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Pharmacokinetics of Mequindox and Its Marker Residue 1,4-Bisdesoxymequindox in Swine Following Multiple Oral Gavage and Intramuscular Administration: An Experimental Study Coupled with Population Physiologically Based Pharmacokinetic Modeling

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Supporting Information

ABSTRACT: Mequindox (MEQ) is a quinoxaline-N,N-dioxide antibiotic used in food-producing animals. MEQ residue in animal-derived foods is a food safety concern. The tissue distribution of MEQ and its marker residue 1,4-bisdesoxymequindox (M1) were determined in swine following oral gavage or intramuscular injection twice daily for 3 days. The experimental data were used to construct a flow-limited physiologically based pharmacokinetic (PBPK) model. The model predictions correlated with available data well. Monte Carlo analysis showed that the times needed for M1 concentrations to fall below limit of detection (5 μg/kg) in liver for the 99th percentile of the population were 27 and 34 days after oral gavage and intramuscular administration twice daily for 3 days, respectively. This population PBPK model can be used to predict depletion kinetic profiles and tissue residues of MEQ's marker residue M1 in swine and as a foundation for scaling to other quinoxaline-N,N-dioxide antibiotics and to other animal species.

KEYWORDS: *food safety, mequindox, physiologically based pharmacokinetic (PBPK) modeling, quinoxaline-N,N-dioxide antibiotics, swine*

INTRODUCTION

Mequindox (MEQ), 3-methyl-2-quinoxalinacetyl-1,4-dioxide, is a quinoxaline-N,N-dioxide antibiotic that is administered via oral gavage or intramuscular (IM) administration for 3−5 days for the treatment of clinical infections caused by *Treponema hyodysenteriae*, *Escherichia coli*, or *Salmonella sp*. in swine, chickens, and cattle in China since the 1980s.[1−3] However, to our best knowledge, the official maximum residue levels (MRL) or withdrawal periods for MEQ in food animals have not yet been established. The use of MEQ in food animals and its potential toxicity to humans have led to an increasing concern about MEQ residues in animal-derived foods.

Multiple studies have shown that excessive exposure to MEQ produces a range of toxic effects to multiple organ systems, especially the kidney and liver.[4−10] For example, long-term dietary exposure to MEQ at a high dose of 250 mg/kg resulted in adrenal toxicity with disrupted endocrine function in rats.[9] A single dose of 350 mg/kg MEQ caused alterations in energy metabolism, oxidative stress, liver damage, and disturbance of gut microbial activity in mice.[6] MEQ exposure at 250 mg/kg also caused liver dysfunction and formation of reactive oxygen species (ROS) by activating both peroxisomal and mitochondrial β-oxidation of fatty acids as well as promoting an antioxidative response in rats.[5] Several short-term experiments demonstrated that MEQ is a genotoxic compound that can lead to mutations in bacterial systems and chromosome and DNA damage in vitro and in vivo.[4] To ensure food safety and to protect humans from potential toxic effects of MEQ overexposure via consuming animal-derived foods, it is crucial to understand its pharmacokinetic characteristics and to develop a quantitative tool that can be used to predict depletion kinetic profiles and tissue residues of MEQ.

The metabolism and disposition of MEQ have been studied in multiple veterinary species, including pigs, chickens, rats, and goats.[1−3,11−17] Following oral gavage or IM administration, MEQ is absorbed rapidly, with the oral bioavailability, IM bioavailability, oral total body clearance being 25.4%, 98.1%, and 2.28 L/h/kg, respectively.[2] In the body, MEQ is rapidly distributed throughout most tissues, metabolized extensively, and then excreted primarily via urine. Following incubation of MEQ with rat, chicken, or pig liver microsomes, 10 metabolites have been observed, with M1 (1,4-bisdesoxymequindox) being the most abundant metabolite.[16] M1 and liver were proposed to be the marker residue and target tissue of MEQ in swine.[3]

Physiologically based pharmacokinetic (PBPK) modeling is a computational process that simulates the absorption, distribution, metabolism, and excretion of compounds in the body

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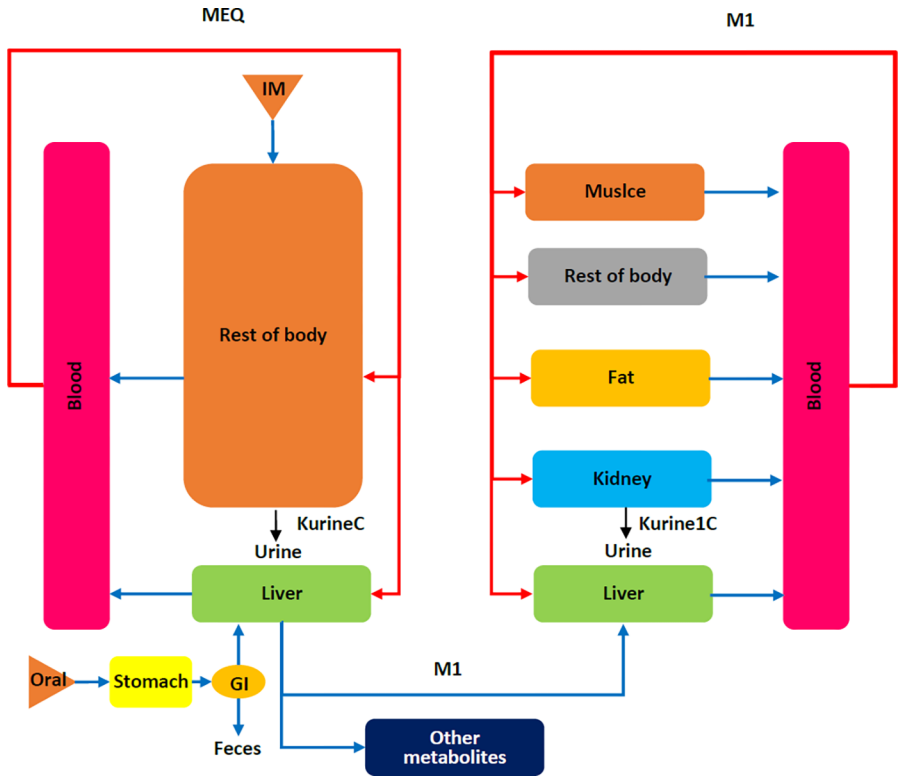

Figure 1. Schematic diagram for the PBPK model for MEQ and its major metabolite M1 in swine. Oral and IM represent oral gavage and intramuscular administration doses (mg/kg), respectively. For descriptions of parameters, refer to Table 1 and Table S4. Model code in MMD file is provided in the Supporting Information.

based on interrelationships among key physiological, biochemical, and physicochemical determinants using mathematical equations.[18−22] The advantages of PBPK models in the field of veterinary medicine are their ability to predict tissue concentrations of veterinary drugs and their metabolites in the target tissue in food-producing animals.[22,23] Multiple PBPK models have been developed for different animal drugs including oxytetracycline, tulathromycine, flunixin, enrofloxacin.[24−35] For quinoxaline antibiotics, PBPK models are available in pigs for olaquindox (OLA),[28] cyadox (CYA),[24,27] and quinocetone (QCT).[36] The recently published QCT PBPK model has also been extrapolated to MEQ, but because of lack of data, the derived MEQ model can only simulate MEQ disposition following single oral gavage; thus, PBPK models for MEQ following multiple oral or IM exposure are not available. Monte Carlo simulation is a statistical method that is applied to obtain numerical results based on repeated random sampling from a certain probability distribution. This method is widely used in mathematical modeling to study biomedical problems,[37,38] as well as PBPK models, to estimate tissue residues and withdrawal intervals.[33,39] The objective of this study was to determine the tissue depletion profiles of MEQ and its marker residue M1 in swine following oral gavage or IM injection twice daily for 3 days and then use the newly collected data to develop a PBPK model to simulate the depletion of MEQ and M1 in swine. Monte Carlo sampling technique was incorporated into the PBPK model to address the interindividual variability and to predict depletion kinetic profiles to help establish MEQ withdrawal periods.

MATERIALS AND METHODS

Chemicals and Reagents. MEQ (99.8%) was provided by the China Institute of Veterinary Drug Control (Beijing, China). M1 (98.0%) was obtained from the College of Veterinary Medicine, China Agricultural University (Beijing, China). HPLC-grade acetonitrile was purchased from Thermo Fisher Scientific Inc. (MA, USA). Ultrapure water was produced using a Milli-Q system (Millipore, MA, USA). Other reagents and chemicals were of analytical grade and supplied by the Guangzhou Chemical Regent Factory (Guangzhou, China). Stock standard solutions (1.0 mg/mL) were prepared by dissolving MEQ and M1 in methanol. Working mixed standard solutions were prepared by dilution of the stock standard in methanol.

Animals. One-hundred twenty healthy castrated crossbred (Duroc × Landrace × large white) swine (90−100 days, 50.0 ± 5.1 kg) were purchased from Guangzhou Lizhi Agricultural Co., Ltd. The swine were housed in ten 8 m × 10 m pens and acclimatized for 1 week under standard environmental conditions (25 ± 2 °C, 50−60% relative humidity) before the experiment in the Laboratory Animal Center of South China Agricultural University, Guangzhou, China. Swine were ear tagged and group-fed with commercial feed purchased from Jinxinnong Technology Co., Ltd. (Shenzhen, China) twice daily, with water available ad libitum. The approximate daily intake for each swine was 2 kg/day. The feed was screened to be MEQ free using a published HPLC method and the limit of detection (LOD) of the method was 200 μg/kg.[40] All procedures were conducted in accordance with Institutional Animal Care and Use Committee (IACUC) protocols of South China Agricultural University.

Residue Depletion Experiments of MEQ in Swine. The 120 healthy swine were randomly allocated to three experimental groups: A (54 swine), B (42 swine), and C (24 swine). In Group A, 45 animals were exposed to MEQ via oral gavage at 10 mg/kg twice daily for 3 consecutive days, and nine animals were left untreated as control animals. For oral gavage, a V-trough was used to restraint the swine. A mouth gag was inserted gently in the mouth, making sure the hole of the pin was slightly off center. Next, a catheter was inserted with a bit

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of water to elicit the swallowing reflex, and then MEQ was injected and the catheter was rinsed swiftly without delay. The carrier of MEQ was 0.5% carboxymethylcellulose sodium. At 0.16, 0.25, 0.5, 1, 3, 5, 7, 9, and 11 days after the last dosing, one control animal and five medicated animals were randomly slaughtered by exsanguination following the guidelines provided by the American Veterinary Medical Association. Plasma, liver (cross-section of lobes), kidney (composite from combined kidneys), muscle (loin), and fat (skin with fat in natural proportions) were collected and immediately frozen at −20 °C until further analysis. In Group B, 35 animals were exposed to MEQ via oral gavage at 10 mg/kg twice daily for 3 consecutive days, and seven animals were left untreated as control animals. At 0.5, 1, 3, 5, 7, 9, and 11 days after the last oral dosing, one control animal and five medicated animals were randomly slaughtered, and the plasma and tissue samples (liver, kidney, muscle, and fat) were collected and immediately frozen at −20 °C until further analysis. In Group C, 20 animals were exposed to MEQ via IM administration at 5 mg/kg twice daily for 3 consecutive days, and four animals were untreated as control animals. IM administration was given on the right side of the neck on Day 1 and then on the left side of the neck on Day 2, and finally on the right side of the neck on Day 3. The injection sites were not marked for testing residues and the injection site subcompartment was not included in our PBPK model. At 7, 9, 11, and 14 days after the last dosing, one control animal and five treated animals were randomly slaughtered and the plasma and tissue samples (liver, kidney, muscle and fat) were collected and immediately frozen at −20 °C until further analysis. Sample preparation and analyte determination were adopted from the method reported by our laboratory.[41] Briefly, the method involved acid hydrolysis, purification by solid-phase extraction, and subsequent analysis with liquid chromatography−tandem mass spectrometry using electrospray ionization operated in positive polarity with a total run time of 15 min. Additional information on these experiments can be found in Supporting Information Tables S1−S3.

PBPK Modeling for MEQ and Its Marker Residue M1 in Swine. On the basis of the previous PBPK models for OLA,[28] CYA,[24,27] and flunixin[35] in pigs, the present model was designed to include two submodels for MEQ and M1, respectively. The MEQ submodel consisted of three compartments, including blood, liver, and rest of body; meanwhile, the M1 submodel consisted of seven compartments, including blood, liver, kidney, muscle, fat, and rest of body (Figure 1). The other minor metabolites were pooled together and modeled as a single compartment. The liver was modeled as an individual compartment in the MEQ submodel because the liver is the major organ of drug biotransformation. The liver, kidney, muscle, and fat were modeled as individual compartments in the M1 submodel because these organs are common edible tissues and relevant to food safety. Additionally, it was necessary to include a lumped compartment to account for disposition of MEQ and M1 to the rest of body. All compartments were assumed to be blood flow-limited and well-stirred. Exposure of MEQ via oral gavage and IM administration was included in the model.

The oral gavage of MEQ was described with a two-compartment model (Figure 1) based on Buur et al.[33] and Lin et al.[26] Briefly, it was assumed that following oral gavage MEQ was immediately available in the stomach, and distributed into the intestine by gastric emptying, governed by the gastric emptying rate constant (K_{st}, 1/h). Once in the intestine, drug absorption and elimination were controlled by intestinal absorption rate constant (K_a, 1/h) and intestinal transit rate constant (K_{int}, 1/h), respectively. These processes were assumed to be linear. Drug absorption from the injection site was described with a two-compartment absorption model, as detailed in the PBPK model for tulathromycin.[31] Briefly, the amount injected initially at the site was modeled as distributing between two compartments (site1 and site2) with absorption occurring from site1. The rate constants for distribution of MEQ from the central (site1) to the peripheral (site2) and site2 to site1 were K_{12} (1/h) and K_{21} (1/h), respectively. Repeated oral exposure paradigms were described with the REPEAT/EXPOSURE function as detailed in the PBPK models for penicillin G and the herbicide atrazine.[42,43]

The rate of change for MEQ and M1 in each tissue compartment was described using mass balance differential equations as described previously.[26,27] Both MEQ and M1 are excreted mainly via urine. Urinary elimination of MEQ and M1 was described with a first-order elimination rate equation in the kidney compartment. Example equations describing MEQ and M1 mass balance, and equations simulating repeated oral gavage, IM administration, hepatic metabolism, and urine clearance, were provided and explained in the Supporting Information. Berkeley Madonna (Version 8.3.23.0, University of California at Berkeley, CA) was used to develop the model and run all simulations. Model codes are provided in the Supporting Information and also available from our Web site (http://iccm.k-state.edu/).

Model Parametrization. Physiological parameters (Table S4, Supporting Information), such as tissue volumes and blood flow rates, were from literature,[33,35,43] and body weight was calculated as an average of the data from the residue depletion experiments. For the chemical-specific parameters, the tissue/plasma partition coefficients (PCs) of M1 were measured experimentally. In brief, the swine were placed in the sling and a topical anesthetic was applied to the ear. The skin was disinfected with 70% alcohol and the over-the-needle catheter was inserted approximately 5−10 mm to the ear vein. The carrier of M1 was dimethylformamide. M1 solution (0.5 mg/mL) was infused into 4 swine (90−100 days, 50.5 ± 4.3 kg) via the ear vein at a rate of 2 mL/min. The plasma M1 concentration was monitored at 10, 30, 60, and 90 min after administration to determine the time when steady-state was attained. The blood sampling procedure is as follows: (1) palpate the sternum, manubrium, and the first rib; (2) disinfect the skin and insert the needle approximately 5−10 mm cranially to the manubrium sterni and approximately 15 mm laterally in an angle of 45−60° in to the jugular fossa, aiming at the dorsal end of the opposite shoulder blade; (3) apply or activate the vacuum as soon as the skin has been penetrated and advance until the vessel is reached and a flash back is seen; (4) after removing the needle, apply good pressure for a minute or so on the injection site to reduce the risk of hematoma. Then all swine were sacrificed according to the guidance provided by American Veterinary Medical Association for euthanasia. Blood, liver, kidney, muscle, and fat samples were collected and analyzed using LC−MS/MS method as previously described.[41] The PCs for noneliminating tissue (liver, muscle, and fat) and eliminating tissue (kidney) were calculated using eqs 1 and 2, respectively:

$$P_t = \frac{C_{T,SS}}{C_{B,SS}} \quad (1)$$

$$P_t = \frac{C_{T,SS}}{C_{B,SS}(1 - E)} \quad (2)$$

where P_t is the PCs of M1; $C_{T,SS}$ and $C_{B,SS}$ represent the steady-state concentrations of M1 in tissues (liver, kidney, muscle, and fat) and plasma, respectively; and E is the renal extraction rate, which is equal to the renal clearance divided by the blood flow through kidney.

The renal clearance (Cl or Kurine1 used in the model) of M1 was measured in the following experiment. Four swine (90−100 days, 51 ± 9.5 kg) were placed in the sling and a topical anesthetic was used to sedate the animal. The skin was disinfected with 70% alcohol and then a 21 g needle was inserted approximately 5−10 mm to the ear vein with a bolus injection of M1 (0.5 mg/kg). After the needle was removed, certain pressure was applied for a minute or so on the site to reduce the risk of hematoma. The swine were housed individually in metabolism cages, which allowed for separate collection of urine and feces. Blood samples (5 mL) were collected via the cranial vena cava before and at 5 h after administration. Urine was collected during the entire experiment (a period of 10 h) with their volumes recorded accurately. Plasma and urine sample preparation and determination were adopted from the method reported by our laboratory.[41] The Cl was calculated by eq 3:

$$\mathrm{Cl} = \frac{dX/dt}{C} \quad (3)$$

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Table 1. Chemical-Specific Parameters Used in the Monte Carlo Analysis[a]

parameter	symbol	mean	SD	CV	lower bound	upper bound
Oral Absorption Rate Constants for MEQ (/h)						
gastric emptying rate constant	K_{st}	0.50	1.50×10^{-01}	0.30	2.694×10^{-01}	8.514×10^{-01}
intestinal absorption rate constant	K_a	0.04	1.20×10^{-02}	0.30	2.155×10^{-02}	6.811×10^{-02}
intestinal transit rate constant	K_{int}	0.40	1.20×10^{-01}	0.30	2.155×10^{-01}	6.811×10^{-01}
IM Absorption Rate Constants for MEQ (/h)						
IM absorption rate constant	K_{im}	1.00	3.00×10^{-01}	0.30	5.388×10^{-01}	1.703×10^{00}
distribution rate from the central to the peripheral	K_{12}	0.10	3.00×10^{-02}	0.30	5.388×10^{-02}	1.703×10^{-01}
distribution rate from the peripheral to the central	K_{21}	0.05	1.50×10^{-02}	0.30	2.694×10^{-02}	8.514×10^{-02}
Tissue/Plasma Partition Coefficient for MEQ (Unitless)						
liver	PL	2.40	4.80×10^{-01}	0.20	1.596×10^{00}	3.470×10^{00}
rest of body	PR	0.40	8.00×10^{-02}	0.20	2.661×10^{-01}	5.783×10^{-01}
Tissue/Plasma Partition Coefficient for M1(Unitless)						
liver	PL1	2.40	4.80×10^{-01}	0.20	1.596×10^{00}	3.470×10^{00}
kidney	PK1	2.00	4.00×10^{-01}	0.20	1.330×10^{00}	2.891×10^{00}
muscle	PM1	0.40	8.00×10^{-02}	0.20	2.661×10^{-01}	5.783×10^{-01}
fat	PF1	0.80	1.60×10^{-01}	0.20	5.321×10^{-01}	1.157×10^{00}
rest of body	PR1	0.40	8.00×10^{-02}	0.20	2.661×10^{-01}	5.783×10^{-01}
hepatic metabolic rate [/(h kg)]	KmC	0.05	1.50×10^{-02}	0.30	2.694×10^{-02}	8.514×10^{-02}
Fraction of MEQ Metabolized to M1 (Unitless)	Frac	0.10	3.00×10^{-02}	0.30	5.388×10^{-02}	1.703×10^{-01}
Percentage of Plasma Protein Binding (Unitless)						
MEQ	PB	0.25	7.500×10^{-02}	0.30	1.347×10^{-01}	4.257×10^{-01}
M1	PB1	0.25	7.500×10^{-02}	0.30	1.347×10^{-01}	4.257×10^{-01}
Urinary Elimination Rate Constant (L/h/kg)						
MEQ	KurineC	0.10	3.000×10^{-02}	0.30	5.388×10^{-02}	1.703×10^{-01}
M1	Kurine1C	0.01	3.000×10^{-03}	0.30	5.388×10^{-03}	1.703×10^{-02}

[a]All chemical-specific parameters were assumed to be in log-normal distribution.

Table 2. Residue Levels of M1 in Tissues and Plasma of Swine from the Three Experimental Groups

		tissues[a] (μg/kg)				
experimental group	days postdose	liver	kidney	muscle	fat	plasma[a] (μg/kg)
A	0.16	493 ± 159	388 ± 128	70.2 ± 38.9	142 ± 81.5	190 ± 102
	0.25	499 ± 170	395 ± 134	71.6 ± 39.6	146 ± 79.0	193 ± 112
	0.5	489 ± 179	391 ± 113	70.8 ± 28.8	145 ± 84.8	191 ± 114
	1	440 ± 176	353 ± 129	64.2 ± 30.6	131 ± 70.6	172 ± 107
	3	214 ± 84.9	172 ± 81.0	31.8 ± 18.9	64.6 ± 36.3	84.4 ± 53.9
	5	92.2 ± 42.6	75.2 ± 42.8	13.8 ± 5.8	28.0 ± 17.6	36.8 ± 25.8
	7	45.4 ± 25.0	36.8 ± 19.0	8.6 ± 3.2	13.6 ± 6.3	18.0 ± 10.3
	9	28.6 ± 17.3	24.6 ± 14.0	ND	9.2 ± 2.3	8.8 ± 1.9
	11	14.2 ± 6.9	11.8 ± 7.4	ND	ND	ND
B	0.5	498 ± 179	411 ± 115	75.4 ± 31.3	144 ± 82.7	211 ± 105
	1	418 ± 178	342 ± 136	60.0 ± 33.5	120 ± 59.9	162 ± 105
	3	224 ± 87.8	165 ± 77.0	35.4 ± 21.5	68.6 ± 37.0	89.8 ± 53.2
	5	96.6 ± 43.0	74.4 ± 43.1	12.6 ± 5.0	32.2 ± 18.7	38.4 ± 26.2
	7	45.4 ± 25.2	39.2 ± 22.0	8.8 ± 2.1	15.4 ± 6.2	19.4 ± 11.3
	9	25.6 ± 15.0	22.6 ± 12.6	ND	ND	8.4 ± 2.1
	11	14.0 ± 6.2	12.2 ± 7.5	ND	ND	ND
C	7	199 ± 100	152 ± 78.3	28.4 ± 15.6	49.0 ± 16.7	72.6 ± 31.1
	9	80.8 ± 50.0	60.6 ± 27.0	15.0 ± 9.1	35.0 ± 18.8	49.0 ± 16.7
	11	40.4 ± 25.1	20.8 ± 8.9	8.0 ± 2.2	16.0 ± 5.9	19.0 ± 11.2
	14	12.0 ± 5.0	10.0 ± 3.4	ND	8.0 ± 2.2	8.0 ± 2.8

[a]Each value represents the mean ± SD for five pigs. ND: below the LOD for M1 in the liver, kidney, muscle, fat, and plasma (5 μg/kg).

where Cl is the renal clearance of M1 (L/h); X is the amount of M1 excreted into urine (mass); and C represents the plasma M1 concentration at the midpoint time of the urine collection interval. Other chemical-specific parameters, such as oral and IM absorption rates, hepatic metabolic rates, fraction of drugs metabolized to main metabolites, were estimated by visually fitting to residue depletion data from the experimental Group A. All chemical-specific parameters are provided in Table 1.

Model Evaluation and Extrapolation. After model calibration with Group A data set, the model was evaluated by comparing model simulations with experimental data set not used in the model calibration including experimental Group B data set and published data set from Huang et al.[3] The model was then extrapolated to simulate IM exposure from experimental Group C data set. On the basis of World Health Organization (WHO) PBPK modeling guidelines,[19] if the simulations were generally within a factor of 2 of

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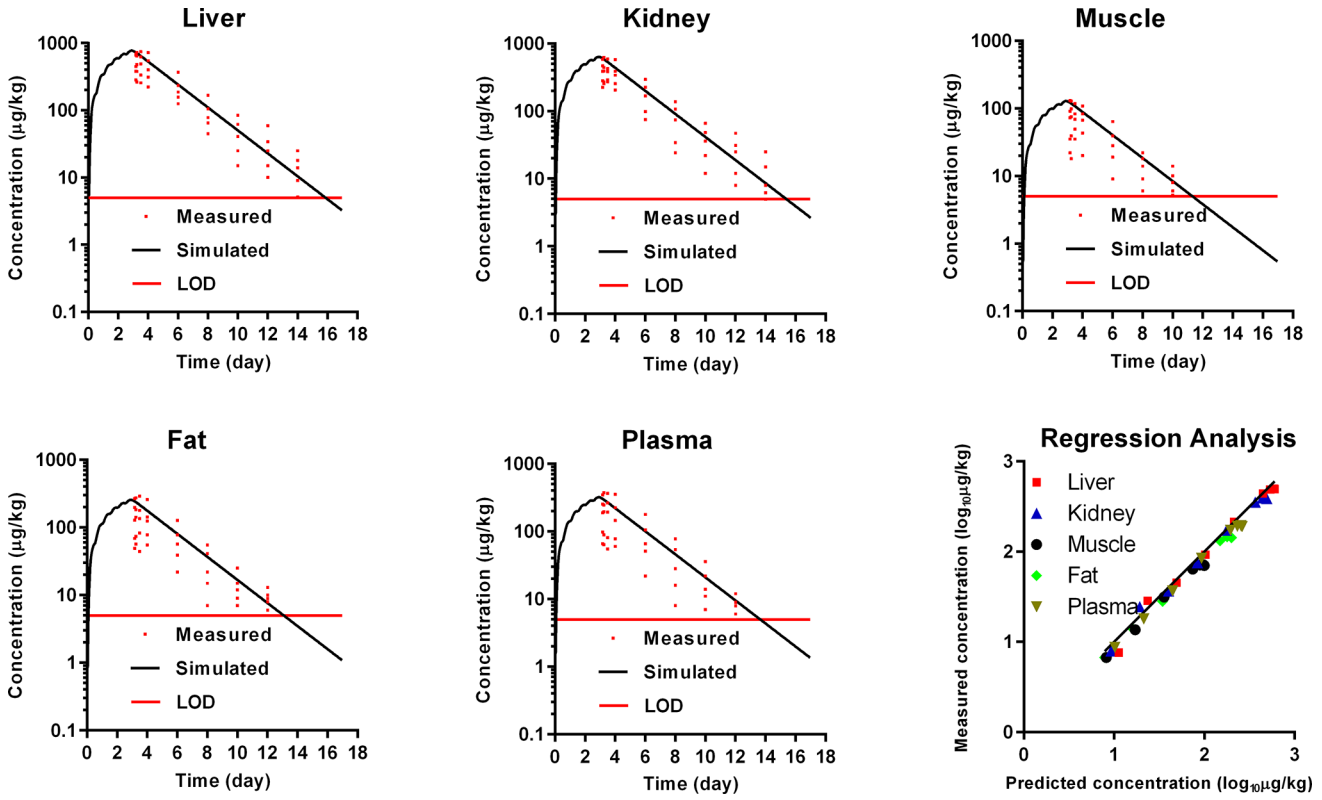

Figure 2. Model calibration with the oral gavage data. Comparison of model predictions (solid line) and observed data (squares) for M1 concentrations in liver, kidney, muscle, fat, and plasma of swine exposed to MEQ via oral gavage at 10 mg/kg twice daily for 3 consecutive days. Result of regression analysis between model predictions and observed data is shown. The determination coefficient R^2 value is 0.99.

the measured values, the model was considered reasonable and validated. The goodness-of-fit between predicted and observed plasma and tissue concentrations were evaluated by model convergence, visual inspection, and further analyzed with linear regression analysis after log-transformation using GraphPad Prism 6 (GraphPad Software Inc., La Jolla, CA).[35]

Sensitivity Analysis. A normalized sensitivity analysis was performed to determine which parameters had high impacts on critical model outputs, including 24-h area under the time concentration curves (AUCs) of M1 in liver, kidney, muscle, fat, and plasma. The normalized sensitivity coefficient (NSC) was calculated using the following equation:[42,44]

$$\mathrm{NSC} = \frac{\Delta r}{r} \times \frac{p}{\Delta p} \quad (4)$$

where p is the original parameter value, Δp is 1% of the original parameter value, r is the model output derived from the original parameter value, and Δr is the change of the model output resulting from 1% increase in the parameter value. Parameters with values of $|\mathrm{NSC}| \geq 0.5$ and $0.5 > |\mathrm{NSC}| \geq 0.2$ were considered highly and moderately sensitive, respectively.[26]

Monte Carlo Analysis. Monte Carlo analysis was implemented to evaluate the impact of uncertainties of parameter values on tissue residue predictions. Normal distributions were assumed for physiological parameters, including body weight, cardiac output, blood flows, and tissue volumes, while chemical-specific parameters were assumed to be log-normally distributed (Table 1 and Table S4, Supporting Information). Probabilistic distributions (variability) of model parameter values were derived from previous reported interindividual variability.[43] Each Monte Carlo simulation included 1000 iterations. To ensure the physiological plausibility of randomly selected physiological parameters, that is, the sum of the fractional blood flows equals 1 and the sum of the fractional tissue volumes equals 1, randomly selected physiological model parameters were adjusted in a fractional manner to maintain mass balance. Berkeley Madonna was used to run Monte Carlo analysis as described by Li et al.[43]

Model Application. Coupled with Monte Carlo analysis, the PBPK model was employed to estimate depletion kinetic profiles of M1 in liver, kidney, muscle, fat, and plasma for 1000 swine following oral gavage or IM administration twice daily for 3 consecutive days. The time when the values of the 99th percentile of simulated M1 residue concentrations below the LOD in liver, kidney, muscle, fat, and plasma (LOD = 5 μg/kg for M1 in all matrices) was determined.

RESULTS AND DISCUSSION

Residue Depletion Study. In this study, residue depletion experiments were conducted and extensive data sets were collected. MEQ residue concentrations were below the LOD (LOD = 4 μg/kg for MEQ) in tissues and plasma at 4 h after the last drug administration. The concentrations of M1 in plasma and tissues for three experimental groups were shown in Table 2. The raw concentration data in individual animals were provided in the Supporting Information (Table S1 for Group A, Table S2 for Group B, and Table S3 for Group C). The LOD for M1 in the liver, kidney, muscle, fat, and plasma was 5 μg/kg. Concentrations of M1 residues in liver were nominally greater than in other tissues. The highest concentrations of M1 in liver were 499 ± 170, 498 ± 179, and 199 ± 100 μg/kg measured in Groups A, B, and C, respectively. Among all tissues, the depletion kinetic profile of M1 in the liver was slower than in other tissues, and M1 was still detected in the liver consistently on days 11, 11, and 14 after the last dosing at concentrations of 14.2 ± 6.9, 14.0 ± 6.2, and 12.0 ± 5.0 μg/kg for Groups A, B, and C, respectively. Compared with the depletion of the total residues of MEQ in liver, the $t_{1/2}$ value of M1 in liver was 1.67 days, which was exactly the same as those of the total residues.[3]

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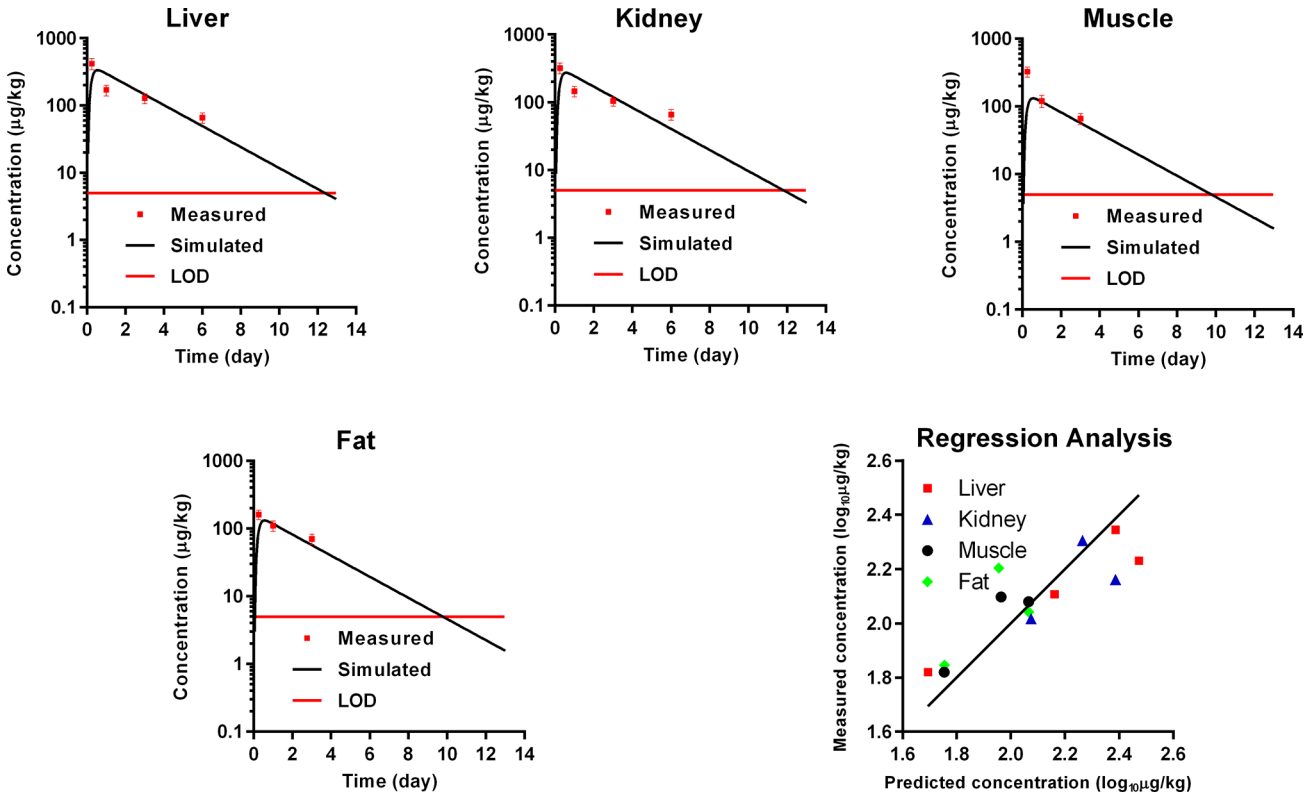

Figure 3. Evaluation of the oral gavage model with independent tissue data. Comparison of model predictions (solid line) and observed data (squares) for M1 concentrations in liver, kidney, muscle, and fat of swine exposed to MEQ suspension via single oral gavage of MEQ suspension at 10 mg/kg from Huang et al.[3] Result of regression analysis between model predictions and observed data is shown. The determination coefficient R^2 value is 0.75.

These results suggest that liver could be the target tissue of MEQ and M1 could be its marker residue in swine.

Model Calibration. During our model calibration process, we found that the present model with MEQ submodel consisting of three compartments and M1 submodel without enterohepatic circulation had relatively better predictions than the recently published MEQ PBPK model that included enterohepatic circulation in the M1 submodel.[36] This was consistent with the facts that no MEQ could be detected in any swine edible tissues, and M1 can only be detected in feces at the early time points up 12 h after oral gavage.[3] The present modeling approach was consistent with PBPK models for other drugs (e.g., ceftiofur, enrofloxacin, flunixin, and sulfamethazine).[35] All existing quinoxaline-N,N-dioxide PBPK models are coded in acslX (Aegis Technologies Group, Inc., Huntsville, AL), which was discontinued in 2015. The present model developed using Berkeley Madonna is unique and important because previous quinoxaline-N,N-dioxide PBPK models may need to be recoded using Berkeley Madonna.[20] Our model provides a foundation for recoding existing models and for scaling to other quinoxaline-N,N-dioxide antibiotics and to other animal species.

Measured M1 concentrations in liver, kidney, muscle, fat, and plasma up to 11 days in swine exposed to MEQ via oral gavage at 10 mg/kg twice daily for 3 consecutive days were compared to simulated data (Figure 2). Overall, the model-simulated concentrations correlated with the measured data well for all tissues, especially at later time points (9−11 days), which is the inference time frame of concern to this tissue residue model. Results of linear regression analyses between model-simulated and measured plasma and tissue concentrations of M1 were shown in Figure 2. The determination coefficient (R^2) value was 0.99, which confirmed excellent overall goodness-of-fit.

Model Evaluation and Extrapolation. After model calibration, Group B experimental data set and published data set were utilized to evaluate the model performance. As shown in Figure 3, the model properly simulated M1 depletion kinetic process in the tissues of swine exposed to MEQ via single oral gavage at 10 mg/kg, which was considered validated according to the WHO model precision criteria, which indicated that the model could be used to conduct exposure duration extrapolation.[19] Likewise, the model estimations were in reasonable agreement with Group B experimental data set (Figure S1). Eventually, following IM administration, model simulations using swine-specific absorption rate constants matched the Group C experimental data accurately (Figure 4). These simulation results suggest that the oral gavage model has been successfully extrapolated to simulate M1 disposition following IM administration of MEQ.

Sensitivity Analysis. NSCs for all 38 model parameters were calculated for five dose metrics (24-h AUCs for M1 in the liver, kidney, muscle, fat, and plasma) and two exposure routes (oral and IM), which resulted in a total of 380 NSCs. Of these NSCs, only parameters with at least one absolute value of NSC more than or equal to 0.2 were presented in Table 3. Body weight (BW), liver volume, hepatic metabolic rate of MEQ (KmC), fraction of MEQ metabolized to M1 (Frac), and urine elimination rate constant of MEQ (KurineC) had high influence on all selected dose metrics regardless of exposure route with NSCs values of 0.68, 0.63, 0.72, 1.00, and −0.51, respectively. Kidney and muscle dose metrics were highly sensitive to kidney and muscle PCs with NSC values of 0.99

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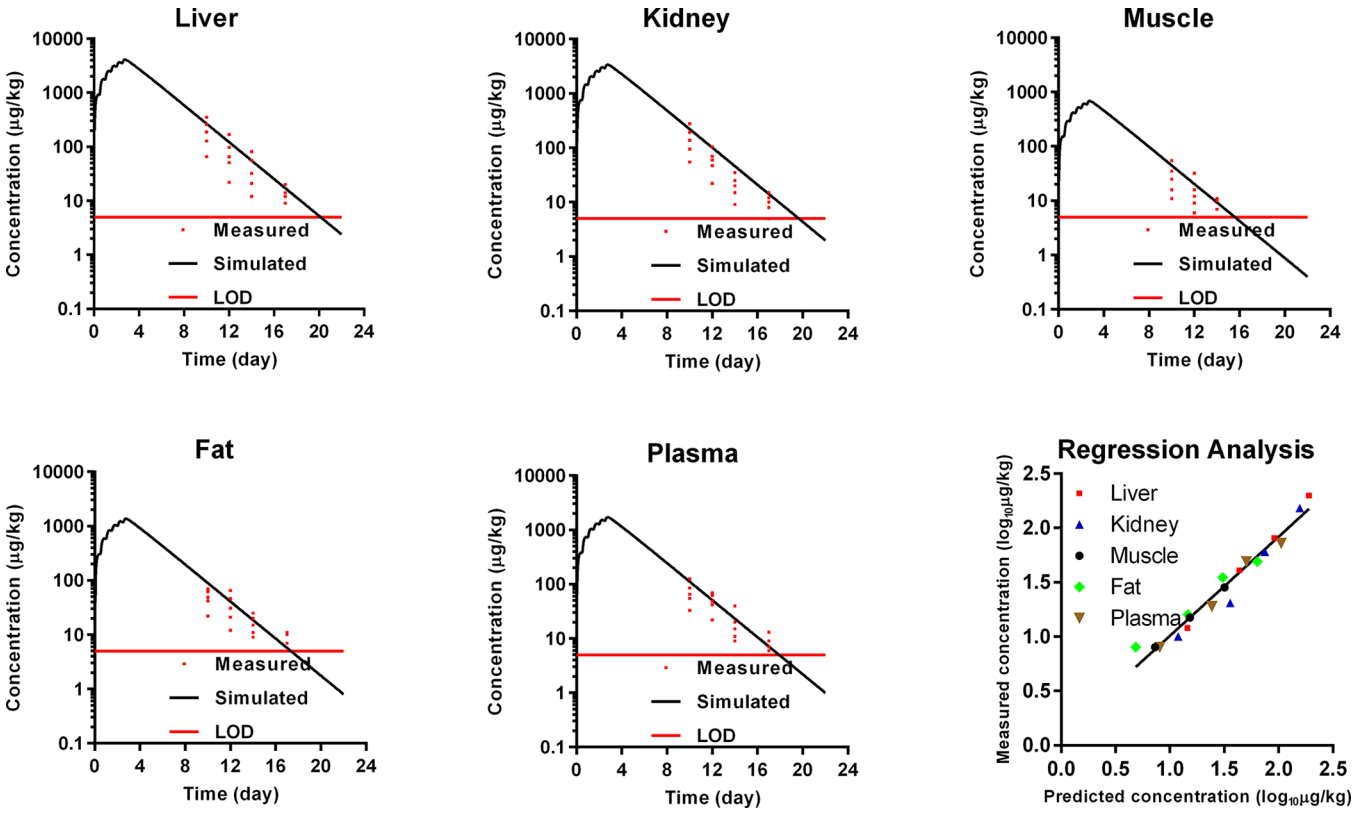

Figure 4. Evaluation of the model with tissue and plasma data from the IM administration study. Comparison of model predictions (solid line) and observed data (squares) for M1 concentrations in liver, kidney, muscle, fat, and plasma of swine exposed to MEQ suspension via IM injection at 5 mg/kg twice daily for 3 consecutive days. Result of regression analysis between model predictions and observed data is shown. The determination coefficient R^2 value is 0.96.

Table 3. NSCs of Moderately to Highly Sensitive Parameters on Selected Plasma and Tissue Dose Metrics Following Multiple Oral Gavage and IM Exposure Paradigms[a]

	multiple oral gavage (10 mg/kg)					multiple IM exposure (5 mg/kg)[c]				
parameter[b]	AUCCL1	AUCCK1	AUCCM1	AUCCF1	AUCCV1	AUCCL1	AUCCK1	AUCCM1	AUCCF1	AUCCV1
BW	0.68	0.68	0.68	0.68	0.68	0.68	0.68	0.68	0.68	0.68
VLC1	0.63	0.63	0.63	0.63	0.63	0.63	0.63	0.63	0.63	0.63
K_a	0.92	0.92	0.92	0.92	0.92	-	-	-	-	-
K_{int}	−0.80	−0.80	−0.80	−0.80	−0.80	-	-	-	-	-
PL	0.81	0.31	0.31	0.31	0.31	0.81	0.31	0.31	0.31	0.31
PK1	-	0.99	-	-	-	0.99	-	-	-	-
PM1	-	-	0.85	-	-	-	-	0.85	-	-
PF1	−0.34	−0.34	−0.34	0.64	−0.34	−0.34	−0.34	−0.34	0.64	−0.34
KmC	0.72	0.72	0.72	0.72	0.72	0.72	0.72	0.72	0.72	0.72
Frac	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
KurineC	−0.51	−0.51	−0.51	−0.51	−0.51	−0.51	−0.51	−0.51	−0.51	−0.51

[a]- indicates a |NSC| smaller than 0.2. [b]Only parameters with at least one absolute value of NSC greater than 0.2 are presented. [c]AUCCL1, AUCCK1, AUCCM1, AUCCF1, and AUCCV1 represent 24-h area under M1 concentration curves in the liver, kidney, muscle, fat, and plasma, respectively. IM, intramuscular.

and 0.85, respectively, independent of exposure route. As expected, intestinal absorption rate constant (K_a) and intestinal transit rate constant (K_{int}) had high impact on all dose metrics after oral exposure with NSCs values of 0.92 and −0.80, respectively.

Monte Carlo Analysis. The present population PBPK model considered the probabilistic distributions of all model parameters. The distributions and variabilities of physiological parameters were previously collected, to the extent possible, directly from or calculated based on original experimental data.[43] The default coefficients of variance were used only for parameters without experimental data.[45−47] Thus, the present Monte Carlo simulations may represent a more realistic range of tissue M1 residue concentrations across a diverse population of animals than the measured data range from the residue depletion studies that were based on a limited number of animals. Monte Carlo analysis was performed to account for the interindividual variability across the population. Only sensitive parameters were subjected to Monte Carlo analysis in previous PBPK model.[25,27,33,47] The present model tested all parameters

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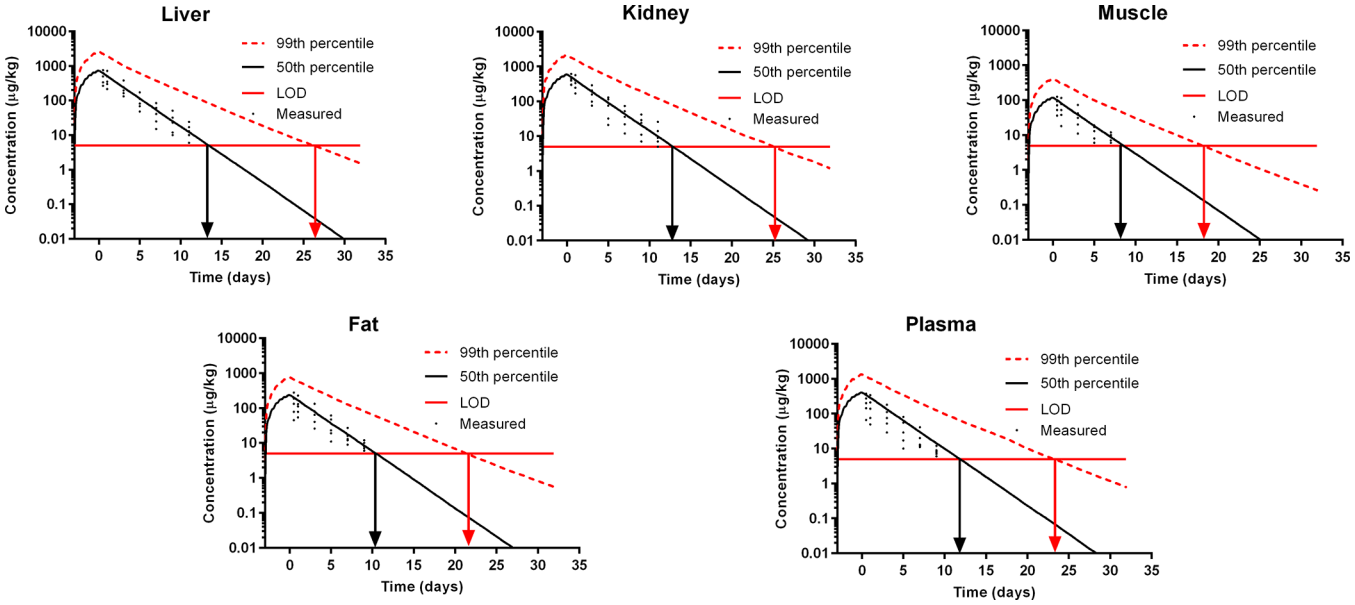

Figure 5. Monte Carlo analysis of the oral gavage model. Comparison of model predictions (solid line, 50th percentile; dotted line, 99th percentile) and observed data (squares) for M1 concentrations in liver, kidney, muscle, fat, and plasma of swine exposed to MEQ suspension via oral gavage at 10 mg/kg twice daily for 3 consecutive days. The Monte Carlo analysis included 1000 iterations.

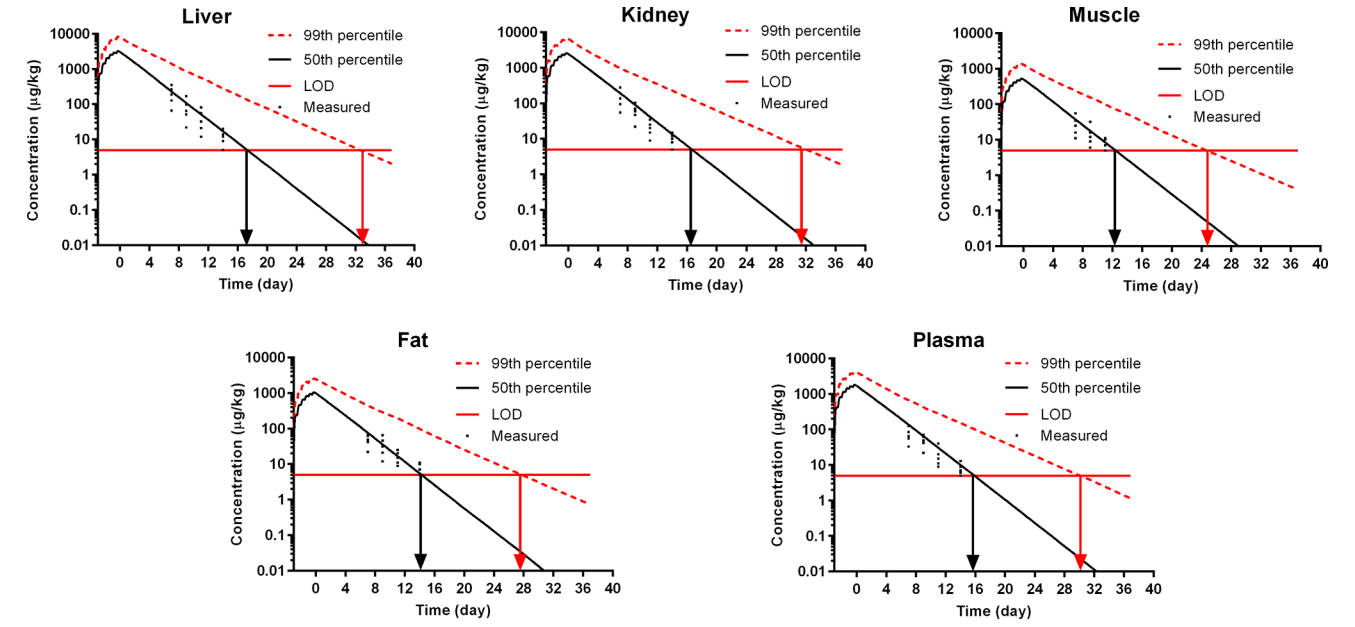

Figure 6. Monte Carlo analysis of the intramuscular (IM) injection model. Comparison of model predictions (solid line, 50th percentile; dotted line, 99th percentile) and observed data (squares) for M1 concentrations in liver, kidney, muscle, fat, and plasma of swine exposed to MEQ via IM injection at 5 mg/kg twice daily for 3 consecutive days. The Monte Carlo analysis included 1000 iterations.

that allow generating more realistic population predictions for food-producing animals, which has been applied for PBPK modeling for human drugs and environmental pollutants.[46,48] A representative Monte Carlo simulation was compared to measured concentrations in tissues of individual swine after multiple oral gavage and IM administration as presented in Figures 5 and 6, respectively. Overall, the measured data were within the 99th percentile of the population predictions generated by Monte Carlo simulations. However, the Monte Carlo analysis did not consider the correlation or covariance between parameters, which requires an advanced Bayesian method with Markov chain Monte Carlo simulation[49] that is an objective of our future study.

Model Application. As presented in Figures 5 and 6, liver tissue had the slowest depletion profiles after either oral gavage or IM administration. Monte Carlo simulations based on the present PBPK model suggest that the times needed for M1 concentrations to fall below the LOD in the liver for the 99th percentile of the population were 27 and 34 days after oral gavage and IM administration twice daily for 3 consecutive days, respectively. To our best knowledge, there are no officially established MRL or withdrawal periods for MEQ. Therefore, we are not able to make any comparison with the statutory

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withdrawal periods. Additionally, since there is no an established MRL, there is not enough information to calculate withdrawal period. Thus, we simply interpret our results as the time when no detectable concentrations of the M1 residue to be found in tissues for the 99th percentile of the population based on the current analytical method. However, once official MRL (or tolerance) is established, our results may help establish an appropriate withdrawal period.

In conclusion, we have successfully developed a population PBPK model for MEQ and its marker residue M1 in swine following multiple oral gavage and IM administration. Evaluation with multiple experimental data sets suggests reliable predictive ability of plasma and tissue depletion profiles of M1. Monte Carlo analysis was successfully incorporated into the PBPK model to predict depletion kinetic profiles and tissue residues of M1 in edible tissues in a diverse population of swine.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jafc.7b01740.

Mass balance differential equations; equations describing repeated oral gavage and intramuscular injection; equation describing liver metabolism; equation describing urine clearance; residue depletion experimental data; physiological parameter distributions; evaluation result of oral gavage model; model code (PDF)

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Notes

The authors declare no competing financial interest.

■ ABBREVIATIONS USED

AUC, area under the time−concentration curve; CYA, cyadox; IACUC, Institutional Animal Care and Use Committee; IM, intramuscular; LOD, limit of detection; M1, 1,4-bisdesoxymequindox; MEQ, mequindox; MRL, maximum residue level; NSC, normalized sensitivity coefficient; OLA, olaquindox; PBPK, physiologically based pharmacokinetic; PC, tissue/plasma partition coefficient; QCT, quinocetone; ROS, reactive oxygen species; WHO, World Health Organization

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