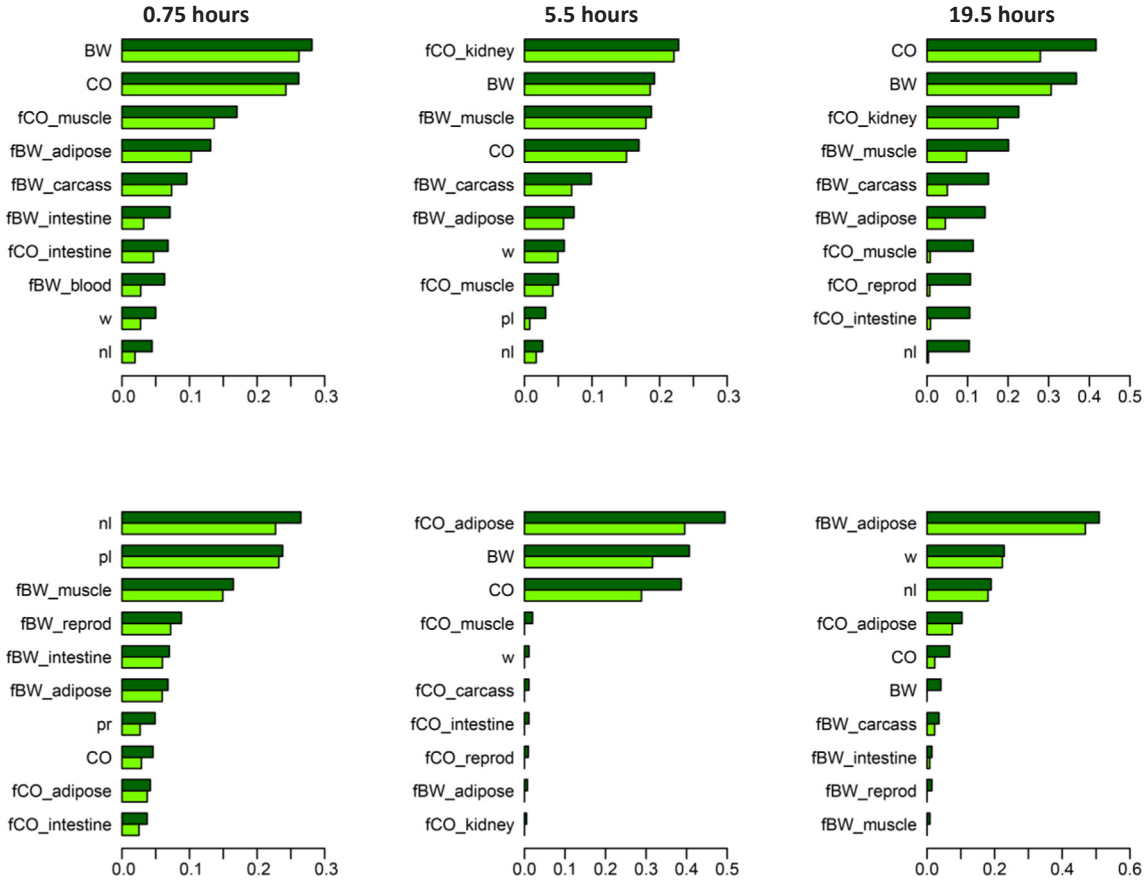


Fig. 2. Sensitivity analysis of the chicken PBK model applied to melamine (upper panel) and deltamethrin (lower panel). Sobol' sensitivity analysis indices were estimated for the blood concentrations at three time points: 0.75, 5.5, and 19.5 h. Sobol's total indices (TI) are presented in dark green and Sobol's first-order indices (FOI) in light green. Parameters were ordered according to the TI. The eleven most influencing parameters according to the total sensitivity indices are shown. BW: body weight, CO: cardiac output, fCO_tissue: fraction cardiac output of a specific tissue; fBW_tissue: fraction body weight of a specific tissue; tissue constituents neutral lipids (nl), polar lipds (pl), proteins (pr) and water (w). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Sooud, 1997; Liu et al., 2018; Wang et al., 2018). Deviations between predicted concentrations and experimental data for florfenicol may be explained by the fact that the current PBK model in chicken does not include quantitative information to model efflux transporters since such data are scarce in the literature (Nebbia, 2001; Schrickx and Fink-Gremmels, 2008). Most information available on transporters in chicken include expression and probe substrates in liver and intestine of Multiple drug resistance 1-gene (MDR1/ABCB1 encoding P-gp), multi-drug resistance-associated protein 2 (MRP2/ABCC2) and Breast Cancer Resistant Protein (ABCG2) encoding for membrane proteins from the ABC superfamily (Antonissen et al., 2017; Guo et al., 2013; Guo et al., 2016; Guo et al., 2014; Liu et al., 2018; Osselaere et al., 2013b). Currently, selective transport can only be taken into account in the model when partition coefficients are measured as they are poorly predicted by QSAR models and including active transport across blood-tissue barriers may improve predictions in a mechanistic way for relevant chemicals.

Overall, literature data on tissues concentrations of the included

Table 6
Chemical specific kinetic parameters collected for the case studies.

Parameter	Unit	Melamine	Monensin	Salinomycin sodium	Fipronil	Florfenicol	Deltamethrin	Sanguinarine
k_{abs}	1/min	0.0059[a]	0.064[b]	0.061[c]	0.01[g]	0.022[d]	0.064[e]	0.01[g]
$Cl_{hepatic}$	L/min/kg	0	0.006[h]	0.006[g]	0.00013[g]	0.003[g]	0.001[g]	0.76[f]
Cl_{renal}	L/min/kg	0.0029[i]	0	0	0	0	0	0

Data were retrieved from:
[a] Poapolathep et al. (2015).
[b] Henri et al. (2017).
[c] Atef et al.)1993).
[d] Shen et al. (2003).
[e] Huyuk and Eraslan (2017).
[f] Hu et al. (2018).
[g] Estimated.
[h] *In vitro in vivo* extrapolation.
[i] Allometric scaling.

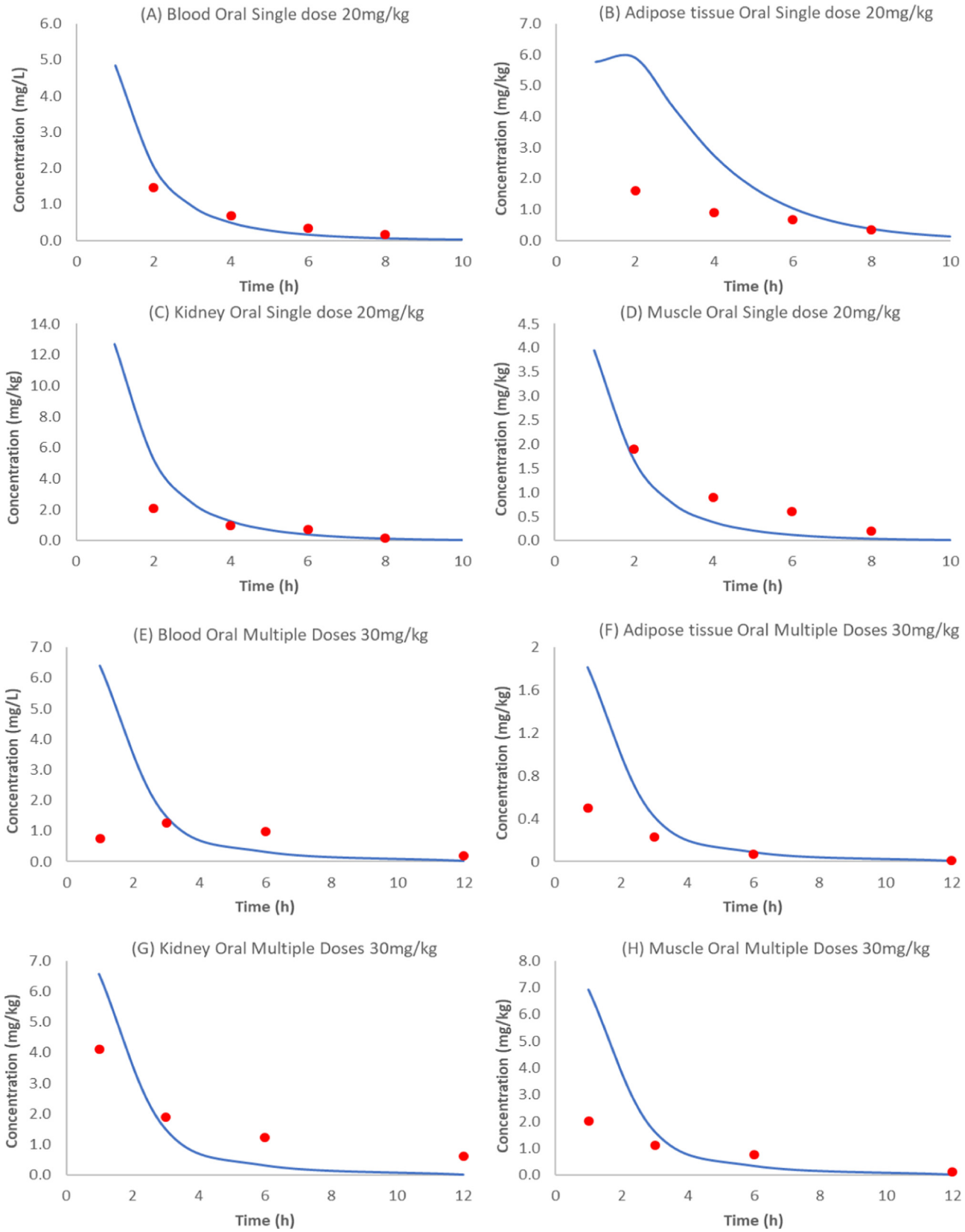


Fig. 3. Validation of the generic chicken PBK model for salinomycin (A-D) and florfenicol (E-H). Comparison of model predictions (solid lines) and observed data (red dots) are shown for concentrations of both salinomycin and florfenicol in blood, adipose tissue, kidney, and muscle from chicken exposed to salinomycin via a single oral dose (A-D; 20 mg/kg), and to florfenicol via multiple oral doses (E-H; 30 mg/kg). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

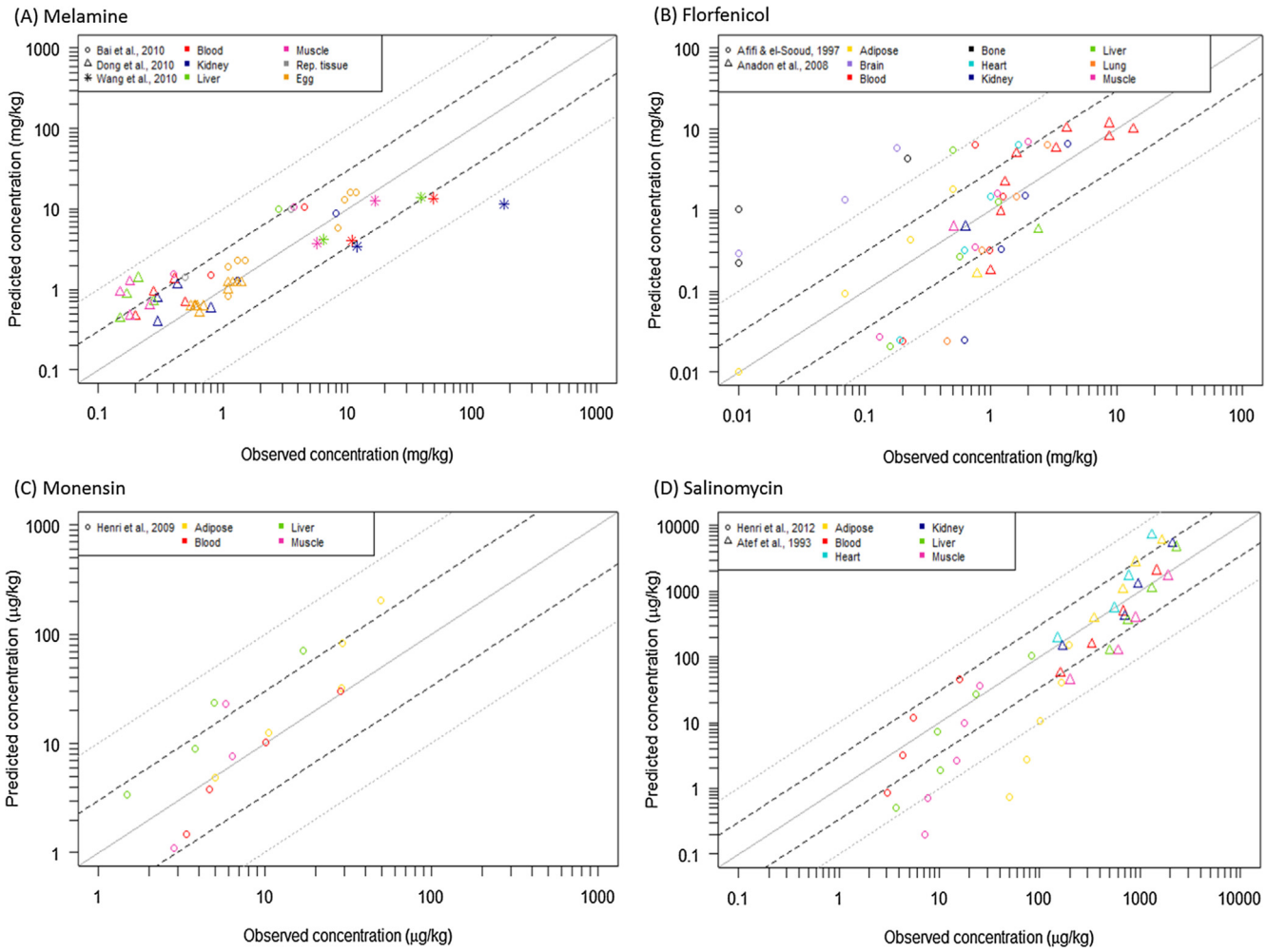


Fig. 4. Comparison between quantities measured in chicken and PBK model predictions for four chemicals in various organs. Dotted lines represent 3-fold and 10-fold changes. Data in FC < 3, 3 < FC < 10, FC > 10 for the chemicals: melamine (80%, 18%, 2%), florfenicol (51%, 30%, 19%), monensin (75%, 25%, 0%), salinomycin (63%, 28%, 9%). Organs and references of experimental dataset obtained are indicated in legends: colours and shapes represent organs and studies, respectively.

chemicals were limited, so the quality of the included papers is of high relevance for the reliability of the model performance. Therefore, study design and availability of ADME parameters for model calibration may impact model performance and validation. First, chemical uptake has been modelled in chicken after feed ingestion and intestinal absorption as the major relevant exposure route for environmental contaminants and feed additives. While oral absorption directly impacts on internal concentrations, it is required as a model input variable and was well described in the literature for most of the compounds (Atef et al., 1993; Henri et al., 2017; Huyuk and Eraslan, 2017; Poapolathep et al., 2015; Shen et al., 2003). Exceptions included fipronil for which oral absorption patterns in chicken were not available and sanguinarine for which absorption was very low and absorption rate were not reported due to low plasma concentrations (Hu et al., 2018). For melamine and salinomycin, the study design involved *ad libitum* feeding patterns through contaminated feed, leading to large variability of oral intake in chicken (Bai et al., 2010; Dong et al., 2010; Henri et al., 2009; Henri et al., 2012). Such study design may introduce variability in time dependent patterns of chemical intake impacting internal concentrations. In contrast, PBK model predictions for salinomycin using data from intra-crop administration as a controlled route for chemical intake resulted in more accurate predictions (Atef et al., 1993; Henri et al., 2012).

Table 7 provides the overall performance of the model for the prediction of tissues and egg concentrations expressed in fold changes compared with the experimental data. Overall, accuracy of the model predictions across compounds was best for egg concentrations with 97% within a 3-fold of the experimental data, followed by blood and kidney (82% and 76%) and other organs (57%-67%). Eggs form an important storage compartment for lipophilic contaminants and veterinary drug residues. In addition, the 1999 dioxin and the 2017 fipronil crises provide examples that egg transfers of lipophilic compounds are also important to consider for human exposure assessment (EFSA, 2018b; 2019; Goetting et al., 2011; Pajurek et al., 2019). Current limitations in PBK models include partitioning of lipophilic chemicals between blood and tissues which is dependent on blood lipid fraction and in chicken, such fraction varies with diet and physiological state such as laying and may introduce variability in egg residue predictions (Máchal, 2000; Peebles et al., 2004; Pinchasov et al., 1994). In the egg compartment, residue profiles can be different between yolk and albumen as part of the egg formation process. Inclusion of both yolk and albumen compartments in the PBK model would support better predictions of residue profiles in this process of egg formation (Hekman and Schefferlie, 2011).

3.4. Open source chicken PBK model: Summary of model evaluation

Evaluation of the generic PBK model in chicken (*Gallus gallus domesticus*) using the WHO criteria is summarised in Table 8 namely scope and purpose of the model, model structure and mathematical implementation, parameter estimation and analysis, model calibration

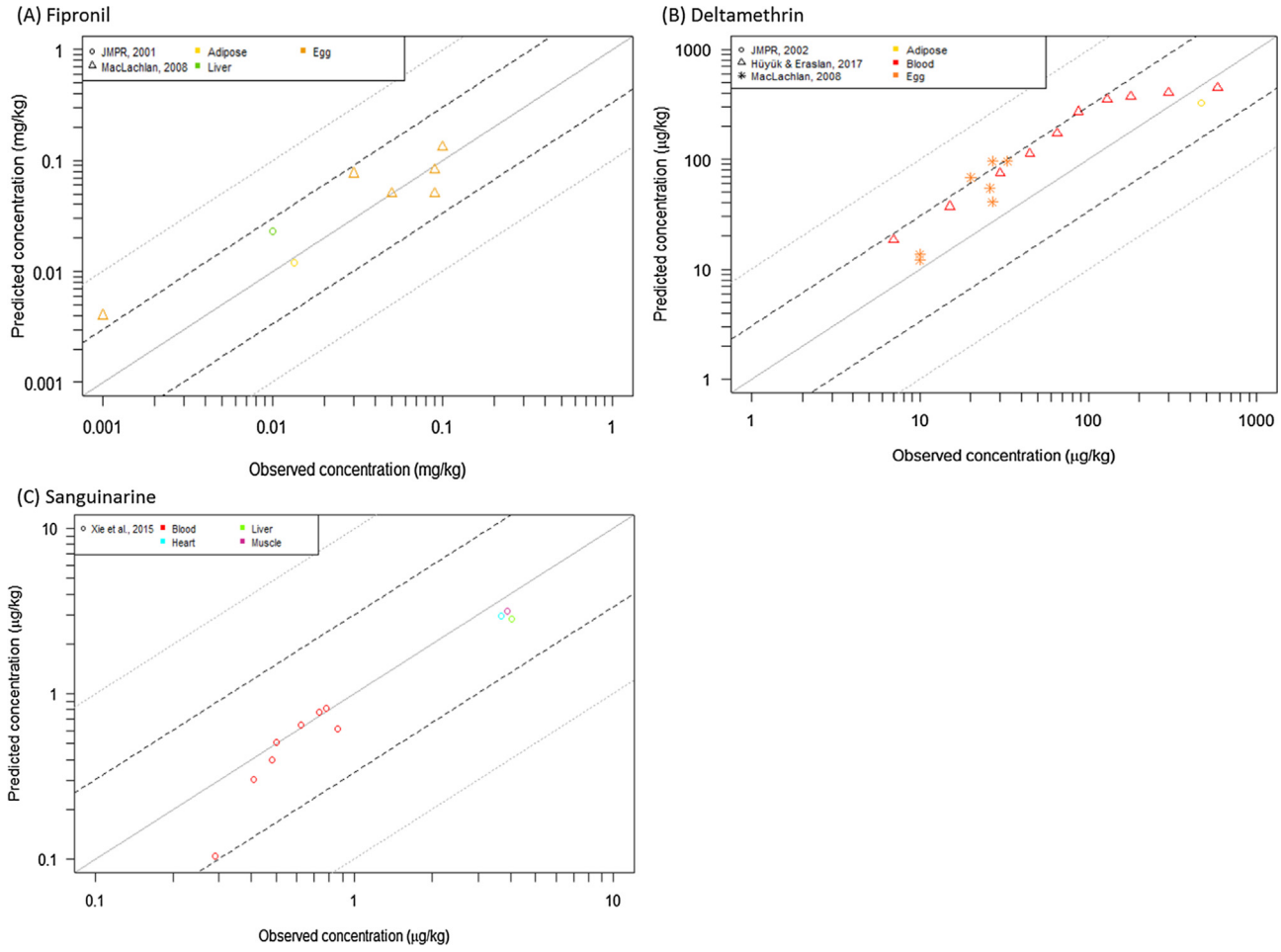


Fig. 5. Comparison between quantities measured in chicken and PBK model predictions for three chemicals in various organs. Dotted lines represent 3-fold and 10-fold changes (FC). Data in FC < 3, 3 < FC < 10, FC > 10 for the chemicals: fipronil (88%, 12%, 0%), deltamethrin (83%, 17%, 0%), sanguinarine (100%, 0%, 0%). Organs and references of experimental dataset obtained are indicated in legends: colours and shapes represent organs and studies, respectively.

Table 7
Validation of the generic chicken PBK model: Overall performance for the prediction of organs, tissues, blood and egg concentrations.

Organ	FC < 3	3 < FC < 10	FC > 10
Adipose tissue	57%	33%	10%
Blood	82%	18%	0%
Heart	67%	33%	0%
Kidney	76%	12%	12%
Liver	61%	35%	4%
Muscle	58%	34%	8%
Egg	97%	3%	0%

and validation and model documentation. In the future, this table can provide practical means to increase transparency in model evaluation for non-PBK specialists and increase the confidence in using such generic models for risk assessment and regulatory purposes.

4. Conclusions and future recommendations

This manuscript describes the development of a generic open source PBK model in chicken (*Gallus gallus domesticus*) through integration of *meta*-analysed physiological parameters into an R-based algorithm. The generic model can be applied to predict blood, tissue and egg concentrations in chicken for risk assessment and can also provide input data for analysis of carry over and residues in human exposure assessment. Model evaluation has been performed using WHO criteria i.e. model purpose, mathematical representation, computer implementation, model calibration and validation. Global sensitivity analysis has been illustrated for melamine (hydrophilic) and deltamethrin (lipophilic) to identify the major physiological variables contributing to the overall variance of the model outputs. Methods such as e-FAST, Sobol Plots or Lowry plots can be recommended as future systematic tools to determine parameters of the PBK model which have little influence on model outputs so that they can be fixed to improve computational speed (Hsieh et al., 2018; McNally et al., 2011; McNally et al., 2018).

Model calibration and validation was performed for seven compounds of relevance to food and feed safety with predictions of blood, tissue and egg concentrations and these are in good agreement with published data. While most model input parameters still rely on physiological data and *in vivo* chemical-specific data, future opportunities to predict internal concentrations of chemicals using *in vitro* kinetic data (V_{max}, K_m, intrinsic clearance) as model inputs and QIVIVE models are increasingly highlighted in the literature and have been explored here for the predictions of monensin residues in chicken (Lautz et al., 2019). However, such *in vitro* kinetic data are still anecdotic in the literature for chicken and other avian test species (i.e. turkey, quail etc.). Hence, the developments of *in vitro* test systems in avian species is recommended to support the generation of such datasets while reducing *in vivo* testing. In addition, data collection on the relative expression and activity of phase I (e.g. cytochrome P-450 isoforms (CYP) etc.), phase II (UDP-glucuronyltransferase set etc.) and transporters (P-glycoprotein, organic anion transporter proteins (OATPs) etc.) using combination of genomic data, *in vivo* and *in vitro* assays will further

Table 8
Evaluation of the generic PBK chicken model according to WHO criteria.

Category	Characteristic
Scope and purpose of the model	- Model purpose: generic PBK model - Species: Chicken - Age, life stage(s), sex, exposure window(s): adult, males and females, single and multiple doses - Exposure route(s), and dose metric(s): Oral - Target organs and tissues: whole body, blood, organs and tissues, eggs
Model structure and mathematical description	- Graphical representation of the model available - 12 compartments including eggs - Steady-state and differential calculations - Mass balance equations given
Computer implementation	- Model implemented in R - Model codes and syntax available
Parameter estimation and analysis	- Anatomical and physiological parameter values from the literature or predicted - Physicochemical and biochemical parameter values from literature or predicted
Model calibration and validation	- Global sensitivity analysis performed - Model calibrated with measured data from 7 compounds - Calibration data adequately reported - Model validation against independent data - Validation data reported (Figs. 4 and 5) - Variability analysis of the model predictions: predicted versus experimental data expressed as fold changes (Table 7)
Model documentation	- Peer-reviewed model - Publicly available model

improve QIVIVE based PBK models (Dorne and Fink-Gremmels, 2013; Fink-Gremmels, 2008; Gusson et al., 2006; Martinez et al., 2018). In this context, CYP expression and activities in chicken and other bird species are becoming increasingly available and could constitute a starting point for such data collection. The current generic model can be modified, and applied to other avian species of relevance to food and feed safety such as ducks, turkey, goose and quails. This would require data mining and collection from databases and the available literature of physiological parameters, enzyme activities, calibration, validation using available kinetic for relevant chemicals.

Comparative *in vitro* studies revealed that, despite a very low CYP content, broiler chick liver microsomes are more efficient than those from horses, cattle, pigs, farmed rabbits and rats in CYP-mediated oxidation of aromatic model substrates (e.g. 7-ethoxycoumarin, benzo (a)pyrene, aminopyrine, aniline) as well as the ionophore coccidiostatic monensin (Nebbia et al., 2001; Nebbia et al., 2003). More recently, the relative expression of hepatic CYP isoforms (CYP 1A4, 1A5, 1B1, 1C1, 2C23a, 2C23b, CYP2C45, CYP2D49, CYP3A37 and CYP3A80) in chicken has been characterised using available genome databases for *Gallus gallus domesticus* to identify the most important ones (CYP2C45 > CYP1A5 > CYP2C23a > CYP3A37) while the remaining CYPs were barely detectable. Interestingly, no gender-related differences between male and female chickens were observed with regards to relative expression of hepatic CYP isoforms (Watanabe et al., 2013). CYP intestinal expression and activities in chicken have been detected for CYP1A, CYP2C and CYP3A isoforms and characterised for their involvement in pre-systemic metabolism of chemicals. This is of particular relevance for feed additives, pesticides and contaminants administered by the oral route (Kulcsar et al., 2017; Osselaere et al., 2013a; Osselaere et al., 2013b).

It is foreseen that integration of open sources databases reporting physiological and chemical parameters as well as model codes into open source workflows such as the US-EPA computational dashboard and the EFSA TKPlate will provide increase the confidence in these models for risk assessment and regulatory purposes (Baas et al., 2018; Dorne et al., 2018; Pearce et al., 2017; Williams et al., 2017).

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CRediT authorship contribution statement

L.S. Lautz: Conceptualization, Methodology, Formal analysis, Writing - original draft. **C. Nebbia:** Writing - original draft, Writing - review & editing. **S. Hoeks:** Software, Visualization. **R. Oldenkamp:** Software. **A.J. Hendriks:** Supervision, Writing - review & editing. **A.M.J. Ragas:** Supervision, Writing - review & editing. **J.L.C.M. Dorne:** Supervision, Writing - review & editing, Project administration.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: This work was supported by the European Food Safety Authority (EFSA) [Contract number: EFSA/SCER/2014/06].

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