REVIEW ARTICLE

Physiological parameter values for physiologically based pharmacokinetic models in food-producing animals. Part I: Cattle and swine

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Abstract

Physiologically based pharmacokinetic (PBPK) models for chemicals in food animals are a useful tool in estimating chemical tissue residues and withdrawal intervals. Physiological parameters such as organ weights and blood flows are an important component of a PBPK model. The objective of this study was to compile PBPK-related physiological parameter data in food animals, including cattle and swine. Comprehensive literature searches were performed in PubMed, Google Scholar, ScienceDirect, and ProQuest. Relevant literature was reviewed and tables of relevant parameters such as relative organ weights (% of body weight) and relative blood flows (% of cardiac output) were compiled for different production classes of cattle and swine. The mean and standard deviation of each parameter were calculated to characterize their variability and uncertainty and to allow investigators to conduct population PBPK analysis via Monte Carlo simulations. Regression equations using weight or age were created for parameters having sufficient data. These compiled data provide a comprehensive physiological parameter database for developing PBPK models of chemicals in cattle and swine to support animal-derived food safety assessment. This work also provides a basis to compile data in other food animal species, including goats, sheep, chickens, and turkeys.

KEYWORDS
blood flow, food safety, organ weight, physiologically based pharmacokinetic model, withdrawal interval

1 | INTRODUCTION

Physiologically based pharmacokinetic or toxicokinetic (PBPK or PBTK) models are increasingly used in various fields, including human health risk assessment (Andersen, Clewell, Gargas, Smith, & Reitz, 1987; Tan, Worley, Leonard, & Fisher, 2018; WHO, 2010), animal health risk assessment (Lautz, Oldenkamp, Dorne, & Ragas, 2019), environmental or ecological risk assessment (Grech et al., 2017), drug discovery and development (EMA, 2018; FDA, 2018; Shebley et al., 2018), as well as animal-derived food safety assessment (Li,

Mainquist-Whigham, et al., 2019; Lin, Gehring, Mochel, Lavé, & Riviere, 2016). PBPK models are powerful tools that can simulate the concentration of a xenobiotic in tissues of interest and allow for extrapolations across species, doses, and routes of administration, as well as from in vitro to in vivo (IVIVE) and from one compound to another (i.e., read-across). These unique strengths result from the use of two key components of a PBPK model, that is, chemical-specific parameters (e.g., partition coefficients and metabolic rates) and species-specific physiological or anatomical parameters (e.g., cardiac output, organ weights, and blood flow rates).

The use of accurate species-specific physiological parameters is essential in the development, validation, extrapolation, and application of a PBPK model. In particular, proper characterization of the variability of each physiological parameter within and between species is important to build stochastic population PBPK models to quantify the variability of simulation results given an exposure paradigm. As such, multiple review articles have comprehensively compiled PBPK-related physiological parameters in multiple species, mainly laboratory mice, rats, dogs, and humans (Brown, Delp, Lindstedt, Rhomberg, & Beliles, 1997; Davies & Morris, 1993; ICRP, 2002). These studies greatly facilitate the development of PBPK models in laboratory animals and humans and have been extensively cited.

In terms of food-producing animals such as the cattle, swine, goats, sheep, chickens, and turkeys, there are limited sources that compile physiological parameters useful for PBPK models. Upton (2008) reports physiological parameters in sheep and swine, but only the mean value of each parameter is provided and the study is based on the standard sizes of sheep (i.e., 45 kg) and swine (i.e., 25 kg) commonly used in biomedical research, which are smaller than animals used in food production. Brown et al. (1997) also provide physiological parameters for goats and cattle, but their focus is on laboratory animals and humans, and only the mean values for several organ weights in goats and cattle are provided. In Lin, Gehring, et al. (2016), physiological parameters for common food-producing animals are only summarized. The focus of this article is on the principles, methodology and existing applications of PBPK models, thus the physiological values are primarily based on previously published PBPK models, rather than based on original experimental studies. A recent mini-review on physiological parameters in swine, cattle, and sheep has been published (Lautz, Dorne, Oldenkamp, Hendriks, & Ragas, 2019). However, this study does not consider different production classes (i.e., calves vs. adult beef cattle vs. dairy cows) or breed differences, and the values of multiple parameters are not available. Overall, despite the recent increase in the number of published PBPK models in food animals (Lautz, Oldenkamp, et al., 2019; Lin, Gehring, et al., 2016), useful compilations of PBPK-related physiological parameters in food animals are still deficient.

The objective of this manuscript is to compile a comprehensive review on PBPK-related physiological parameters in food-producing animals, including cattle and swine. These parameters include body weight, cardiac output, organ weights, blood flow rates, hematocrit, and volume fractions of blood in organs. For each parameter in each species, unless data are not available, the pooled mean and standard deviation (*SD*) were analyzed from original experimental studies in order to quantify the variability of each parameter. The extracted raw data are provided in the Appendices S1–S5, S6–S11, and S12–S17, and the calculated mean and *SD* values are presented in the manuscript. Due to the large amount of data, the present manuscript focuses on cattle and swine. Subsequent publications will include data from other food-producing species, including goats, sheep, chickens, and turkeys. The ultimate goal of this project is to provide a reference physiological parameter database for the development of PBPK models for drugs and environmental chemicals in food-producing animals.

2 | METHODS

2.1 | Literature search

All data used in this study were extracted from previously published experimental research manuscripts from peer-reviewed journals or book chapters. These relevant publications were identified through the use of multiple search engines, including PubMed (https://www.ncbi.nlm.nih.gov/pubmed), Google Scholar (https://scholar.google.com/), ProQuest (https://search.proquest.com/), and ScienceDirect (https://www.sciencedirect.com/) with related key words. The Kansas State University Interlibrary Loan service provided full text of those papers that were not subscribed by Kansas State University Libraries. For the first-round literature search, the combination of general key words for animal species and physiological parameters was used. The animal species-specific keywords for cattle used in the literature search were "Cattle," "Cow," "Bull," or "Bovine"; for calves were "Calf," "Calves," or "Young Cattle"; and for swine were "Pig," "Swine," "Sow," "Barrow," "Boar," "Gilt," "Hog," "Stag," or "Porcine." The terms for physiological parameters used in the literature search were "Organ Weight," "Tissue Volume," "Blood Flow," "Vascular Space," or "Residual Blood Volume." The literature was primarily screened based on information in their titles and abstracts. In order to increase the number of manuscripts, specific key words were used for the second-round literature search. For tissue volumes of specific organs or tissues, the following key words, such as "Heart," "Kidneys," "Liver," "Lungs," "Spleen," "Brain," "Stomachs," "Intestines," "Muscle," "Adipose," "Fat," "Blood," "Bone," "Pancreas," "Adrenal Glands (Adrenals)," "Thyroid," "Thymus," or "Carcass Composition," were used for a more targeted literature search. The key words "Hepatic Blood Flow," "Myocardial Blood Flow," "Pulmonary Blood Flow," "Renal Blood Flow," or "Muscular Blood Flow" were used for searching more specific parameters related to blood flow. The "Residual Blood Volume" and "Vascular Space" were used with specific organ names to obtain more relevant literature on the parameter of the volume percentage of blood in each organ.
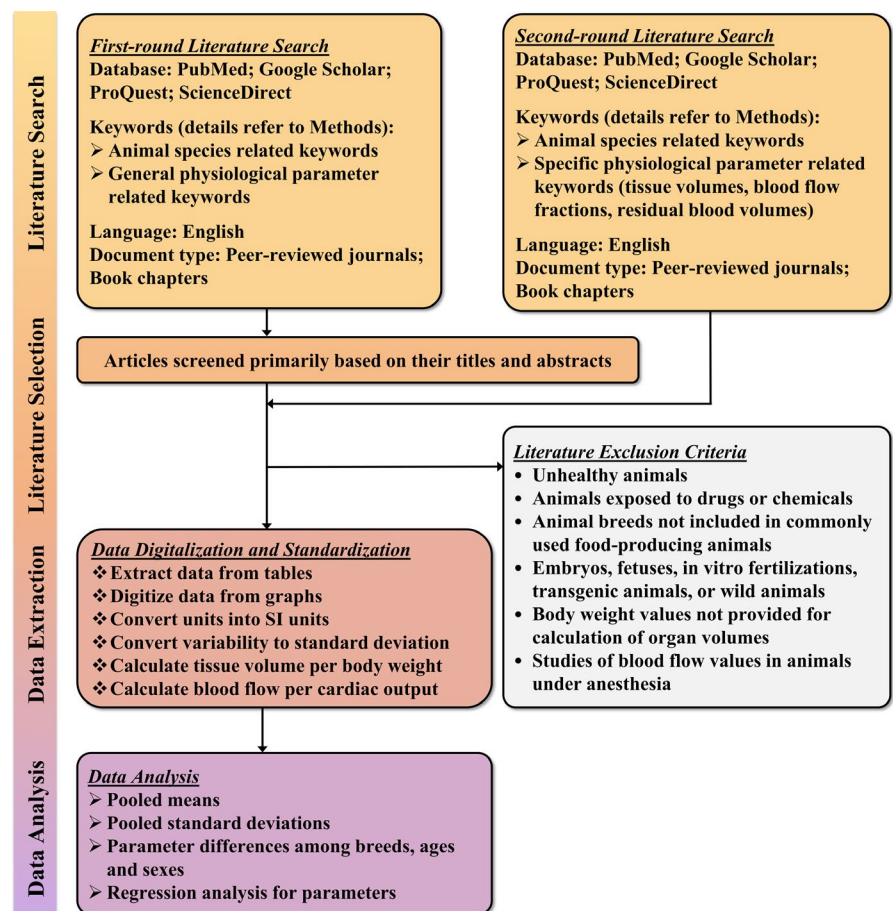
2.2 | Literature selection criteria

Please refer to Figure 1 for a detailed workflow of the literature search, and inclusion and exclusion criteria. In brief, all data used in the study were from healthy animals. The selected studies from all the literature of cattle and swine must have implemented a method for randomization, and these studies must be controlled trials with at least one control group (i.e., healthy animals). Only the controlled group animals were involved in the calculation, if the treatment factors had significant impacts on values of the physiological parameters. For tissue or organ volumes, studies must have included measures of final body weights or directly reported the initial body weight and the daily weight gain. If no body weight value was reported, the fractions of tissue volume per body weight had to be reported directly. For the studies used to calculate blood flow fractions, only values measured on conscious animals were involved. No data were collected from fetuses, in vitro fertilizations, transgenic animals, or wild animals. The studies or data sets for breeds with gene mutations significantly affecting the physiological parameters were excluded. For example, double-muscled cattle breeds (Shahin, Berg, & Price, 1986), which have higher tissue volume of muscle and lower tissue volume of fat compared to the same breed without gene mutations, were not involved in the data analysis. For adult cattle physiological parameters, all experimental studies included had to report the physiological parameters for cattle over 10 months.

Studies with species such as bison, buffalo, and yak were removed, and only studies with cattle breeds commonly used for food products (i.e., Jersey and Holstein for dairy cows and Angus and Hereford for beef cattle) were included for further analysis. For calves, only young cattle under 350 kg and/or under age of ten months old were included for physiological data calculation. The calves might be fed with different diets (e.g., milk, milk replacer, hay, or concentrate), but not exposed to drugs or toxic agents. For physiological parameters of swine, experimental studies for swine with all ages were included. Data for minipigs were removed, and only studies with swine breeds commonly used for meat production (i.e., Yorkshire, Landrace, Large White, Duroc, and Hampshire) were included for further analysis.

2.3 | Data digitalization and standardization

The physiological parameter data were extracted directly into Excel spreadsheets from papers that reported these values in tables. When the relevant data were shown graphically, the graphic data were extracted and digitized with WebPlotDigitizer (version 4.1). Since data from different studies were presented in different units, all data were converted into International System of Units (SI), and finally into the units commonly used in PBPK modeling. Briefly, gram (g) and kilogram (kg) were used as units for mass; minute (min) and hour (h) were used for time units, and milliliter

FIGURE 1 A flow chart for the process of literature search, selection, data extraction, and analysis for physiological parameters in adult cattle, calves, and swine [Colour figure can be viewed at wileyonlinelibrary.com]

(mL) and liter (L) were used as units for volumes. The reported standard errors were converted into standard deviations using Equation 1. The organ weights and blood flows to organs were calculated into organ weight fractions and blood flow fractions by dividing the body weight and cardiac output, respectively. As both values for physiological parameters involved in the calculation may have means and standard deviations, Equations 2 and 3 were used to calculate means and standard deviations for organ weight and blood flow fractions. Equations 4 and 5 were used to calculate the combinations of means and standard deviations from studies with different animal numbers (i.e., the pooled mean and the pooled standard deviation). Details for these equations and examples are provided in the Appendix S18.

$$SD = SE \times \sqrt{N} \tag{1}$$

$$MEAN\_ind = \frac{MEAN\_a}{MEAN\_b} \tag{2}$$

$$SD\_ind = MEAN\_ind \times \sqrt{\left(\frac{SD\_a}{MEAN\_a}\right)^2 + \left(\frac{SD\_b}{MEAN\_b}\right)^2} \tag{3}$$

$$MEANtotal = \frac{MEAN1 \times N1 + MEAN2 \times N2 + MEAN3 \times N3}{N1 + N2 + N3} \tag{4}$$

$$SDtotal = \sqrt{\frac{SD1^2 \times N1 + SD2^2 \times N2 + SD3^2 \times N3}{N1 + N2 + N3}} \tag{5}$$

Here, SE is the standard error; SD is the standard deviation; N is the number of animals in the study used; MEAN_ind is the mean after calculation from an individual study; MEAN_a and MEAN_b are the mean values used to calculate relative organ weights (i.e., MEAN_a is the organ weight and MEAN_b is the body weight) or blood flow fractions (i.e., MEAN_a is the blood flow to an organ and MEAN_b is the cardiac output); SD_a and SD_b are the standard deviations used to calculate relative organ weight (SD_a is the SD of organ weight and SD_b is the SD of body weight) or blood flow fractions (SD_a is the SD of the blood flow to an organ and SD_b is the SD of cardiac output); MEAN1, MEAN2, and MEAN3 are the means from studies 1, 2, and 3 (if more than 3 studies were used, MEAN4, MEAN5, and so on were used); SD_ind is the standard deviation after calculation from an individual study; SD1, SD2, and SD3 are the standard deviations from studies 1, 2, and 3; MEANtotal is the pooled mean for all data; N1, N2, and N3 are the number of animals in individual studies; SDtotal is the pooled standard deviation for all data from studies 1, 2, and 3.

The mean values in all tables provided in this document are weighted arithmetic means with the number of animals used in each experiment as weight. For adult cattle and swine, the studies not reporting data variabilities were not included to calculate the pooled standard deviation. For calves, the weights from papers not reporting standard deviation or standard error values were treated as one.

2.4 | Statistical analysis

The values of physiological parameters were extracted from the tables with values of all production classes for beef cattle and dairy cows. The physiological parameters for dairy cows were calculated based on data from female Holstein or Jersey cattle breeds. These values were also filtered for the two most commonly used beef cattle breeds, Angus and Hereford. The comparison of organ weights for potential sex differences in beef cattle was also carried out with Student's t test. The Student's t test was also used to identify the potential differences of available physiological parameters between beef cattle and dairy cows, and between commonly used breeds in beef cattle (i.e., Angus vs. Hereford) and in dairy cows (i.e., Jersey vs. Holstein). The values of $p < .05$ were considered statistically significant. For calves, regression analyses were performed for body weight with age, and for all other parameters with body weight. Regression models were only considered acceptable when the coefficients of determination (R^2) were larger than or equal to .75.

3 | RESULTS

3.1 | Body weight

For beef-use cattle, there is no specific age for market use. From the "Blue Book" of the U.S. National Residue Program of the U.S. Department of Agriculture's Food Safety and Inspection Service (USDA/FSIS), the bovine category includes cattle with a wide age range starting from bob veal up to beef cows, dairy cows, and bulls (USDA, 2019c). Previous experimental studies that reported cattle across different ages were included in current research. The average market weight for adult cattle was reported as 552 kg (Meyer, Hess, Paisley, Du, & Caton, 2014), and the average market weight for swine in 1980 was 110 kg and in 2015 was 128 kg (Tokach, Goodband, & O'Quinn, 2016). According to the latest USDA Daily Cattle and Swine Reports in November 2019, the average market weights for beef cattle and swine were 621 (USDA, 2019a) and 131 kg (USDA, 2019b), respectively.

Body weights in calves younger than 10 months are age and breed dependent and can range from 20 kg to over 350 kg. However, in the food animal industry, male Holstein calves are commonly used as sources of veal. Body weight and age selection were first based on the criteria of veal calves which are male calves predominantly from the dairy industry. Excluding all the data from female and/or adult and/or other breeds of cattle, a fourth-order polynomial regression was generated from available data in young Holstein male calves:

$$BW = B0 + B1*Age + B2*Age^2 + B3*Age^3 + B4*Age^4 \tag{6}$$

where BW represents body weight in kg, Age resembles age values in days, $B0 = 41.04$, $B1 = 0.5584$, $B2 = 0.001787$, $B3 = -1.549e\text{-}006$, $B4 = -1.332e\text{-}009$. The R^2 value was .9709. The growth curve is shown in Figure 2, and all data and the regression analysis are included in the
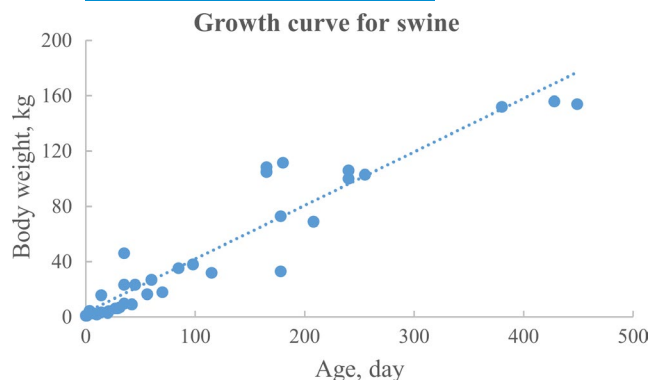
Growth curve for calves
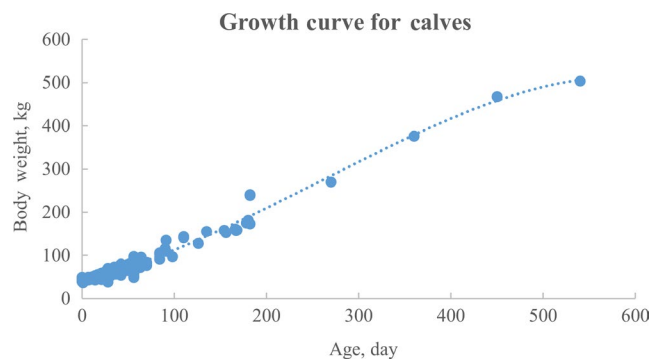
FIGURE 2 The growth curve for calves from 0 day to about 550 days. Data from 213 animals in 18 studies (Abu-Tarboush et al., 1996; Andrighetto et al., 1999; Arrayet et al., 2002; Bailey & Mears, 1990; Castells et al., 2012; Eaton et al., 1972; Groenewegen et al., 1990; Kahl et al., 1977; Kerr et al., 1991; Khan et al., 2007; Montoro et al., 2013; Shakeri et al., 2014; Soltan, 2009; Stabel et al., 1993; Tamate et al., 1962; Terré et al., 2007; Vogstad et al., 2015; Woelfel et al., 1964) were used to establish the growth curve [Colour figure can be viewed at wileyonlinelibrary.com]

Appendix S6. In brief, a total of 213 data points from 18 publications (Abu-Tarboush, Al-Saiady, & Keir El-Din, 1996; Andrighetto, Gottardo, Andreoli, & Cozzi, 1999; Arrayet et al., 2002; Bailey & Mears, 1990; Castells, Bach, Araujo, Montoro, & Terre, 2012; Eaton, Rousseau, Hall, Frier, & Lucas, 1972; Groenewegen, McBride, Burton, & Elsasser, 1990; Kahl, Wrenn, & Bitman, 1977; D. E. Kerr, Manns, Laarveld, & Fehr, 1991; Khan et al., 2007; Montoro, Miller-Cushon, DeVries, & Bach, 2013; Shakeri, Riasi, & Alikhani, 2014; Soltan, 2009; Stabel, Spears, & Brown, 1993; Tamate, McGilliard, Jacobson, & Getty, 1962; Terré, Devant, & Bach, 2007; Vogstad et al., 2015; Woelfel, Rousseau, Kersting, Nielsen, & Lucas, 1964) involving 763 animals were extracted to generate the regression Equation 6. These studies used different methods for milk feeding, weaning, or provided different diets. Body weight values for Holstein calves were included in the analysis when the corresponding age parameters were reported in the literature.

For swine, body weights are reported from birth to around 450 days, with the range from 1 kg to over 150 kg being included in the regression analysis. Data from 13 studies (Adeola & King, 2006; Doornenbal, Tong, & Sather, 1986; Hansard, 1956; Kaensombath, Neil, & Lindberg, 2013; Lee & Woyengo, 2018; Lundeen, Manohar, & Parks, 1983; Miller & Ullrey, 1987; Owsley, Orr, & Tribble, 1986; Rehfeldt, Tuchscherer, Hartung, & Kuhn, 2008; Ruusunen, Partanen, Pösö, & Puolanne, 2007; Smit & Beltranena, 2017; Velayudhan, Schuh, Woyengo, Sands, & Nyachoti, 2017; Wise, Young, & Pond, 1993) involving 712 animals were used for the regression analysis. The body weight data for both sexes were included. The growth curve for swine is shown in Figure 3. The data and the regression analysis are included in Appendix S12 of the Supporting Information. The regression equation is as follows:

$$BW = B0 + B1 * Age \qquad (7)$$

where BW represents body weight in kg, Age resembles age values in days, $B0 = 3.37$ and $B1 = 0.387$. The R^2 value was .8799.

Growth curve for swine

FIGURE 3 The growth curve for swine from 0 day to about 450 days. Data from 712 animals in 13 studies (Adeola & King, 2006; Doornenbal et al., 1986; Hansard, 1956; Kaensombath et al., 2013; Lee & Woyengo, 2018; Lundeen et al., 1983; Miller & Ullrey, 1987; Owsley et al., 1986; Rehfeldt et al., 2008; Ruusunen et al., 2007; Smit & Beltranena, 2017; Velayudhan et al., 2017; Wise et al., 1993) were used to establish the growth curve [Colour figure can be viewed at wileyonlinelibrary.com]

Typically in PBPK models, study-specific body weight is used for model calibration or evaluation using a specific data set. However, the average market weight is required for predicting tissue drug or chemical residue withdrawal intervals using population analysis with Monte Carlo simulations for PBPK models of drugs in food-producing animals (Buur, Baynes, Smith, & Riviere, 2006; Li, Gehring, Riviere, & Lin, 2017). In addition, most of the existing PBPK models do not consider growth when using body weight in food animals, especially in adults because the therapeutic scenarios of drug usage usually last for only a short period. However, even for the short therapeutic period, the body weight growth may be considerable in calves. Therefore, it is important to incorporate the growth curve into PBPK models of calves. Furthermore, when simulating a long period of exposure to feed additives or environmental toxicants, the growth curve definitely needs to be considered in a PBPK model. In this regard, recent PBPK models that simulate lifetime exposure to a chemical in chickens have incorporated growth curves for relevant physiological parameters (Henri, Carrez, Méda, Laurentie, & Sanders, 2017; Zeng et al., 2019). Another recent PBPK model for doxycycline in grass carp also considers body weight gain because the model simulation period is relatively long due to the substantially extended withdrawal interval estimates of 41–74 days depending on the target tissue (Xu, Li, Chou, & Lin, 2020).

3.2 | Organ weight

In the literature, typically the organ weight or mass values, rather than organ volume values are reported. However, PBPK model compartments are defined by the compartments' volumes rather than their weights (Brown et al., 1997). Since the density of most visceral organs is approximately 1.00 g/cm^3 (most organs have densities ranging from 1.02 to 1.06 g/cm^3, except for bone and skin), the mass-to-volume conversion is often not required in PBPK

TABLE 1 Relative organ weight (percent body weight) or tissue volume for adult cattle (including beef cattle and dairy cows)

	Mean	SD	Number of animals	Number of studies	References
Adrenal glands	0.006	0.002	716	3	1–3
Adipose tissue	12.27	5.21	301	9	4–11, 48
Blood	4.31	0.87	893	9	1, 12–19
Bone	8.66	1.49	40	2	11, 20
Brain	0.08	0.01	812	2	1, 21
GI tract	5.98	1.28	107	6	4, 6, 14, 22–24
Reticulorumen	1.76	0.45	339	7	15, 16, 22, 25–28
Reticulum	0.26	0.07	696	1	1
Rumen	1.75	0.35	869	4	1, 14, 29, 30
Omasum	0.85	0.22	948	6	1, 15, 16, 22, 25, 27
Abomasum	0.37	0.10	948	6	1, 15, 16, 22, 25, 27
Intestines					
Small intestine	1.06	0.24	1,158	10	1, 14–17, 22, 25, 27, 29, 31
Large intestine	0.78	0.21	919	8	1, 14–17, 22, 25, 31
Cecum	0.08	0.01	168	3	17, 25, 27
Colon	0.39	0.02	93	1	27
Heart	0.40	0.07	1,828	28	1–4, 14–18, 22, 24, 26–42
Kidneys	0.21	0.04	2,159	29	1–4, 6, 14–20, 22, 24–34, 35, 37, 40, 42, 43
Liver	1.23	0.21	2,256	32	1–4, 6, 14–20, 23–33, 36, 37, 40, 41, 43–46
Lungs	0.77	0.20	1,773	21	1, 2, 4, 32, 15–18, 22, 24, 26–30, 33, 34, 37–39, 42
Muscle	36.10	11.73	83	2	11, 47
Pancreas	0.09	0.02	1,319	12	1, 32, 15, 17, 22, 26, 24, 27, 30, 38, 39, 43
Spleen	0.18	0.05	1,642	22	1, 3, 4, 10, 14–18, 22, 24–28, 30, 32–34, 39, 41, 45
Thyroid	0.006	0.002	696	1	1
Thymus	0.030	0.018	728	3	1, 24, 26
Rest of body	29.67				

Note: The studies involved in the relative organ weight calculations are as follows: 1. Matthews et al. (1975); 2. Buntyn et al. (2017); 3. Garrett et al. (1968); 4. DiCostanzo et al. (1991); 5. Velazco et al. (1997); 6. Andrew et al. (1994); 7. Robelin (1981); 8. De Paula et al. (2013); 9. Fernandez et al. (1996); 10. Sainz et al. (1995); 11. Keane (2011); 12. Hansard et al. (1953); 13. Larsen et al. (2017); 14. Rumsey et al. (1996); 15. Long et al. (2010); 16. Rotta, Valadares Filho, et al. (2015); 17. McCurdy et al. (2010); 18. Hansard (1956); 19. Swett et al. (1933); 20. Faulkner et al. (1989); 21. Ballarin et al. (2016); 22. Sharman et al. (2013); 23. Sprinkle et al. (1998); 24. Schumann et al., (2007); 25. Reynolds et al. (2004); 26. Remling et al. (2017); 27. Mader et al. (2009); 28. Fitzsimons et al. (2014); 29. Jenkins and Ferrell, (1997); 30. Wood et al. (2013); 31. Scheaffer, Caton, Bauer, and Reynolds (2001); 32. Terry et al. (1990); 33. Early, McBride, and Ball (1990); 34. Schlegel, Bergen, Schroeder, VandeHaar, and Rust (2006); 35. Olivares et al. (2019); 36. McEvoy, Sinclair, Broadbent, Goodhand, and Robinson (1998); 37. Fiems, Boucque, and Cottyn (1993); 38. Long et al. (2012); 39. Talton et al. (2014); 40. Murphy and Loerch (1994); 41. Bourg, Tedeschi, Wickersham, and Tricarico (2012); 42. Sainz and Bentley (1997); 43. Burciaga-Robles et al. (2010); 44. Moseley, Paulissen, Goodwin, Alaniz, and Claflin (1992); 45. Lawler, Taylor, Finley, and Caton (2004); 46. Robertson, Wilson, and Morris (1967); 47. Shahin and Berg, (1985a); 48. Fonseca et al. (2017).

models. Therefore, the present study considers the terms "relative organ weight" and "relative tissue volume" and "relative organ volume" operationally equivalent assuming water density for all organs.

Organ weights or tissue volumes for adrenal glands, adipose tissue, blood, bone, brain, gastrointestinal tract (GI tract), heart, kidneys, liver, lungs, muscle, pancreas, spleen, thyroid, and thymus were obtained for cattle from previously reported data. The raw data and data analysis

processes can be found in Appendix S1. Organ weights or tissue volumes in adult cattle operationally defined as either age older than 10 months or body weight larger than 350 kg including both beef cattle and dairy cows are summarized in Table 1. The calculation of cattle organ weights or tissue volumes was based on both sexes with commonly used breeds, including Friesian, Jersey, Angus, Hereford, and Holstein. In addition, the organ weight or tissue volume data for beef cattle only and dairy cows only are shown in Tables 2 and 3, respectively.

TABLE 2 Relative organ weight (percent body weight) or tissue volume for beef cattle

	Mean	SD	Number of animals	Number of studies	References
Adrenal glands	0.004	0.001	20	2	1, 2
Adipose tissue	12.18	5.06	276	7	3, 4, 5–12
Blood	3.99	0.68	105	7	13, 14, 16–21
Bone	8.66	1.49	40	2	12, 22
GI Tract	5.17	0.73	90	5	4, 16, 23–27
Reticulorumen	1.81	0.53	215	5	17, 23, 24, 27, 28
Omasum	0.65	0.17	128	3	17, 23, 27
Abomasum	0.28	0.13	128	3	17, 23, 27
Intestines					
Small intestine	1.00	0.19	318	6	14, 16, 17, 19, 23, 27, 29
Large intestine	0.87	0.29	79	4	14, 16, 17, 19, 23
Cecum	0.08	0.03	132	2	19, 27
Colon	0.39	0.07	93	1	27
Heart	0.43	0.08	1,012	24	2–4, 14, 16, 17, 19, 20, 23, 24, 26–30, 32–41
Kidneys	0.21	0.05	1,282	23	2–4, 14, 16, 17, 19–21, 23, 24, 26–30, 32, 33, 35, 37, 40, 42–44
Liver	1.22	0.18	1,379	27	2–4, 14, 16, 17, 19–30, 32, 35, 36, 39, 40, 42–45
Lungs	0.85	0.25	977	19	2, 4, 14, 17, 19, 20, 23, 24, 26–30, 32, 33, 36–38, 41
Muscle	36.10	11.73	83	2	12, 46
Pancreas	0.09	0.02	611	11	14, 17, 19, 23, 24, 26, 27, 30, 37, 38, 42
Spleen	0.19	0.06	810	19	3, 4, 11, 14, 16, 17, 19, 20, 23, 24, 26–28, 30, 32, 33, 38, 40, 44
Thymus	0.09	0.02	20	1	24
Testes	0.10	0.02	104	3	47–49
Rest of body	30.72				

Note: The studies involved in the relative organ weight calculations are as follows: 1. Matthews et al. (1975); 2. Buntyn et al. (2017); 3. Garrett et al. (1968); 4. DiCostanzo et al. (1991); 5. Velazco et al. (1997); 6. Andrew et al. (1994); 7. Robelin (1981); 8. De Paula et al. (2013); 9. Fernandez et al. (1996); 10. Fonseca et al. (2017); 11. Sainz et al. (1995); 12. Keane (2011); 13. Hansard et al. (1953); 14. Terry et al. (1990); 15. Larsen et al. (2017); 16. Rumsey et al. (1996); 17. Long et al. (2010); 18. Rotta, Valadares Filho, et al. (2015); 19. McCurdy et al. (2010); 20. Hansard (1956); 21. Swett et al. (1933); 22. Faulkner et al. (1989); 23. Sharman et al. (2013); 24. Remling et al. (2017); 25. Sprinkle et al. (1998); 26. Schumann et al., (2007); 27. Mader et al. (2009); 28. Fitzsimons et al. (2014); 29. Jenkins and Ferrell, (1997); 30. Wood et al. (2013); 31. Scheaffer et al. (2001); 32. Early et al. (1990); 33. Schlegel et al. (2006); 34. Olivares et al. (2019); 35. McEvoy et al. (1998); 36. Fiems et al. (1993); 37. Long et al. (2012); 38. Talton et al. (2014); 39. Murphy and Loerch (1994); 40. Bourg et al. (2012); 41. Sainz and Bentley (1997); 42. Burciaga-Robles et al. (2010); 43. Moseley et al. (1992); 44. Lawler et al. (2004); 45. Robertson et al. (1967); 46. Shahin and Berg, (1985a); 47. Weisgold and Almquist (1979); 48. Unruh et al. (1986); 49. Killian and Amann, (1972).

The organ weights between commonly used breeds for dairy cattle (Jersey vs. Holstein) and beef cattle (Angus vs. Hereford) were compared. Since dairy cattle data were from multiple studies, and the number of animals was large, nearly all relative organ weight parameters were significantly different between Jersey and Holstein, except volumes for heart, liver, lung, and mammary gland (Table 4). For beef cattle, relative weights of adipose tissue, liver, lung, and spleen were significantly different between Angus and Hereford (Table 5). The sex differences for organ volumes are shown in Table 6. All relative organ weights were significantly different between sexes. Even though the statistical tests showed significant differences, some of those relative organ weight values were quite close between breeds and between sexes. For example, the relative blood volume in percentage of body weight was 4.33% for Jersey and 4.52% for Holstein, and the relative heart volume was 0.42% for males and 0.41% for females. This was, in part, because these parameter values were based on the pooled data from multiple studies involving a large number of animals.

For calves, relative organ weight values were available for the adrenal glands, adipose tissue, bone, blood, brain, GI tract, stomachs (reticulorumen, omasum, abomasum), intestines (small intestine, large intestine), heart, kidneys, liver, lungs, muscle, pancreas, skin, spleen, and thyroid (Table 7). Data were from calves that met the inclusion criteria mentioned earlier, but were independent of sex, diet,

or breed (Table 7). Relative organ weight for adipose tissue in calves is summarized in Table 8 with data from 3 studies (Gill et al., 1987; Morgan, 1969; Santos et al., 2013). All data and data analysis processes for organ weights in calves are provided in the Appendix S7.

The relative organ weight values were plotted against the corresponding body weight with a fitted linear trend line. Heart relative weights were observed to be body weight dependent with a R^2 value of .7509. Settlemire, Hibbs, and Conrad (1964) have also provided weights of several organs, but the values were outliers when compared to other available data. Therefore, the calculated weighted arithmetic mean did not include this study. The results for the regression analyses of relative organ weights with body weight or age for calves are provided in the "Tissue Volume Calcu&Regression" tab of the Appendix S7.

Relative organ weight values were obtained for the adrenal glands, adipose tissue, bone, blood, stomach, intestines (small intestine and large intestine), heart, kidneys, liver, lungs, muscle, pancreas, spleen, thyroid, thymus, and skin for swine. All data and data analysis processes for relative organ weights in swine are included in the Appendix S13 of Supporting Information. Relative organ weight values for swine based on data from both sexes with all age range and with commonly used breeds for meat production, including Yorkshire, Landrace, Large White, Duroc, and Hampshire are summarized in Table 9. We also calculated these parameter values for each sex. The results for males and females are shown in Tables 10 and 11, respectively. The reported average market weight for swine in 1980 was 110 kg and in 2015 was 128 kg from the study by Tokach et al. (Tokach et al., 2016). In Table 12, relative organ weights were

TABLE 3 Relative organ weight (percent body weight) or tissue volume for dairy cows

	Mean	SD	Number of animals	Number of studies	References
Adrenal glands	0.006	0.002	696	1	1
Adipose tissue	13.21	6.64	25	1	2
Blood	4.35	0.90	788	3	1, 4, 5
Brain	0.08	0.01	696	1	1
GI tract	8.20	2.28	25	1	2
Reticulorumen	1.68	0.25	124	1	5
Reticulum	0.26	0.07	696	1	1
Rumen	1.55	0.33	696	1	1
Omasum	0.89	0.23	820	3	1, 3, 5
Abomasum	0.38	0.09	820	3	1, 3, 5
Intestines					
Small intestine	1.09	0.25	840	4	1, 3, 5, 6
Large intestine	0.77	0.20	840	4	1, 3, 5, 6
Cecum	0.08	0.01	36	1	3
Heart	0.37	0.06	804	3	1, 5, 6
Kidneys	0.22	0.05	865	5	1–3, 5, 6
Liver	1.25	0.25	865	5	1–3, 5, 6
Lungs	0.68	0.15	784	2	1, 5
Pancreas	0.08	0.02	696	1	1
Spleen	0.17	0.04	820	3	1, 3, 5
Thyroid	0.006	0.002	696	1	1
Thymus	0.03	0.02	696	1	1
Mammary gland (nonlactating)	1.68	0.81	55	3	7, 8, 9
Mammary gland (lactating)	3.18	0.71	22	1	7
Mammary gland (pregnancy)	2.29	0.54	7	1	7
Uterus	1.09	0.24	40	1	10
Ovaries	0.003	0.001	187	3	11–13
Corpora Lutea	0.0008	0.0003	187	3	11–13
Rest of body	67.06				

Note: The studies involved in the relative organ weight calculations are as follows: 1. Matthews et al. (1975); 2. Andrew et al. (1994); 3. Reynolds et al. (2004); 4. Larsen et al. (2017); 5. Rotta, Valadares Filho, et al. (2015); 6. Scheaffer et al. (2001); 7. Smith and Baldwin, (1974); 8. Harrison, Reynolds, and Little (1983); 9. Swanson and Poffenbarger, (1979); 10. Rotta, Valadares Filho, et al. (2015), 11. Segerson, Hansen, Libby, Randel, and Getz (1984); 12. Ireland, Coulson, and Murphree (1979); 13. Freetly et al. (2014).

TABLE 4 Relative organ weight (percent body weight) or tissue volume for dairy cows in breeds of Jersey and Holstein

	Jersey			Holstein			t test
	Mean	SD	Number of animals	Mean	SD	Number of animals	p
Adrenal glands	0.008	0.003	346	0.004	0.001	350	2.4E-90*
Blood	4.33	0.88	346	4.52	0.92	350	.00544*
Brain	0.09	0.01	346	0.07	0.01	350	1E-107*
GI tract							
Reticulum	0.33	0.08	346	0.19	0.05	350	1E-118*
Rumen	2.08	0.42	346	1.02	0.21	350	3E-117*
Omasum	1.18	0.30	346	0.66	0.16	350	3E-192*
Abomasum	0.50	0.11	346	0.29	0.08	350	1E-106*
Intestines							
Small intestine	1.37	0.32	346	0.82	0.20	350	2E-112*
Large intestine	1.01	0.25	346	0.55	0.14	350	1E-129*
Heart	0.38	0.06	346	0.37	0.07	350	.19742
Kidneys	0.22	0.05	346	0.25	0.05	375	1.9E-17*
Liver	1.35	0.28	346	1.31	0.27	375	.0555
Lungs	0.69	0.16	346	0.70	0.14	350	.60003
Pancreas	0.09	0.02	346	0.08	0.02	350	1.4E-07*
Spleen	0.18	0.04	346	0.16	0.04	350	1.7E-18*
Thyroid	0.008	0.003	346	0.004	0.002	350	2.6E-97*
Thymus	0.04	0.02	346	0.02	0.01	350	1.7E-32*
Mammary gland (nonlactating)	1.67	0.74	13	1.77	0.38	10	.65921
Mammary gland (lactating)	3.14	0.50	7	3.20	0.79	15	.83425

Note: Data were extracted from studies by Andrew et al. (1994) and Matthews et al. (1975). Please refer to the Appendix S1 Tab "Tissue Vol Comp Summary" in Supporting Information for details about these data.

*Significant differences between the two breeds with $p < .05$.

TABLE 5 Relative organ weight (percent body weight) or tissue volume for beef cattle in breeds of Angus and Hereford

	Angus			Hereford			t test
	Mean	SD	Number of animals	Mean	SD	Number of animals	p
Adipose tissue	22.20	1.63	14	14.00	3.53	3	.0013*
Small intestine	1.12	0.10	33	1.06	0.14	16	.1334
Heart	0.44	0.04	47	0.43	0.06	24	.3427
Kidneys	0.22	0.03	47	0.23	0.04	24	.1125
Liver	1.19	0.11	47	1.06	0.15	24	.0002*
Lungs	0.88	0.12	47	0.76	0.16	24	.0012*
Spleen	0.16	0.03	33	0.24	0.06	8	.0014*

Note: Data are from studies by DiCostanzo et al. (1991), Early et al. (1990), Hansard et al. (1953), Jenkins and Ferrell (1997), Keane (2011), Shahin and Berg (1985a), and Sharman et al. (2013). For details about these data, please refer to the Appendix S1 Tab "Tissue Vol Comp Summary" in Supporting Information.

*Significant differences between the two breeds with $p < .05$.

calculated with data from swine with the body weight in the range of 65–160 kg.

The relative organ weights of cattle and swine across different ages or production classes are provided (Table 2 for beef cattle, Table 3 for dairy cows, Table 7 for calves, and Table 12 for market-age swine), which can be used to establish PBPK models specific for food animals with a certain age or for a certain production class. The relative organ weights for different sexes are also available (Table 3 for dairy cows, Table 6 for male and female beef cattle, Table 10 for male swine, and Table 11 for female swine). These data can be applied

TABLE 6 Relative organ weight (percent body weight) or tissue volume for male and female beef cattle

	Male			Female			t test
	Mean	SD	Number of animals	Mean	SD	Number of animals	p
Body weight (kg)	419.00	46.90	1,172	369.00	58.00	506	8.1E-61*
Adipose Tissue	11.30	4.46	193	22.20	6.77	14	1.2E-08*
Heart	0.42	0.08	556	0.41	0.08	389	.0056*
Kidneys	0.21	0.04	786	0.22	0.04	371	2.7E-08*
Liver	1.26	0.20	853	1.11	0.13	401	4.3E-52*
Lungs	0.92	0.25	482	0.66	0.26	419	5.7E-48*
Pancreas	0.09	0.02	318	0.07	0.02	229	9.4E-35*
Spleen	0.19	0.06	476	0.12	0.04	219	4.5E-54*

Note: Data for this table are from 33 studies (Bourg et al., 2012; De Paula et al., 2013; DiCostanzo et al., 1991; Early et al., 1990; Faulkner et al., 1989; Fernandez et al., 1996; Fiems et al., 1993; Fitzsimons et al., 2014; Fonseca et al., 2017; Garrett et al., 1968; Jenkins & Ferrell, 1997; Long et al., 2010, 2012; McEvoy et al., 1998; Moloney, Allen, Ross, Olson, & Convey, 1990; Moseley et al., 1992; Murphy & Loerch, 1994; Olivares et al., 2019; Remling et al., 2017; Robelin, 1981; Robertson et al., 1967; Rumsey et al., 1996; Sainz & Bentley, 1997; Sainz et al., 1995; Schlegel et al., 2006; Shahin & Berg, 1985b; Sprinkle et al., 1998; Swanson & Poffenbarger, 1979; Swett et al., 1933; Talton et al., 2014; Terry et al., 1990; Velazco et al., 1997; Wood et al., 2013). Please refer to the Appendix S1 Tab "Tissue Vol Comp Summary" in Supporting Information for more details.

*Significant differences between the two sexes with $p < .05$.

to develop PBPK models for each sex to explore the potential sex differences in the pharmacokinetics of a chemical. Relative organ weights for commonly used breeds of beef cattle (Table 4) and dairy cows (Table 5) are also included.

3.2.1 | Adrenal glands

The adrenal gland data for cattle were obtained from three different studies (Buntyn et al., 2017; Garrett, Heitman, & Booth, 1968; Matthews, Swett, & McDowell, 1975). The adrenal glands constitute approximately 0.006% of the body weight in cattle (including both beef cattle and dairy cows) (Table 1). The adrenal gland data for calves were reported only in Sangild et al. (2000). The adrenal glands constitute approximately 0.007% of the body weight in calves (Table 7). The relative organ weight of adrenal glands does not seem to significantly change due to age or body weight in cattle. As shown in Table 9, the relative organ weight of adrenal glands in swine is 0.005%. These values in cattle and swine are similar to the range of relative weights of adrenal glands reported in mice (0.01%–0.04%), rats (0.01%–0.03%), dogs (0.004%–0.014%), and humans (~0.02%) (Brown et al., 1997).

3.2.2 | Adipose tissue

The weight of adipose tissue reflects the weight of dissectible fat tissue only. The mean relative weight of adipose tissue in cattle was 12.27%, and the reported values were in a wide range of 6.6%–24% based on the data from 9 different studies (Andrew, Waldo, & Erdman, 1994; De Paula, Tedeschi, Paulino, Fernandes, & Fonseca, 2013; DiCostanzo, Meiske, & Plegge, 1991; Fernandez, Monin, Culioli, Legrand, & Quilichini, 1996; Fonseca et al., 2017;

Keane, 2011; Robelin, 1981; Sainz, De la Torre, & Oltjen, 1995; Velazco et al., 1997; Table 1). The calculated relative adipose tissue weight for calves was 6.95% ± 1.96% (mean ± SD) based on data from three studies (Gill et al., 1987; Morgan, 1969; Santos et al., 2013). The reported values of relative adipose tissue weights from individual studies are summarized in Table 8. The relative adipose tissue weights for cattle reported in a previous review was in the range of 15%–20% (Lin, Gehring, et al., 2016), and the value of 15% was used in the PBPK models for cattle (Li, Cheng, et al., 2019; Li et al., 2017; Li, Gehring, Riviere, & Lin, 2018). These values are within the range of 6.6%–24% reported in the present study. In swine, the calculated relative adipose tissue weight was 15.44% ± 2.65% (Table 9). These values in swine are close to those in cattle. The reported relative adipose tissue weights are 7% in mice and rats, 15% for dogs, and 21.4% for humans (Brown et al., 1997). The average values of 12.27% in cattle and 15.44% in swine fall in the range from 7% to 21.4% in mice, rats, dogs, and humans, and the reported value ranges in cattle and swine include more variability from different breeds of animals from available experimental studies.

3.2.3 | Blood

The calculated mean relative blood volume in cattle was 4.31% based on data from 893 animals of 9 studies (Hansard, 1956; Hansard, Butler, Comar, & Hobbs, 1953; Larsen et al., 2017; Long, Prado-Cooper, Krehbiel, DeSilva, & Wettemann, 2010; Matthews et al., 1975; McCurdy, Krehbiel, Horn, Lancaster, & Wagner, 2010; Rotta, Filho, et al., 2015; Rumsey, Elsasser, Kahl, Moseley, & Solomon, 1996; Swett, Matthews, Miller, & Graves, 1933) (Table 1). This value is close to the reported mean value of 4% for cattle in a previous review article (Lin, Gehring, et al., 2016). Based on data from 5 studies using 52 animals in total, the average relative volume of the blood in

TABLE 7 Relative organ weight (percent body weight) or tissue volume for calves

	Mean	SD	Number of animals	Number of studies	References
Adrenal glands	0.007	0.002	7	1	1
Adipose tissue	6.95	1.96	112	3	2–4
Blood	6.91	0.37	52	5	5–9
Bone	13.29	4.06	76	2	2, 3
Brain	0.54	0.14	7	1	1
GI tract	5.47	3.61	148	5	3, 4, 10–12
Stomachs	2.22	0.69	315	7	3, 10–15
Reticulorumen	1.23	0.59	279	6	10–15
Omasum	0.38	0.17	279	6	10–15
Abomasum	0.38	0.08	286	7	1, 10–15
Intestines	2.39	1.47	146	5	1, 3, 10–12
Small intestine	1.15	0.64	110	4	1, 10–12
Large intestine	0.53	0.20	110	4	1, 10–12
Heart	0.51	0.13	228	9	1, 3, 4, 7, 10, 16–19
Kidneys	0.39	0.07	119	6	1, 3, 4, 7, 14, 16
Liver	2.87	0.36	475	12	1, 3, 4, 7, 10, 12, 14, 16–18, 20
Lungs	1.23	0.29	195	5	1, 4, 7, 10, 16
Muscle	33.90	1.61	76	2	2, 3
Pancreas	0.08	0.00	93	1	10
Spleen	0.26	0.07	192	6	1, 3, 7, 10, 17, 22
Thyroid	0.03	0.01	7	1	1
Thymus	0.23	0.09	13	3	1, 17, 21
Rest of body	27.34				

Note: The studies involved in the relative organ weight calculations are as follows: 1. Sangild et al. (2000); 2. Santos et al. (2013); 3. Morgan (1969); 4. Gill et al. (1987); 5. Waldern, Johnson, and Blosser (1963); 6. Hansard et al. (1953); 7. Hansard (1956); 8. Rhodes, Paterson, Kerley, Garner, and Laughlin (1991); 9. Conrad et al. (1958); 10. Mader et al. (2009); 11. Lineweaver and Hafez (1969); 12. Taylor-Edwards, Burrin, Holst, McLeod, and Harmon (2011); 13. Cozzi et al. (2002); 14. Kristensen et al. (2007); 15. Khan et al. (2011); 16. Martin et al. (2010); 17. Stabel et al. (1993); 18. Williams et al. (1987); 19. Manohar et al. (1982); 20. Fernandez et al. (1996); 21. Biolatti et al. (2005); 22. Settlemire et al. (1964).

calves was approximately 6.95% of the body weight (Table 7). The calculated relative blood volume for swine was 4.12% based on data of 302 animals from 5 different studies (Hansard, 1956; Johnson et al., 2015; Kerr, Yen, Nienaber, & Easter, 2003; Ruusunen et al., 2007; Wiseman et al., 2007) (Table 9). The value in swine reported here is close to the calculated mean value for cattle. However, these values in cattle and swine are relatively lower than the reported values of 4.9% for mice, 7.4% for rats, 8.2% for dogs, and 7.9% for humans (Brown et al., 1997). Also, the mean value of 4.12% is lower than the previously reported value of 6% for swine (Lin, Gehring, et al., 2016; Upton, 2008).

3.2.4 | Bone

The calculated mean relative bone weight was 8.66% for cattle based on data from two different studies (Faulkner, McKeith, Berger, Kesler, & Parrett, 1989; Keane, 2011; Table 1). The average value for relative bone weight in calves was 13.29% (Table 7). This was calculated based on values reported in two studies ranging from 9% to

18% of the body weight (Morgan, 1969; Santos et al., 2013). The calculated mean value for swine was 10.7% based on values from two studies (Quinious & Noblet, 1995; Ruusunen et al., 2007) (Table 9). The calculated mean values for cattle, calves, and swine are in the range of 7.3%–14.3% for the species of mice, rats, dogs, and humans (Brown et al., 1997).

3.2.5 | Brain

The calculated mean value for relative brain weight in cattle was 0.08% based on data from two different studies (Ballarin et al., 2016; Matthews et al., 1975; Table 1). The reported brain weights for cattle are consistently within the range of 400–500 g. The data for relative brain weight in calves were obtained only from Sangild et al. (2000), with the mean value of 0.54% derived from the experiment with 7 calves (Table 7). The relative brain weight for swine was 0.22% based on one study (Mitchell, Scholz, Wange, & Song, 2001). The relative brain weight for cattle is much lower, and for calves and swine are slightly lower than the reported values

TABLE 8 Relative organ weight (percent body weight) or tissue volume for adipose tissue in calves

Volume (percent body weight)	Note	Numbers of animals	References
4.21		10	1
5.58		10	
6.15		10	
5.97		10	
3.38		9	2
4.58		9	
5.70		9	
5.61		9	
10.73		36	3
0.34	Perirenal fat	2	4
0.41	Perirenal fat	2	
0.43	Perirenal fat	2	
0.45	Perirenal fat	2	
5.42	Visceral fat	93	5

Note: The studies involved in the calculations are as follows: 1. Santos et al. (2013); 2. Morgan (1969); 3. Gill et al. (1987); 4. Kristensen et al. (2007); 5. Mader et al. (2009).

in other species, which are in the range of 0.6% in rats to 2.0% in humans (Brown et al., 1997). This may be due to the fact that the value of brain weight has been shown in allometric analyses of pharmacokinetic drug data to not scale with body weight across species (Huang & Riviere, 2014).

3.2.6 | Gastrointestinal tract

The contents of GI tract were excluded in the calculation of values for weight of the total GI tract and individual segments of the GI tract. The calculated mean value for relative weight of total GI tract was 5.98% for cattle (Table 1). The sum of relative weights of the small and large intestines and stomachs, including the reticulum, rumen, omasum, and abomasum, was 5.08%. The value was not exactly equal to 5.98% because all these values were mean values calculated from different studies. Without GI tract contents, the GI tract, including reticulum, rumen, omasum, abomasum, small intestine, and large intestine, constituted about 5.47% of the body weight in calves (Table 7). Three studies (Cozzi et al., 2002; Khan, Weary, & von Keyserlingk, 2011; Kristensen, Sehested, Jensen, & Vestergaard, 2007) reported only stomach data but not organ weights for intestines. Although a trend of decreasing relative organ weights of intestines with increasing body weights was found for calves when plotting values of different sections of the GI tract to body weight, a lack of data for calves with body weight around 250–350 kg prevents a conclusion for this trend. The results for the regression analysis of GI tract organ weights with body weights are included in the Appendix S7 tab "Tissue Volume Calcu&Regression" in the

Supporting Information. By combining organ weights of stomach and intestines, the calculated mean relative GI tract weight was 4.3% for swine (Table 9). The relative GI tract weight of swine is close to the values reported for mammals without a ruminant digestive system (e.g., 4.2% for mice, 2.7% for rats, 3.7% for dogs, and 1.7% for humans) (Brown et al., 1997). However, the calculated values are higher in cattle and calves, which may be due to the large relative weight of the forestomachs.

The food effects are an important consideration in the PBPK simulation of drug absorption through GI tract in humans (Li, Zhao, Pan, & Wagner, 2018). The changes of gastric emptying rate, pH in GI lumen, and increase of splanchnic and hepatic blood flow by food intake can impact oral absorption of drugs in humans (FDA, 2002; Rose, Turner, Neuhoff, & Jamei, 2017). The food effects on oral absorption of drugs in food-producing animals, especially in ruminant animals are less studied than in humans. However, considering that the rumen content can have a major metabolic activity and its acidic pH can play a major ion trapping effect (as for sulfonamides) (Ratz, Maas, Semjen, van Miert, & Witkamp, 1995), it is also anticipated that the rumen content plays an important role in oral absorption of drugs in ruminants. During the literature search process of this study, we have also identified data on the weight of GI tract contents in cattle (Fitzsimons, Kenny, & McGee, 2014; Reynolds, Dürst, Lupoli, Humphries, & Beever, 2004; Sharman et al., 2013) and swine (Pond, Jung, & Varel, 1988). It is also important to know that different diets would have different impacts on the pH of digesta (Ma, Li, Qiao, Huang, & Han, 2002), the digesta flow kinetics (Pond, Pond, Ellis, & Matis, 1986), and on the weight of ruminant contents which ranges from 4.5 to 9.6 g/kg body weight (Sharman et al., 2013). Since the digesta-related parameter values are highly dependent on the diet, these parameters should be considered on a case-by-case basis when incorporating into a PBPK model.

3.2.7 | Heart

The calculated mean relative heart weight was 0.4% for cattle as shown in Table 1, and the calculated values for beef cattle and dairy cows were 0.43% and 0.37%, respectively (Tables 2 and 3). The relative organ weight of the heart was about 0.51% of the whole body of calves ranging from 0.39% to 0.73% (Table 7). Heimbecker (1969) suggested the range is 0.3%–1.4% in calves. When plotting the relative heart weight values to the corresponding body weight values, a regression with $R^2 = .7509$ was found: $Y = -0.00001X + 0.0076$, where Y represents relative heart weight and X represents body weight in kilograms. Results for the regression analysis of heart organ weights with body weights are presented in the Appendix S7 tab "Tissue Volume Calcu&Regression" in the Supporting Information. The calculated mean relative heart organ weight for swine was 0.37% shown in Table 9. These values are all in the range of relative heart weights from 0.3% to 0.8% reported in mice, rats, dogs, and humans (Brown et al., 1997).

TABLE 9 Relative organ weight (percent body weight) or tissue volume for swine

	Mean	SD	Number of animals	Number of studies	References
Adrenal glands	0.005	0.001	111	3	1–3
Adipose tissue	15.44	2.65	244	6	4–9
Blood	4.12	0.46	302	5	1, 8, 10–12
Bone	10.70	0.92	166	2	6, 8
Brain	0.22	0.18	37	1	13
GI tract					
Stomach	0.61	0.09	2,069	17	11, 14–29
Intestines	3.69	0.64	140	2	11, 30
Small intestine	2.19	0.39	626	18	1, 8, 14–19, 21, 22, 24, 25–29, 31, 32
Large intestine	1.47	0.39	282	11	1, 14, 15, 17–19, 21, 22, 25, 27, 28
Cecum	0.20	0.03	135	5	16, 17, 19, 20, 29
Colon	1.68	0.24	59	3	19, 20, 33
Heart	0.37	0.07	2,555	28	1, 8, 10, 11, 13–17, 20–29, 31, 34–41
Kidneys	0.37	0.11	3,261	32	1, 3, 8–10, 13–17, 19–29, 31, 34–37, 39–44
Liver	2.04	0.33	4,992	39	1–3, 8–17, 19–29, 31, 33–46
Lungs	0.90	0.20	419	10	10, 11, 15, 17, 24, 25, 29, 38, 39, 41
Muscle	36.32	2.66	110	3	6, 19, 34
Pancreas	0.15	0.11	421	10	1, 8, 15, 16, 21, 22, 27–29, 33, 37, 47
Spleen	0.20	0.06	3,817	23	1, 8, 10, 12, 14, 16, 17, 21–25, 27–29, 3, 34, 37, 39, 41–45
Thyroid	0.011	0.010	158	6	3, 17, 20, 35, 37, 46
Thymus	0.28	0.03	8	1	1
Skin	5.28	0.81	166	2	6, 8
Rest of body	19.29				

Note: The studies involved in the relative organ weight calculations are as follows: 1. Kerr et al. (2003); 2. Wise et al. (1993); 3. Stahly and Cromwell (1979); 4. Doornenbal et al. (1986); 5. Hood and Allen (1977); 6. Quinious and Noblet (1995); 7. O'Hea and Leveille (1969); 8. Ruusunen et al. (2007); 9 Shelton, Southern, LeMieux, Bidner, and Page (2004); 10. Hansard (1956); 11. Wiseman et al. (2007); 12. Johnson et al. (2015); 13. Mitchell et al. (2001); 14. Tranquilli et al. (1982); 15. Phuc and Hieu (1993); 16. Agyekum, Slominski, and Nyachoti (2012); 17. Kaensombath et al. (2013); 18. Miller and Ullrey (1987); 19. Pond, Varel, Dickson, and Haschek (1989); 20. Velayudhan et al. (2017); 21. Chen, Lewis, Miller, and Yen (1999); 22. Chen, Miller, Lewis, Wolverton, and Stroup (1995); 23. Cliplef and McKay (1993); 24. Critser, Miller, and Lewis (1995); 25. Kaensombath and Lindberg (2012); 26. Pond et al. (1988); 27. Koong, Nienaber, Pekas, and Yen (1982); 28. Koong, Nienaber, and Mersmann (1983); 29. Yen, Nienaber, Klindt, and Crouse (1991); 30. Adeola and King (2006); 31. Moughan, Smith, and Stevens (1990); 32. Cera, Mahan, Cross, Reinhart, and Whitmoyer (1988); 33. Jin, Reynolds, Redmer, Caton, and Crenshaw (1994); 34. Anugwa, Varel, Dickson, Pond, and Krook (1989); 35. Lee and Woyengo (2018); 36. Rehfeldt et al. (2008); 37. Smit and Beltranena (2017); 38. Chiba (1994); 39. Boleman et al. (1995); 40. Owen, Nelssen, Goodband, Tokach, and Friesen (2001); 41. Wang et al. (2011); 42. Brudevold and Southern (1994); 43. Weaver et al. (2013); 44. Lundeen et al. (1983); 45. Tischendorf, Schone, Kirchheim, and Jahreis (2002); 46. Schöne, Kirchheim, Schumann, and Lüdke (1996); 47. Owsley et al. (1986).

3.2.8 | Kidneys

The calculated mean volume for both kidneys was 0.21% for cattle (Table 1). This value is close to the value of 0.26% used in a PBPK model by MacLachlan (2009) and 0.2% used in recent PBPK models for cattle (Li, Cheng, et al., 2019; Li et al., 2017; Li, Gehring, et al., 2018). The kidneys constitute about 0.39% of the body weight in calves (Table 7). In addition, Williams et al. (1987) reported that the relative weight of kidneys with channel fat was about 1.1%. When data were provided for only one kidney (Hansard, 1956), the assumption was made that the weight of both kidneys was equal to twice the weight of the studied organ. The calculated relative weight of both kidneys in swine was 0.37% (Table 9), which is close to the value 0.4% reported in previous review papers (Lin, Gehring, et al., 2016; Upton, 2008).

3.2.9 | Liver

The calculated mean relative liver weight in cattle was 1.23% (Table 1), which is similar to the value of 1.4% used in published PBPK models for cattle (Li, Cheng, et al., 2019; Li et al., 2017; Li, Gehring, et al., 2018) and is close to the reported range of 1.3% to 3% in the review paper (Lin, Gehring, et al., 2016). However, the value is lower than values of 5.5%, 3.4%, 3.3%, and 2.6% reported for mice, rats, dogs, and humans (Brown et al., 1997). In calves, this

TABLE 10 Relative organ weight (percent body weight) or tissue volume for male swine

	Mean	SD	Number of animals	Number of studies	References
Adrenal glands	0.005	0.001	55	2	1, 2
Adipose tissue	14.93	2.61	122	4	3–6
Blood	3.85	0.25	104	3	1, 6, 7
Bone	8.60	0.76	86	2	4, 6
GI tract					
Stomach	0.66	0.11	324	10	6–15
Intestines	3.74	0.40	60	1	7
Small intestine	1.68	0.28	273	10	1, 8–16
Large intestine	1.57	0.40	183	7	1, 8–10, 12, 14, 15
Cecum	0.15	0.02	27	2	1, 13
Heart	0.34	0.05	377	14	1, 6–8, 10–19
Kidneys	0.38	0.10	1,566	16	1, 2, 6, 8–20
Liver	1.76	0.23	246	19	1, 2, 5–21
Lungs	0.80	0.17	200	6	7, 8, 11, 12, 18, 19
Muscle	38.46	2.70	79	3	4, 9, 17
Pancreas	0.15	0.13	297	7	1, 6, 10, 14, 15, 21, 22
Spleen	0.20	0.05	765	11	1, 6, 8, 10–12, 14, 15, 17, 18, 20
Thyroid	0.008	0.001	24	1	1
Thymus	0.28	0.03	8	1	1
Skin	4.47	0.82	86	2	4, 6
Rest of body	21.38				

Note: The studies involved in the tissue volume calculations are as follows: 1. Kerr et al. (2003); 2. Wise et al. (1993); 3. Hood and Allen (1977); 4. Quinious and Noblet (1995); 5. O'Hea and Leveille (1969); 6. Ruusunen et al. (2007); 7. Wiseman et al. (2007); 8. Kaensombath et al. (2013); 9. Pond et al. (1989); 10. Chen et al. (1999); 11. Critser et al. (1995); 12. Kaensombath and Lindberg (2012); 13 Pond et al. (1988); 14. Koong et al. (1982); 15. Koong et al. (1983); 16. Moughan et al. (1990); 17. Anugwa et al. (1989); 18. Boleman et al. (1995); 19. Chiba (1994); 20. Cliplef and McKay (1993); 21. Jin et al. (1994); 22. Owsley et al. (1986). Only data from male swine were used in the calculation in this table.

value was 2.87% (Table 7). The calculated mean relative liver organ weight for swine was 2.04% of body weight (Table 9). This value is close to the value of 2.3% used in recent PBPK models for swine (Li, Cheng, et al., 2019; Li et al., 2017) and in the range of 2%–2.94% for swine reported in the previous review paper (Lin, Gehring, et al., 2016).

3.2.10 | Lungs

The calculated relative weight of lungs for cattle was 0.77% (Table 1), which is close to the value of 0.8% used in PBPK models for cattle (Li et al., 2017; Li, Gehring, et al., 2018). The lungs constitute 1.23% of the body weight in calves with a range of 0.82% to 1.92% (Table 7). Morgan (1969) conducted experiments on 36 calves and showed that lung and trachea weight values ranged from 1.7% to 2.2%. For swine, the calculated mean relative organ weight of lungs was 0.9% (Table 9). This value is similar to the value of 1% for swine in previous review papers (Lin, Gehring, et al., 2016; Upton, 2008) and in one PBPK model for swine (Qian et al., 2017), and to the value of 0.8% in some recent PBPK models for swine (Li, Cheng, et al., 2019; Li et al., 2017).

3.2.11 | Muscle

The calculated mean relative weight of muscle for beef cattle was 36.1% (Tables 1 and 2), which is in the range of 27%–45% reported in a previous review (Lin, Gehring, et al., 2016). The muscle tissue weight data are not available for dairy cows. As shown in Table 7, the weight of muscle is fairly constant and constitutes approximately 33.9% of the body weight in calves. The calculated mean relative tissue weight of muscle in swine was 36.32% (Table 9), which is close to the value of 40% reported in previous review papers (Lin, Gehring, et al., 2016; Upton, 2008) and some PBPK models for swine (Qian et al., 2017; Yuan, Luo, Zhu, Wang, & Liu, 2011), and similar to the value of 35.5% used in PBPK models for swine (Li, Cheng, et al., 2019; Li et al., 2017).

3.2.12 | Pancreas

The calculated mean value was 0.09% for relative weight of pancreas in cattle (Table 1). This value is slightly lower than the reported values in the range of 0.14%–0.7% for mice, rats, dogs, and humans (Brown et al., 1997). The weight of the pancreas constitutes about

TABLE 11 Relative organ weight (percent body weight) or tissue volume for female swine

	Mean	SD	Number of animals	Number of studies	References
Adrenal glands	0.005	0.001	42	1	1
Adipose tissue	13.00	3.06	40	2	2, 3
Blood	3.76	0.28	80	2	3, 4
Bone	10.73	1.00	40	2	2, 3
GI tract					
Stomach	0.63	0.11	131	3	4–6
Intestines	3.47	0.40	60	1	4
Small intestine	1.44	0.31	116	4	5–8
Large intestine	1.04	0.17	42	2	5, 8
Heart	0.36	0.05	196	6	3–8
Kidneys	0.35	0.11	1,318	8	1, 3, 5–10
Liver	1.89	0.28	1,002	8	1, 3–8, 10
Lungs	0.90	0.19	119	2	4, 6
Muscle	34.09	2.37	19	1	2
Pancreas	0.10	0.02	12	1	5
Spleen	0.21	0.07	492	4	5, 6, 9, 10
Uterus	3.28	0.84	42	1	1
Ovaries	0.011	0.002	42	1	1
Corpora Lutea	0.005	0.001	42	1	1
Skin	5.07	0.85	40	2	1, 3
Rest of body	22.14				

Note: The studies involved in the relative organ weight calculations are as follows: 1. Wise et al. (1993); 2. Quinious and Noblet (1995); 3. Ruusunen et al. (2007); 4. Wiseman et al. (2007); 5. Moughan et al. (1990); 6. Chen et al. (1999). Only data from female swine were used in the calculation in this table.

0.08% of the body weight in calves (Table 7), which is close to the value in cattle. Only limited data are available on the weight of the pancreas in calves (Mader et al., 2009). The pancreas organ weight in swine was 0.15% (Table 9), which is close to the reported range of 0.14%–0.7% in other mammalian species (Brown et al., 1997). It should be noted that pancreas along with the thymus can be a component of the "sweetbreads," an edible food product, and thus has tissue residue food safety implications.

3.2.13 | Spleen

Although the spleen represents a small proportion of total body weight, it is important for many physiological functions and can be an important target organ for toxicants. Spleen constitutes approximately 0.18% of the body weight for cattle (Table 1). The average value for calves is 0.26%, which is based on reported values ranging from 0.16% to 0.42% (Hansard, 1956; Mader et al., 2009; Morgan, 1969; Sangild et al., 2000; Settlemire et al., 1964; Stabel et al., 1993) (Table 7). The value for swine is 0.20% (Table 9), which is the same as the relative spleen volume in rats (Brown et al., 1997). All these values in swine and cattle are somewhat

lower than the values 0.35% for mice, 0.27% for dogs, and 0.26% for humans (Brown et al., 1997).

3.2.14 | Thymus

The calculated mean organ weight for thymus was 0.03% of body weight in cattle (Table 1). The value for thymus was based on three different studies (Matthews et al., 1975; Remling et al., 2017; Schumann, Dänicke, Meyer, Ueberschär, & Breves, 2007). In calves, the reported values for thymus are fairly constant with the mean value of 0.23%, and actual values of thymus in calves fall in the range of 360–550 g (Biolatti et al., 2005; Sangild et al., 2000; Stabel et al., 1993) (Table 7). The organ weight of thymus in cattle decreases as the age increases, from 170 g in cattle at 2–3 years to 104 g at over 10 years old (Matthews et al., 1975). The organ weight for thymus was 0.28% of body weight in swine (Table 9). The organ weight of thymus in swine was based on only one study (Matthews et al., 1975). The organ weights of thymus in rats are in the range of 0.08%–0.14% (Brown et al., 1997). The relative organ weights of thymus for swine and calves are higher than the values in rats, but the value in cattle is lower than the value in rats.

TABLE 12 Relative organ weight (percent body weight) or tissue volume for market-age swine

	Mean	SD	Number of animals	Number of studies	References
Body weight (kg)	92.5	4.0	5,521	26	1–26
Adrenal glands	0.005	0.001	79	2	1, 2
Adipose tissue	17.42	2.66	124	4	3–6
Blood	3.45	0.54	176	3	5, 7, 8
Bone	14.31	1.19	88	2	4, 5
GI tract					
Stomach	0.58	0.08	1,811	11	7, 9–18
Intestines	3.01	0.30	72	1	7
Small intestine	1.26	0.23	300	10	9–13, 15–19
Large intestine	1.35	0.32	132	6	9–13, 18
Cecum	0.14	0.02	39	2	16, 17
Colon	0.94	0.10	3	1	16
Heart	0.35	0.05	2,101	16	5, 7, 9, 12–24
Kidneys	0.37	0.10	2,812	17	1, 2, 5, 6, 9, 11–17, 19, 20, 22–24
Liver	2.01	0.25	4,421	21	1, 2, 5–9, 11–20, 22–26
Lungs	0.77	0.14	275	7	7, 9, 15, 17, 18, 22, 24
Muscle	42.63	3.29	24	2	11, 20
Pancreas	0.12	0.03	112	4	12, 13, 17, 18
Spleen	0.21	0.06	3,488	10	8, 9, 12–15, 17, 20, 22, 25
Skin	6.82	0.82	88	2	4, 5
Rest of Body	7.95				

Note: The studies involved in the relative organ weight calculations are as follows: 1. Wise et al. (1993); 2. Stahly and Cromwell (1979); 3. Hood and Allen (1977); 4. Quinious and Noblet (1995); 5. Ruusunen et al. (2007); 6. Shelton et al. (2004); 7. Wiseman et al. (2007); 8.. Johnson et al. (2015); 9. Kaensombath et al. (2013); 10. Miller and Ullrey (1987); 11. Pond et al. (1989); 12. Chen et al. (1999); 13. Chen et al. (1995); 14. Cliplef and McKay (1993); 15. Critser et al. (1995); 16. Pond et al. (1988); 17. Yen et al. (1991); 18. Phuc and Hieu (1993); 19. Moughan et al. (1990); 20. Anugwa et al. (1989); 21. Rehfeldt et al. (2008); 22. Boleman et al. (1995); 23. Owen et al. (2001); 24. Chiba (1994); 25. Tischendorf et al. (2002); 26. Schöne et al. (1996). The calculation of swine relative organ weights in this table was based on data from swine with reported mean body weight of 92.5 kg ranging from 65 to 160 kg.

More data are required to increase our confidence for the relative weight of thymus in swine and cattle.

3.2.15 | Thyroid

The calculated mean organ weight for thyroid was 0.006% of body weight in cattle (Table 1) and 0.03% in calves (Table 7). The relevant data are very limited, only one study (Matthews et al., 1975) is available for thyroid organ weight in beef cattle and no data were found for dairy cows. The actual weights of thyroid increase from around 11 g in calves with 41 kg body weight (Sangild et al., 2000) to 20–40 g in adult cattle (Matthews et al., 1975). Thyroid grows slower compared with the growth of body weight in cattle. The calculated mean organ weight for thyroid was 0.011% of body weight in swine (Table 9). The relative weight of thyroid is in the range of 0.002%–0.009% in rats and in the range of 0.0074%-0.0081% in dogs (Brown et al., 1997). Both the thyroid volumes in cattle and swine are close to or in the range of the values in rats and dogs.

3.2.16 | Mammary glands

The physiological parameters for mammary glands in dairy cows are important for PBPK models related to drugs excreted through milk. The organ weights of mammary glands in nonlactating, pregnant, and lactating cows were obtained, although limited data were available. The mammary glands constitute about 1.68% of body weight for nonlactating cows, 2.29% for pregnant cows, and 3.18% for lactating cows (Table 3).

3.2.17 | Reproductive organs

Limited data were available for reproductive organs. The organ weight of testes is provided in Table 2 for beef cattle as 0.1% of body weight based on three studies (Killian & Amann, 1972; Unruh, Gray, & Dikeman, 1986; Weisgold & Almquist, 1979). The relative organ weights of uterus, ovaries, and corpora lutea were 1.09%, 0.003%, and 0.0008% for dairy cows shown in Table 3, and were 3.28%, 0.011%, and 0.005% for female swine shown in Table 11.

3.2.18 | Mass balance

The value for the rest of body is included in the table to maintain mass balance and to constrain the sum of total relative organ weight fractions to 1. The value for rest of body in Table 1 was 29.67% and in Table 2 was 30.72%, which includes skin, ear, horn, eye, hoof, hair, some of the reproductive organs, and GI tract contents. For dairy cows, the rest of body value was 67.06% in Table 3. This high value is attributed to the fact that muscle weight was not measured separately in dairy cattle and is therefore included in the rest of body estimates. The value for rest of body for calves was 27.34% (Table 7). For swine, the rest of body value in Table 9 was 19.29%.

3.3 | Cardiac output

All cardiac output data in cattle and swine are from unanesthetized, resting animals only. Anesthesia and exercise have impacts on the cardiac output in animals and were therefore excluded from reporting. The cardiac output for adult cattle is summarized in Table 13. The value for cardiac output of calves was calculated based on six different studies (Davis, Collier, McNamara, Head, & Sussman, 1988; Doyle, Patterson, Warren, & Detweiler, 1960; Huntington, Eisemann, & Whitt, 1990; Nienaber, Eisemann, Yen, & Huntington, 1993; Weir, Tucker, Reeves, Will, & Grover, 1974; Whittow, 1965). The mean value of cardiac output for cattle was 5.45 L h^{-1} kg^{-1} body weight. This value is close to the value of 5.67 L h^{-1} kg^{-1} reported in the review by Lin, Gehring, et al. (2016) and the value of 5.97 L h^{-1} kg^{-1} used in recent published PBPK models for cattle (Li, Cheng, et al., 2019; Li et al., 2017). Cardiac output values for calves were calculated based on data only from calves. The original values from each study with reported units are presented in Table 14. The calculated values in the unit of L/h/kg body weight when the body weight data were available for PBPK model use are reported in Table 15. The mean cardiac output value was 9.09 L h^{-1} kg^{-1} from eleven studies and 220 calves (Table 16). Cardiac Output values (L h^{-1} kg^{-1} body weight) were plotted against values of corresponding body weight (kg). Only those studies with explicit body weight (kg) values and those with convertible cardiac output (L h^{-1} kg^{-1} body weight) were included. No significant trend was found for the correlation of cardiac output with body weight, the relevant data and regression analysis are included in the Appendix S10. The body weight-scaled cardiac output value (L h^{-1} kg^{-1} body weight) in calves is higher than that in adult cattle.

The value for cardiac output of swine was calculated based on seven different studies (Duncker et al., 1997; Hannon, Bossone, & Wade, 1990; Lundeen et al., 1983; Manohar & Parks, 1984; Tranquilli et al., 1982; van Woerkens, Duncker, Huigen, Van Der Giessen, & Verdouw, 1990; van Woerkens et al., 1992). The average value of cardiac output for swine was 8.70 L h^{-1} kg^{-1} body weight shown in Table 17. The value reported here is close to the value of 8.543 L h^{-1} kg^{-1} in recent PBPK models for swine (Li, Cheng, et al., 2019; Li et al., 2017). In the review paper by Upton (2008), the cardiac output of swine was reported as 12 L h^{-1} kg^{-1} from Buur,

TABLE 13 Cardiac output (L h^{-1} kg^{-1} body weight) in unanesthetized adult cattle

Mean	SD	Number of animals	Numbers of studies
5.45	1.47	48	6

Note: The value for cardiac output of cattle was calculated based on six different studies (Davis et al., 1988; Doyle et al., 1960; Huntington et al., 1990; Nienaber et al., 1993; Weir et al., 1974; Whittow, 1965).

Baynes, Craigmill, and Riviere (2005) or 20 L h^{-1} kg^{-1} from Vinegar (1999) based on young pigs with body weight of 25 kg. These values are both larger than the value of 8.70 L h^{-1} kg^{-1} for market-age swine analyzed in this study (mean body weight 92.5 kg, Table 12). The data and data analysis for cardiac output for cattle are included in Appendix S4, for calves are in Appendix S10, and for swine are in Appendix S16.

3.4 | Blood flow

The cardiac output value is needed in the calculation of the fraction of blood flow to an organ out of the cardiac output (i.e., fractional cardiac output). For papers that did not provide cardiac output values, the mean cardiac output value from the previous section was used to calculate the mean values of blood flow in individual organs as fractions of cardiac output. The values of blood flow to different organs or tissues are reported as blood flow units of L h^{-1} kg BW^{-1} or mL/min/100 g tissue weight or with the original units reported in the papers, and also by the percent of cardiac output, which can be used directly in PBPK models. The pooled average values of blood flows to organs for adult cattle are summarized in Tables 18 and 19, for beef cattle in Tables 20 and 21, for dairy cows in Tables 22 and 23, for calves in Tables 24-26, and for swine in Tables 27 and 28.

3.4.1 | Gastrointestinal tract

Due to limited data, the blood flow to GI tract was available only for swine and calves. The blood flow fractions in swine to the stomach, small intestine and large intestine were 2.1%, 15.3%, and 5.1% of cardiac output, respectively (Table 28). The sum of these GI tract segment blood flow fractions was 22.5%, which represents the blood flow fraction that gets to the liver through portal vein. This value was very close to the calculated mean value of 19.9% for the portal vein blood flow in swine. The slight difference between these two values was due to these values being calculated based on different experimental studies. The mean value of the blood flow fraction in GI tract for calves was derived from only one study (Conrad, Smith, Vandersall, Pounden, & Hibbs, 1958). This value was 11% (Table 24). The blood flow to GI tract takes 14% of the cardiac output in the rat (Delp, Manning, Bruckner, & Armstrong, 1991), which is close to the values in cattle and swine.

Cardiac output	SD	Unit	Number of animals	References
10.5	2.92	L/min	34	1
28.5	4.68	L/min	27	1
32.1	4.87	L/min	37	1
39.4	6.5	L/min	25	1
8.4	NR	L/min	14	2
158	42.43	mL min^{-1} kg^{-1}	8	3
158	15	mL min^{-1} kg^{-1}	6	3
136	31.11	mL min^{-1} kg^{-1}	8	4
127	29.98	mL min^{-1} kg^{-1}	8	4
1655	NR	L/h	4	5
123	NR	mL min^{-1} kg^{-1}	14	6
7.5	NR	L/min	11	6
154.3	NR	mL min^{-1} kg^{-1}	2	7
4.04	NR	L/min	1	8
32.8	0.98	L/min	6	9
28.6	0.73	L/min	6	9
113	14	mL min^{-1} kg^{-1}	9	10
8.29	0.35	L/min	9	11

Note: NR, not reported in the original study. The studies involved in the cardiac output calculations are as follows: 1. Amory et al. (1993); 2. Weber, Dennison, Fuqua, Speaker, and Hastings (1971); 3. Will, McMurtry, Reeves, and Grover (1978); 4. Busch, Tucker, and Robertshaw (1985); 5. Huntington, Reynolds, and Stroud (1989); 6. Stowe and Good (1960); 7. Waldern et al. (1963); 8. Neuwirth, Norton, Rawlings, Thompson, and Ware (1979); 9. Amory et al. (1995); 10. Manohar et al. (1982); 11. Weber et al. (1972).

3.4.2 | Muscle

The calculated mean blood flow to muscle in cattle was 28% of cardiac output as shown in Table 19. This value is within the range of 18% to 45% reported for cattle in the review paper by Lin, Gehring, et al. (2016). The calculated value was 34.2% of cardiac output in swine shown in Table 28. The value for blood flow fraction of muscle in swine is close to but slightly higher than the value of 29.3% used in PBPK models for swine (Li, Cheng, et al., 2019; Li et al., 2017) and the value of 25% reported in previous review papers (Lin, Gehring, et al., 2016; Upton, 2008) and some other PBPK models for swine (Qian et al., 2017; Yuan et al., 2011). The values of blood flow to muscle in mice, rats, dogs, and humans fall in the range of 16.1 to 29.7% (Brown et al., 1997). The average value for cattle is within this range; however, the value in swine is slightly higher compared with the range.

3.4.3 | Heart

Manohar et al. (1981) and Manohar et al. (1982) both reported myocardial blood flow values in the left and right ventricles, and interventricular septum for calves. Delp et al. (1991) reported interregional differences exist in blood flow to the heart in rats, with the ventricles receiving about twice the flow rate as the atria. Therefore, the summation of the blood flow fractions of both ventricles and septum

accounts for the majority of the heart. The calculated mean blood flow fraction to the heart in calves was 6% (Table 24). The originally reported values of blood flow to heart in units of mL min^{-1} g^{-1} tissue or mL min^{-1} kg BW^{-1} are provided in Table 25, and the converted values in units of L h^{-1} kg BW^{-1} are provided in Table 26. Similar to calves, the heart blood flow in swine was also the sum of the values of septum, right and left ventricles (Tranquilli et al., 1982). The blood flow fraction of heart in swine was 3% (Table 28), which is close to the value of 4.3% in swine reported by Upton (2008). The blood flow to heart is 6.6% in mice, 5.1% in rats, 4.6% in dogs, and 4.0% of cardiac output in humans (Brown et al., 1997). The value of blood flow to heart in cattle is in the range of values reported for mice, rats, dogs, and humans, but the value in swine is slightly lower than this range.

3.4.4 | Kidneys

The value of blood flow to kidneys in cattle was based on 75 animals from four different studies (Deetz, Tucker, Mitchell, & DeGregorio, 1982; Delaquis & Block, 1995; Reynolds, Tyrrell, & Reynolds, 1991a, 1991b). The values of renal blood flow in calves were found in three studies (Huber, 1976; Reynolds, Tyrrell, & Reynolds, 1991b; Wanner, Ziv, Nicolet, Noelpp, & Roesler, 1981). The study by Huber (1976) did not provide either body weight or breed. Therefore, the mean value was calculated based only on the other two studies.

TABLE 15 Cardiac output in unanesthetized calves with the unit as L h^{-1} kg^{-1} body weight

QCC (L h^{-1} kg BW^{-1})	SD	Number of animals	References
12.75	5.06	34	1
10.03	2.05	27	1
9.77	1.95	37	1
8.00	1.81	25	1
5.31	NR	14	2
9.48	2.55	8	3
9.48	0.9	6	3
8.16	1.87	8	4
7.62	1.8	8	4
8.36	NR	4	5
7.38	NR	14	6
7.09	NR	11	6
9.26	NR	2	7
5.92	NR	1	8
9.38	0.32	6	9
7.23	0.24	6	9
6.78	2.52	9	10

Note: NR, not reported in the original study. The studies involved in the cardiac output calculations are as follows: 1. Amory et al. (1993); 2. Weber et al. (1971); 3. Will et al. (1978); 4. Busch et al. (1985); 5. Huntington et al. (1989); 6. Stowe and Good (1960); 7. Waldern et al. (1963); 8. Neuwirth et al. (1979); 9. Amory et al. (1995); 10. Manohar et al. (1982).

TABLE 16 Cardiac output (L h^{-1} kg^{-1} body weight) in unanesthetized calves

Mean	SD	Number of animals	Numbers of studies
9.09	2.77	220	11

Note: The studies involved in the cardiac output calculations are as follows: 1. Amory et al. (1993); 2. Weber et al. (1971); 3. Will et al. (1978); 4. Busch et al. (1985); 5. Huntington et al. (1989); 6. Stowe and Good (1960); 7. Waldern et al. (1963); 8. Neuwirth et al. (1979); 9. Amory et al. (1995); 10. Manohar et al. (1982); 11. Weber et al. (1972).

The originally reported values of blood flow to kidney in units of mL/min or mL min^{-1} m^{-2} or L/h is provided in Table 25, and the converted values in units of L h^{-1} kg BW^{-1} are provided in Table 26. The calculated mean values for renal blood flow fractions in cattle, calves, and swine were 10% (Table 19), 10% (Table 24), and 11.4% (Table 28), respectively. Those values were close to each other and fell within the reported range of renal blood flow for cattle of 9%–11%, and for swine of 10%–14% in a previous review article (Lin, Gehring, et al., 2016). For other animal species, the value was 9.1% for mice, 14.1% for rats, 17.3% for dogs, and 17.5% of cardiac output for humans (Brown et al., 1997). The values of blood flow to kidneys in cattle and swine all fell in the range of 9.1% to 17.5%.

TABLE 17 Cardiac output (L h^{-1} kg^{-1} body weight) in unanesthetized swine

Mean	SD	Number of animals	Numbers of studies
8.70	1.62	83	7

Note: The value for cardiac output of swine was calculated based on seven different studies (Duncker et al., 1997; Hannon et al., 1990; Lundeen et al., 1983; Manohar & Parks, 1984; Tranquilli et al., 1982; van Woerkens et al., 1990, 1992).

3.4.5 | Liver

Liver blood flow is composed of hepatic artery and portal vein. The total blood flow in liver, represented as a combination of blood flow in the hepatic artery and portal vein, is commonly used in PBPK models. The hepatic blood flow in cattle was 46% (Table 19), which was within the reported range of 35%–53% in a previous review article (Lin, Gehring, et al., 2016) and close to the value of 40.5% in published PBPK models for cattle (Li, Cheng, et al., 2019; Li et al., 2017). The value for hepatic blood flow fraction in calves was 30% of cardiac output (Table 24). The value was slightly lower than the value in cattle. The originally reported values of blood flow to liver in units of L/min or L/h is provided in Table 25, and the converted values in unit of L h^{-1} kg BW^{-1} is provided in Table 26. The originally reported values of blood flow to hepatic artery in units of mL min^{-1} kg BW^{-1}, L/min, or L h^{-1} kg BW^{-1} is provided in Table 25, and the converted values in unit of L h^{-1} kg BW^{-1} is provided in Table 26. The blood flow fractions of hepatic artery and portal vein in swine are reported in Table 28. By combining these two values, the value of hepatic blood flow fraction in swine was 24.3% of cardiac output. This value fell in the range of 24%–30.5% in a previous review paper (Lin, Gehring, et al., 2016) and was close to the value of 27.3% used in PBPK models for swine (Li, Cheng, et al., 2019; Li et al., 2017). The values of blood flow to liver are in the range of 16.1%–29.7%, blood flow through hepatic artery in the range of 2.0%–4.6%, and through portal vein in the range of 14.1%–25.1% in mice, rats, dogs, and humans (Brown et al., 1997). The blood flow to liver in cattle was higher than the values for swine, mice, rats, dogs, and humans, which may be due to the ruminant digestive system in cattle.

3.4.6 | Lungs

The blood flow to lungs in calves was achieved based on data from one study (Rudolph & Yuan, 1966), which was reported as 50% in Table 24. The blood flow values in the original reported unit of L/min are shown in Table 25, and in the unit of L h^{-1} kg BW^{-1} are reported in Table 26. In the PBPK model, the blood flow to the lung compartment is typically considered as 100% cardiac output (Brown et al., 1997). The values reported for calves stand for the blood flow to the bronchial region.

	Mean	SD	Number of animals	Number of studies	References
Muscle	1.51	0.28	13	2	1, 2
Kidneys	0.55	0.45	75	4	3–6
Liver	2.51	1.17	331	8	3, 6, 7–12
Hepatic artery	0.44	0.34	152	2	8, 10
Portal vein	2.12	1.02	399	9	3, 6–13
Uterus	0.0041	0.0036	12	3	14–16
Ovaries	0.0003	0.0001	3	1	15
Testes	0.0015	0.0005	14	1	17

TABLE 18 Regional blood flow (L h^{-1} kg^{-1} body weight) distribution in adult cattle

Note: The studies involved in the regional blood flow calculations are as follows: 1. Eisemann, Huntington, and Ferrell (1987); 2. Eisemann, Huntington, and Ferrell (1988); 3. Reynolds, Tyrrell, and Reynolds (1991a); 4. Delaquis and Block (1995); 5. Deetz et al. (1982); 6. Reynolds et al. (1991b); 7. Huntington et al. (1990); 8. Røjen, Theil, and Kristensen (2011); 9. Lescoat, Sauvant, and Danfær (1996); 10. Ellis et al. (2016); 11. Huntington et al. (1989); 12. Whitt et al. (1996); 13. Reynolds and Huntington (1988); 14. Ford, Chenault, and Echternkamp (1979); 15. Ford and Chenault (1981); 16. Rawy et al. (2018); 17. Barros Adwell et al. (2018).

	Mean	SD	Number of animals	Number of studies	References
Muscle	28	9	13	2	1, 2
Kidneys	10	9	75	4	3–6
Liver	46	25	331	8	3, 6, 7–12
Hepatic artery	8	7	152	2	8, 10
Portal vein	39	22	399	9	3, 6–13
Uterus	0.08	0.07	12	3	14–16
Ovaries	0.005	0.002	3	1	15
Testes	0.03	0.01	14	1	17

TABLE 19 Regional blood flow distribution as percent cardiac output in adult cattle

Note: The studies involved in the regional blood flow calculations are as follows: 1. Eisemann et al. (1987); 2. Eisemann et al. (1988); 3. Reynolds et al. (1991a); 4. Delaquis and Block (1995); 5. Deetz et al. (1982); 6. Reynolds et al. (1991b); 7. Huntington et al. (1990); 8. Røjen et al. (2011); 9. Lescoat et al. (1996); 10. Ellis et al. (2016); 11. Huntington et al. (1989); 12. Whitt et al. (1996); 13. Reynolds and Huntington (1988); 14. Ford et al. (1979); 15. Ford and Chenault (1981); 16. Rawy et al. (2018); 17. Barros Adwell et al. (2018).

All raw data and data calculations for blood flow fractions for cattle are provided in Appendix S2, for calves are provided in Appendix S8, and for swine are included in Appendix S14.

3.5 | Vascular space

The vascular space or volume fraction of blood in organs and tissues is one of the important physiological parameters for PBPK models with diffusion-limited (also known as permeability-limited or membrane-limited) compartment structures. Vascular space is also described as residual blood volume in tissues or organs. For chemicals with large molecular weight as well as many nanoparticles, the transmembrane process is the rate-limited step for chemical distribution. In membrane-limited PBPK models, the organ compartments are divided into compartments of organ tissue and residual blood (Godin et al., 2010; Lin, Monteiro-Riviere, & Riviere,

2016; Tornero-Velez et al., 2010; Yoon, Kedderis, Yan, & Clewell, 2015). Hansard (1956) reported values of residual blood volumes in nine different organs, including spleen, lungs, liver, kidneys, pituitary gland, adrenal gland, heart, pancreas, and muscles in cattle, sheep, and swine, which are shown in Table 29 for adult cattle, Table 30 for calves, Table 31 for growing swine, and Table 32 for aged swine (mean BW: ~297 kg). Compared to the values reported in Table 30 of Brown et al. (1997), the fractions in heart, liver, and lungs for cattle and swine seem to be lower than those of the mouse, rat, dog, and human perhaps due to species difference or variability in the measurement. The fraction values in other organs in cattle and swine fall within the reported ranges of mice, rats, dogs, and humans (Brown et al., 1997). For vascular space in muscle of calves, two studies were found for calculation and comparison as shown in Table 33. Macdougall, Bremner, and Dalgarno (1973) reported four residual blood volume fractions from different muscles. Hansard (1956) reported two values, both higher than those

TABLE 20 Regional blood flow (L h⁻¹ kg⁻¹ BW) distribution in beef cattle

	Mean	SD	Number of animals	Number of studies	References
Muscle	1.51	0.28	13	2	1, 2
Kidneys	0.62	0.41	54	3	3–5
Liver	2.40	1.23	285	7	3, 5–10
Hepatic artery	0.40	0.35	111	1	8
Portal vein	2.05	1.07	353	8	3, 5–11
Testes	0.0015	0.0005	14	1	12

Note: The studies involved in the regional blood flow calculations are as follows: 1. Eisemann et al. (1987); 2. Eisemann et al. (1988); 3. Reynolds et al. (1991a); 4. Deetz et al. (1982); 5. Reynolds et al. (1991b); 6. Huntington et al. (1990); 7. Lescoat et al. (1996); 8. Ellis et al. (2016); 9. Huntington et al. (1989); 10. Whitt et al. (1996); 11. Reynolds and Huntington (1988); 12. Barros Adwell et al. (2018).

TABLE 21 Regional blood flow distribution as percent cardiac output in beef cattle

	Mean	SD	Number of animals	Number of studies	References
Muscle	28	9	13	2	1, 2
Kidneys	11	8	54	3	3–5
Liver	44	25	285	7	3, 5–10
Hepatic artery	7	7	111	1	8
Portal vein	38	22	353	8	3, 5–11
Testes	0.03	0.01	14	1	12

Note: The studies involved in the regional blood flow calculations are as follows: 1. Eisemann et al. (1987); 2. Eisemann et al. (1988); 3. Reynolds et al. (1991a); 4. Deetz et al. (1982); 5. Reynolds et al. (1991b); 6. Huntington et al. (1990); 7. Lescoat et al. (1996); 8. Ellis et al. (2016); 9. Huntington et al. (1989); 10. Whitt et al. (1996); 11. Reynolds and Huntington (1988); 12. Barros Adwell et al. (2018).

TABLE 22 Regional blood flow distribution (L h⁻¹ kg⁻¹ BW) in dairy cows

	Mean	SD	Number of animals	Number of studies	References
Kidneys	0.36	0.53	21	1	1
Liver	3.17	0.63	41	2	2, 3
Hepatic artery	0.54	0.30	41	2	2, 3
Portal vein	2.65	0.58	41	2	2, 3
Mammary gland	0.71	0.25	119	2	4, 5
Uterus	0.0041	0.0036	12	3	6–8
Ovaries	0.0003	0.0001	3	1	6

Note: The studies involved in the regional blood flow calculations are as follows: 1. Delaquis and Block (1995); 2. Røjen et al. (2011); 3. Ellis et al. (2016); 4. Lescoat et al. (1996); 5. Davis et al. (1988); 6. Ford et al. (1979); 7. Ford and Chenault (1981); 8. Rawy et al. (2018).

in Macdougall et al. (1973). The mean value of around 1% for cattle and swine from Hansard (1956) was similar to the value of 1% for dogs and humans, but was less than the value of 4% in mice and rats (Brown et al., 1997).

All raw data and data calculations for vascular space for cattle are provided in Appendix S3, for calves in Appendix S9, and for swine in Appendix S15.

3.6 | Hematocrit

Hematocrit, also known as Packed Cell Volume (PCV), is the proportion of red blood cells in the total volume of blood. Hematocrit for

cattle and swine were calculated based on previously reported data. Hematocrit for cattle of both sexes with different ages was pooled together (Table 34), and the value was 37.8%. Hematocrit values were collected as the baseline for calves (Table 35). The hematocrit value for calves was 33.7%. Hematocrit values for swine of all ages are shown in Table 36 and for different age groups are shown in Table 37. The average value of hematocrit in swine was 41.2%, and values of hematocrit slightly increase from 39.9% to 43.3% with the increase of age.

Hematocrit was not included in previous reviews for physiological parameters in either laboratory animals or food animals (Brown et al., 1997; Lin, Gehring, et al., 2016; Upton, 2008). In the PBPK models for drugs and chemicals in laboratory animals and humans,

	Mean	SD	Number of animals	Number of studies	References
Kidneys	7	10	21	1	1
Liver	58	19	41	2	2, 3
Hepatic artery	10	6	41	2	2, 3
Portal vein	49	17	41	2	2, 3
Mammary gland	13	6	119	2	4, 5
Uterus	0.075	0.069	12	3	6–8
Ovaries	0.005	0.002	3	1	6

TABLE 23 Regional blood flow distribution as percent cardiac output in dairy cows

Note: The studies involved in the regional blood flow calculations are as follows: 1. Delaquis and Block (1995); 2. Røjen et al. (2011); 3. Ellis et al. (2016); 4. Lescoat et al. (1996); 5. Davis et al. (1988); 6. Ford et al. (1979); 7. Ford and Chenault (1981); 8. Rawy et al. (2018).

	Mean	SD	Number of animals	Number of studies	References
GI tract	11	4	8	1	1
Heart	6	2	21	2	2, 3
Kidneys	10	3	30	2	4, 5
Liver	30	11	12	2	4, 6
Hepatic artery	4	1	17	2	6, 7
Portal vein	28	9	62	12	4, 6–16
Lungs	46	25	16	1	17

TABLE 24 Regional blood flow distribution as percent cardiac output in calves

Note: The studies involved in the regional blood flow calculations are as follows: 1. Conrad et al. (1958); 2. Manohar et al. (1981); 3. Manohar et al. (1982); 4. Reynolds et al. (1991a); 5. Wanner et al. (1981); 6. Ortigues, Martin, Durand, and Vermorel (1995); 7. Durand, Bauchart, and Levaivre (1984); 8. McGilliard, Thorp, and Thorp (1971); 9. Fries and Conner (1961); 10. Huntington et al. (1989); 11. Harmon and Avery (1987); 12. Wangsness and McGilliard (1972); 13. Huntington and Prior (1983); 14. Huntington et al. (1989); 15. Carr and Jacobson (1968); 16. Durand, Bauchart, Lefaivre, and Donnat (1988); 17. Rudolph and Yuan (1966).

the hematocrit is applied to facilitate the prediction of chemical concentrations in plasma. However, for PBPK models in food animals, the values of hematocrit were not commonly used, due to limited information in pharmacokinetic and drug depletion studies in food animals. For example, the blood to plasma ratio of drugs, which helps to calculate drug distributed to red blood cells, is not commonly measured or reported in drug distribution studies in food animals. Many pharmacokinetic studies do not report details for blood sample preparation, and the drug concentrations in blood samples may be from serum, plasma, or whole blood. In addition, the pharmacokinetic and drug depletion studies in food animals conducted across a wide range of time used very different analytical methods, including radioactive techniques, immunoassay, or analytical chemistry methods. When performing new pharmacokinetic studies in food animals, the inclusion of hematocrit in PBPK models would help improve the prediction of drug concentrations in blood or plasma. All raw data and data analysis for hematocrit for cattle are provided in Appendix S5, for calves in Appendix S11, and swine in Appendix S17.

4 | DISCUSSION

To develop a PBPK model for a xenobiotic in an organism, the most accurate method of collecting physiological parameter values is by direct measurement of the values in animals of the same species, strain/breed, and age as the target animals used in the pharmacokinetic or tissue residue depletion studies. However, this is practically unfeasible, scientifically unnecessary, and ethically questionable since many physiological parameters in different animals of different strains/breeds and ages have been reported. One of the future directions of PBPK model applications is to serve as an alternative method to animal experimentation (i.e., to develop a PBPK model using in vitro and in silico methods for animal-free risk assessment) (Fabian et al., 2019). Therefore, it is important to have a physiological parameter database for developing PBPK models in the future. The main contribution of the present report is to provide a detailed and comprehensive compilation of PBPK-related physiological parameters in different production classes of cattle (i.e., calve, beef cattle, and dairy cows) and swine (i.e.,

TABLE 25 Original data for regional blood flow distribution in calves

	Mean	SD	Unit	Number of animals	Reference
Heart	2.83		mL min^{-1} g^{-1} tissue	12	1
	4.32	0.20	mL min^{-1} kg^{-1} BW	9	2
Kidneys	210.00		L/h	1	3
	235.00		L/h	1	3
	186.00		L/h	1	3
	200.00		L/h	1	3
	681.70	14.90	mL/min	NA	4
	351.00	125.70	mL min^{-1} m^{-2}	26	5
Liver	714.50	193.01	L/h	4	3
	3.00	NR	L/min	4	6
	3.02	NR	L/min	4	6
Hepatic artery	4.40	1.20	mL min^{-1} kg^{-1}	4	7
	5.70	NR	L h^{-1} kg^{-1} BW	5	7
	0.46	NR	L/min	4	6
	0.44	NR	L/min	4	6
Lungs	3		L/min	1	9
	4.1		L/min	1	9
	3.6		L/min	1	9
	2.9	1.3	L/min	16	10

Note: NR, not reported in the original study. 1. Manohar et al. (1981), 2. Manohar et al. (1982), 3. Reynolds et al. (1991a), 4. Huber (1976), 5. Wanner et al. (1981), 6. Ortigues et al. (1995), 7. Durand et al. (1984), 8. Durand et al. (1988), 9. Reeves and Leathers (1964b), 10. Rudolph and Yuan (1966).

TABLE 26 Converted data for regional blood flow distribution in unit of L h^{-1} kg^{-1} BW in calves

	Mean	SD	Unit	Number of animals	Reference
Heart	0.69		L h^{-1} kg^{-1} BW	12	1
	0.26	0.01	L h^{-1} kg^{-1} BW	9	2
Kidneys	0.67		L h^{-1} kg^{-1} BW	1	3
	0.70		L h^{-1} kg^{-1} BW	1	3
	0.60		L h^{-1} kg^{-1} BW	1	3
	0.62		L h^{-1} kg^{-1} BW	1	3
	0.90		L h^{-1} kg^{-1} BW	26	4
Liver	2.21		L h^{-1} kg^{-1} BW	4	3
	2.99		L h^{-1} kg^{-1} BW	4	5
	3.01		L h^{-1} kg^{-1} BW	4	5
Hepatic artery	0.26	0.07	L h^{-1} kg^{-1} BW	4	6
	0.34		L h^{-1} kg^{-1} BW	5	6
	0.46		L h^{-1} kg^{-1} BW	4	5
	0.44		L h^{-1} kg^{-1} BW	4	5
Lungs	4.14	1.84	L h^{-1} kg^{-1} BW	16	8

Note: 1. Manohar et al. (1981), 2. Manohar et al. (1982), 3. Reynolds et al. (1991a), 4. Wanner et al. (1981), 5. Ortigues et al. (1995), 6. Durand et al. (1984), 7. Durand et al. (1988), 8. Rudolph and Yuan (1966).

growing swine, market-age swine, and aged swine). This study is expected to serve as a reference for the development of future PBPK models for drugs and xenobiotics in cattle and swine. This study also provides a methodology basis for ongoing studies compiling physiological parameters for other food-producing animals, such as goats, sheep, chickens, and turkeys.

	Mean	SD	Number of animals	Number of studies	References
Brain	80.92	12.93	26	2	1, 2
Thyroid	206.00	126.00	9	1	3
Adrenal	152.16	87.77	43	4	1–3, 5
Pancreas	149.00	51.00	9	1	3
Muscle	10.10	6.86	45	4	1, 2, 4, 5
Skin	7.58	3.28	34	3	1, 2, 5
Kidneys	361.63	84.48	35	3	1–3
Hepatic artery	22.28	18.71	43	4	1–3, 5
Spleen	193.98	91.84	43	4	1–3, 5
Stomach	59.42	35.27	43	4	1–3, 5
Small intestine	82.84	37.34	43	4	1–3, 5
Large intestine	57.00	15.00	9	1	3

Note: The regional blood flows of swine were calculated based on the following studies: 1. Duncker et al. (1997); 2. van Woerkens et al. (1990); 3. Manohar and Parks (1984); 4. Lundeen et al. (1983); 5. van Woerkens et al. (1992).

Swine blood flow (percent cardiac output)					
	Mean	SD	Number of animals	Number of studies	References
Brain	1.5	0.4	35	3	1–3
Thyroid	0.13	0.08	9	1	4
Adrenal glands	0.06	0.04	43	4	2–5
Pancreas	1.4	0.5	9	1	4
Muscle	34.2	30.6	45	4	2, 3, 5, 6
Skin	3.5	1.6	34	3	2, 3, 5
Heart	3.0	0.6	9	1	1
Kidneys	11.4	3.2	56	5	1–4, 7
Hepatic artery	4.4	2.9	55	5	1–4, 6
Portal vein	19.9	4.6	32	3	8–10
Spleen	3.1	1.2	52	5	1–5
Stomach	2.1	1.1	34	4	1, 3, 5
Small intestine	15.3	7.7	52	5	1–5
Large intestine	5.1	1.1	18	2	1,4

Note: The regional blood flow fractions of swine were calculated based on the following studies: 1. Tranquilli et al. (1982); 2. Duncker et al. (1997); 3. van Woerkens et al. (1990); 4. Manohar and Parks (1984); 5. van Woerkens et al. (1992); 6. Lundeen et al. (1983); 7. Hannon et al. (1990); 8. Yen, Nienaber, Hill, and Pond (1989); 9. O'Connor et al. (1992); 10. Yen and Killefer (1987). If no cardiac output reported in a specific study, the regional blood flow fractions were calculated using the average cardiac output of swine reported in Table 17.

In this database, the mean, standard deviation, and range of values of each parameter from different studies were calculated to characterize the biological and experimental variability associated with each parameter. Only the original studies that reported values obtained experimentally were used as sources of data analysis. To avoid the bias inherent to repeated use of the same data in the analysis, the default organ weight estimates used in published PBPK models were not used to calculate the mean values reported in this manuscript. The standard deviation and range of values of each parameter are important as these data are needed to conduct stochastic population PBPK analysis to quantify the population variability via statistical approaches, such as Monte Carlo simulations. These data can better characterize the animal population variability since direct measurement of physiological parameters in a few animals from a highly homogeneous population is unlikely to accurately characterize the variability of the particular animal

TABLE 29 Vascular space or volume fraction of blood (% of organ weight, unitless) in organs and tissues of adult cattle

	Mean	SD
BW (kg)	383.7	46.3
Spleen	34.5	8.3
Lungs	20.3	2.6
Liver	7.7	1.5
Kidneys	6.6	0.5
Pituitary gland	4.6	0.9
Adrenal glands	3.8	0.3
Heart	3.7	0.6
Pancreas	3.4	0.8
Loin muscle	1.0	0.3
Gastrocnemius muscle	1.0	0.2

Note: Very limited studies were identified for the residual blood volume in organs of cattle. All data reported in the table were from the study of Hansard (1956) with values from 4 animals.

TABLE 30 Vascular space or volume fraction of blood (% of organ weight, unitless) in organs and tissues for calves

	Mean	SD
Adrenal glands	3.0	0.2
Heart	2.6	0.4
Kidneys	3.7	0.3
Liver	7.9	2.5
Lungs	25.1	1.8
Muscle	*	*
Pancreas	2.5	0.5
Pituitary gland	3.4	0.7
Spleen	31.3	1.7

Note: Very limited studies were identified for the residual blood volume in organs of calves. All data reported in the table were from the study of Hansard (1956) with values from 3 animals. * Please refer to Table 33 for more details related to muscle.

TABLE 31 Vascular space or volume fraction of blood (% of organ weight, unitless) in organs and tissues for growing swine

	Mean	SD
BW (kg)	20.9	12.6
Spleen	14.6	1.9
Lungs	24.8	2.9
Liver	5.7	0.5
Kidneys	7.2	0.3
Adrenal glands	4.9	0.8
Heart	3.1	0.3
Pancreas	2.2	0.1
Loin muscle	1.5	0.4
gastrocnemius muscle	0.80	0.02

Note: Very limited studies were identified for the residual blood volume in organs of growing swine. All data reported in the table were from the study of Hansard (1956) with values from 3 animals.

TABLE 32 Vascular space or volume fraction of blood (% of organ weight, unitless) in organs and tissues for aged swine

	Mean	SD
BW (kg)	281.1	29.1
Spleen	10.0	0.1
Lungs	24.0	0.9
Liver	8.0	0.6
Kidneys	9.1	3.2
Adrenal glands	4.5	0.9
Heart	3.6	0.5
Pancreas	2.3	0.3
Loin muscle	0.91	0.01
Gastrocnemius muscle	0.8	0.1

Note: Very limited studies were identified for the residual blood volume in organs of aged swine. All data reported in the table were from the study of Hansard (1956) with values from 3 animals.

population. Although calculation of the mean and standard deviation in this way is useful to characterize the population variability, it does not solely represent the variability of the data for individuals within a species. Instead, the standard deviations reported in this manuscript could be due to multiple factors, including true biological variability, sampling error, interlaboratory variation, and differences in the measurement techniques employed. Therefore, while the present data are useful in characterizing the population variability of physiological parameters, caution should be taken when interpreting the results.

To facilitate the application of the data presented in this manuscript, for all parameters, the values in the tables are presented in a format that can be directly used in a PBPK model. If the original studies use a different unit, the values are converted to the unit commonly used in PBPK modeling. Values in original units are available

in the Supplementary Excel files. Consequently, the values in this manuscript can be directly compared to published values in existing PBPK models for cattle and swine (Lin, Gehring, et al., 2016), and also be compared with values in other mammals (Brown et al., 1997). These comparisons are performed and discussed throughout the manuscript in order to verify that the values are biologically plausible (i.e., do not substantially deviate from the commonly reported values).

When available, values for the weights or blood flows of different regions within a particular organ or tissue system (e.g., stomach and small and large intestines of the GI tract, or hepatic artery and portal vein of the total blood flow to the liver) are provided. The sum of individual values of different regions may be occasionally different from the measured total value of the particular organ or tissue system. These differences are mainly because different values could be taken from different references, not due to oversights or failure

Mean	SD	Number of animals	Notes	References
0.46	0.21	3	*Longissimus dorsi*	1
0.40	0.14	3	*Biceps femoris*	
0.38	0.23	3	*Semimembranosus*	
0.33	0.07	3	*Semitendinosus*	
0.39	0.09	3	Mean of all muscles measured	
1.23	0.06	3	Loin muscle	2
0.97	0.12	3	Gastrocnemius muscle	

TABLE 33 Vascular space or volume fraction of blood (% of organ weight, unitless) in muscle for calves

Note: Very limited studies were identified for the residual blood volume in muscle of calves. All data reported in the table were from the studies of 1. MacDougall et al. (1973) and 2. Hansard (1956).

TABLE 34 Hematocrit (%) for adult cattle

Mean	SD	Number of animals	Numbers of studies
37.8	3.3	230	6

Note: The hematocrit value of cattle was calculated based on 6 studies (Braun, Camenzind, & Ossent, 2003; Doyle et al., 1960; Lawrence, Kenny, Earley, Crews, & McGee, 2011; Nascimento et al., 2015; Røjen et al., 2011; Weir et al., 1974).

TABLE 35 Hematocrit (%) for calves

Mean	SD	Number of animals	Numbers of studies
33.7	4.6	81	7

Note: Final *SD* was calculated excluding data without reported *SD* values. The hematocrit value of calves was calculated based on 7 studies (Bisgard, Ruiz, Grover, & Will, 1974; Fasules, Tryka, Chipman, & Van Devanter, 1994; Manohar et al., 1982; Reeves & Leathers, 1964a, 1964b; Reynolds et al., 1991b; Will et al., 1978).

TABLE 36 Hematocrit (%) for swine

BW (kg)	Mean	SD	Number of animals	Numbers of studies
56.3	41.2	5.0	684	10

Note: The hematocrit value of swine was calculated based on 10 studies (Brudevold & Southern, 1994; DeGoey, Wahlstrom, & Emerick, 1971; Gowanlock, Mahan, Jolliff, Moeller, & Hill, 2013; Groce et al., 1973; Honeyfield, Froseth, & Barke, 1985; Hyun, Ellis, Curtis, & Johnson, 2005; Russett, Krider, Cline, & Underwood, 1979; Shelton et al., 2004; Veum, Ledoux, Shannon, & Raboy, 2009; Weaver et al., 2013). The calculation of swine hematocrit in this table involved data from swine of all ages.

to select between alternative values, as discussed in a previous review article (Davies & Morris, 1993).

The present study fills many data gaps in the recently published review article on physiological parameters in cattle, swine, and sheep (Lautz, Dorne, et al., 2019). For example, in the study by Lautz, Dorne, et al. (2019), many parameter values are not available, such as physiological parameters in calves, blood flows in the kidney and reproductive organs (i.e., testes, uterus, and ovaries) in beef cattle and dairy cows, as well as vascular space or volume fraction of blood in organs (i.e., % organ weight) in cattle and swine. These parameters were tabulated in the present manuscript. In Lautz, Dorne, et al. (2019), physiological parameter values are presented, but without discussion on the consistency with values reported in existing PBPK models. As a result, it is difficult to evaluate the validity of their parameter values. For example, the blood flows to the liver as a fraction of cardiac output are 24.6% and 66.0% in beef cattle and dairy cattle, respectively, in Lautz, Dorne, et al. (2019). Since these two values are both for adult animals in the same species and the major difference is lactating vs. nonlactating, this large difference is hard to interpret biologically. This difference could be due to inter-study variation, but the specific reference(s) for each parameter are not provided and there is no discussion on the validity of the parameter values, it is difficult to identify the reasons. In the present study, the blood flows to the liver as a fraction of cardiac output are 44% and 58% in beef cattle and dairy cows, respectively. These values are consistently with the previously reported values of 40.5% for beef cattle (Li, Cheng, et al., 2019) and 40.5%–53% for dairy cows (Leavens et al., 2014; Li, Gehring, et al., 2018). Since many physiological parameters were determined in studies published decades ago with different methods, they are of high variability. When selecting physiological parameter values to use in a PBPK model, it is important to consider whether the parameter value is biologically plausible and whether it is consistent with values reported in existing literature. Overall, compared to the mini-review by Lautz, Dorne, et al. (2019), the present study provides a comprehensive database on PBPK-related physiological parameters in cattle and swine in the context of their potential application to food animal safety endpoints, as well as providing a detailed discussion on the validity of the parameter values reported.

The present summary of physiological parameter values can serve as a reference database for the development of new PBPK models of drugs and environmental chemicals in different production classes of cattle and swine. However, readers should be aware of several caveats associated with the use of default parameter values in PBPK models. The reported values are for healthy, unanesthetized, and

TABLE 37 Hematocrit (%) for swine in different age groups

Age	BW (kg)	Mean	SD	Number of animals	Numbers of studies	References
Young	17.6	39.9	5.4	315	7	1–7
Growing	65.6	40.1	6.4	113	2	6, 8
Finishing	95.2	43.3	3.7	256	4	2, 8–10

Note: The hematocrit value of swine was calculated based on 10 studies including 1. Brudevold and Southern (1994); 2. DeGoey et al. (1971); 3. Hyun et al. (2005); 4. Russett et al. (1979); 5. Veum et al. (2009); 6. Groce et al. (1973); 7. Weaver et al. (2013); 8. Gowanlock et al. (2013); 9. Honeyfield et al. (1985); 10. Shelton et al. (2004). The values of hematocrit for swine in this table were calculated based on different age groups.

resting animals. However, as reviewed by Brown et al. (1997), many factors can change physiological parameter values, especially organ blood flows. These factors include disease, physical activity, anesthesia, food intake, age, sex, posture, and treatment with common drugs, as well as unintended or unreported exposure to toxicants (e.g., mycotoxins in feed). For example, liver is an important organ for elimination of drugs that are extensively metabolized and liver is a commonly included organ in PBPK models. Liver dysfunction due to disease (e.g., cirrhosis) or exposure to chemicals (e.g., carbon tetrachloride) can markedly change hepatic blood flow by over a fourfold range from half normal flow to twice normal flow (Brown et al., 1997; Nies, Shand, & Wilkinson, 1976). This will greatly change elimination of drugs with a high hepatic extraction ratio and intrinsic hepatic clearance. Liver dysfunction can also change the hepatic metabolic capacity (e.g., decreased enzyme expression or activity) (Brown et al., 1997), resulting in altered metabolite to parent drug ratios and extended withdrawal times for different drugs in cattle and swine; and this effect is drug- and species-specific (Lin, Vahl, & Riviere, 2016).

One of the main applications of PBPK models in food animals is to predict extralabel withdrawal intervals of drugs, which could range from days to months, depending on the drug and species. When running a PBPK model for an extended simulation period in growing animals, it is important to consider age-dependent physiological changes. Age-dependent increases in body weight of chickens have been incorporated into recently published PBPK models (Henri et al., 2017; Zeng et al., 2019). The present study provides growth curves for calves and young swine for developing PBPK models in growing calves and swine. Potential age- or body weight-dependence of other physiological parameters was also analyzed, but due to limited data, only the relative heart weight was found to be significantly associated with the body weight. The raw data are provided in the Supplementary Excel files. Once new data are available, further studies are needed to determine whether other parameters are age-dependent.

Another potential application for the data in this report is to serve as a basis for the creation of virtual populations of cattle and swine in computer software programs or web-based interfaces for rapid development of PBPK models. In this regard, virtual populations in different species, including mice, rats, dogs, and humans have been incorporated into commercial PBPK modeling software programs, such as Simcyp (Certara USA, Inc.) and GastroPlus (Simulations Plus, Inc.). These software programs have been shown to be useful to efficiently create PBPK models for drugs in preclinical species and humans, facilitating drug discovery and development. Both the US Food and Drug Administration and European Medicines Agency have accepted PBPK simulation results based on virtual populations from Simcyp and GastroPlus (EMA, 2018; FDA, 2018). However, currently, neither Simcyp nor GastroPlus has included food-producing animal species in their software. To create virtual animal populations, besides physiological parameters, biochemical parameters, such as the expression levels and activities of different drug-metabolizing enzymes in different organs (e.g., liver and intestine) are needed. Several studies have attempted to characterize the ontogeny of hepatic and intestinal P450 protein abundance and enzyme activity in pigs (Millecam et al., 2018; Schelstraete et al., 2019), but such studies are still limited in cattle, which requires further investigation. Overall, the present study serves as a critical step toward creating virtual populations of cattle and swine in PBPK modeling software programs.

In conclusion, the present manuscript provides a comprehensive compilation and a reference database of physiological parameter values for developing PBPK models of drugs and environmental chemicals in different production classes of cattle and swine. This study serves a methodology basis for compiling PBPK-related physiological parameters for other food animal species, such as chickens, turkeys, goats, and sheep. This study represents as a first step toward creating virtual populations of cattle and swine in computer software programs or web-based interfaces for rapid development and application of PBPK models in the field of animal health and animal-derived food safety assessment. Reviews such as the present manuscript strengthen the ability to build PBPK models as outlined in the World Health Organization and US Environmental Protection Agency PBPK modeling guidelines (EPA, 2006; WHO, 2010).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

ZL, JER, LAT, REB, JLD, and TWV discussed and designed this project. ML did the literature search on beef cattle, dairy cows and swine, extracted the data into Excel files, analyzed the data, and presented the data as Tables and Figures. YSW did the literature search on calves, extracted the data into Excel files, analyzed the data, and presented the data as Tables and Figures. YSW double checked all data presented in the Excel files. ZL double checked all data presented in the Tables of the manuscript. ZL and ML co-drafted the manuscript. All authors contributed to data interpretation and provided critical comments on the manuscript. All authors approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.