

Supplementary Material

Transfer of Polychlorinated Dibenzop-dioxins and Dibenzofurans (PCDD/Fs) and Polychlorinated Biphenyls (PCBs) from Oral Exposure into Cow's Milk - Part II: Toxicokinetic Predictive Models for Risk Assessment

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Chapter S-1: 2-compartment model

The matrix form of this model is given by

$$\frac{d}{dt}A(t) = MA(t) + I, \quad (S1)$$

with transition matrix M given by

$$\begin{pmatrix} -k_{Cent-Fat} - k_{Milk} & k_{Fat-Cent} \\ k_{Cent-Fat} & -k_{Fat-Cent} \end{pmatrix} \quad (S2)$$

and the input vector

$$I = \begin{pmatrix} F_{abs}Dose \\ 0 \end{pmatrix} \quad (S3)$$

for the given quantity vector

$$A(t) = \begin{pmatrix} A_{Cent}(t) \\ A_{Fat}(t) \end{pmatrix}. \quad (S4)$$

Chapter S-2: The original model by Derks

The matrix form of this model is given by

$$\frac{d}{dt}A(t) = MA(t) + I \quad (S5)$$

with transition matrix M given by

$$\begin{pmatrix} -\frac{F_Q Q_{Fat} + \sum_i Q_i}{V_{Blood}} & \frac{F_Q Q_{Fat}}{F_Q Q_{Fat}} & \frac{Q_{Liver}}{V_{Liver} P_{Liver}} & \frac{Q_{Slow}}{V_{Slow} P_{Slow}} & \frac{Q_{Udder}}{V_{Udder} P_{Udder}} \\ \frac{F_Q Q_{Fat}}{F_Q Q_{Fat}} & -\frac{F_{Fat} P_{Fat}}{V_{Fat} P_{Fat}} & 0 & 0 & 0 \\ \frac{Q_{Liver}}{V_{Liver} P_{Liver}} & 0 & -\frac{Q_{Liver}}{V_{Liver} P_{Liver}} - k_{met} & 0 & 0 \\ \frac{Q_{Slow}}{V_{Slow} P_{Slow}} & 0 & 0 & -\frac{Q_{Slow}}{V_{Slow} P_{Slow}} & 0 \\ \frac{Q_{Udder}}{V_{Udder} P_{Udder}} & 0 & 0 & 0 & -\frac{Q_{Udder}}{V_{Udder} P_{Udder}} - \frac{CLM}{V_{Udder}} \end{pmatrix} \quad (S6)$$

and the input vector

$$I = \begin{pmatrix} 0 \\ 0 \\ F_{abs} Dose \\ 0 \\ 0 \\ 0 \end{pmatrix} \quad (S7)$$

for the given state, or “quantity”, vector

$$A(t) = \begin{pmatrix} A_{Blood}(t) \\ A_{Fat}(t) \\ A_{Liver}(t) \\ A_{Rich}(t) \\ A_{Slow}(t) \\ A_{Udder}(t) \end{pmatrix}. \quad (S8)$$

Chapter S-3: Derks model without udder compartment

The matrix form of this model is given by

$$\frac{d}{dt}A(t) = MA(t) + I \quad (S9)$$

with transition matrix M given by

$$\begin{pmatrix} -\frac{F_Q Q_{Fat} + \sum_i Q_i}{V_{Blood}} - CL_{Milk} P_{Milk} & \frac{F_Q Q_{Fat}}{V_{Fat} P_{Fat}} & \frac{Q_{Liver}}{V_{Liver} P_{Liver}} & \frac{Q_{Rich}}{V_{Rich} P_{Rich}} & \frac{Q_{Slow}}{V_{Slow} P_{Slow}} \\ \frac{F_Q Q_{Fat}}{V_{Blood}} & -\frac{F_Q Q_{Fat}}{V_{Fat} P_{Fat}} & 0 & 0 & 0 \\ \frac{Q_{Liver}}{V_{Blood}} & 0 & -\frac{Q_{Liver}}{V_{Liver} P_{Liver}} - k_{met} & 0 & 0 \\ \frac{Q_{Rich}}{V_{Blood}} & 0 & 0 & -\frac{Q_{Rich}}{V_{Rich} P_{Rich}} & 0 \\ \frac{Q_{Slow}}{V_{Blood}} & 0 & 0 & 0 & -\frac{Q_{Slow}}{V_{Slow} P_{Slow}} \end{pmatrix} \quad (S10)$$

and the input vector

$$I = \begin{pmatrix} 0 \\ 0 \\ F_{abs} Dose \\ 0 \\ 0 \end{pmatrix} \quad (S11)$$

for the given quantity vector

$$A(t) = \begin{pmatrix} A_{Blood}(t) \\ A_{Fat}(t) \\ A_{Liver}(t) \\ A_{Rich}(t) \\ A_{Slow}(t) \end{pmatrix}. \quad (S12)$$

Chapter S-4: The original fugacity model by McLachlan

As this model only contains a single differential equation it can be reformulated into the form

$$\frac{d}{dt}(f_{Fat}(t)V_{Fat}Z_{Fat}) = Mf_{Fat}(t) + I. \quad (S13)$$

Here

$$M = \left(1 - \frac{D_{Dig-Blood}Dose}{D_{Blood}D_{Dig}}\right)^{-1} \frac{D_{Blood-Fat}^2}{D_{Blood}} - D_{Blood-Fat}, \quad (S14)$$

$$I = \left(1 - \frac{D_{Dig-Blood}Dose}{D_{Blood}D_{Dig}}\right)^{-1} \left(\frac{D_{Dig-Blood}D_{Blood-Fat}Dose}{D_{Blood}D_{Dig}}\right). \quad (S15)$$

with

$$D_{Blood} := D_{Dig-Blood} + D_{Milk} + D_{Blood-Fat} + D_{Blood-Meta}, \quad (S16)$$

$$D_{Dig} := D_{Dig-Blood} + D_{Exc} + D_{Dig-Meta}. \quad (S17)$$

The other two fugacities can then be calculated by

$$f_{Blood} = \left(1 - \frac{D_{Dig-Blood}Dose}{D_{Blood}D_{Dig}}\right)^{-1} \left(\frac{D_{Blood-Fat}f_{Fat}}{D_{Blood}} + \frac{D_{Dig-Blood}Dose}{D_{Blood}D_{Dig}}\right) \quad (S18)$$

$$f_{Dig} = \frac{Dose + f_{Blood}D_{Blood-Dig}}{D_{Dig}} \quad (S19)$$

Chapter S-5: The fugacity model by Binelli

The matrix form of this model is given by

$$\frac{d}{dt}f(t) = Mf(t) + I \quad (\text{S20})$$

with transition matrix M given by

$$\begin{pmatrix} -\frac{D_{Exc} + D_{Dig-Meta}}{V_{Dig}Z_{Dig}} & \frac{D_{Blood-Dig}}{V_{Dig}Z_{Dig}} & 0 \\ \frac{D_{Blood-Dig}}{V_{Blood}Z_{Blood}} & -\frac{D_{Blood-Dig} + D_{Blood-fat} + D_{Milk} + D_{Blood-Meta}}{V_{Blood}Z_{Blood}} & \frac{D_{Blood-Fat}}{V_{Blood}Z_{Blood}} \\ 0 & \frac{D_{Blood-Fat}}{V_{Fat}Z_{Fat}} & -\frac{D_{Blood-Fat}}{V_{Fat}Z_{Fat}} \end{pmatrix} \quad (\text{S21})$$

and the input vector

$$I = \begin{pmatrix} \frac{D_{Grass}f_{Grass} + D_{Conc}f_{Conc} + D_{Soil}f_{Soil}}{V_{Dig}Z_{Dig}} \\ 0 \\ 0 \end{pmatrix} \quad (\text{S22})$$

for the given quantity vector

$$f(t) = \begin{pmatrix} f_{Dig}(t) \\ f_{Blood}(t) \\ f_{Fat}(t) \end{pmatrix}. \quad (\text{S23})$$

Chapter S-6: MacLachlans PBPK model

The matrix form of this model is given by

$$\frac{d}{dt}A(t) = MA(t) + I \quad (\text{S24})$$

(S25)

$$\begin{pmatrix}
-\frac{F_Q Q_{Fat} + \sum_i Q_i}{V_{Blood}} & \frac{F_Q Q_{Fat}}{V_{Fat} P_{Fat}} & \frac{Q_{Liver}}{V_{Liver} P_{Liver}} & \frac{Q_{Muscle}}{V_{Muscle} P_{Muscle}} & \frac{Q_{Kidney}}{V_{Kidney} P_{Kidney}} & \frac{Q_{Rest}}{V_{Rest} P_{Rest}} & \frac{Q_{Udder}}{V_{Udder} P_{Udder}} & 0 \\
\frac{F_Q Q_{Fat}}{V_{Blood}} & -\frac{F_Q Q_{Fat}}{V_{Fat} P_{Fat}} & 0 & 0 & 0 & 0 & 0 & 0 \\
\frac{Q_{Liver}}{V_{Blood}} & 0 & -\frac{Q_{Liver}}{V_{Liver} P_{Liver}} - \frac{k_{met}}{P_{Liver}} & 0 & 0 & 0 & 0 & F_{abs} k_a \\
\frac{Q_{Liver}}{V_{Blood}} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\frac{Q_{Muscle}}{V_{Blood}} & 0 & 0 & -\frac{Q_{Muscle}}{V_{Muscle} P_{Muscle}} & 0 & 0 & 0 & 0 \\
\frac{Q_{Kidney}}{V_{Blood}} & 0 & 0 & 0 & -\frac{Q_{Kidney}}{V_{Kidney} P_{Kidney}} & 0 & 0 & 0 \\
\frac{Q_{Rest}}{V_{Blood}} & 0 & 0 & 0 & 0 & -\frac{Q_{Rest}}{V_{Rest} P_{Rest}} & 0 & 0 \\
\frac{Q_{Rich}}{V_{Udder}} & 0 & 0 & 0 & 0 & 0 & -\frac{Q_{Udder}}{V_{Udder} P_{Udder}} - \frac{CL_M P_{Udder}}{V_{Udder}} & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & -k_a
\end{pmatrix}$$

with transition matrix M given by

and the input vector

$$I = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ Dose \end{pmatrix} \quad (\text{S26})$$

for given quantity vector

$$A(t) = \begin{pmatrix} A_{Blood}(t) \\ A_{Fat}(t) \\ A_{Liver}(t) \\ A_{Muscle}(t) \\ A_{Kidney}(t) \\ A_{Rest}(t) \\ A_{Udder}(t) \\ A_{Rumen}(t) \end{pmatrix}. \quad (\text{S27})$$

Chapter S-7: Solving the linear differential equations

A stable linear differential equation of the form

$$\frac{d}{dt}A(t) = MA(t) + I \quad (\text{S28})$$

with a n -dimensional matrix M (stability $\Rightarrow M$ is invertible) and constant vector I has a unique solution, which is given by

$$A(t) = x^* + e^{Mt}(x_0 - x^*) \quad (\text{S29})$$

with

$$x^* = -M^{-1}I \quad (\text{S30})$$

and x_0 being the starting condition. Additionally, it holds true that

$$A(t) \xrightarrow{t \rightarrow \infty} x^*, \quad (\text{S31})$$

which means that x^* is the steady state of our system.

Note that the stability condition for the equation (S28) is met if and only if the real parts of all eigenvalues of M are all negative. Intuitively, this means that if the input vector $I \equiv 0$ then for any given starting contamination the systems total contamination would converge to 0 over time, which is always given for our systems due to the constant excretion via milk fat, i.e. for all here presented models the differential equation (S28) is stable.

During the depuration phase our system can be described by the following differential equation

$$\frac{d}{dt}A_D(t) = MA_D(t) \quad (\text{S32})$$

and it's solution is given by

$$A_D(t) = e^{Mt}x_{0,D}, \quad (\text{S33})$$

where $x_{0,D}$ is starting vector of the depuration phase. Note here that we do not need the stability assumption from above for this solution to be valid.

For deriving a more explicit formula using either equation (S29) or equation (S33), the most difficult part to write down explicitly is the exponential e^{Mt} . This can be simplified if M is diagonalizable, i.e., there exists an invertible matrix S such that

$$M = SDS^{-1} \quad (\text{S34})$$

with D being diagonal matrix containing the eigenvalues of M on it's diagonal. Then

$$e^{Mt} = Se^{Dt}S^{-1} = \sum_{i=1}^n C_i e^{\lambda_i t}, \quad (\text{S35})$$

where C_i are constant matrices and λ_i are the eigenvalues of M , which means that the exponential rate constants are given by the eigenvalues of M . The eigenvalues λ_i can be quite efficiently computed via numerical methods.

Note that the diagonalization condition is met if all eigenvalues of M are unique, i.e. we have n different eigenvalues.