Simulation of Residue Accumulation and Elimination in Growing Animals

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1. *Introduction*

Exposure assessments involving dioxins and related compounds often include food chain pathways that require estimates of bioconcentration or biotransfer factors (BCF or BTF) in food producing animals. Ideally, BCFs should be measured at steady state, which has rarely been attained except in some measurements of milk concentrations in lactating cattle. Typical applications of pharmacokintic models to estimate BCFs at steady state, or measurements of environmental concentrations at presumed steady state, assume implicitly that inputs, pool sizes, and daily elimination rates are relatively constant; however, these factors are dynamic and change markedly during growth, fattening, and lactation[1]. A simple model was devised to examine the effects of changing feed intake and fat pool size during growth on the predicted concentrations of lipophilic residues in body fat. Pigs were used for this illustration because more adequate growth and composition data bases are available for this species, and there are fewer variations in the management and feeding of pigs during growth than other food animal species. A disadvantage of using pigs as a model is that less residue data are available for validation.

2. *Model Description*

The model covers the period from birth through the weight of 120 kg, which exceeds the typical slaughter weight in the U. S. The major assumptions of this model are that low concentrations of lipophilic compounds, including the dioxin-like compounds, are distributed uniformly in a single body fat compartment, and that accumulation and elimination are passive processes with rates proportional to concentrations. The change in body burden (ΔB) during a short time increment is

$$\Delta B = aI_{Comp} - kB \qquad (1)$$

where a is the absorption coefficient, I_{Comp} is the amount of ingested compound, k is the elimination (metabolism and/or excretion) rate constant, and B is the body burden. The body burden at time (t) is

$$B = B_{Initial} + \sum_{t=0}^{n} \Delta B \qquad (2)$$

and the concentration (C) in body fat at any time is

$$C = B/F \qquad (3)$$

where F is the quantity of body fat.

Table 1. Constants ± SE for Equation (5) predicting fat and protein composition of the growing pig.

Constant	Protein	Fat
a	0.1332943 ± 0.1302344	0.1117987 ± 0.3808369
b	0.0315458 ± 0.0066451	0.0378761 ± 0.0194319
c	0.0002274 ± 0.0000806	-0.0000064 ± 0.0002358
d	-0.0000001 ± 0.0000003	0.0000046 ± 0.0000008

The intake of a compound under environmental conditions is a function of the concentration of the compound in feed and the amount of feed consumed, which under *ad libitum* feeding is a function of body weight. The energy concentration of the diet also affects intake and a value of 14 MJ/kg was assumed to be typical of commercial swine diets when adapting the following equation from a National Research Council evaluation of feed intake of farm animals[2].

$$I_{Feed} = 4.003(1 - e^{-0.01768W}) \quad (4)$$

where I_{Feed} is intake of feed (kg/day), e is the base of the natural logarithms, and W is body weight (kg). This equation is valid for weights from 10 to 120 kg.

A serial slaughter experiment by Doornenbal[3-5] provided data to derive growth curves for the model. The data covered a range in age from 44 to 210 days and in weight from 10 to 130 kg. Data for the quantities (kg) of fat (F) and protein (P) were fitted to the following empirical equation by a general linear models procedure[6].

$$F \text{ or } P = a + bt + ct^2 + dt^3 \quad (5)$$

where t is time as days and a, b, c, and d are constants. Values of the constants for fat and protein equations are in Table 1. The fat and protein equations were then used as predictors of fat-free body mass (W_{FFB}), empty body weight (W_{Emp}) and live weight (W) using equations from Kielanowski[7].

$$W_{FFB} = 6.012P^{0.892} \quad (6)$$

$$W_{Emp} = W_{FFB} + F \quad (7)$$

$$W = (W_{Emp})/0.95 \quad (8)$$

Equations (1) through (8) were incorporated into a computer program. All simulations were run using time increments of a day, and provision was made for altering initial conditions and exposure scenarios.

3. *Model Simulations and Discussion*

A typical simulation result that involved animals exposed to a constant concentration of a compound in the diet from weaning at 50 days through 220 days of age is shown in Figure 1. The curves represent three absorption coefficients that are comparable to the absorption of 2,3,7,8-tetrachlordibenzo-*p*-dioxin (TCDD) from corn oil, normal diet, and soil as compiled by Fries and Paustenbach[1]. Elimination was assumed to be negligible in keeping with the 7-yr half-life of TCDD in man[8]. The magnitudes of the curves are proportional to the assumed absorption rates as stipulated in Eq. (1). An interesting feature of these

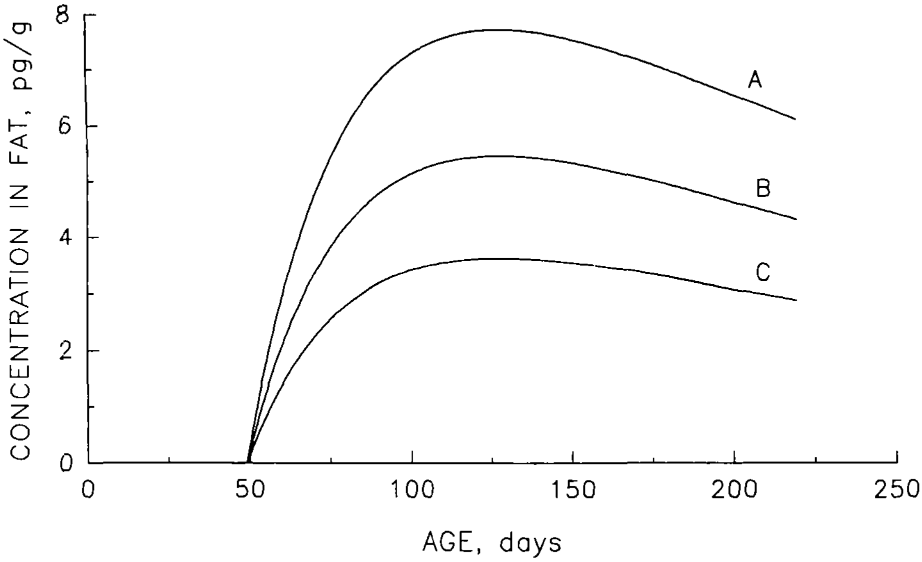

Figure 1. Simulated concentration of residues in fat pigs fed a diet with a constant residue concentration of 1 pg/g from 50 to 220 days of age. Assumed absorption rates of 85% (A), 60% (B), and 40% (C) are illustrated. Excretion and metabolism are considered negligible.

simulations is that the predicted concentrations peaked at about 100 days and then declined even though feed intake increased and concentration in the diet remained constant. This observation reflects the shift in energy partitioning from protein deposition to fat deposition as the animals age. The maximum predicted BFCs were 7.7 for 85% absorption (Curve A) and 5.4 for 60% absorption (Curve B). These values agree well with our previous conclusion, based on a review of the halogen hydrocarbon literature, that the maximum BFC for TCDD in nonlactating animals would be in the range of 5 to 6[1].

The general validity of the model was evaluated by comparing model predictions with observed values in the literature. One result is shown in Table 2. Pigs in this study had been unintentionally fed a feed containing chlordane and heptachlor residues[9]. The decline in concentration of these compounds was measured after the animals were placed on an uncontaminated diet. The recalcitrance of these compounds is confirmed by the finding that dilution in the enlarged body fat pool accounts for all of the concentration decline. A similar finding might be expected with the 2,3,7,8-substituted dioxins, which are resistant to metabolic degradation.

In addition to predicting concentrations of residues for assessment purposes, model simulations also can be used to identify gaps and deficiencies in the existing data bases and theories. When the model was used to predict residue accumulation, predicted values were consistently greater than observed values, which suggests inadequacies in selecting appropriate absorption coefficients and elimination rate constants. Absorption coefficients usually must be selected from studies with laboratory species that may not applicable to the diets of farm

Table 2. Predicted and observed concentrations of chlordane and heptachlor residues in 77-day old pigs fed an uncontaminated diet. Observed data are from Raisbeck et al[9].

	Heptachlor, ppm		Oxychlordane, ppm	
Age, days	Predicted	Observed	Predicted	Observed
77	35.1	35.1	4.8	4.8
98	20.7	17.5	2.8	3.1
119	14.0	13.7	1.9	2.2
140	10.2	8.7	1.4	1.6
161	7.8	7.3	1.1	1.4

animals. Rates of metabolism were inferred from the rates of concentration decline in excess of decline due to dilution. This method may underestimate the true metabolic rate if transport from fat to blood is the rate-limiting step in elimination.

The effect of changing feeding practices on residue accumulation and concentrations is an area that requires examination because the livestock industry is changing to meet consumer demand for meat with a lower fat content. This result can be attained restricting energy intake. At a given weight, pigs fed restricted energy deposit more protein and less fat in the body, but they consume more feed to reach that weight. If the assumptions in the model are correct, energy restriction would cause greater total accumulations and concentrations in fat from a given concentration of environmental contaminants like dioxins.

4. *References*

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