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Generic physiologically based kinetic modelling for farm animals: Part I. Data collection of physiological parameters in swine, cattle and sheep

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ABSTRACT

Physiologically based kinetic (PBK) models for farm animals are of growing interest in food and feed safety with key applications for regulated compounds including quantification of tissue concentrations, kinetic parameters and the setting of safe exposure levels on an internal dose basis. The development and application of these models requires data for physiological, anatomical and chemical specific parameters. Here, we present the results of a structured data collection of anatomical and physiological parameters in three key farm animal species (swine, cattle and sheep). We performed an extensive literature search and meta-analyses to quantify intra-species variability and associated uncertainty of the parameters. Parameters were collected for organ weights and blood flows in all available breeds from 110 scientific publications, of which 29, 48 and 33 for cattle, sheep, and swine, respectively. Organ weights were available in literature for all three species. Blood flow parameter values were available for all organs in sheep but were scarcer in swine and cattle. Furthermore, the parameter values showed a large intra-species variation. Overall, the parameter values and associated variability provide reference values which can be used as input for generic PBK models in these species.

1. Introduction

Physiologically based kinetic (PBK) models are increasingly being used by scientific advisory bodies and regulatory authorities to estimate internal concentrations of chemicals or their metabolites in a various body fluids and tissues (Paini et al., 2017). These models can be applied to support exposure assessment to perform route-to-route extrapolation, to evaluate biomonitoring data, to characterise variability between individuals, and to quantify variability and uncertainty in physiological and kinetic parameters (Beaudouin et al., 2010; Bois et al., 2010; EFSA, 2014; Fierens et al., 2016; Huizer et al., 2014; McNally et al., 2012). In the pharmacology field, PBK models are also applied in drug discovery and development (EMA, 2018).

PBK models are built by integrating mathematical relationships describing the kinetics of a chemical in different physiological compartments of an organism processes. A number of parameters are required to build a PBK model and these can be divided into physiological/anatomical descriptors (e.g., blood flow, organ volumes), and biochemical descriptors (e.g., partition coefficients, protein binding) (EFSA, 2014; WHO, 2010). Biochemical descriptors are chemical-specific, whereas the physiological and anatomical descriptors are species-specific. It is foreseen that systematic data collection of physiological parameters in relevant species, and the creation of open source databases will support the development and application of PBK models in risk assessment (Madden et al., 2019). In addition, quantification of variability and uncertainty associated with these parameters (e.g. Marchov Chain Monte Carlo) and global sensitivity analysis using probabilistic approaches, are becoming increasingly important to investigate key variables that impact on model outputs and to support validation of the models (Bois et al., 2010; Li et al., 2019a).

Over twenty years ago, Brown et al. (1997) published a thorough comparative data collection of physiological and anatomical parameters for four standard laboratory test species and humans which provided a basis to develop generic PBK models for those species. Especially for human, various databases have been described (Madden et al., 2019). For fish species, an anatomical and physiological database for four species (rainbow trout, fathead minnow, zebra fish and European stickleback) has recently been published (Grech et al., 2019). For sheep and swine, only limited data have been published, e.g. mean physiological data for one sheep breed (Merino) and small pigs (25 kg), both often used for preclinical drug studies (Upton, 2008). Thorough data for anatomical and physiological parameters in a range of farm

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Table 1
Keywords applied in the extensive literature searches for the data collection of physiological and anatomical parameters in swine, cattle and sheep.

Type	Keywords
Species	< cow / cattle > OR < swine > OR < sheep / ewe > OR
Biological and physiological variables	< 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 > OR < muscle >

species and breeds are currently lacking, impeding the development of generic open source PBK models and this has been highlighted in recent review papers (Lautz et al., 2019b; Li et al., 2019a; Lin et al., 2016).

This paper aims to perform a systematic data collection on physiological and anatomical parameters for swine, cattle and sheep as key farm animal species by means of extensive literature searches and meta-analyses. A part II of this manuscript describes the development of the generic PBK models in swine, cattle and sheep, their validation using global sensitivity analysis as well as case studies to predict blood and tissue concentrations for compounds that are renally excreted (Lautz et al., 2019a).

2. Material and methods

2.1. Extensive literature search

Extensive literature searches were conducted in PubMed and Google Scholar until December 2018 to identify all relevant peer-reviewed publications reporting physiological parameters, such as organ volumes and blood flow rates, using relevant keywords described in Table 1. Each reference identified in the extensive literature searches and its associated bibliography were screened for relevance based on title and abstract. In a next step, the full text of each individual study was scrutinised and evaluated critically for their relevance. Parameter values for body weight, organ weight, and values for blood flow distribution were extracted when available for healthy, mature animals. Animals were classified as healthy when no information on altered health conditions were given. When parameters for healthy animals were not available, healthy, juvenile animals (pigs > 25 kg, sheep and cattle: ruminants only) were included. Data for animals fed on a conventional (grass, corn-based) diet were included. In contrast, data for animals fed an altered diet such as protein rich or protein poor diet, or with added supplements were excluded to collect all parameters under physiological conditions. Data for animals with non-typical traits (e.g. obese animals), kept under adverse environmental conditions, or exposed to drugs or toxic agents, were excluded. Mean values for organ weight, represented as a fraction of body weight, were only derived if studies explicitly provided body weight data or data presented as percent body weight. If organ blood flow was reported in ml/100 g/min or similar units, the mean organ weight was used to calculate the percent of cardiac output.

2.2. Meta-analyses

From the data collection, meta-analyses were performed for each physiological parameter and species obtained. All studies assumed that the physiological and biological parameters followed a normal distribution (arithmetic mean and standard deviation). Organ weight and blood flow fractions were calculated based on the reported arithmetic mean (AM) and standard deviation (SD) (Equations 1 & 2):

$$\mathbf{AM_{f,i}} = \frac{\mathbf{AM_{O,i}}}{\mathbf{AM_B}} \tag{1}$$

where $AM_{f,i}$ is the arithmetic mean body weight or blood flow fraction for organ i; $AM_{O,i}$ is the arithmetic mean weight or blood flow for organ i; and AM_B is the arithmetic mean body weight or cardiac output;

$$\mathbf{SD_{f,i}} = \mathbf{AM_{f,i}} \bullet \sqrt{\left(\frac{\mathbf{SD_{O,i}}}{\mathbf{AM_{O,i}}}\right)^2 + \left(\frac{\mathbf{SD_B}}{\mathbf{AM_B}}\right)^2 - 2 \bullet \frac{\mathbf{SD_{O,i}} \bullet \mathbf{SD_B}}{\mathbf{AM_{O,i}} \bullet \mathbf{AM_B}} \bullet \rho[\mathbf{O_i}, \mathbf{B}]} \tag{2}$$

Where, $SD_{f,i}$ is the standard deviation of the body weight or blood flow fraction for organ i; $SD_{O,i}$ is the standard deviation of body weight or blood flow for organ i; SD_B is the standard deviation of the body weight or cardiac output; $\rho[O_i, B]$ is the Pearson's correlation coefficient between the organ weight or blood flow and body weight or cardiac output, respectively. When $\rho[O_i, B]$ was not given, no correlation was assumed ($\rho[O_i, B] = 0$).

When multiple studies were available for the assessed parameter, the studies were combined using the method described by Ragas and Huijbregts (1998), in which AM and SD were combined based on the sample size of the respective studies (Equation 3 & 4):

$$\mathbf{AM_{combined}} = \frac{\sum_{x=1}^{x=n} \mathbf{N_x} \bullet \mathbf{AM_x}}{\sum_{x=1}^{x=n} \mathbf{N_x}} \tag{3}$$

$$\mathbf{SD^2_{combined}} = \frac{\sum_{x=1}^{x=n} [(\mathbf{N_x} - 1) \bullet \mathbf{SD_x^2} + \mathbf{N_x} \bullet \mathbf{AM_x^2} - 2 \bullet \mathbf{N_x} \bullet \mathbf{AM_x} \bullet \mathbf{AM_{combined}} + \mathbf{N_x} \bullet \mathbf{AM^2_{combined}}]}{(\sum_{x=1}^{x=n} \mathbf{N_x}) - 1} \tag{4}$$

Where, $AM_{combined}$ represents the combined mean; AM_x is the mean of study x; SD_x is the standard deviation of individual study x; N_x is the sample size of study x; and n is the number of studies to be combined.

The original dataset reporting all anatomical and physiological parameters included in the meta-analyses is available in excel format on EFSA knowledge junction under the DOI: 10.5281/zenodo.3433224 with a Creative Common Attribute 4.0 license.

Since dairy cattle and beef cattle are selected for on different traits (i.e. milk yield versus meat yield), a two-tailed Student *t-test* ($p < 0.001$) was performed to test for significant intra-species differences between dairy cattle and beef cattle.

3. Results

3.1. Anatomical and physiological parameters

Anatomical and physiological parameters were retrieved from 110 scientific publications, i.e. 29 for cattle, 48 for sheep, and 33 for swine. For each species, data was collected for organ weights (adipose tissue, blood, brain, bone, heart, intestine, kidney, liver, lung, muscle, and mammary tissue) and blood flows. In order to get representative physiological values covering the whole species, various breeds were included. For cattle the data on the following breeds were included: Aberdeen Angus, Angus x Gelbvieh, Angus x Hereford, Angus x Simmental, Ayrshire, Braunvieh, Charolais, Friesian x Ayrshire, Gelbvieh, Guernsey, Hereford, Holstein, Holstein x Friesian, Holstein x Gyr, Jersey, Jersey x Limousin, Limousin, Pinzgauer, Red Poll, Salers, Simmental, and Swedish Red and white. For sheep most data §was available for Merino sheep, however also other breeds were described, such as Clun Forest, Dorper, East Friesian, Friesian, INRA 401, Lacaune, Leicester x Swaledale, Omani, Rambouillet, Romney Marsh, Santa Ines,

Table 2
Mean organ weights of cattle, sheep, and swine as percentage of body weight.

Species		Body weight	Adipose tissue	Blood	Brain	Carcass	Heart	Intestine	Kidney	Liver	Lung	Muscle	Mammary gland	References
Cattle	N	38976	3663	70	1116	3705	1566	71	1557	1592	1541	54	23	1-21
	BW (%)	526.1	18.4	3.8	0.1	12.8	0.4	1.7	0.2	1.3	0.8	34.0[a]; 47.0[b]	2.2	
	CV (%)	14	26	12	14	16	15	27	14	16	33	21[a], 16[b]	34	
	ρ(BW,OW)	–	0.94	0.96	0.74	NA	0.96	0.41	0.92	0.93	0.91	NA	NA	
Sheep	N	21231	86	102	133	62	309	84	242	293	207	62	75	22-53
	BW (%)	58.4	19.2	4.7	0.2	9.8	0.4	5.4	0.3	1.5	1.1	35.3	1.7	
	CV (%)	21	39	21	26	16	21	19	24	22	28	24	49	
	ρ(BW,OW)	–	0.9	NA	0.73	NA	0.39	NA	NA	NA	NA	NA	NA	
Swine	N	18221	15860	216	46	497	2562	206	458	2523	150	NA	54-76	54-76
	BW (%)	108.0	17.6	3.0	0.1	9.3	0.4	3.2	0.3	1.7	0.8	45.0	NA	
	CV (%)	15	27	18	68	21	23	24	21	19	27	6	NA	
	ρ(BW,OW)	–	NA	NA	0.72	0.95	0.95	NA	0.92	0.91	0.75	0.98	NA	

N: sample size (number of individuals); BW%: percentage body weight; CV: coefficient of variation; rho: ρ(BW,OW); Bodyweight in kg; NA: not available; [a] muscle fraction of dairy cattle; [b] muscle fraction for beef cattle.
*Cattle 1-21: (*Ballarin et al., 2016; Bellmann et al., 2004; Crile and Quiring, 1940; Ellis et al., 2016; Holt et al., 1968; Holtenius and Björnhag, 1989; Hunter, 2010; Jenkins and Ferrell, 1997; Jurie et al., 2007; Long et al., 2010, 2012; Martinez et al., 2006; McDowell et al., 1987; Morris et al., 2010; Nephawe et al., 2004; Pfuhl et al., 2007; Ren et al., 2002; Rotta et al., 2015; Swett, 1937; von Soosten et al., 2012; Wood et al., 2013*)*.
*Sheep 22-53: (*Barnes et al., 1983; Bennett, 1973; Boxenbaum, 1980; Brown and Swan, 2014; Burrin et al., 1990; Carlson et al., 2009; Charismidou et al., 2000; Clarke et al., 2001; Delavaud et al., 2007; Ebinger, 1974; Gardner et al., 2005; Grace, 1983; Graham et al., 1982; Hales and Fawcett, 1993; Holt et al., 1968; Holtenius and Björnhag, 1989; Jenkinson et al., 1995; Juca et al., 2016; Kamalzadeh et al., 1998; Louey et al., 2005; Mahgoub and Lodge, 1998; McCutcheon et al., 1993; Metcalfe et al., 1962; Moss et al., 2005; Neville et al., 2008; Norberg et al., 2005; Pethick and Lindsay, 1982; Reed et al., 2007; Sinclair et al., 2010; Swanson et al., 2008; Tilahun et al., 2014; Wallace et al., 2002*)*.
*Swine 54-76: (*Andersson-Eklund et al., 1998; Fraga et al., 2009; García-Valverde et al., 2008; He et al., 2015; Holt et al., 1968; Hunter, 2010; Kerr et al., 1995; Kruska and Rohrs, 1974; Martinez et al., 2006; Martinsen et al., 2015; Minervini et al., 2016; Moughan et al., 1990; Müller et al., 2000; Nieto et al., 2012; Njoku et al., 2015; Orcutt et al., 1990; Pekas, 1983; Quinious and Noblet, 1995; Razmaite et al., 2009; Ruusunen et al., 2007; Thein et al., 2003; Tranquilli et al., 1982; Wiseman et al., 2007; Yang and Lin, 2010*)*.

Sarda, Swifter, Targhee, and Western Whiteface. For swine, physiological values for the following breeds were available: Duroc, Duroc x Large White x Yorkshire, Landrace and Landrace crossbreeds, Meishan, Pietrain, Purebred, Wild Boar, Yorkshire, and York x Hampshire. Meta-analyses were conducted to characterise the intra-species variability of the parameters and their associated uncertainty.

Results of the meta-analyses for the most common physiological and anatomical parameter values expressed as percentage of body weight are provided in Table 2. A distinction between dairy cattle and beef cattle was made the weight fraction of muscle, due to significant differences. The highest intra-species variability was observed in the fraction of brain weight for swine, the fraction of adipose tissue for sheep, and the fraction of lung tissue in cattle. For other parameters, the coefficient of variation was below 30%.

Results of the meta-analyses of blood flow parameter values as percentage of cardiac output are presented in Table 3. A significant difference was observed between dairy cattle and beef cattle for kidney and liver blood flows. Due to these differences, blood flows for dairy cattle and beef cattle are reported separately. From the three species included, sheep is the only one, for which blood flow to each organ was reported in literature. Large intra-species variability for blood flow was observed, especially for the percentage blood flow through the hepatic artery. In sheep and swine, blood flow fractions through the muscles also shows high intra-species variability.

4. Discussion & conclusion

Here, extensive literature searches and structured data collection on physiological and anatomical parameters in three key farm animal species (swine, cattle and sheep) are described. Subsequently, meta-analyses were performed to quantify intra- and inter-species variation in those parameters. Such information can for example be used to perform a Monte Carlo simulation to analyse the impact of inter-individual variability and uncertainty on PBK predictions (Huizer et al., 2012).

Organ weights for all three species were available in literature. The larger variability observed in the brain weight fractions in swine might be caused by large differences in body weight influencing the brain-to-body ratio (Minervini et al., 2016). The variability observed in adipose tissue fractions in sheep might be caused by differences between male and female, but also various breeds (Bennett, 1973; Clarke et al., 2001; Delavaud et al., 2007). It should be noted that the reported organ weight fractions cannot be used directly as input for PBK models since PBK model compartments are defined by volume rather than mass. The density of most organs is ranging from 1.02 to 1.06, meaning mass-to-volume conversion is not necessary (Brown et al., 1997). Blood flow parameter values were available for all organs in sheep but were very limited in cattle. For swine, blood flow parameter values were available for juvenile pigs (body weight range 25–38 kg); however, none were available for mature pigs. Furthermore, the parameter values showed a large variation, which may reflect true intra-species differences, but it is more likely that the observed variation is caused by interlaboratory variability using different experimental techniques for blood flow measurements (Brown et al., 1997). With regard to blood flow, experimental studies using radiolabelled microsphere techniques, originally reported by Rudolph and Heymann (1967), have become the preferred method of choice for measuring the distribution of blood flow among and within organs in animals (Hoffman et al., 1977). In addition, data for studies using other techniques for blood flow measurements were also included, such as those using a thermodilution or indicator-dilution method (Bergman et al., 1971; Fleet and Mepham, 1985; Freetly and Ferrell, 1997; Ullman et al., 2001). Consequently, blood flow parameters characterising the vascular system in these three species are likely to have considerable uncertainty.

The meta-analyses provide estimates for organ weights and tissue blood flows expressed in percentage of body weight or cardiac outputs. The means of the included parameters do not add up to 100 % of body weight or cardiac output. Variability and uncertainty are associated with these estimates particularly because of inter-study variability and data gaps in the availability of physiological parameters for each species. Allometric scaling between species can be used to estimate mean physiological parameters to fill such data gaps as inputs for PBK modelling for individuals using a mean scaling exponent of 0.75. For intra-species differences, the exponent applied shows higher variation

Table 3
Average blood flows of cattle, sheep, and swine as percentage of cardiac output.

Species		Cardiac output	Adipose tissue	Brain	Carcass	Heart	Kidney	Liver HA	Liver PV	Lung	Muscle	Mammary gland	References
Dairy Cattle	N	89	1	NA	NA	NA	15	163	163	NA	1	14	1-10
	CO (%)	59.7	6.8	NA	NA	NA	1.6	11.8	54.2	NA	1.9	16.5	
	CV (%)	21	24	NA	NA	NA	19	62	33	NA	30	25	
Beef Cattle	N	89	1	NA	NA	NA	NA	140	140	NA	1	NA	
	CO (%)	59.7	6.8	NA	NA	NA	NA	3.1	21.5	NA	26.3	NA	
	CV (%)	21	24	NA	NA	NA	NA	75	30	NA	31	NA	
Sheep	N	77	15	41	5	40	131	56	80	8	21	40	11-30
	CO (%)	6.4	2.3	1.9	6.6	4.5	14.3	2.6	38.5	3.0	33.2	7.4	
	CV (%)	26	46	39	42	42	51	123	39	54	104	46	
Swine	N	228	11	20	NA	17	17	37	37	11	11	NA	31-41
	CO (%)	10.9	11.0	23.0	NA	4.2	9.8	4.7	17.8	2.1	29.2	NA	
	CV (%)	34	66	56	NA	43	38	77	32	63	63	NA	

N: sample size (number of individuals); CO%: percentage cardiac output; CV: coefficient of variation; Cardiac output in L/min; Liver HA: liver hepatic artery; Liver PV: Liver portal vein; NA: not available; no correlation assumed between cardiac output and blood flow.
*Cattle 1-10: (*Bell et al., 1976; Boonsanit et al., 2012; Doyle et al., 1960; Ellis et al., 2016; Fisher and Dalton, 1961; Hallowell et al., 2007; Lomax and Baird, 1983; McDowell et al., 1987; Purdie et al., 2008; Will et al., 1962*).*
*Sheep 11-30: (*Barnes et al., 1983; Bergman et al., 1971; Di Giantomasso et al., 2003; Dodic et al., 2001; Evans et al., 1998; Fegler and Hill, 1958; Fleet and Mepham, 1985; Freetly and Ferrell, 1997; Hales, 1973, 1976; Hales and Fawcett, 1993; Liu et al., 2015; Norberg et al., 2005; Pethick and Lindsay, 1982; Runciman et al., 1984, 1986; Talke et al., 2000; Thompson, 1980; Ullman et al., 2001; Von Engelhardt and Hales, 1977*).*
*Swine 31-41: (*Carretero et al., 2010; Kuipers et al., 1999; Kurita et al., 2002, 2013; Lundeen et al., 1983; Mosing et al., 2015; Shih et al., 2013; Stonestreet et al., 1998; Thein et al., 2003; Tranquilli et al., 1982; van Essen et al., 2018).

(0.3–1.8) and quantifying intra-species variability and uncertainty for the whole population is more challenging because of data gaps (Feldman and McMahon, 1983; Glazier, 2005; Lindstedt and Schaeffer, 2002). In order to fill in such data gaps for physiological parameters (e.g. blood flow and organ weights), authors have proposed to include a 30% default coefficient of variation associated with mean parameter values in the model to provide quantify intra-species variability and uncertainty for the whole population (Clewell and Clewell, 2008). Finally, global sensitivity analysis for the PBK model is recommended to assess the influence of each parameter on the final model output (Hsieh et al., 2018; McNally et al., 2011).

Overall, the anatomical and physiological parameters reported in the present study provide reference values for the development of generic PBK models and other allometric scaling models in cattle, swine and sheep. It is foreseen that such data collection can be performed for other species of farm animals (e.g. chicken, goat, duck, salmon) and vertebrate species of ecological relevance (e.g. quail and other birds, test fish species) in adults and other life-stages (Li et al., 2019a, b). In addition, such anatomical and physiological data should be available as open source databases to allow the scientific community to use and update the datasets when more data become available. In order to facilitate the further use of physiological databases in the field of food and feed safety and risk assessment, the anatomical and physiological databases for the three species have been harmonised with those previously described for fish (Grech et al., 2019) and are available for download on EFSA's knowledge junction together with the codes for the generic PBK models described in the associated manuscript (Lautz et al., 2019a).

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.toxlet.2019.10.021.

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