

Appendix D: Model Equations

D1: Delta Model

Chemical Abbreviations

DLM: deltamethrin

Compartment Abbreviations

BRN: brain
F: fat
GI: gastrointestinal
L: liver
PL: portal-liver
S: slowly-perfused tissue
R: richly-perfused tissue
P: plasma
E: erythrocytes

Primary Symbols

A_j : amount of deltamethrin in tissue j (μmol)
 V_j : volume of tissue j (L)
 Q_j : flow in tissue j (L/h)
 PC_j : tissue/plasma partition coefficient of tissue j
 PA_j : permeability-surface area product of tissue j (L/h)
 PV_j : plasma volume fraction of tissue j
 K_s : gastric absorption rate constant (h^{-1})
 K_i : intestinal absorption rate constant (h^{-1})
 K_{si} : GI transfer rate constant (h^{-1})

$V_{\text{max}1}$: maximum rate of metabolism of DLM in liver via oxidative metabolism ($\mu\text{mol/h}$)
 $V_{\text{max}2}$: maximum rate of metabolism of DLM in liver via hydrolytic metabolism ($\mu\text{mol/h}$)
 $V_{\text{max}3}$: maximum rate of metabolism of DLM in plasma via hydrolytic metabolism ($\mu\text{mol/h}$)
 $V_{\text{max}F}$: fecal excretion rate constant ($\mu\text{mol/h}$)

K_{m1} : concentration at half saturation for clearance of DLM in liver via oxidative metabolism ($\mu\text{mol/L}$)
 K_{m2} : concentration at half saturation for clearance of DLM in liver via hydrolytic metabolism ($\mu\text{mol/L}$)
 K_{m3} : concentration at half saturation for clearance of DLM in plasma via hydrolytic metabolism ($\mu\text{mol/L}$)
 K_{mF} : half saturation for fecal excretion ($\mu\text{mol/L}$)

The brain, and rapidly perfused tissues were modeled as flow-limited compartments, indicating that the rate of transfer of DLM to the j -th tissue is limited by the rate at which the chemical in plasma reaches the compartment.

$$V_j \frac{dC_j}{dt} = Q_j \left(C_a - \frac{C_j}{PC_j} \right) \quad (D1.1)$$

where concentration of DLM in the flow-limited tissue is defined as:

$$C_j = \frac{A_j}{V_j} \quad (D1.2)$$

The concentration of DLM in the arterial plasma, C_a , is defined as:

$$C_a = \frac{A_p}{V_p} \quad (D1.3)$$

The rate of absorption of DLM from the lumen into the blood supply of the GI tract was described empirically using two compartments. The uptake kinetic constants include stomach and intestinal absorption rate constants (i.e., K_s and K_i , respectively) and the gastric-emptying rate constant, K_{si} . The rate of change in the stomach (D1.4) and intestine (D1.4) are as follows:

$$\frac{dA_s}{dt} = K_s A_s - K_{si} A_i \quad (D1.4)$$

$$\frac{dA_i}{dt} = K_{si} A_s - K_i A_i - rFECPO \quad (D1.5)$$

where A_s and A_i are the amount of DLM in stomach and intestine, and $rFECPO$ is the competing rate of fecal elimination ($\mu\text{mol/h}$) from the intestinal lumen:

$$rFECPO = \frac{V \max F \times C_i}{K_m F + C_i} \quad (D1.6)$$

C_i is the concentration in the intestine and is defined as A_i/V_{gij} , where V_{gij} is the volume of gastric juice. The rate of change in the GI compartment is thus:

$$V_{GI} \frac{dC_{GI}}{dt} = Q_{GI} \left(C_a - \frac{C_{GI}}{PC_{GI}} \right) + \frac{dA_s}{dt} + \frac{dA_i}{dt} \quad (D1.7)$$

Ingested DLM is primarily absorbed from the GI tract into the portal vein and transported directly to the liver. The movement of compound in and out of the liver is described by the equation:

$$V_L \frac{dC_L}{dt} = Q_L \left(C_a - \frac{C_L}{PC_L} \right) + Q_{PL} \left(C_{PL} - \frac{C_L}{PC_L} \right) - rCYP - rCaE \quad (D1.8)$$

where $rCYP$ and $rCaE$ correspond to oxidative and hydrolytic clearance in the liver:

$$rCYP = \frac{V_{max1} \times C_L}{K_{m1} + C_L}, \quad (D1.9)$$

$$rCaE = \frac{V_{max2} \times C_L}{K_{m2} + C_L} \quad (D1.10)$$

The fat and slowly perfused tissues were modeled as diffusion-limited compartments. We assume that the rate of transfer of DLM to the j -th tissue is limited by the rate of transfer across cellular membrane. The movement in and out of the vascular space (D1.11) and tissue space (D1.12) are mediated by the permeability surface-area product (PA_j) in the following equations:

$$\frac{dA_jP}{dt} = Q_j (C_a - C_jP) + PA_j (CV_j - C_jP) \quad (D1.11)$$

$$\frac{dA_j}{dt} = PA_j (C_jP - CV_j) \quad (D1.12)$$

Where the concentration in the plasma-vascular space, C_jP (D1.13), tissue space (D1.14), and venous-equilibrated concentration (D1.15) are defined as:

$$C_jP = A_jP / PV_j \times V_j \quad (D1.13)$$

$$C_j = A_j / (1 - PV_j) \times V_j \quad (D1.14)$$

$$CV_j = C_j / PC_j \quad (D1.15)$$

The plasma volume fraction of the j -th tissue, PV_j , was based on the blood volume fraction (BV_j):

$$PV_j = BV_j \times PV_{Blood} / (1 - [BV_j(1 - PV_{Blood})]) \quad (D1.16)$$

The concentration of chemical in venous plasma:

$$CV = (QF \times CFP + QS \times CSP + QBRN \times CVBRN \dots \quad (D1.17)$$

$$+ QR \times CVR + (QL + QPL)CVL) / QP$$

And, the rate of change of DLM in the arterial plasma:

$$\frac{dAP}{dt} = QP(CV - CA) + PAE((CE/PCE) - CA) \dots \quad (D1.18)$$

$$- rCaEP + rIV$$

where $rCaEP$ corresponds to hydrolytic clearance in the plasma:

$$rCaEP = \frac{V_{max} \times 3 \times CV}{Km + 3 \times CV} \quad (D1.19)$$

and, where rIV is the rate of iv dosing. The movement of DLM in and out of the red blood cells is governed by the equation:

$$\frac{dAE}{dt} = PAE \left(Ca - \frac{CE}{PCE} \right) \quad (D1.20)$$