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REVIEW ARTICLE

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Physiological parameter values for physiologically based pharmacokinetic models in food-producing animals. Part II: Chicken and turkey

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Abstract

Physiologically based pharmacokinetic (PBPK) models are growing in popularity due to human food safety concerns and for estimating drug residue distribution and estimating withdrawal intervals for veterinary products originating from livestock species. This paper focuses on the physiological and anatomical data, including cardiac output, organ weight, and blood flow values, needed for PBPK modeling applications for avian species commonly consumed in the poultry market. Experimental and field studies from 1940 to 2019 for broiler chickens (1–70 days old, 40 g - 3.2 kg), laying hens (4–15 months old, 1.1–2.0 kg), and turkeys (1 day–14 months old, 60 g –12.7 kg) were searched systematically using PubMed, Google Scholar, ProQuest, and ScienceDirect for data collection in 2019 and 2020. Relevant data were extracted from the literature with mean and standard deviation (*SD*) being calculated and compiled in tables of relative organ weights (% of body weight) and relative blood flows (% of cardiac output). Trends of organ or tissue weight growth during different life stages were calculated when sufficient data were available. These compiled data sets facilitate future PBPK model development and applications, especially in estimating chemical residue concentrations in edible tissues to calculate food safety withdrawal intervals for poultry.

KEYWORDS
blood flow, Food Animal Residue Avoidance Databank (FARAD), food safety, organ weight, physiologically based pharmacokinetic (PBPK) model

1 | INTRODUCTION

The world poultry industry generally includes the major species, chickens (*Gallus gallus domesticus*) and turkeys (*Meleagris gallopavo*), and the minor species of guinea fowls, ducks, quails, pheasants, partridges, and others, with the categorization varying between continents (e.g., turkeys are considered a major species in the United States, but a minor species in European and Asian countries). The U.S. poultry industry is the world's largest producer and second largest exporter of poultry meat (USDA, 2019b). Since 1970, the

amount of chicken meat available for human consumption per capita has more than doubled (USDA, 2019a) and the national production of poultry meat (broiler chicken, other chicken, turkey, and other poultry) has been comparable to the total of beef and pork production. In 2018, broiler chickens produced 42.6 billion pounds of meat, whereas beef and pork yielded 26.5 and 26.1 billion pounds, respectively (USDA, 2019c), with the estimated consumer retail expenditures on chickens generating $95 billion in 2019 (NCC, 2019a).

Growth of poultry production and consumption raises significant concerns in food safety, violative drug residues, and estimated drug withdrawal intervals (Baynes et al., 2016; Chen et al., 2019). Readers are referred to Li et al. (2017) for detailed definition of withdrawal intervals. In the United States, legislation such as the Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA) makes it legal for drugs to be used in an extralabel manner provided that several conditions set forth by AMDUCA and US FDA are met. Similarly, in the European Union and United Kingdom, the cascade prescription system permits veterinarians to prescribe extralabel medicines to animals in accordance with the cascade (De Briyne et al., 2014; Loeb, 2019). It is a requirement that the estimation of a withdrawal interval be based on scientific data, thus creating a need for tools to predict drug withdrawal intervals after extralabel use (Riviere et al., 2017). Physiologically based pharmacokinetic (PBPK) modeling is a robust tool for estimating drug tissue residues and withdrawal intervals in food-producing animals after approved FDA label or extralabel drug use and can be used for extrapolation across species, production classes, or therapeutic regimens (Li, Cheng, et al., 2019; Li, Mainquist-Whigham, et al., 2019; Lin et al., 2016).

To date, several PBPK models for poultry, primarily chickens, have been published and are useful for the above-mentioned applications (Cortright et al., 2009; Henri et al., 2017; Yang et al., 2014, 2015; Zeng et al., 2019). The growing use of PBPK models in veterinary medicine and food safety assessment has created the need for a comprehensive physiological parameter database for different food-producing animal species. Physiological parameter values for PBPK modeling have been comprehensively compiled for laboratory animal species and humans (Brown et al., 1997; Davies & Morris, 1993; ICRP, 2002), but such data are still deficient for food-producing animals.

Our objective is to compile a comprehensive PBPK-related physiological parameter database for food-producing animals, including cattle (*Bos taurus taurus* or *Bos taurus indicus*) for veal calves, beef cattle, and dairy cattle, swine (*Sus scrofa domesticus* or *Sus domesticus*), chickens for broiler chickens and laying hens, turkeys for growing turkeys, as well as sheep (*Ovis aries*) and goats (*Capra aegagrus hircus*). Literature-extracted physiological parameters include body weight, organ/tissue weight, cardiac output, regional blood flow, and hematocrit. Values are presented as pooled mean and standard deviation (*SD*) derived from original experimental or field study data. Extracted raw data and analysis processes are provided in the Appendix S1–S8. Compiled tables of individual parameters are presented in the manuscript. This manuscript is part two of three in a larger series for food animals (Li et al., 2020; Lin et al., 2020). The ultimate goal of the project is to provide data for a curated reference physiological database for the development of PBPK models for drugs and environmental chemicals in different species of production animals intended for human consumption.

2 | METHODS

2.1 | Literature search strategy

Relevant studies published from 1940 to 2019 were identified from the following electronic databases: PubMed, Google Scholar, ProQuest, and ScienceDirect. Data were searched using the keywords listed below. Primarily, comprehensive studies were identified using keywords combining species criteria: chicken, domestic fowl, broiler, laying hen, turkey poult, turkey hen, turkey tom, and tissue volume, organ weight, or blood flow. Next, the more specific parameter was searched using keywords including adrenal glands, adipose, fat, blood, bone, brain, stomachs, crop, proventriculus, gizzard, ventriculus, intestines, small intestines, duodenum, ileum, jejunum, large intestines, cecum, colon, heart, kidneys, liver, lungs, muscle, pancreas, spleen, thyroid, or thymus for organ/tissue weights. For blood flow, combined with species criteria, one of the following keywords was used: hepatic blood flow, myocardial blood flow, pulmonary blood flow, renal blood flow, and muscular blood flow. For reproductive organs/tissues, the following keywords were used: reproductive organs, reproductive tissues, oviduct, uterus, infundibulum, isthmus, magnum, shell gland, vagina, ovary, testis, and testes. Due to the majority USDA-approved drug administration routes being *per os* (PO), the retention or passage time and rate of ingesta were included in the literature search with the keywords being passage time OR emptying time OR retention time AND broiler OR turkey.

2.2 | Inclusion and exclusion criteria

Figure 1 provides a workflow of the literature search process, the inclusion and exclusion criteria. Briefly, all physiological data provided in this document were from healthy chickens and turkeys. Studies using broiler chickens were all included, regardless of the specific strains mentioned in the references (including the main strains: Cobb 500, Ross 308, and Hubbard F15). Both sexes and ages less than eight weeks were included in this study since the market age of general broiler chickens is typically six to seven weeks (NCC, 2019b). As for laying hen production class, initially both sexes were included in the data search. Females were later separated from the general pool of laying species for calculation because some studies only used males of the typical laying hen production class for research purposes. For turkeys, the values in the tables represent actual experimental data from those animals with body weights listed and have not been extrapolated from other data. No data were collected from embryos, in vitro fertilizations, wild or scavenger birds. Studies with unusual body weight values relative to age were excluded considering modern poultry husbandry (e.g., if the body weight is outside the range of mean $\pm$ 3 * *SD*). No animal

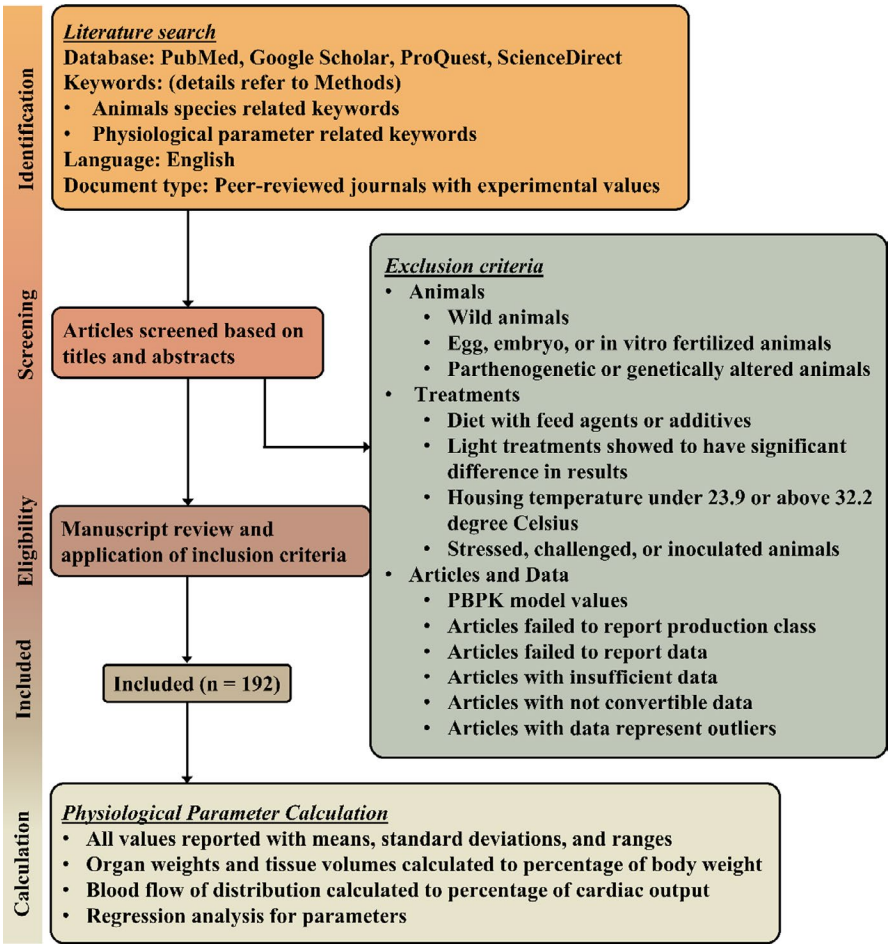

FIGURE 1 A flowchart of the literature search process, inclusion and exclusion criteria, as well as data analysis for physiological parameters in chickens and turkeys [Colour figure can be viewed at wileyonlinelibrary.com]

subjects included were physiologically stressed according to each cited study. Only values from naïve control groups were included.

2.2.1 | Strains, lines, breeds, and market age

For the purpose of meat production, selected genetic lines have improved over the last 50 years such that broiler chickens reared in intensively housed production systems currently achieve market weights at 35–42 days of age (MacLachlan, 2010). The mean market age for broiler chickens reported by the National Chicken Council for the last three years is 47 days (NCC, 2019b). Main strains, lines, or breeds analyzed in this research included Cobb 500, Ross 308, Hubbard F15, and their crossbreeds for broiler chickens; and White Leghorn, New Hampshire, Rhode Island Red, Barred Plymouth Rock, and their crossbreeds for laying hens. Although none of the literature adopted free-range systems and/or organic production, it is worth noting that these housing conditions require longer time periods for animals to reach market weight and therefore feed to gain ratio would need to be taken into consideration in parameter fitting. In addition, it was reported that male lines resulted primarily from selection for growth and carcass traits, and female lines for carcass and reproductive traits (Melnychuk et al., 1997). Although selection breeding nowadays may result in difference carcass characteristics between sexes, animal subjects in this research were not considered to be affected. Therefore, both male and female lines were included in the calculation. Strains of turkeys included Nicholas Large White turkeys and British United Turkeys (B. U. T.) 6 as both were commonly used in commercial and laboratory settings.

2.2.2 | Diet

Only animal groups that were labeled full-fed or fed ad libitum were included. No values from animals under diet restrictions were used. Diets formulated as standard commercial diets to meet breeder-recommended nutrient levels and NRC nutrient requirement of poultry were adopted (NRC, 1994; Renema et al., 1995). Groups fed with extra feed agents, feed additives, additional enzymes, mycotoxins, or artificially contaminated feeds were excluded.

2.2.3 | Sex effects

An effect of sex on live weight is usually observed in poultry, males being heavier than females. In this study though, the sex effect was not considered due to the fact that marketed broiler chickens include both sexes and that sex is often not specified in the literature.

TABLE 1 Relative organ weight (% body weight) in broiler chickens of all ages

Organ/Tissue	Mean	*SD*	Number		Range	Reference
			Animal subjects	Studies		
Adipose Tissue	13.4 (male)		10	1		1
	15.1 (female)		10	1		1
Coelomic (Abdominal) Fat	2.14	0.68	863	5	0.5–4.30	2–6
Adrenal Glands	0.014	0.0022	140	1	0.0095–0.0255	7
Blood	4.83	0.98	27	3	1.10–7.02	8–10
Bursa of Fabricius	0.19	0.05	489	9	0.07–0.28	5, 6, 11–17
Gallbladder	0.12	0.01	68	2	0.094–0.158	18, 19
Heart	0.54	0.12	7,476	17	0.35–1.10	2, 4, 6, 8, 11, 12, 16, 20–29
Liver	2.14	0.47	8,667	22	1.75–4.75	4, 5, 6, 8, 11–13, 15, 16, 18, 20, 22–27, 29, 30–33
Muscle	57.12	14.73	70	2	40.15–66.65	8, 34
Pectoral (Breast) Muscle	23.46	4.01	78	2	18.12–25.3	5, 34
Pancreas	0.29	0.03	501	7	0.20–0.55	6, 11, 13, 15, 18, 20, 30
Pulmonary Parenchyma (Lungs)	0.71	0.10	265	6	0.50–1.04	8, 20–22, 27, 35
Renal Parenchyma (Kidneys)	0.64	0.10	58	4	0.56–0.87	8, 20, 26, 36
Skin/Feathers	13.38	2.82	10	1		8
Spleen	0.11	0.04	552	11	0.07–0.22	5, 6, 11–17, 20, 23
Thymus	0.50	0.09	10	1		11
Pre-intestinal GI Tract (Stomachs)	3.50	0.68	660	1	1.25–9.05	4
Ingluvies (Crop)	0.50		13	1		20
Proventriculus	0.36	0.05	479	5	0.29–0.59	6, 11, 13, 20, 30
Ventriculus (Gizzard)	1.25	0.44	6,646	11	1.02–7.11	5, 6, 8, 11, 13, 15, 20, 24, 25, 30, 31
Intestine	3.50	0.82	6,339	5	0.70–17.1	15, 21, 24, 27, 31
Small intestine	3.13	0.32	472	5	2.67–7.49	6, 11, 13, 15, 30
Duodenum	1.20	0.05	130	3	1.17–1.47	6, 15, 18
Jejunum	1.92	0.16	114	2	1.84–3.29	6, 15
Ileum	1.37	0.17	114	2	1.29–2.73	6, 15
Large Intestine	1.42	0.10	6	1		15
Ceca	0.50	0.10	183	1	0.30–0.53	6, 11, 13, 20, 32
Colon	0.18	0.03	10	5		11
Ovary	0.043	0.010	180	1	0.03–0.05	4
Testes	0.050	0.026	360	1	0.03–0.1	4
Rest of body (Remainder of Body)	12.37 (both sexes)					

Note: Blank field indicates not applicable or data not available.

1. Becker et al. (1981), 2. Boostani et al. (2010), 3. Kalavathy et al. (2003), 4. Leeson and Summers (1980), 5. Park and Kim (2014), 6. Sadeghi et al. (2012), 7. Deaton et al. (1969), 8. Cortright et al. (2009), 9. May et al. (1971), 10. Rzasa et al. (1974), 11. Awad et al. (2009), 12. Baarendse et al. (2006), 13. Ghahri et al. (2013), 14. Heckert et al. (2002), 15. Lee et al. (2003), 16. Rath et al. (2006), 17. Toghyani et al. (2010), 18. Khosravinia (2016), 19. Peebles et al. (1997), 20. Adeyemi et al. (2008), 21. Bowes and Julian (1988), 22. Buys (1999), 23. Deeb (2002), 24. Gaya et al. (2006), 25. Moraes et al. (2002), 26. Pastuszewska et al. (2001), 27. Tickle et al. (2014), 28. Wideman (1999), 29. Yersin et al. (1992), 30. Çabuk et al. (2006), 31. Dyubele et al. (2010), 32. Józefiak et al. (2006), 33. O'Hea and Leveille (1969), 34. Hussein et al. (2019), 35. Wideman et al. (1996), 36. Glahn et al. (1990).

2.2.4 | Environmental effects

Sources for data variability included different factors such as altitude, light cycle, and light duration (Hobbs & Moreng, 1976; USDA, 2013). Recommended light intensity during different growth stages is available in the Poultry Industry Manual (USDA, 2013). In Yahav et al. (2000), although the animals were under different treatments of light intensity, the result showed no significant difference

TABLE 2 Relative organ weight (% body weight) in broiler chickens of market age (42–49 days)

Organ/Tissue	Mean	*SD*	Number		Range	Reference
			Animal Subjects	Studies		
Adipose Tissue						
Coelomic (Abdominal) Fat	3.25	0.66	120	1	3–3.5	1
Adrenal Glands	0.01	0.002	40	1	0.0095–0.0103	2
Blood	4.83	0.98	27	3	1.1–7.02	3–5
Bursa of Fabricius	0.15	0.004	262	3	0.07–0.2	6–8
Gallbladder	0.094	0.004	8	2	0.09–0.1	9, 10
Heart	0.52	0.12	6,338	8	0.38–0.69	1, 3, 11–16
Liver	2.04	0.48	7,531	10	1.76–3.78	1, 3, 6, 9, 11, 14–18
Muscle	40.15	0.081	10	1		3
Pancreas	0.25	0.01	369	4	0.2–0.33	6, 9, 11 ,17
Pulmonary Parenchyma (Lungs)	0.61	0.09	114	7	0.5–0.71	3, 11, 13, 14, 16, 19, 20
Renal Parenchyma (Kidneys)	0.57	0.12	30	2	0.56–0.58	3, 11
Skin/Feathers	13.38	2.82	10	1		3
Spleen	0.12	0.03	275	4	0.1–0.16	6–8, 11
Pre-intestinal Gastrointestinal Tract (Stomachs)	2.18	0.4	120	1	2.05–2.3	1
Ingluvies (Crop)	0.5		13	1		11
Proventriculus	0.29	0.03	361	3	0.29–0.33	6, 11, 17
Ventriculus (Gizzard)	1.17	0.34	6,434	6	1.13–3.2	3, 6, 11, 15, 17, 18
Intestine	3.43	0.81	6,256	4	0.7–5.34	13, 15 ,16, 18
Small intestine	2.69	0.26	348	2	2.67–3.31	6, 17
Testes	0.03	0.01	120	1		1
Rest of Body (Remainder of Body)	28.39					

Note: Blank field indicates not applicable or data not available.

1. Leeson and Summers (1980), 2. Deaton et al. (1969), 3. Cortright et al. (2009), 4. May et al. (1971), 5. Rzasa et al. (1974), 6. Ghahri et al. (2013), 7. Heckert et al. (2002), 8. Toghyani et al. (2010), 9. Khosravinia (2016), 10. Peebles et al. (1997), 11. Adeyemi et al. (2008), 12. Boostani et al. (2010), 13. Bowes and Julian (1988), 14. Buys (1999), 15. Gaya et al. (2006), 16. Tickle et al. (2014), 17. Çabuk et al. (2006), 18. Dyubele et al. (2010), 19. Wideman et al. (1996), 20. Wideman (1999).

between relative weight values for pectoral muscle, fat, and testes. Therefore, all values regardless of light treatment were adopted for calculation in this study.

2.3 | Data analysis

Data analysis and calculation were based on the method described in detail in Part I of this series of manuscripts (Lin et al., 2020). In brief, the mean values in the tables provided are weighted arithmetic means with the numbers of animals used in each experiment as a weighting factor. Number of animals was considered as one when studies did not report the number of animals. With the exception of May et al. (1971) where values were presented as male and female without specifying the number of animal subjects. For this, we assigned the number of animals used as two subjects. The *SD* values reported in this document were derived from the *SD* in individual studies with the number of animals as a weighting factor. Studies without *SD* values were excluded in pooled *SD* calculation. Reported blood flow values were extracted and calculated as absolute and relative values (% of cardiac output). During data extraction, total animal numbers were calculated with consideration of mortality during the research period. When applicable, organ weights immediately after death were assumed to be representative of the true physiological value (Bowes & Julian, 1988). For organs of bilateral pairs (i.e., kidneys and testes), reported value of the unilateral organ was multiplied by two when no significant difference was reported.

TABLE 3 Relative organ weight (% body weight) for laying hens

Organ/Tissue	Mean	*SD*	Number		Range	Reference
			Animal Subjects	Studies		
Adrenal Glands	0.0057	0.0038	28	1		1
Blood	6.30	1.33	4	1		2
Brain	0.089	0.01	19	2	0.071–0.1	1, 3
Heart	0.30	0.065	21	1		1
Liver	2.49	0.49	25	2	2.352–2.621	3, 4
Pancreas	0.15	0.02	13	1		4
Pulmonary Parenchyma (Lungs)	0.66	0.20	12	1		3
Renal Parenchyma (Kidneys)	0.76	0.13	25	2	0.747–0.763	3, 4
Spleen	0.15	0.06	637	3	0.101–0.157	1, 3, 5
GI Tract						
Ingluvies (Crop)	0.055		10	1		6
Proventriculus	0.19	0.04	23	2	0.045–0.3	4, 6
Ventriculus (Gizzard)	0.70	0.11	23	2	0.333–0.979	4, 6
Duodenum	0.27	0.06	13	1		4
Jejunum	0.42	0.08	13	1		4
Ileum	0.26	0.08	13	1		4
Ceca	0.045		10	1		6
Colon and rectum	0.019		10	1		6
Ovary	1.91	0.28	24	1	0.36–2.85	7
Infundibulum	0.13	0.033	49	3	0.053–0.182	7, 8, 9
Magnum	1.24	0.28	49	3	0.3–1.55	7, 8, 9
Isthmus	0.29	0.066	49	3	0.113–0.411	7, 8, 9
Uterus[a]	0.72	0.13	49	3	0.32–0.81	7, 8, 9
Vagina	0.20	0.028	24	1	0.11–0.26	7
Rest of Body (Remainder of Body)	82.60					

Note: Blank field indicates not applicable or data not available.

1. DeSantis et al. (1975), 2. Bond and Gilbert (1958), 3. Wolfenson et al. (1978), 4. Wolfenson et al. (1981), 5. Norton and Wolfe (1949), 6. Martínez et al. (2015), 7. Niezgoda et al. (1982), 8. Wolfenson et al. (1978), 9. Wolfenson et al. (1981).

[a]Uterus was used as the parameter in the original study even the hens were reproductively active.

3 | RESULTS

Results of the pooled physiological parameters for chickens and turkeys, including organ/tissue weight, gastrointestinal retention time, cardiac output, regional blood flow, and hematocrit, are summarized in Tables 1–23. Each parameter value is compared to values from published reports of physiological parameters for PBPK modeling in other species, including mice, rats, dogs, humans, cattle, and swine (Brown et al., 1997; Davies & Morris, 1993; Lin et al., 2020; Upton, 2008), as well as currently available PBPK models for chickens (Cortright et al., 2009; Henri et al., 2017; MacLachlan, 2010; Yang et al., 2014, 2015; Zeng et al., 2019). Tables 24 and 25 present overall comparisons of our compiled data with data from a recently published PBPK model in domestic chickens (Lautz et al., 2020).

3.1 | Organ weight

Tables 1–5 summarize the values for the weight fraction of organs and tissues typically represented in PBPK models for broiler chickens of all ages, broiler chickens at market age (42–49 days old), layers, turkeys of all ages, and turkeys at market age (16–20 weeks old),

TABLE 4 Relative organ weight (% body weight) for turkeys of all ages

Organ/Tissue	Mean	*SD*	Number		Range	Reference
			Animal Subjects	Studies		
Total lipid[a]	18.1	2.04	156	4	7.48–24.8	1–4
Coelomic (Abdominal) Fat	1.42	0.47	40	3	0.75–2.05	4, 5, 6
Adrenal Glands	0.019	0.0045	1,793	2	0.01–0.02	7, 8
Blood	0.68	0.23	10	1		9
Brain	0.21	0.035	10	1		9
Bursa of Fabricius	0.18	0.060	106	14	0.05–0.2	10–23
Heart	0.51	0.075	2,194	20	0.32–0.74	8–10, 12, 15–18, 23–34
Liver	2.62	0.36	2,811	29	0.83–4.27	2, 5, 8–12, 15–17, 19, 21, 23, 25–27, 29–31, 33–42
Muscle	43.1	6.37	10	1		9
Pancreas	0.30	0.078	1,672	12	0.08–0.42	8, 19, 21, 23, 29–31, 33, 37, 38, 41, 43
Pulmonary Parenchyma (Lungs)	0.83	0.122	949	4	0.27–0.89	8, 9, 30, 31
Renal Parenchyma (Kidneys)	0.95	0.12	1,052	9	0.26–1.1	8, 9, 19, 21, 29, 30, 33, 37, 41
Skin/Feathers	11.73	2.04	10	1		9
Spleen	0.073	0.023	1,793	19	0.042–0.29	8, 10–18, 20, 21, 27, 29–31, 33, 36, 44
Thymus	0.26	0.015	56	3	0.14–0.30	13, 20, 45
Pre-intestinal Gastrointestinal Tract (Stomachs)						
Ingluvies (Crop)	0.34	0.071	298	2	0.31–0.43	23, 35
Proventriculus	0.43	0.059	208	6	0.11–0.74	19. 21, 23, 27, 31, 45
Ventriculus (Gizzard)	2.15	0.25	398	14	0.86–3.42	5, 9, 19, 23, 26, 27, 29–31, 33, 37, 38, 40, 45
Small Intestine	4.85	0.43	144	5	2.05–7.15	26, 30, 36, 43, 46
Duodenum	1.68	0.16	130	4	0.69–2.01	13, 23, 46, 47
Jejunum	2.55	0.50	142	5	1.35–3.12	12, 13, 23, 46, 47
Ileum	2.13	0.22	70	3	1.07–2.28	12, 23, 46
Ovary	0.27	0.30	596	4	0.008–1.54	2, 8, 40, 48
Oviduct	1.03	0.22	299	5	0.03–1.39	2, 35, 39, 40, 48
Stroma[b]	0.18	0.05	112	2	0.16–0.25	2, 48
Testes	0.025	0.07	501	4	0.01–0.36	5, 8, 22, 49
Rest of Body (Remainder of Body)	12.6 (male) 11.2 (female)					

Note: Blank field indicates not applicable or data not available.

1. Hurwitz et al. (1988), 2. Melnychuk et al. (1997), 3. Plavnik and Hurwitz (1991), 4. Renema et al. (1994), 5. Hulet and Brody (1986)), 6. Jankowski and Nevarez (2010), 7. Davis and Siopes (1985), 8. Hobbs and Moreng (1976), 9. Cortright et al. (2009), 10. Bayyari, Huff, Balog, et al. (1997), 11. Bayyari, Huff, Rath, et al. (1997), 12. Danicke et al. (2007), 13. Fasina et al. (2006), 14. Gore and Qureshi (1997), 15. Huff et al. (1998), 16. Huff et al. (2000), 17. Huff et al. (2001), 18. Huff et al. (2005), 19. Kubena et al. (1991), 20. Li et al. (2000), 21. McKenzie et al. (1998), 22. Rozenboim et al. (1990), 23. Shapiro et al. (1998), 24. Ali and Czarnecki (1987), 25. Fairchild and Christensen (2000), 26. Ferket and Sell (1989), 27. Hamilton et al. (1985), 28. Hoffmann et al. (2016), 29. Kubena et al. (1997), 30. Marsden (1940), 31. Nestor et al. (2005), 32. Pierpont et al. (1985), 33. Tilley et al. (2017), 34. Wu et al. (1994), 35. Crouch et al. (2002) 36. Grimes et al. (2008), 37. Kubena et al. (1995a), 38. Kubena et al. (1995b), 39. Lilburn and Nestor (1993), 40. Rauber et al. (2007), 41. Richards et al. (1987), 42. Rosebrough et al. (1981), 43. Moran and McGinnis (1967), 44. Fadly and Nazerian (1984), 45. Chang et al. (1981), 46. Fan et al. (1997), 47. Applegate et al. (2005), 48. Renema et al. (1995), 49. Yahav et al. (2000).

[a]Total lipid extraction method; please refer to the text for details.

[b]Stroma: Stroma was defined as the ovary without large follicles. Please refer to the text for more details.

respectively. In PBPK modeling, a compartment is typically defined by its volume rather than its weight (Brown et al., 1997), but in the literature usually the organ weight or mass, instead of the organ volume, is reported. Nevertheless, the mass-to-volume conversion is often not required in PBPK modeling because the density of the majority of 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 (1.92 g/cm^3 for marrow-free bone) and adipose tissue (0.916 g/cm^3) (Brown et al., 1997). Therefore, in line with previous review articles on PBPK-related physiological parameters (Brown et al., 1997; Lin et al., 2020), in this study the terms "organ weight" and "organ volume" and "tissue volume" are considered operationally equivalent assuming water density for all organs. Furthermore, when evaluating the measurement of organ weights, methods of termination should be taken into consideration. The common practice of industrial poultry processing is to pass the birds through an electrified water-bath while shackled, followed by exsanguination to termination. However, most of the experimental study references did not provide the detailed method of slaughtering. This can lead to some differences in organ weights when applying the data from this study to the chickens and turkeys in the field.

3.1.1 | Adipose tissue

Three methods were formerly reported to acquire the adipose tissue: dissection, chemical extraction, and dual-energy x-ray absorptiometry technique (Brown et al., 1997). Careful dissection was suggested to be able to yield accurate values for the adipose tissue content of the animal, minus the visceral organs. Total lipid using chemical extraction was determined gravimetrically after extraction with a 2:1 mixture of chloroform:methanol (Folch et al., 1957). In this study, only methods of dissection and chemical extraction were found to include in the data pool. In most of the literature providing values for coelomic fat weight, the parameter was indicated as "abdominal fat pad." In the present study, these two terms were considered equivalent and only the term "coelomic fat" was used to avoid confusion and ambiguity for PBPK modelers. Relative adipose tissue and coelomic fat weight values were summarized in Tables 1, 2, 4, and 5, for broiler chickens and turkeys, respectively. No adipose tissue data were available for layers.

In the present study, mean total adipose tissue for all broiler chickens was reported as 13.4% and 15.1% for males and females, respectively (Table 1). No data were available for total adipose tissue specifically for broiler chickens of market age. Coelomic fat weights from 863 chickens between 7 and 70 days old were collected from five studies (Boostani et al., 2010; Kalavathy et al., 2003; Leeson & Summers, 1980; Park & Kim, 2014; Sadeghi et al., 2012), and the average value was 2.14% of total body weight. Coelomic fat was found to represent 16% and 12% of the total fat for males and females, respectively. The mean adipose tissue values of male and female broiler chickens are comparable with those reported in Lin et al. (2020) where the relative weight of adipose tissue was 12.27% for cattle and 15.44% for swine. The acquired value is higher than that reported in Cortright et al. (2009) which was 5.23% from the experimental data and the optimized value of 5%. A linear regression analysis was performed to examine the relationship between the age of chickens in days (x-axis; independent variable) and the coelomic fat weight (%; y-axis; dependent variable). As shown in Tab "OWS_Broiler" of Appendix S2, the results showed that there was a significant association between the age and the coelomic fat weight with $R^2 = .90$. The regression equation is shown below:

TABLE 5 Relative organ weight (% body weight) for turkeys at market age (16–20 weeks)

Organ/Tissue	Mean	*SD*	Number		Range	Reference
			Animal Subjects	Studies		
Adipose Tissue	14.9		6	1		1
Bursa of Fabricius	0.06	0.008	6	1		2
Heart	0.36	0.02	28	2	0.32–0.41	3, 4
Liver	1.58	0.3	208	3		3, 5, 6
Muscle	41.1	2.46	108	5		1, 7–10
GI Tract						
Ingluvies (Crop)	0.42		72	1		5
Proventriculus	0.12	0.01	66	1	0.11–0.12	10
Ventriculus (Gizzard)	1.20		8	1		3
Small Intestine	2.05		8	1		3
Testes	0.11	0.07	16	2	0.06–0.15	2, 11

Note: Blank field indicates not applicable or data not available.

1. Plavnik and Hurwitz (1991), 2. Rozenboim et al. (1990), 3. Ferket and Sell (1989), 4. Hoffmann et al. (2016), 5. Crouch et al. (2002), 6. Rosebrough et al. (1981), 7. Barbour and Lilburn (1995), 8. Rozenboim et al. (1990), 9. Nestor et al. (1987), 10. Nestor et al. (2005), 11. Yahav et al. (2000).

TABLE 6 Relative total lipid weight (% body weight ± *SD*) for turkeys

Age (week)	Reference			
	Hurwitz et al. (1988)	Melnychuk et al. (1997)	Plavnik and Hurwitz (1991)	Renema et al. (1994)
14	8.27			
15	8.50			
16			14.9	
28				13.7 ± 1.98
33		23.8		
34				
40				14.0 ± 1.98
48				13.3 ± 2.20

Note: Blank field indicates lack of data from the reference.

TABLE 7 Relative coelomic fat weight (% body weight ± *SD*) for turkeys

Age (week)	Reference	
	Jankowski et al. (2017)	Renema et al. (1994)
16	2.05	
28		1.86 ± 0.54
40		1.73 ± 0.54
48		1.61 ± 0.56

Note: Blank field indicates lack of data from the reference.

$$y = 0.0007x - 0.0024.$$

Becker et al. (1981) provided regression data for male and female broiler chickens between coelomic fat and body weight. Their reported R^2 values of .24 and .28 indicate that birds with a very small body size may have limited coelomic fat and that diets, strains, or other experimental procedures may affect the weight of coelomic fat.

For turkeys, values for total lipid content were acquired from four studies (Hulet & Brody, 1986; Melnychuk et al., 1997; Plavnik & Hurwitz, 1991; Renema et al., 1994) yielding a value of 18.1% of total body weight (Table 4). This value is higher than the reported relative adipose tissue volumes of 7% for mice and rats, 15% for dogs, but is lower than 21.4% for humans (Brown et al., 1997). Coelomic fat values were also collected due to potential food safety concern and data availability, yielding a mean of 1.42% of total body weight based on three studies (Hulet & Brody, 1986; Jankowski & Nevarez, 2010; Renema et al., 1994) (Table 4). In addition, for the turkeys of market age, the relative adipose tissue weight was found to be 14.9% from Plavnik and Hurwitz (1991) (Table 5). Tables 6 and 7 summarize the acquired data of fractional values of adipose tissue for turkeys of different ages. Hulet and Brody (1986) reported the relative coelomic fat weight was 0.69% around age of 28 weeks in turkeys. However, the relative weight at week 34 in this study was reported to be 0.075% of total body weight, which was considered too low and raised concern about the accuracy regarding this specific value. Therefore, this study was not included in the presented tables.

3.1.2 | Adrenal Glands

The adrenal glands constitute 0.014% of body weight in broiler chickens based on 140 animals as reported by Deaton et al. (1969) (Table 1). For broiler chickens of market age, this value was similar to that reported for broiler chickens of all ages, at 0.01% of total body weight for 40 animals (Table 2). For layers, adrenal glands are of 0.0057% of total body weight (Table 3). Adrenal glands have not been considered in any of the currently available PBPK models for chickens. In turkeys, adrenal glands constitute 0.019% of body weight based on two studies (Davis & Siopes, 1985; Hobbs & Moreng, 1976) as shown in Table 4. Davis and Siopes (1985) conducted a study to determine the effect of light duration on turkey poult performance and adrenal function, in which the adrenal weight values were measured in 97 turkeys. The reported values ranged from 6.7 to 16.8 mg/100 g body weight for turkeys from one to eight weeks old under naturally occurring light duration. These values are comparable to those reported by Brown et al. (1997) where mice, rats, dogs, and humans are 0.01%–0.04%, 0.01%–0.031%, 0.004%–0.014%, and approximately 0.02%, respectively. The weight value of adrenal glands for layers is similar to the value for adult cattle (0.006%), calves (0.007%), and swine (0.005%) (Lin et al., 2020).

3.1.3 | Blood

The calculated mean relative blood volume for broiler chickens was 4.83% found in three studies with a total of 27 animals (Cortright et al., 2009; May et al., 1971; Rzasa et al., 1974) (Tables 1 and 2). For layers, mean relative weight for blood, 6.30% of total body weight, was based on Deaton et al. (1969) with 4 animal subjects (Table 3). These calculated values are comparable with the relative blood weights reported in Lin et al. (2020) for cattle (4.31%), calves (6.95%), and

TABLE 8 Relative pectoral (breast) muscle weight (% body weight ± *SD*) for turkeys

Age (week)	Reference										
	Applegate et al. (2008)	Barbour and Lilburn (1995)	Jankowski et al. (2017)	Kang et al. (1985)	Nestor et al. (1987)	Nestor et al. (2005)	Plavnik and Hurwitz (1990)	Plavnik and Hurwitz (1991)	Renema et al. (1994)	Velleman et al. (2010)	Yahav et al. (2000)
1				8.91							
2		11.6		14.2							
4		14.3		16.5						21.0	
6		15.4									
8				16.7	15.3		20.0			19.4	
9		17.2									
10		18.5									
12		19.6									
14		20.1									
16		19.9	22.4		19.0	22.0		20.0		24.3	
18								19.8			
19		24.2									
20	18.2 ± 0.45				20.3						21.1 ± 0.40
21		24.7									
26										28.2	
28									29.3 ± 2.26		
35										32.1	
40									25.0 ± 2.26		
45										34.1	
48									23.5 ± 2.45		
54										33.9	

Note: Blank field indicates lack of data from the reference.

TABLE 9 Relative pectoral (breast) and leg muscle weight (% body weight) for turkeys

	Reference						
Age (week)	Barbour and Lilburn (1995)	Jankowski et al. (2017)	Kang et al. (1985)	Nestor et al. (1987)	Nestor et al. (2005)	Plavnik and Hurwitz (1990)	Plavnik and Hurwitz (1991)
1			11.5				
2	29.1		17.2				
4	32.7		19.9				
6	35.1						
8			20.6	31.0		39.0	
9	39.4						
10	40.8						
12	42.5						
14	42.2						
16	41.7	41.1		38.0	43.1		39.0
19	45.1						
20				39.6			
21	46.1						39.6

Note: Blank field indicates lack of data from the reference.

TABLE 10 Gastrointestinal retention time (hour) for broiler chickens

		Number				
Parameter	Age	Animal Subjects	Studies	Mean ± *SD*	Range	Reference
T1	7–21 days	245	4	1.18 ± 0.39	0.75–1.63	1–4
T50	7–21 days	257	5	6.44 ± 1.58	4.96–8.89	1–5
MRT	7–72 days	423	6	9.25 ± 4.76	4.95–18.77	1, 2, 4, 6–8

Note: 1. Almirall and Esteve-Garcia (1994), 2. Lázaro et al. (2003), 3. Sieo et al. (2005), 4. Rochell et al. (2012), 5. Hetland and Svihus (2001), 6. Vergara et al. (1989), 7. Ferrando et al. (1987), 8. Dänicke et al. (1997).

swine (4.12%). Relative blood weight for turkeys was only reported in Cortright et al. (2009) at a value of 0.68%. This is considerably lower when compared to that for other domestic animals, perhaps due to the residual blood volume in the wet organs (Table 4). Additional studies are needed to confirm this parameter value in turkeys.

3.1.4 | Brain

The brain weight value was identified in two studies (DeSantis et al., 1975; Wolfenson et al., 1978) for layers and accounted for 0.089% of total body weight (Table 3). No brain weight value was identified for broiler chickens. In Brown et al. (1997), the brain was reported to constitute 1.7% of body weight in mice, 0.6% in rats, 0.8% in dogs, and 2.0% in humans. Mean relative brain weight in cattle, calves, and swine was reported to be 0.08%, 0.54%, and 0.22% of total body weight, respectively, in Lin et al. (2020). The relative brain weight value calculated for layers was lower than mice, rats, dogs, humans, calves, and swine, but was comparable to that of the cattle. For turkeys, the relative brain weight value was 0.21% from Cortright et al. (2009) and was comparable to that of swine.

3.1.5 | Bursa of Fabricius

For broiler chickens of all ages, the mean relative weight of the bursa of Fabricius was 0.19% of total body weight identified in nine studies with a total of 489 animals (Awad et al., 2009; Baarendse et al., 2006; Ghahri et al., 2013; Heckert et al., 2002; Lee et al., 2003; Park & Kim, 2014; Rath et al., 2006; Sadeghi et al., 2012; Toghyani et al., 2010) (Table 1). For broiler chickens of market age, the value, 0.15% of total body weight, was slightly lower (Table 2). No value for this parameter was identified in layers. For turkeys, 0.18% was calculated to be the mean relative weight for the bursa of Fabricius based on 14 studies with a total of 106 animals (Bayyari et al., 1997; Bayyari, Huff, Rath, et al., 1997; Danicke et al., 2007; Fasina et al., 2006; Gore & Qureshi, 1997; Huff, Huff, Balog, & Rath, 1998, 2000; Kubena et al., 1991; Li et al., 2000; McKenzie et al., 1998; Rozenboim et al., 1990; Shapiro et al., 1998) (Table 4). When narrowing the criteria of the age of turkeys down to 16–20 weeks old, the weight of the bursa of Fabricius drops to 0.06% of body weight based on Rozenboim et al. (1990) perhaps due to involution later in life. The bursa of Fabricius is found exclusively within the class Aves and has no known homologue in any other class of vertebrates (Glick, 1955). It develops

TABLE 11 Mean retention time (MRT, min, mean ± *SD*) for sections of the gastrointestinal tract for broiler chickens

Reference	Van der Klis et al. (1990)	Shires et al. (1987)	Moquet et al. (2018)	Enting et al. (2007)	Van der Klis et al. (1993)	Gutierrez del Alamo et al. (2009)	Weurding et al. (2001)	Palander et al. (2010)
Age/body weight	44 days	body weight adjusted to 792.8 g	22–23 days	22 weeks	35 days	30 days	27–28 days	21 days/42 days
Animal Subjects	*n* = 32	*n* = 59	*n* = 15	*n* = 5	*n* = 42	*n* = 48	*n* = 120	*n* = 5 /*n* = 4
Esophagus + Ingluvies		7.4						
Ingluvies	49.5 ± 12		72	148				
Proventriculus + Ventriculus	54 ± 29.7		24	218				
Proventriculus		4.2						
Ventriculus		50.2						
Small Intestine	186 ± 28.3		91		144			
Duodenum		7.2			4			
Proximal Duodenum	4.5 ± 3.5							
Distal Duodenum	5 ± 2.8							
Jejunum + Ileum						153.5 ± 30.3	161.3 ± 13.7	
Jejunum		59.5		542				
Proximal Jejunum	30 ± 9.9				16	11.8 ± 3.2	18 ± 3.4	
Distal Jejunum	54.5 ± 9.2				40	36.4 ± 7.4	42.9 ± 5.3	
Ileum	92 ± 2.8	86.4		408	79			41.6 ± 10.2/108.3 ± 37.1
Proximal Ileum						46.9 ± 11	46.7 ± 6.2	
Distal Ileum						58.4 ± 15.1	53.8 ± 8.4	
Ceca + Colon			4					
Ceca		78.7		180				
Colon				222				
Rectum	41 ± 21.2							
Colon + Cloaca		44.4						
Total	330.5 ± 91.2	338	191	1,718				

Note: Blank field indicates not applicable or data not available.

TABLE 12 Mean retention time (MRT, min) in ileum for turkeys[a]

Age	Number of animal subjects	Mean	*SD*	Range
21 days	7	38.0	4.3	34.8–42.9
42 days	4	40.9	6.9	35.1–48.5

[a]Palander et al. (2010).

in young birds and involutes completely in older birds (Forbes, 1877). It was found in Ring Dove and Common Pigeons that bursa involution is usually complete by the time of sexual maturity (Riddle, 1928). In Glick (1955), the bursa regresses between 4–7 weeks in White Leghorns and 8–13 weeks in Rhode Island Reds. Although it has not been included in any published poultry PBPK studies, the bursa of Fabricius is a primary lymphoid organ and should be considered when the pharmacokinetics of a drug involves organs of lymphocyte origin.

3.1.6 | Gallbladder

For broiler chickens, the relative weight values for gallbladder were identified in two studies with 68 animals (Khosravinia, 2016; Peebles et al., 1997). The mean value was 0.12% (Table 1). This value for broiler chickens at market weight was calculated to be 0.094% from the same studies with 8 animals (Table 2). No value for gallbladder was identified for layers or turkeys. Among the common laboratory, farm, and food production animals with gallbladders, no absolute or relative weight values were reported in compiled data for mammals (Brown et al., 1997). In an avian study by Williams (2005), a trend of increasing volume of gallbladder was observed associated with the age of healthy avian. We were unable to identify such a trend in the weight values due to the scarce data in relation to age or body weight. The compartment of gallbladder has not been included in any published poultry PBPK studies.

3.1.7 | Heart

For broiler chickens of all ages, broiler chickens of market weight, layers, turkeys of all ages, and turkeys of market weight, the heart represented 0.54%, 0.52%, 0.30%, 0.51%, and 0.36%, of the body weight, respectively (Tables 1–4). The fractional organ weight of the heart of approximately 0.50% of body weight in chickens and turkeys is comparable with that in other species, including mice (0.50%), rats (0.33%), dogs (0.78%), and humans (0.47%) (Brown et al., 1997), as well as 0.4% for cattle and 0.37% for swine (Lin et al., 2020). In Cortright et al. (2009), relative heart weight acquired from ten chickens with the mean body weight of 2.7 kg was 0.42% but was not included in the PBPK model as an individual compartment.

3.1.8 | Liver

The liver constitutes 2.14%, 2.04%, 2.49%, and 2.62% of the body weight in broiler chickens of all ages, broiler chickens of market age, layers, and turkeys of all ages, respectively (Tables 1–4). In Cortright et al. (2009), the experimentally measured value was 2.24% for liver parameter, whereas the optimized value in chickens was 2.4%. For turkeys, the mean value of fractional organ weight of liver at

TABLE 13 Cardiac output (L hr^{-1} kg^{-1} body weight) for chickens

Production Class	Mean	*SD*	Number		Range	References
			Animal Subjects	Studies		
All Chickens	9.88	2.07	320	17	7.26–13.08	1–17
All Broilers	10.2	2.22	193	13	8.1–12.86	2, 3, 7–17
Broilers of Market Age (42–49 days)	10.17	7.44	37	5	8.4–11.9	7, 11, 12, 14, 16
Layers	9.91	5.37	127	6	7.26–13.08	1, 4, 5, 6, 9, 10

Note: 1. Boelkins et al. (1973), 2. Chapman and Wideman (2002), 3. Merrill et al. (1981), 4. Moynihan and Edwards (1975), 5. Niezgoda et al. (1982), 6. Sapirstein and Hartman (1959), 7. Stebel and Wideman (2008), 8. Sturkie and Eiel (1966), 9. Sturkie (1967), 10. Vogel and Sturkie (1963), 11. Wideman, 1999), 12. Wideman and French (1999), 13. Wideman et al. (1999), 14. Wideman et al. (2000), 15. Wideman et al. (2001), 16. Wideman and Erf (2002), 17. Wideman et al. (2005).

TABLE 14 Cardiac output (L hr^{-1} kg^{-1} body weight) for turkeys

Production Class	Mean	*SD*	Number		Range	Reference
			Animal Subjects	Studies		
All turkeys	6.87	1.46	40	2	4.87–11.6	1, 2
Turkeys of market age (16–20 weeks)	7.22	1.42	30	2	4.87–11.6	1, 2

Note: 1. Boulianne et al. (1993), 2. Romvari et al. (2004).

TABLE 15 Regional blood flow (L hr^{-1} kg^{-1} BW) for chickens

Organ/Tissue	Mean	*SD*	Number		Range	Reference
			Animal Subjects	Studies		
Adrenal Glands	0.0142	0.0089	48	5	0.0039–0.0239	1–5
Cerebrum	0.0006		5	1		4
Cerebellum	0.0001	6.52942E−05	13	2	0.0001–0.0002	1, 4
GI Tract						
Proventriculus	0.11	0.04	39	4	0.06–0.17	2, 4–6
Ventriculus (Gizzard)	0.084	0.013	39	4	0.067–0.096	3–6
Duodenum	0.47	0.11	41	5	0.21–0.49	1–6
Jejunum	0.46		13	1		5
Ileum	0.21		13	1		5
Colon	0.012	0.001	16	2	0.012–0.013	1, 6
Heart	0.54	0.03	18	2	0.52–0.56	1, 3
Liver	2.50		12	1		7
Hepatic Artery	1.33	0.39	60	6	0.84–1.81	1–6
Portal Vein	1.56	0.75	18	2	0.85–1.92	7, 8
Muscle						
Pectoral Muscle	0.75	0.11	23	2	0.69–0.84	3, 5
Pancreas	0.066	0.031	49	5	0.03–0.11	1 ,2 ,4–6
Pulmonary (Lungs)	5.59	0.7	25	2	5.09–6.43	9, 10
Renal (Kidneys)	1.99	1.23	60	6	0.92–4.08	1–6
Skin	1.49	0.31	39	3	1.2–1.77	4–6
Spleen	0.40	0.24	46	5	0.08–0.75	1–4, 6
Testes	0.006		9	1		2

Note: Blank field indicates not applicable or data not available.

1. Boelkins et al. (1973), 2. Merrill et al. (1981), 3. Sapirstein and Hartman (1959), 4. Wolfenson et al. (1978), 5. Wolfenson et al. (1981), 6. Arad et al. (1993), 7. Purton (1975), 8. Sturkie and Abati (1975), 9. Chapman and Wideman (2002), 10. Wideman et al. (2001).

market age derived from three studies (Crouch et al., 2002; Ferket & Sell, 1989; Hoffmann et al., 2016) involving 208 animals was 1.58% (Table 5), lower than that of other production classes but falls between the acquired value (1.32%) and model-fitted value (2%) used in the PBPK study of Cortright et al. (2009). The calculated mean values in chickens and turkeys are lower but comparable to those reported in mammalian species: 5.49% in mice, 3.66% in rats, 3.29% in dogs, and 2.57% in humans (Brown et al., 1997). These values are slightly higher but considered similar to the values of cattle and swine which are 1.23% and 2.04%, respectively (Lin et al., 2020).

3.1.9 | Muscle

For broiler chickens, muscle weight was calculated to be 57.12% from two studies (Cortright et al., 2009; Hussein et al., 2019) (Table 1). The values for pectoral muscle were extracted from Hussein et al. (2019) and Park and Kim (2014) based on 70 animals with mean value of 23.46% of body weight (Table 1). Trivedi et al. (2015) provided values of net edible meat weight, yielding a fraction of 60% of gross weight in broiler chickens. Hussein et al. (2019) included some parts of bone when taking the measurement of the muscles. Therefore, the value in Table 1 for muscle is a slight overestimation. For turkeys, the reported value consists of breast muscles and leg muscles which are the main consumed product on the market. Breast muscles consist of *pectoralis major* and *minor*; leg muscles comprise the edible thigh and drumsticks, mainly representing *gastrocnemius* and *peroneus longus*. In this study, breast muscle weight was found to be similar to total leg muscle weight for turkeys. Muscles in sum yield 43.1% of total body weight (Table 4) for turkeys of all ages and 41.1% for turkeys of market age (Table 5). Age-related differences in the breast muscle of turkeys have been reported in eleven studies (Table 8) and seven reported the fraction of combined breast and leg muscles (Table 9). Assuming for chickens, breast muscle weight is similarly equivalent to leg muscle weight, the total edible meat weight for chickens would yield 46.92%. The above-mentioned values are then similar to the value acquired and fitted in Cortright et al. (2009) which were 40% and 43% for chickens and turkeys, respectively. They are also similar to the values reported in Brown et al. (1997) where fractional muscle weight was 40.4% in rats and

TABLE 16 Regional blood flow (% cardiac output) for chickens

Organ/Tissue	Mean	*SD*	Number		Range	Reference
			Animal subjects	Studies		
Adrenal Glands	0.14	0.09	48	5	0.04–0.24	1–5
Cerebrum	0.0058		5	1		4
Cerebellum	0.0013	0.0007	13	2	0.0008–0.0017	1, 4
GI Tract						
Proventriculus	1.11	0.43	39	4	0.65–1.69	2, 4–6
Ventriculus (Gizzard)	0.85	0.13	39	4	0.68–0.97	3–6
Duodenum	4.76	1.11	41	5	2.12–4.95	1–6
Jejunum	4.64		13	1		5
Ileum	2.09		13	1		5
Colon	0.12	0.01	16	2	0.12–0.13	1, 6
Heart	5.07	0.27	18	2	4.9–5.28	1, 3
Liver	25.26		12	1		7
Hepatic Artery	13.43	3.99	60	6	8.47–18.28	1–6
Portal Vein	14.03	7.64	18	2	8.63–19.43	7, 8
Muscle						
Pectoral Muscle	7.64	1.14	23	2	6.94–8.55	3, 5
Pancreas	0.67	0.31	49	5	0.29–1.12	1 ,2 ,4–6
Pulmonary (Lungs)	56.59	7.12	25	2	51.54–65.13	9, 10
Renal (Kidneys)	20.12	12.44	60	6	9.26–41.27	1–6
Skin	15.05	3.13	39	3	12.19–17.88	4–6
Spleen	4.03	2.44	46	5	0.84–7.59	1–4, 6
Testes	0.061		9	1		2

Note: Blank field indicates not applicable or data not available.

The sum of the values for regional blood flow for chickens is 91.6% excluding pulmonary blood flow since after the alveolar gas exchange, the oxygen-rich blood continues to nutritionally supply other organs and in PBPK modeling, the fractional blood flow to lungs is typically assumed to be 100%. The fractional blood flow to the rest of body is 8.4% which includes the head, neck, and bones. The regional blood flow to reproductive tract is summarized in Tables 19–21.

1. Boelkins et al. (1973), 2. Merrill et al. (1981), 3. Sapirstein and Hartman (1959), 4. Wolfenson et al. (1978), 5. Wolfenson et al. (1981), 6. Arad et al. (1993), 7. Purton (1975), 8. Sturkie and Abati (1975), 9. Chapman and Wideman (2002), 10. Wideman et al. (2001).

45.7% in dogs. Total muscle weight fraction to body weight values in broiler chickens and turkeys are higher than those of cattle and swine which were reported as 36.1% and 36.32%, respectively (Lin et al., 2020). No muscle weight data for layers were identified in the available literature.

TABLE 17 Blood flow in different muscles regions for layers

Region	mL min^{-1} g^{-1} tissue[a]	
	Mean	*SD*
Pectoralis major	0.049	0.029
External abdominal oblique	0.214	0.039
Gastrocnemius	0.107	0.010

[a]Wolfenson et al. (1981); Crossbred of white leghorn × rhode island red hens.

3.1.10 | Pancreas

From over 2,100 animal subjects, the average values of relative weight of the pancreas for broiler chickens and turkeys of all ages were calculated to constitute 0.29% and 0.30% of the body weight, respectively (Tables 1 and 4). It was 0.25% for broiler chickens of market weight based on four studies and 369 animal subjects (Adeyemi et al., 2008; Çabuk et al., 2006; Ghahri et al., 2013; Khosravinia, 2016) (Table 2). There were no data identified for turkeys of market age. The relative pancreas weight in layers was calculated to be 0.15% (Table 3). These values are comparable with those reported by Brown et al. (1997) with 0.32% for rats, 0.23% for dogs, and 0.14% for humans. Comparing to the cattle (0.09%) and swine (0.15%) (Lin et al., 2020), the values for broiler chickens and turkeys are higher. As of now, the pancreas had not been included in any of the available PBPK models for avian.

3.1.11 | Pulmonary parenchyma (Lungs)

The pulmonary parenchyma compartment is commonly referred as the lung compartment in existing poultry PBPK models (Lautz et al., 2020; Yang et al., 2014, 2015). Based on the data from eleven studies involving over 1,200 animal subjects (Adeyemi et al., 2008; Bowes & Julian, 1988; Buys, 1999; Cortright et al., 2009; Hobbs & Moreng, 1976; Marsden, 1940; Nestor et al., 2005; Tickle et al., 2014; Wideman, 1999; Wideman et al., 1996; Wolfenson et al., 1978), the mean relative weight of pulmonary parenchyma for broiler chickens of all ages, broiler chickens of market age, layers, and turkeys of all ages are approximately 0.71%, 0.61%, 0.66%, and 0.83% of the body weight, respectively (Tables 1-4). These values are comparatively higher than the weight used in the PBPK studies for chickens (Yang et al., 2014, 2015), which was 0.54% of body weight experimentally derived from 10 chickens in Cortright et al. (2009). Our calculated values are comparable with those reported in Brown et al. (1997) which were 0.73% in mice, 0.50% in rats, 0.82% in dogs, and 0.76% in humans. Comparing to the values of relative weight of lungs in cattle and swine (Lin et al., 2020), 0.77% and 0.9%, respectively, the calculated values for birds are within the range considering body composition.

3.1.12 | Renal parenchyma (Kidneys)

Renal tissue constitutes about 0.64% in broiler chickens, 0.57% in market-age broiler chickens, 0.76% in layers, and 0.95% of the body weight in turkeys of all ages (Tables 1–4). This value was not identified for turkeys of market age. For broiler chickens, the value falls between the experimental data which was 0.58% and the fitted value of 0.64% in the PBPK study of Cortright et al. (2009). For turkeys, our value is slightly lower than that in Cortright et al. (2009) which was 0.8%. The relation of renal tissue to the trend of these values is opposite when comparing that of mammals in regard of body sizes: 1.67% in mice, 0.73% in rats, 0.55% in dogs, 0.44% in humans (Brown et al., 1997), 0.37% in swine, and 0.21% in cattle (Lin et al., 2020). The avian kidney, unlike the unipapillate kidneys of mammals, is not divided into distinct cortical and medullary regions. Rather, the cortical region of the avian kidney is composed of many cortical units coalescing to form the medullary regions (Whittow, 1999). In addition, the composition of total nephron population in avian varies from species to species, generally being 85% reptilian-type and 15% mammalian-type nephrons (Braun & Dantzler, 1972; Whittow, 1999).

3.1.13 | Salt gland

No relative weight value of salt gland was identified in the literature. Salt gland has been identified in avian living in habitats where fresh water is limited or the intake of high concentrations of electrolytes is part of the normal diet. Here, salt gland severs an alternate route for ion regulation with parallelly arranged epithelial tubules and blood vessels (Gerstberger & Gray, 1993; Whittow, 1999). The counter-direction of fluid flow facilitates the secretion of concentrated sodium chloride. Therefore, when considering the salt metabolism of the avian in a PBPK model, the presence or absence of a salt gland can impact osmoregulation but more experimental data on absolute weight of salt gland are needed.

TABLE 18 Blood flow in different skin regions for layers

	mL min^{-1} g^{-1} tissue[a]	
Region	**Mean**	***SD***
Metatarsal	0.095	0.050
Back	0.067	0.039
Pectoral (Breast)	0.050	0.017

[a]Wolfenson et al. (1981); Crossbred of White Leghorn × Rhode Island Red hens.

3.1.14 | Skin/Feathers

The relative weight of skin/feather values was only identified in Cortright et al. (2009) as 13.38% and 11.73% for broiler chickens and turkeys, respectively (Tables 1 and 4). The values for broiler chickens of all ages also account for that of broiler chickens of market age since the data were collected at 42 days of age (Table 2). No skin/feather data were identified for layers. Although there was no individual value for skin or feathers, this parameter accounts for a good portion of the total body weight, ranking only after muscle mass and adipose tissue.

3.1.15 | Spleen

The weight of the spleen represents 0.11%, 0.12%, 0.15%, and 0.073% of total body weight in broiler chickens of all ages, broiler chickens of market age, layers, and turkeys of all ages, respectively (Tables 1–4). No data for weight of the spleen were found for turkeys of market age. These values are low compared to the values reported in Brown et al. (1997), which were 0.35%, 0.20%, 0.27%, and 0.26% for mice, rats, dogs, and humans, respectively. Comparing to those of domestic animals, cattle (0.18%) and swine (0.20%) (Lin et al., 2020), the calculated values for avian are relatively low as well. The compartment of spleen has not been incorporated in any of the currently available avian PBPK models.

3.1.16 | Thymus

The value for thymus weight was reported in Awad et al. (2009) for ten 35-day-old broiler chickens (Table 1), representing 0.50% of total body weight. This value is higher than the values reported by Brown et al. (1997) where thymus weighted 0.12% and 0.22% of total body weight in male and female mice, and 0.09 and 0.13% of total body

weight in male and female rats, respectively. In Lin et al. (2020), thymus occupies 0.03% of total body weight in cattle and 0.28% in swine. The relative weight in broiler chickens identified is higher than the values presented in Brown et al. (1997) and Lin et al. (2020). Additional data are needed to increase our confidence for the relative weight of thymus in broiler chickens. No value for layers was found. For turkeys, mean relative thymus weight was identified to be 0.26% of total body weight in three studies with 56 animals (Chang et al., 1981; Fasina et al., 2006; Li et al., 2000). The range was 0.14%–0.30% which is comparable to those reported in Brown et al. (1997) and Lin et al. (2020).

3.1.17 | Gastrointestinal tract (GIT)

According to a search of "poultry, all use classes" in the Veterinarian's Guide to Residue Avoidance Management (VetGRAM) (Riviere et al., 2017), the most common route of administration for US Food and Drug Administration approved drugs is oral administration (PO) as water or feed additives. The main site of absorption for these drugs is the small intestine, which emphasizes the importance of this section of the GIT. Different sections of the GIT have not been comprehensively incorporated into any of published poultry PBPK models. In the current study, different sections of GIT are examined and presented with calculated mean values.

3.1.18 | Pre-intestinal section of the gastrointestinal tract (Stomachs)

This section includes the crop (ingluvies), proventriculus, and gizzard (ventriculus). All the reference literature used the common names (crop, proventriculus, and gizzard) as the parameter in individual studies. In Henri et al. (2017), the crop was considered important in avian pharmacokinetics for PO drug administration since the time to reach the absorption site small intestine is longer (i.e., rate-limiting) than the time to cross the intestinal barrier. For broiler chickens of all ages (Table 1), the weight of the pre-intestinal GIT accounts for 3.5% of total body weight based on Leeson and Summers (1980). The weight value for the crop is 0.50% identified in Adeyemi et al. (2008). Proventriculus was reported as 0.36% based on the data from five studies of 479 animals (Adeyemi et al., 2008; Awad et al., 2009; Çabuk et al., 2006; Ghahri et al., 2013; Sadeghi et al., 2012). In addition, the values for the gizzard were identified in eleven studies with 6,646 animals yielding 1.25% of the total body weight. The value calculated in the current study is comparable to the experimental value reported by Cortright et al. (2009) with the relative weight of gizzard as 1.31%. For broiler chickens of market age (Table 2), the pre-intestinal GIT weight is 2.18% based on Leeson and Summers (1980). Calculated from six studies (Adeyemi et al., 2008; Çabuk et al., 2006; Cortright et al., 2009; Dyubele et al., 2010; Gaya et al., 2006; Ghahri et al., 2013), the relative organ weights for crop, proventriculus, and gizzard are 0.50%, 0.29%, and 1.17%, respectively, in broiler chickens of market age (Table 2). For layers, the overall weight of this section was not found but the values for crop, proventriculus, and gizzard are 0.055%, 0.19%, and 0.70%, respectively (Table 3). They are lower than those for broiler chickens, but reasonable due to the hypertrophy of reproductive structures in the layers. For turkeys of all ages (Table 4), crop, proventriculus, and gizzard account for 0.34%, 0.43%, and 2.15% of total body weight; for turkeys of market age (Table 5), the values of these three compartments are 0.42%, 0.12%, and 1.20%, respectively. The discrepancy between values may derive from the intrinsic design of the individual experiments: whether the animal subjects were fasted before culling, or they were culled without prior fasting and whether the organ weights were measured with or without ingesta.

3.1.19 | Intestine

For broiler chickens of all ages, relative intestine weight was calculated to be 3.50% from five studies of 6,339 animal subjects (Bowes & Julian, 1988; Dyubele et al., 2010; Gaya et al., 2006; Lee et al., 2003; Tickle et al., 2014). Among these animals, 6,256 were identified as broiler chickens within market-age range, yielding the mean of 3.43% (Bowes & Julian, 1988; Dyubele et al., 2010; Gaya et al., 2006; Tickle et al., 2014) (Tables 1 and 2). For layers or turkeys, total intestine was not found. Note that the organ weight values for intestine provided in this study were considered only when the individual experimental study indicated the measured organ as "intestine" or "total intestine" but not a summation of the weight values of small intestine and large intestine.

3.1.20 | Small intestine

For the small intestine, including duodenum, jejunum, and ileum, the fractional total organ values are 3.13%, 2.69%, 4.85%, and 2.05% for broiler chickens of all ages, broiler chickens of market age, turkeys of all ages, and turkeys of market age, respectively (Tables 1, 2, 4, and 5). The total small intestine parameter was not identified for layers. The values for broiler chickens and turkeys are comparable with those reported in Brown et al. (1997) with 2.53% for mice, 1.40% for rats, 2.22% for dogs, and 0.91% for humans and those in Lin et al. (2020) with 1.06% for cattle and 2.19% for swine. Data between the segments of small intestine are within reasonable range considering body composition and the active/inactive reproductive organs: Duodenum, jejunum, and ileum are 1.20%, 1.92%, and 1.37% from three studies (Khosravinia, 2016; Lee et al., 2003; Sadeghi et al., 2012) for broiler chickens of all ages (Table 1), 0.27%, 0.42%, and 0.26% for layers from Wolfenson et al. (1981) (Table 3), and 1.68%, 2.55%, and 2.13% for turkeys of all ages (Table 4). No segmental small intestine data were found for broiler chickens or turkeys of market age.

TABLE 19 Regional blood flow (L hr^{-1} kg^{-1} BW) for sections of the reproductive tract for layers

Section	Mean	*SD*	Number		Range	Reference
			Animal subjects	Studies		
Ovary	1.63	0.47	30	1	0.86–2.09	1
Infundibulum	0.031	0.007	64	5	0.017–0.035	2–6
Magnum	0.51	0.08	67	6	0.36–0.56	2–7
Isthmus	0.12	0.04	59	5	0.05–0.15	2–6
Uterus	0.17	0.14	8	1	0.09–0.29	4
Shell Gland[a]	0.55	0.21	63	5	0.31–0.86	2, 3, 5–7
Vagina	0.04	0.008	34	2	0.03–0.04	3, 6

Note: Blank field indicates not applicable or data not available.

1. Niezgoda et al. (1982), 2. Hrabia et al. (2005), 3. Moynihan and Edwards (1975), 4. Scanes et al. (1982), 5. Wolfenson et al. (1981), 6. Wolfenson et al. (1978), 7. Arad et al. (1993).

[a]Shell gland is technically the same as uterus. However, the term shell gland is more commonly used in studies where laying hens are in reproductive stages, whereas the term uterus is used in studies where the animals are in nonreproductive phases. As a result, the blood flow fraction to the shell gland is higher than that to the uterus.

TABLE 20 Regional blood flow (% cardiac output) for sections of the reproductive tract for layers

Section	Mean	*SD*	Number		Range	Reference
			Animal Subjects	Studies		
Ovary	16.46	4.74	30	1	8.63–21.14	1
Infundibulum	0.32	0.07	64	5	0.28–0.35	2–6
Magnum	5.12	0.82	67	6	3.6–5.65	2–7
Isthmus	1.18	0.37	59	5	0.53–1.53	2–6
Uterus	1.67	1.36	8	1	0.95–2.88	4
Shell Gland[a]	5.1	2.1	63	5	3.1–8.69	2, 3, 5–7
Vagina	0.42	0.084	34	2	0.33–0.45	3, 6

Note: Blank field indicates not applicable or data not available.

1. Niezgoda et al. (1982), 2. Hrabia et al. (2005), 3. Moynihan and Edwards (1975), 4. Scanes et al. (1982), 5. Wolfenson et al. (1981), 6. Wolfenson et al. (1978), 7. Arad et al. (1993).

[a]Shell gland is technically the same as uterus. However, the term shell gland is more commonly used in studies where laying hens are in reproductive stages, whereas the term uterus is used in studies where the animals are in nonreproductive phases. As a result, the blood flow fraction to the shell gland is higher than that to the uterus.

TABLE 21 Blood flow (% cardiac output) in reproductive tract regions of layers during different stages of oviposition

Position of developing egg	Blood flow (% of cardiac output)[a]					
	Ovary	Infundibulum	Magnum	Isthmus	Uterus/Shell Gland[b]	Vagina
No Egg	8.6	0.30	3.23	0.49	3.38	0.25
Magnum	16.8	0.20	5.21	0.39	2.90	0.31
Isthmus	16.7	0.19	3.83	0.98	3.01	0.26
Uterus/Shell Gland[b]	19.0	0.50	3.18	0.62	7.72	0.33
Oviposition	21.1	0.48	2.78	0.56	3.27	0.48

[a]Niezgoda et al. (1982).

[b]The term "uterus" was used as the parameter in the original study although the hens were reproductively active.

TABLE 22 Hematocrit (%) for chickens

Production class	Mean	*SD*	Number		Range	Reference
			Animal Subjects	Studies		
All chickens	32	2.76	568	20	23.7–46.7	1–20
Broilers of all ages	31	2.57	433	11	23.7–38.2	3, 5, 7–10, 13, 15–17, 20
Broilers of market age (42–49 days)	30.7	2.45	198	6	25–34.6	3, 5, 13, 15–17
Layers	31.4	5.1	39	5	27–37	1, 2, 6, 14, 19

Note: 1. Bailey and Nishimura (1984), 2. Bond and Gilbert (1958), 3. Buys (1999), 4. Cloud et al. (1992), 5. Jankowski and Nevarez (2010), 6. Koike et al. (1983), 7. May et al. (1971), 8. Rath et al. (2006), 9. Rodnan et al. (1957), 10. Sadeghi et al. (2012), 11. Sturkie and Eiel (1966), 12. Sturkie (1967), 13. Toghyani et al. (2010), 14. Whittow et al. (1964), 15. Wideman Jr (1999), 16. Wideman et al. (1999), 17. Wideman et al. (2000), 18. Wideman et al. (1993), 19. Wyse and Nickerson (1971), 20. Yersin et al. (1992).

TABLE 23 Hematocrit (%) for turkeys

Mean	*SD*	Number		Range	Reference
		Animal Subjects	Studies		
35.5	2.26	100	8	30.3–39.3	1–8

Note: 1. Allen et al. (1981), 2. Bayyari, Huff, Rath, et al. (1997), 3. Huff et al. (1996), 4. Huff et al. (2010), 5. Kubena et al. (1995a), 6. Kubena et al. (1997), 7. Ledoux et al. (1996), 8. Weibking et al. (1993).

TABLE 24 Relative organ weight values (% total body weight) comparison with data from Lautz et al. (2020)

Organ/Tissue	Current study				Lautz et al. (2020)	
	Broilers		Layers		Mixed chicken population	
	BW (%)	*SD*	BW (%)	*SD*	BW (%)	*SD*
Adipose tissue	13.4 (male)				10.7	2.57
	15.1 (female)					
Blood	4.83	0.98	2.36	3.4	7.1	1.28
Brain			0.071	0.0038	0.3	0.12
Heart	0.54	0.12	0.3	0.066	0.6	0.12
Kidney	0.64	0.10	0.76	0.011	0.8	0.26
Liver	2.14	0.47	2.49	0.19	2.4	0.41
Lung	0.71	0.10	0.66	0.20	0.8	0.22
Muscle	65.61	1.47			40.8	5.30
Intestines	3.50	0.82	0.992[a]	0.12	3.9	2.22
Reproductive Tissues			4.49[b]	0.42	2.8	0.11

Note: Blank field indicates not applicable or data not available.

BW (%): Values for organs or tissues normalized as percentages of total body weight.

[a]Sum of the values of different intestinal segments from Table 3.

[b]Sum of the different sections in female reproductive tract from Table 3.

3.1.21 | Large intestine

The value reported as "large intestine" was found as 1.42% of body weight in broiler chickens in only one study (Lee et al., 2003) (Table 1). In five studies (Adeyemi et al., 2008; Awad et al., 2009; Ghahri et al., 2013; Józefiak et al., 2006; Sadeghi et al., 2012), values for ceca were identified and the average value was calculated to be 0.50% from 183 animals; and colon was identified and calculated as 0.18% in one study with ten broiler chickens (Awad et al., 2009) (Table 1). No data for this parameter were identified for broiler chickens of market age. In Table 3, relative weight values are listed: 0.045% for ceca and 0.019% for colon and rectum in layers. The values calculated for layers were lower than the ones for broiler chickens. No data for large intestine, ceca, colon, or rectum were found for turkeys. Although no weight value for cloaca was able to be identified, the lower GIT of avian, including digestive ceca, colon, and cloaca, serves an important role in the regulation of the composition of the extracellular excreta and osmoregulation in addition to the kidneys (Whittow, 1999). A retrograde peristalsis generated by the cloaca recovers proteins, water, and salts from the urine as the osmolality of the ureteral urine being sensed by a vanilloid type receptor in the cloaca (Braun, 1999; Souza et al., 2011; Whittow, 1999). None of the published chicken PBPK models incorporated urine reflux mechanism. These available PBPK models commonly adopted the approach used to simulate urine excretion in mammals to describe the process in chickens, assuming they are similar. However, this is worth consideration in PBPK models for poultry when urinary excretion is included in the pharmacokinetics.

TABLE 25 Regional blood flow values (% cardiac output) comparison with data from Lautz et al. (2020)

	Current study		Lautz et al. (2020)	
Organ/Tissue	**CO (%)**	***SD***	**CO (%)**	***SD***
Adipose Tissue			1.5	0.45
Brain			0.4	0.08
Cerebrum	0.0058			
Cerebellum	0.0013	0.0007		
Carcass			12.4	3.72
Heart	5.07	0.27	5.5	1.82
GI Tract[a]	13.57	0.97	17.1	6.67
Kidneys	20.12	12.44	11.4	3.31
Liver	13.43[b]	3.99	6.6	2.84
Lungs	56.59	7.12	3	0.9
Muscles	7.64	1.14	19.8	5.94
Reproductive tissue	12.14[c]	2.290	14.3	3.72

Note: Blank field indicates not applicable or data not available.

CO (%): blood flow normalized as percentage of cardiac output.

[a]GI Tract: Values in the present study include blood flow to proventriculus, ventriculus, and intestines; values from Lautz et al. (2020) include only intestines.

[b]Liver: Value here represents blood flow in the hepatic artery.

[c]Reproductive tissue value is the sum of infundibulum, magnum, isthmus, shell gland (uterus in reproductive stage), and vagina. Please refer to Tables 20 and 21 for blood flow fractions of different segments of reproductive tissue at different oviposition stages.

3.1.22 | Female reproductive organs

PBPK models may include reproductive organs as individual compartments when egg production is accounted for; therefore, values of related organs from broiler chickens, layers, and turkeys were adopted from the literature and included in this study. For female broiler chickens, even though it is not significant due to sexual immaturity, the weight of the ovary was identified as 0.043% body weight (Bayyari, Huff, Balog, et al., 1997; Hobbs & Moreng, 1976; Melnychuk et al., 1997; Renema et al., 1995) (Table 1). For the layers, weight values of the ovary were acquired after removal of ovulated follicles (Renema et al., 1995). The ovarian relative weight values were identified in two studies with 24 animals (Bond & Gilbert, 1958; DeSantis et al., 1975), with calculated average value being 1.91% (Table 3). Anatomically, the shell gland is the same as the uterus. However, "shell gland" is more commonly used in studies with the layers being in reproductive stages, whereas "uterus" is used in studies with the layers either in or out of the reproductive stages. Values for different segments of the oviduct, namely infundibulum, magnum, isthmus, and uterus (shell gland), were identified in three studies among 49 animal subjects (DeSantis et al., 1975; Wolfenson et al., 1978, 1981) representing 0.13%, 1.24%, 0.29%, and 0.72% of total body weight, respectively (Table 3). The value for vagina of 0.20% of total body weight in layers was identified in DeSantis et al. (1975). For turkeys, the average value of 0.27% of body weight for ovary was calculated from four studies with 596 animal subjects (Hobbs & Moreng, 1976; Melnychuk et al., 1997; Rauber et al., 2007; Renema et al., 1995) (Table 4). Although the values for the other segments of the oviduct were not identified in the literature, the total oviduct weight was calculated to account for 1.03% of the total body weight. One point worth noted is that the parameter stroma was identified in two studies focused on reproductive traits in turkey hens (Melnychuk et al., 1997; Renema et al., 1995). Stroma was defined as "total ovary minus large yellow follicles with a diameter greater than 10 mm" in Melnychuk et al. (1997) and "ovary without large follicles" in Renema et al. (1995). The total number of animal subjects in these two studies was 112, yielding the mean of 0.18% of total body weight with *SD* of 0.046% (Table 4). Comparing to the data reported in Lin et al. (2020), the value of uterus/shell gland from this study is lower than that of female swine (3.28%). As for relative weight of ovary, it is higher in the layers than in the female swine, where the bilateral ovaries accounted for 0.011% of total body weight.

3.1.23 | Male reproductive organs

The testes account for 0.05% body weight for all broiler chickens which is reasonably low due to sexual immaturity (Table 1). This phenomenon can also be observed in the lower value as that for broiler

chickens of market age being 0.03%, considering the growth in other tissues (Table 2). However, the comparison of turkeys of all ages with those of market age shows otherwise. The testes in turkeys of all ages account for 0.025% of body weight (Table 4), whereas turkeys of market age are 0.11% of body weight (Table 5) since the turkeys reach sexual maturity at about 10 months of age (Cecil & Bakst, 1991).

3.1.24 | Mass balance

The values for the relative weight of the rest of the body are included in the tables to maintain mass balance and to constrain the sum of total relative organ weight fractions to 100%. The values for rest of body in Table 1 were 12.37% for male and female broiler chickens. This value included head, neck, part of bones, eyes, metatarsi, phalanges, digits, gut contents, cloaca, and part of the reproductive tract which are considered immature at the market age of broiler chickens. In Table 2, the rest of body accounts for 28.39% of total body weight for broiler chickens of market age. With the inclusion of testes, this value accounts for that of male market-age broiler chickens and includes head, neck, bone, eyes, metatarsi, phalanges, digits, gut contents, and cloaca. One can calculate this for female market-age broiler chickens which the rest of body weight is 28.42% of the total body weight and the whole reproductive tract will be accounted for in addition to the above-mentioned organs and tissues. In Table 3, the relative weight for the rest of body was 82.60% for layers. The high value mainly attributes to the inclusion of all the muscles, along with adipose tissue, head, neck, feathers, skin, bones, eyes, metatarsus, phalanges, digits, and gut contents. This presents an uncertainty of this compartment, raising a need to measure the weights of additional individual organs in layers. For turkeys, the values for the rest of body, considering available reproductive organs, were 12.6% and 11.2% for males and females, respectively, as shown in Table 4. The age-related adipose tissue and muscle values are described in Tables 6 and 7 for adipose tissue weights and in Tables 8 and 9 for muscle weights. In addition, due to the scarcity of data, the rest of body weight was not calculated for the turkeys of market age.

3.2 | Gastrointestinal retention time

The mean, *SD*, and range of the commonly used parameters of GI retention time for broiler chickens are presented in Table 10. To determine the retention time, capsules containing markers of either chromium, titanium, or ruthenium compounds were administered PO to calculate the values of T1, the time at which 1% of the marker intake was excreted, T50, the time necessary to excrete 50% of the marker administered, and mean retention time (MRT). The MRTs were calculated from the equation proposed by (Coombe & Kay, 1965):

$$\mathrm{MRT} = \frac{\sum x_i \times t_i}{\sum x_i}$$

where x_i is the amount of marker excreted at the *i*th collection at time t_i after administration.

The values for T1 (hr) were calculated from 245 chickens ranging from 7 to 21 days old from four studies with a mean and *SD* of 1.18 ± 0.39 (Almirall & Esteve-Garcia, 1994; Lázaro et al., 2003; Rochell et al., 2012; Sieo et al., 2005). T50 (hr) was calculated from 257 animals from five studies (Almirall & Esteve-Garcia, 1994; Hetland & Svihus, 2001; Lázaro et al., 2003; Rochell et al., 2012; Sieo et al., 2005). The mean and *SD* were 6.44 ± 1.58. The mean for MRT (hr) was 9.25 with a *SD* of 4.76 from 423 animals of six studies (Almirall & Esteve-Garcia, 1994; Dänicke et al., 1997; Ferrando et al., 1987; Lázaro et al., 2003; Rochell et al., 2012; Vergara et al., 1989). This value ranged from 4.95 (Vergara et al., 1989) to 18.77 (Lázaro et al., 2003), even though animals of close ages and similar measuring approaches were used.

Table 11 lists the available data from eight studies for the MRT in different sections of the GIT for broiler chickens. A number of factors are considered to affect the values of GI retention time: the age of the avian (Almirall & Esteve-Garcia, 1994), feed intake level (Dänicke et al., 1997; Siegerstetter et al., 2018), diet composition, exposure to moisture, endogenous and supplemental enzymes (Classen et al., 2016; Svihus, 2014), light/dark exposure (Shynkaruk et al., 2019), and the anatomical site of digesta retention (Dänicke et al., 1997). Therefore, a direct comparison of the measurements of gastrointestinal retention time or food passage rate among different studies is difficult. Although similar research methods had been applied, the values for retention time in ileum observed in Palander et al. (2010) both for 21-day-old boilers (41.6 min) and turkeys (38.0 min) and for 42-day-old turkeys (40.9 min) were shorter than those reported by Danicke et al. (1999) for 24-day-old broiler chickens (129–140 min) or Weurding et al. (2001) for 28-day-old broiler chickens (100.5 min). Dänicke et al. (1997) suggested that a decrease in food intake level reduces food passage rate and therefore an increased retention time. In Hetland and Svihus (2001), the inclusion of coarsely ground oat hulls gave significantly more rapid feed passage than a diet containing finely ground oat hulls. This finding is in accordance with the general theory that insoluble fiber shortens retention times in monogastrics. In terms of anatomical site of potential digesta retention, Dänicke et al. (1997) and Shannon and McNab (1972) pointed out that the retention of marker in the ceca may be responsible for incomplete marker recovery, because cecal emptying may only occur once every 24 to 48 hr, suggesting a shift in the dynamics of excretion.

For turkeys, limited data were acquired for GI retention time. Table 12 presents MRT in ileum for turkeys based on Palander et al. (2010). In comparison, the values of retention time increased from 3 to 6 weeks of age considerably more in broiler chickens than in turkeys. It is safe to assume that broiler chickens are nearer to their physiological maturity at six weeks of age than turkeys.

If the drug is administered PO in food-producing animals, intestinal retention time can be decreased due to experimental inoculation or pathological events (Shane et al., 1985). Overall, the digesta retention time in the GIT can affect the animal's performance, nutrient

digestibility, and drug metabolism for orally administered drugs. Therefore, when taking gastrointestinal retention time into account in PBPK modeling, it is suggested to consider the factors that contribute to the variability of this parameter.

3.3 | Cardiac output

The mean value of cardiac output for chickens is 9.88 L hr^{-1} kg^{-1} body weight with 10.2 L hr^{-1} kg^{-1} body weight for broiler chickens of all ages, 10.17 L hr^{-1} kg^{-1} body weight for broiler chickens of market age, and 9.91 L hr^{-1} kg^{-1} body weight for layers (Table 13). The values we calculated from the experimental data are slightly lower than that adopted in Cortright et al. (2009), which was 11.2 L hr^{-1} kg^{-1} body weight from model fitting and in Yang et al. (2014) and Yang et al. (2015), where cardiac output was assumed to be 15 L hr^{-1} kg^{-1} body weight. Based on two studies including 40 animals (Boulianne et al., 1993; Romvari et al., 2004), the mean value of cardiac output for turkeys of all ages and of market age was calculated to be 6.87 L hr^{-1} kg^{-1} and 7.22 L hr^{-1} kg^{-1} body weight, respectively (Table 14). In MacLachlan (2010), cardiac output for turkeys was adopted from other literature and was reported as the range of 4.86–6.88 L hr^{-1} kg^{-1}. The cardiac output values in chickens and turkeys are similar to those in adult cattle, calves, and market-age swine, which are 5.45, 9.09, and 8.70 L hr^{-1} kg^{-1}, respectively (Lin et al., 2020).

3.4 | Regional blood flow

The majority of the literature which reported convertible regional blood flow values used layers of the same breed (e.g., male White Leghorn) as animal subjects with two exceptions (Chapman & Wideman, 2002; Wideman et al., 2001), where broiler chickens were the animal subjects. Due to insufficient data in our search, no data are provided for regional blood flow in turkeys; therefore, all results described below refer to chickens only. Overall, Table 15 provides absolute regional blood flow values in the unit of L hr^{-1} kg^{-1} BW, and Table 16 provides relative values as % cardiac output. In general, radioactive microsphere method is the main approach to measure regional blood flow following the underlying principle that the microspheres do not recirculate in the vascular system. However, Wolfenson et al. (1981) mentioned that microspheres of 15 μm diameter may recirculate if they pass through arteriovenous anastomoses larger than 15 μm in diameter. The bypassing microspheres can later be trapped in the capillary bed in the lungs, kidneys, or liver leading to no measurable residual radioactivity in other tissues (Boelkins et al., 1973; Odlind, 1978). Therefore, the results presented here are estimates of regional blood flow in different organs, but the results in liver, kidney, and lungs may also partly be derived from microspheres passing through arteriovenous anastomoses in the lower body (Wolfenson et al., 1981).

3.4.1 | Adrenal glands

Values for regional blood flow to adrenal glands were identified in five studies (Boelkins et al., 1973; Merrill et al., 1981; Sapirstein & Hartman, 1959; Wolfenson et al., 1978, 1981). Mean value was calculated to be 0.0142 L hr^{-1} kg^{-1} BW (Table 15) which took up 0.14% of cardiac output (Table 16). It is comparable to the values in rats (0.3%), dogs (0.2%), and humans (0.3%) reported by Brown et al. (1997).

3.4.2 | Brain

The blood flow to cerebrum was 0.0006 L hr^{-1} kg^{-1} BW from five animals based on one study (Wolfenson et al., 1978), and was 0.0001 L hr^{-1} kg^{-1} BW to cerebellum from thirteen animals in two studies (Boelkins et al., 1973; Wolfenson et al., 1978) (Table 15), which represented 0.0058% and 0.0013% of cardiac output, respectively (Table 16). These values are lower than the data reported in Brown et al. with the regional blood flow to the brain being 12% of cardiac output in both male and female humans as well as that in swine reported in Lin et al. (2020) as 1.5% cardiac output.

3.4.3 | Gastrointestinal Tract

Regional blood flow values were identified in six studies with a total of 41 animals (Arad et al., 1993; Boelkins et al., 1973; Merrill et al., 1981; Sapirstein & Hartman, 1959; Wolfenson et al., 1978, 1981), including the proventriculus, gizzard, and all parts of small intestine and colon (Tables 15 and 16). Values for the crop, ceca, or cloaca were not found. All of the six studies used layers for the experiments. The calculated mean for proventriculus was 0.11 L hr^{-1} kg^{-1} BW, yielding 1.11% of cardiac output. The calculated mean for gizzard was 0.084 L hr^{-1} kg^{-1} BW, yielding 0.85% of cardiac output. Mean regional blood flow values for the sections of the small intestines, duodenum, jejunum, and ileum, were 0.47, 0.46, and 0.21 L hr^{-1} kg^{-1} BW which were 4.76%, 4.64%, and 2.09% of cardiac output, respectively. Blood flow to colon was found to be smaller than that to any other segments of the GIT, calculated to be 0.12% of cardiac output. In Lin et al. (2020), values of blood flow to GIT were reported to be 22.5% and 11% of cardiac output for swine and calves, respectively. The GI regional blood flow was reported to be 14% of cardiac output in anesthetized rats (Delp et al., 1991). In the current study, the summation of the available data of blood flow to GIT was 13.57% of cardiac output, which is comparable to that reported in rats, but lower than that of swine, and higher than of calves.

3.4.4 | Heart

Values for regional blood flow to the heart (aka, coronary arteries) were found in two studies including eighteen animals (Boelkins

et al., 1973; Sapirstein & Hartman, 1959). The mean value was 0.54 L hr^{-1} kg^{-1} BW and 5.07% of cardiac output (Tables 15 and 16). It is comparable with the regional blood flow values reported by Brown et al. (1997) where the values were 6.6% in mice, 5.1% in rats, 4.6% in dogs, and 4.0% of cardiac output in humans. Comparing to the values provided by Lin et al. (2020), this value for broiler chickens is between the regional blood flow to heart for calves (6%) and that for swine (3%).

3.4.5 | Liver

The blood flow to the liver consists of nutritional and functional blood supplies which are channeled through the hepatic artery and portal vein, respectively. Only when the literature provided solely "total liver blood flow" or indicated such in the method was the value included in this parameter. Otherwise, the blood flow of hepatic artery and portal vein were accounted separately. The mean hepatic blood flow (i.e., hepatic artery plus portal vein) was from Purton (1975) involving 12 animal subjects to be 2.50 L hr^{-1} kg^{-1} BW, which was 25.26% of the cardiac output (Tables 15 and 16). The hepatic artery and portal vein flow were 1.33 and 1.56 L hr^{-1} kg^{-1} BW derived from 60 and 18 animal subjects, accounting for 13.43% and 14.03% of cardiac output, respectively. In the current study, hepatic artery and portal vein blood flow ranged from 8.47% to 18.28% and 8.63% to 19.43% of cardiac output, respectively. These values are within a reasonable fluctuation range considering multiple variables such as splanchnic input into the portal system, the intrahepatic resistance to flow, and the flow in the coccygeal mesenteric vein. The reported values are indicative of normal hepatic function (Purton, 1975). In Lin et al. (2020), hepatic blood flow values were reported as 46% and 24.3% in cattle and swine, respectively. In Brown et al. (1997), hepatic blood flows for the common laboratory animal species were 16.1% for mice, 17.5% for rats, 29.7% for dogs, and 25.0% and 27.0 for male and female humans. In the published PBPK literature (Cortright et al., 2009; Yang et al., 2014, 2015), the regional blood flow to liver was all reported as 20% of cardiac output, which is similar to the calculated mean value in the current study. Overall, our calculated mean hepatic regional blood flow is comparable to the previously published data.

3.4.6 | Muscle

Due to data scarcity, no absolute mean value of blood flow to total muscle compartments in chickens or turkeys was able to be extracted. Pectoral muscle was identified in two studies in chickens (Sapirstein & Hartman, 1959; Wolfenson et al., 1981) and calculated to account for 0.75 L hr^{-1} kg^{-1} BW (Table 15) and 7.64% cardiac output (Table 16). Table 17 summarizes the individual relative blood flow value in three muscles: *pectoralis major*, *external abdominal oblique*, and *gastrocnemius* for layers. In Wolfenson et al. (1981), 8- to 15-month-old crossbred White Leghorn X Rhode Island Red hens were used. Among the three main edible muscle parts documented, blood flow in the control state was the highest in the abdominal region with a relative value of 0.214 ml min^{-1} g^{-1} tissue. This value was not able to be converted to % cardiac output due to the lack to the individual muscle weight. The calculated mean values of muscular regional blood flow in cattle and swine were 28% and 34.2%, respectively (Lin et al., 2020). It was reported in common laboratory animals, blood flow fractions to muscles are 12.2%$^{-1}$9.6% for mice, 27.8% for rats, and 21.7% of cardiac output for dogs (Brown et al., 1997). In Cortright et al. (2009), Yang et al. (2014) and Yang et al. (2015), the regional blood flow to muscle compartment was 35% of cardiac output derived from the model fitting result from Cortright et al. (2009).

3.4.7 | Pancreas

From five studies in chickens with 49 animal subjects (Arad et al., 1993; Boelkins et al., 1973; Merrill et al., 1981; Wolfenson et al., 1978, 1981), we calculated the mean value of relative blood flow to pancreas to be 0.066 L hr^{-1} kg^{-1} BW which pertains 0.67% of cardiac output (Tables 15 and 16). Values for pancreatic regional blood flow were not reported for mice, rats, dogs, or humans in Brown et al. (1997). This value was reported to be 1.4% in swine (Lin et al., 2020).

3.4.8 | Pulmonary parenchyma (Lungs)

In PBPK modeling, fraction of cardiac output to pulmonary parenchyma is generally considered as 100% cardiac output since the pulmonary and systemic cardiac circuits are assumed equal (Yang et al., 2014, 2015). The value provided in the current study, 5.59 L hr^{-1} kg^{-1} BW (Table 15), equivalent to 56.59% of cardiac output (Table 16), is based on pulmonary blood flow measured in the right pulmonary artery. This approximately corresponds to the assumption in Wideman et al. (2001) where the cardiac output was assumed to be twice pulmonary blood flow.

3.4.9 | Renal parenchyma (Kidneys)

Values of renal blood flow in chickens were identified in six studies (Arad et al., 1993; Merrill et al., 1981; Sapirstein & Hartman, 1959; Wolfenson et al., 1981), yielding the mean of 1.99 L hr^{-1} kg^{-1} BW and 20.12% of cardiac output (Tables 15 and 16). Bailey and Nishimura (1984) showed renal blood flow to be 2.4 L hr^{-1} kg^{-1} BW in anesthetized pullets (*Gallus gallus*), which took up around 25.6% of cardiac output, higher than the calculated pooled mean value. Our calculated mean value is similar to the values in the available PBPK models for chickens. It is very close to that reported in Cortright et al. (2009), model-fitted value of blood flow to kidneys of 25%, but about two times higher than that used in Yang et al. (2014) and Yang et al. (2015) which were 12.5% of cardiac

output. This uncertainty deserves additional studies and impacts imposed by the renal portal system should be taken into consideration. The relative renal blood flow in chickens is higher than in adult cattle (10%), calves (10%), swine (11.4%), mice (9.1%), rats (14.1%), dogs (17.3%), and humans (17.5%) (Brown et al., 1997; Lin et al., 2020). The renal portal system in avian is unique with bilaterally located renal portal valves. The valves, acting as sphincters of smooth muscle, can close off the direct flow from the external iliac veins to the caudal vena cava, thus increase renal portal blood flow (Akester, 1967; Whittow, 1999). Urine flow and glomerular filtration rate (GFR) are not included in this study due to it being largely dependent on water intake. However, Yokota et al. (1985) suggested that the rate of glomerular filtration by single nephrons (SNGFR) is lower in avian than in mammals of similar body mass, but the low SNGFR of avian kidneys is counterbalanced by a larger number of nephrons, so the total kidney GFRs are not significantly different between the two groups (Whittow, 1999).

3.4.10 | Skin

The values of blood flow distributed to skin were identified in three studies (Arad et al., 1993; Wolfenson et al., 1978, 1981), yielding 1.49 L hr^{-1} kg^{-1} BW and 15.05% of cardiac output (Tables 15 and 16). Relative blood flow to different portions of skin was examined and documented in Wolfenson et al. (1981). Summarized in Table 18, blood flow values were 0.095, 0.067, and 0.050 ml min^{-1} g^{-1} tissue for metatarsal, back, and breast skin, respectively, during normothermia state. Our calculated result is higher than the values for integument regional blood flow fractions reported as 5.8% of cardiac output in mice and rats, 6% in dogs, and 3.3%-8.6% in humans (Brown et al., 1997) potentially due to additional blood flow to blood (pin) feathers in the avian.

3.4.11 | Spleen

The mean value of relative blood flow to spleen was 0.40 L hr^{-1} kg^{-1} BW which occupied 4.03% of cardiac output, from a total of 46 animals from five studies (Arad et al., 1993; Boelkins et al., 1973; Merrill et al., 1981; Sapirstein & Hartman, 1959; Wolfenson et al., 1978) (Tables 15 and 16). Values for splenic blood flow were not reported for laboratory animals, dogs, or humans in Brown et al. (1997). This value was reported to be 3.1% in swine (Lin et al., 2020).

3.4.12 | Thyroid

The mean value of relative blood flow to thyroid was not included in the tables due to the lack of organ weight data available for conversion. The average of the extracted data was 1.57 ml min^{-1} g^{-1} tissue with the range of 0.33–2.16. All animal subjects were adult layers with the age ranging from 8 to 15 months based on four studies (Boelkins et al., 1973; Sapirstein & Hartman, 1959; Wolfenson et al., 1978, 1981).

3.4.13 | Testes

The blood flow to the testes was identified in one study (Merrill et al., 1981), being 0.006 L hr^{-1} kg^{-1} BW from 9 animals, accounting for 0.061% of cardiac output (Tables 15 and 16).

3.4.14 | Reproductive organs for layers

Values of blood flow distribution for various sections of the reproductive tract in layers are summarized in Tables 19 and 20 with the absolute and relative blood flow values, respectively. The blood flow to reproductive tract of layers accounts for about 25.17% of cardiac output when pooling the different sections together (Table 20). It is higher than that reported in Boelkins et al. (1973) which estimated the total reproductive tract received 15.34% of the cardiac output. In sum, the high distribution of blood flow to the reproductive tract during shell formation marks the importance of the oviduct in the overall metabolism of the layers. Table 21 lists the values of blood flow to reproductive organs during different stages of oviposition acquired from Niezgoda et al. (1982). A total of 24 birds were used in the experiment with ages ranging from 16 to 28 weeks. It shows that the ovary constantly has the highest relative blood flow during any period during oviposition, although blood flow does increase in each part of the reproductive tract as the egg passes through its developmental stages. Anatomically, the shell gland is the same as the uterus. However, the term shell gland is more commonly used in studies where the layers are in reproductive stages, whereas the term uterus is used in studies with the layers either in reproductive or nonreproductive stages. In the current study, we separated the parameters in accordance to the animals' reproductive activity. As a result, the blood flow fraction to the shell gland is higher than that to the uterus.

3.5 | Egg Production

Typically, a healthy chicken laying hen can produce an egg every 25–27 hr with yolks developed prior in the ovary as a cluster of sacs containing ova in follicles. Under normal conditions, the development of the ova occurs over a period of months. As the hen matures, the suitable ova develop through three different stages (small white, small yellow, and large yellow yolk phases) into yolks, while most small white follicles remain dormant. The majority of yolk formation occurs within the ten days before ovulation during which yolk material steadily accumulates (Donoghue, 2005; Donoghue et al., 1997; Goetting et al., 2011). Egg formation process recurs daily. The developing egg passes through different segments of the oviduct following yolk release from the ovary: 15–30 min in the infundibulum where the developed follicle is caught, 3 hr in the magnum for the accumulation of albumen

as the yolk spins down the oviduct, 1.25 hr in the isthmus for the inner and outer membrane syntheses and placing around the albumen, and 20–21 hr in the uterus for shell formation. The completed egg will then be ovipositioned and is ready to be laid (Donoghue, 2005).

Chicken laying hens start to lay at around five months of age and continue to lay for twelve months on average. During the laying cycle, hens may be exposed to drugs or contaminants in various ways including extralabel use of drugs or unintentional cross-contamination in feed which poses a food safety concern (Stafford et al., 2018). Thus, a need for predicting drug residues in eggs has been raised. Predicting drug residues in eggs with PBPK models is a unique challenge since unlike most tissues, eggs act more like an excretory product with extended developing time in the hens' bodies (Donoghue, 2005). The edible component of the eggs, the albumen and yolk, is different in physiological and chemical properties. Several published PBPK models have incorporated eggs with or without albumen and yolk being two separated compartments (Hekman & Schefferlie, 2011; Lautz et al., 2020; Schefferlie & Hekman, 2016). It was suggested that the inclusion of both yolk and albumen compartments can aid in predictions of residue profiles depending on the physiochemical properties of the drug (Lautz et al., 2020; Schefferlie & Hekman, 2016). Readers are referred to Goetting et al. (2011) for a comprehensive review for the information regarding drug pharmacokinetics in laying hens and the deposition of antibiotics, parasiticides, and coccidiostats in eggs.

3.6 | Hematocrit

Hematocrit is a parameter that measures the ratio of the volume of red blood cells to the total blood volume (red blood cells and plasma). It is an important parameter in PBPK modeling in order to convert blood volume and cardiac output to plasma volume and cardiac plasma output, respectively. In addition, with the purpose of diagnosis and establishing a treatment plan, the reference intervals of normal blood components are needed in clinical settings (Clark et al., 2009). In Haile and Chanie (2014), it was reported that chickens typically have a lower hematocrit value that increases with age and that the normal reference intervals of blood components (e.g., leukocytes, lymphocytes, and monocytes) vary in different avian species but due to insufficient data, such trend was not observed in the present review. Summarized in Tables 22 and 23, values of hematocrit were determined in twenty and eight studies for chickens and turkeys, respectively. Six studies were identified to provide the values of hematocrit for broiler chickens of market age, which was calculated to be 30.7%. In addition, the hematocrit values were identified in five studies with 39 animals, yielding the mean of 31.4% for layers. Overall, the mean hematocrit values were 32.0% for chickens regardless of production class and 35.5% for turkeys. These values are comparable to those of adult cattle (37.8%), calves (33.7%), swine (41.2%), sheep (36.15%), and goats (29.38%) (Li et al., 2020; Lin et al., 2020). In Sturkie and Eiel (1966), the mean was 46.7% with a *SD* of 0.963 from 32 chickens, which is higher than most of the values collected in this study but is comparable with Bond and Gilbert (1958) which provided 45% as the mean among 3 animals. In the PBPK studies of Henri et al. (2017), Yang et al. (2014), and Yang et al. (2015), hematocrit value of 33% was utilized to calculate the cardiac plasma output from cardiac output.

4 | DISCUSSION

PBPK models provide a framework for incorporating information on the various production-specific factors that can impact drug and chemical residue depletion which in turn impact assessment of animal-derived food safety (MacLachlan, 2010). The physiological parameters that serve as the base of any PBPK models are therefore essential. This study compiled data of organ/tissue weights and cardiac output along with regional blood flow values and is expected to provide a comprehensive reference for the development of future PBPK models for drugs and environmental chemicals in chickens and turkeys. The physiological data can further be used as initial parameter estimates to explore PBPK model development for ducks, pheasants, and quails, which are classified as major poultry species in other countries.

The physiological parameters used in existing PBPK models for chickens (Cortright et al., 2009; Henri et al., 2017; MacLachlan, 2010; Yang et al., 2014, 2015; Zeng et al., 2019) were model-fitted or derived from Cortright et al. (2009). In the present report, all data were calculated from field and experimental studies which inherently included the variability of individual differences and inevitable experimental errors. Values from published PBPK models were not included in this database to avoid repeated or redundant value insertion in the analysis, but were discussed in each section to validate the calculated results. These *SD* and ranges can be used in PBPK models when population analysis is applied, noting that the individual *SD* and ranges reported from the original literature might have resulted from discrepancies between measurement techniques, which do not reflex true biological variability.

During the preparation of this manuscript, Lautz et al. (2020) reported a generic PBPK model for adult domestic chickens. Comparison of the fractional organ weights and regional blood flows between our study and the Lautz et al. study is presented in Tables 24 and 25, respectively. Overall, most of the physiological parameter values between these two studies are similar despite calculating from different data sources. For example, the calculated heart weight fraction is 0.54% of total body weight in this study, similar to the value of 0.6% in Lautz et al. (2020). The Lautz et al. model was designed to be a generic model and adequately simulated the kinetics of multiple chemicals with diverse physicochemical properties (the Log Kow values ranged from 0.12 to 6.20). However, in their study, data from broiler chickens and layers were pooled together; thus, production class-specific information was not available. Additionally, the egg compartment by Lautz et al. (2020) was assumed to be a well-mixed homogenized

compartment similar to other organ compartments; thus, the physiology (e.g., growth of the follicles) and different components (e.g., yolk and albumen) of eggs were not taken into account. In the present study, we considered different production classes based on the definitions and descriptions in Guidance for Industry #191 published by US FDA (FDA, 2015). We also provide physiological parameters for turkeys, which play a major role in the domestic poultry meat consumption. In addition, we provide the weight and blood flow information for different segments of the reproductive tract during different oviposition stages, which is important when developing a PBPK model for layers. In addition, retention time data of different segments of GIT were provided to aid in simulation of drugs administered PO. Overall, the present study and the study by Lautz et al. (2020) together provide useful information to develop PBPK models for xenobiotics in broiler chickens, laying hens, and turkeys.

Estimating extralabel withdrawal intervals for drugs prescribed by veterinarians is one of the main applications of PBPK models in production animals. Withdrawal intervals widely vary depending on the drug pharmacokinetics, administration routes, and animal production classes. In poultry, particularly, age-dependent parameters of chickens had been utilized in Henri et al. (2017) and Zeng et al. (2019) for chicken life-stage PBPK models. Our present study provides some values of tissue growth as listed in Tables 6-9. These studies can serve as a basis for further development and application of physiologically realistic life-stage PBPK models in chickens of different production classes for other chemicals.

Considering the anatomical and physiological differences between avian species and commonly used laboratory animals, discrepancy in data for the same parameter can be seen. Main body components of vertebrates are similar; however, data availability is relatively scarce for avian species. More experimental research with collected physiological parameters will be needed in order to fill the data gaps for certain parameters such as regional blood flows for turkeys and residual blood volumes for both chickens and turkeys. When physiological data are not available or have not been comprehensively compiled for other avian species (e.g., turkeys, ducks, quails, pheasants), parameter values for chickens can serve as approximate starting values, but species differences (e.g., seasonal variability in Anseriformes testicle size) must be accounted for in order for the models to be accurate. When additional data become available in different avian species, the present database will be able to be updated to fulfill the need of PBPK modeling in poultry.

In conclusion, the present manuscript provides a comprehensive summary of physiological parameters related to PBPK modeling for different production classes of chickens and turkeys. This study identifies data gaps in this field such as the regional blood flow fractions in turkeys, providing a direction for future studies. Data presented in this manuscript can serve as a starting point for creating virtual populations of chickens and turkeys in commercial PBPK modeling software programs or in web-based interactive PBPK interfaces (Li, Cheng, et al., 2019) for rapid development of PBPK models for applications in animal health and poultry-derived food safety assessment. Additional experimental or review studies on the expression and activities of key metabolic enzymes or transporters in major metabolic and excretory organs (e.g., liver, intestine, pancreas, and kidney) at different life stages of chickens and turkeys are needed to create biologically realistic virtual populations of chickens and turkeys.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

ZL, JER, LAT, REB, JLD, and TWV discussed and conceived this project. YSW did the literature search, extracted the data into Excel files, analyzed the data, and presented the data as tables and figures based on advice from ZL. ML contributed to the literature search and data analysis. LAT contributed to the literature search and determination of appropriate references. LAT served as the avian expert. YSW double-checked all data presented in the Excel files. ZL, REB, and LAT double-checked all data presented in the tables of the manuscript. YSW drafted the manuscript. ZL coordinated the project and comprehensively revised 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.

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