Graphical Abstract

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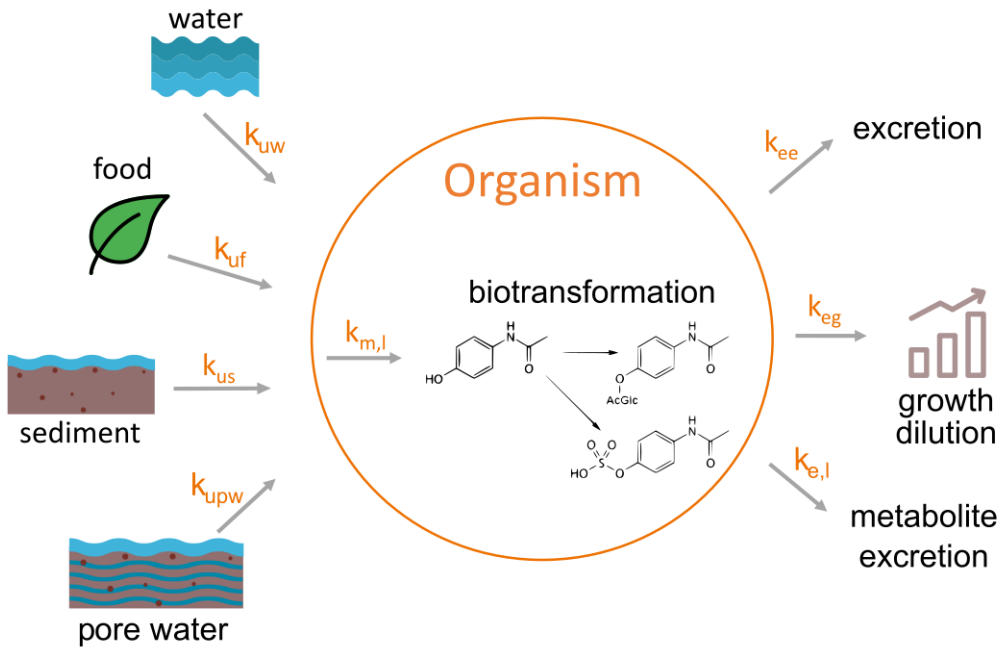

Generic solving of one-compartment toxicokinetic models

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Abstract

This paper gives the full analytical solution of the generic set of ordinary differential equations that define one-compartment toxicokinetic models. These models describe uptake and elimination processes taking place within living organisms when exposed to chemical substances. The models solved in this paper consider living organisms as a unique compartment, into which a parent compound enters via several possible exposure routes and from which it is eliminated as well as its potential metabolites. Benefiting from generic solutions of one-compartment toxicokinetic models is particularly useful when fitting them to experimental data, facilitating the writing of the inference algorithms leading to parameter estimates. Additionally, these models are of crucial interest in environmental risk assessment for the calculation of bioaccumulation metrics as required by regulators in support of decision making when they evaluate dossiers for marketing authorisation of active substances.

Keywords: ordinary differential equations, environmental risk assessment, living organisms, active substances, TK models, bioaccumulation metrics
MSC: 92B05

1. Introduction

In this paper, we consider a very generic one-compartment toxicokinetic (TK) model describing uptake and elimination processes taking place within living organisms when exposed to chemical substances. On a general point

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of view, TK models are of particular interest in Environmental Risk Assessment [6], for example when the calculation of bioaccumulation metrics is required by regulators in support of decision making when they evaluate dossiers for marketing authorisation of active substances.

The generic TK model considered in this paper is a one-compartment model considering organisms as a whole in which compounds may enter and from which these compounds can be eliminated). Note that there exists more complex TK models refining the description of contamination pathways within organisms, distinguishing organs and tissues from physiological hypotheses on potential targets of exposure compounds; such physiologically-based TK (PBTK) models mainly apply for humans [9, 8] or big mammals [3, 5]. The generic one-compartment TK model considered in this paper has the advantage of accounting for several exposure sources (*e.g.*, by water, sediment and/or food), several elimination processes (*e.g.*, direct elimination, dilution by growth and/or biotransformation) and several potential metabolites of the parent chemical compound to which organisms are exposed [7]. This generic TK model is composed of two sets of ordinary differential equations (ODE), one set for the accumulation phase (that includes both bioaccumulation and elimination processes, as those related to the biotransformation of the parent compound into metabolites) and during which organisms are exposed to a given compound; the second one for the depuration phase (with only elimination processes including biotransformation) and during which organisms are transferred into a clean medium. The transition from one set of ODE to the other takes place at time t_c corresponding to the duration of the accumulation phase (see Table 1).

In practice, the exposure concentration to which organisms are exposed may vary over time as in realistic environments, but then, there is no analytical solution of the TK model; only a numerical solution can be calculated in this case with an appropriate algorithm. Our paper thus assumes that the exposure concentration remains constant over time whatever the exposure source. Such an experimental condition can be ensured for most of the chemical compound when performing laboratory experiments. In addition, this assumption allows to provide the exact solution of the full one-compartment TK model by considering as many routes of exposure and as many elimination processes as desired, as well as an infinite number of phase I metabolites, *i.e.*, directly derived from the parent compound to which organisms are exposed. Note that [4] already provided a partially resolved one-compartment TK model but only for the accumulation phase and one exposure route.

2. The one-compartment TK set of ODE

2.1. Accumulation phase ($0 \leqslant t \leqslant t_c$)

The set of ODE describing the accumulation phase ($0 \leqslant t \leqslant t_c$) writes as follows:

$$\begin{cases} \dfrac{dC_p(t)}{dt} = U - (E + M) \times C_p(t) & \text{(1.a)} \\ \dfrac{dC_{m_\ell}(t)}{dt} = k_{m_\ell} \times C_p(t) - k_{e_\ell} \times C_{m_\ell}(t), \, \forall \ell = 1 \dots L & \text{(1.b)} \end{cases}$$

All parameters and variables, with their meaning and units when applicable, are gathered together in Table 1.

Equation (1.a) for the parent compound is a linear first-order ODE with constant coefficients and a second member. Equation (1.a) admits $C_{part}(t) = \frac{U}{E+M} = R$ as a particular solution. Equation (1.a) without its second member writes:

$$\frac{dC_p(t)}{dt} - (E+M) \times C_p(t) = 0 \Leftrightarrow C_p(t) = K \times e^{-(E+M)\times t},\ K \in \mathbb{R}^+ \quad (2)$$

Given the initial condition $C(t=0) = C_0$ ($C_0 \geqslant 0$), we finally get the full analytical solution of Equation (1.a), providing the internal concentration of the parent compound over time during the accumulation phase ($0 \leqslant t \leqslant t_c$) as follows:

$$C_p(t) = (C_0 - R) \times e^{-(E+M)\times t} + R \quad (3)$$

See Table 1 for the definition of parameter R.

Equation (1.b) is also a linear first-order ODE with constant coefficients and a second member, with the following analytical solution when removing its second member:

$$\frac{dC_{m_\ell}(t)}{dt} - k_{e_\ell} \times C_{m_\ell}(t) = 0 \Leftrightarrow C_{m_\ell}(t) = K \times e^{-k_{e_\ell}\times t},\ K \in \mathbb{R}^+,\ \forall \ell = 1 \ldots L \quad (4)$$

The method of variation of a constant consists of writing the general solution of Equation (1.b) as:

$$C_{m_\ell}(t) = K(t) \times e^{-k_{e_\ell}\times t} \quad (5)$$

and to find function $K(t)$ by deriving $C_{m_\ell}(t)$ and re-injecting the result into

Equation (5). The derivative from Equation (1.b) writes:

$$\frac{dC_{m_\ell}(t)}{dt} = \frac{dK(t)}{dt} \times e^{-k_{e_\ell} \times t} - K(t) \times k_{e_\ell} \times e^{-k_{e_\ell} \times t} \tag{6}$$

while the re-injection into Equation (1.b) leads to:

$$\frac{dK(t)}{dt} = k_{m_\ell} \times \left((C_0 - R) \times e^{D_\ell \times t} + R \times e^{k_{e_\ell} \times t} \right) \tag{7}$$

which integrates into:

$$K(t) = k_{m_\ell} \times \left(\frac{C_0 - R}{D_\ell} \times e^{D_\ell \times t} + \frac{R}{k_{e_\ell}} \times e^{k_{e_\ell} \times t} \right) + C,\ C \in \mathbb{R} \tag{8}$$

See Table 1 for the definition of parameter D_ℓ.

The general solution of Equation (1.b) finally writes as follows:

$$C_{m_\ell}(t) = k_{m_\ell} \times \left(\frac{C_0 - R}{D_\ell} \times e^{-(E+M) \times t} + \frac{R}{k_{e_\ell}} \right) + C \times e^{-k_{e_\ell} \times t},\ C \in \mathbb{R} \tag{9}$$

Let's consider the following initial condition $C_{m_\ell}(t = 0) = 0$, biologically meaning that when the accumulation phase starts, organisms are only exposed to the parent compound, so that there are no metabolites within. Then, we finally get the full analytical solution of Equation (1.b) providing the internal concentration of metabolite ℓ over time during the accumulation phase:

$$C_{m_\ell}(t) = k_{m_\ell} \times \left(\frac{C_0 - R}{D_\ell} \times \left(e^{-(E+M) \times t} - e^{-k_{e_\ell} \times t} \right) + \frac{R}{k_{e_\ell}} \times \left(1 - e^{-k_{e_\ell} \times t} \right) \right) \tag{10}$$

2.2. Depuration phase ($t \geq t_c$)

The set of ODE describing the depuration phase ($t \geq t_c$) writes as follows:

$$\begin{cases} \dfrac{dC_p(t)}{dt} = -(E+M) \times C_p(t) & \text{(11.a)} \\ \dfrac{dC_{m_\ell}(t)}{dt} = k_{m_\ell} \times C_p(t) - k_{e_\ell} \times C_{m_\ell}(t),\ \forall \ell = 1 \dots L & \text{(11.b)} \end{cases}$$

All parameters and variables, with their meaning and units when applicable, are gathered together in Table 1.

Equation (11.a) is a linear first-order ODE without a second member, so that it has a general solution of the following form:

$$C_p(t) = K \times e^{-(E+M)\times t},\ K \in \mathbb{R}^+ \tag{12}$$

For the depuration phase and the parent compound, the initial condition comes from the calculation of the internal parent compound concentration at the end of the accumulation phase (*i.e.*, at time $t = t_c$) thanks to solution (3):

$$C_p(t_c) = (C_0 - R) \times e^{-(E+M)\times t_c} + R \tag{13}$$

From the general analytical solution given by Equation (12), we get $C_p(t_c) = Ke^{-(E+M)t_c}$ leading to a constant K in Equation (12) equals to:

$$K = C_0 - R + R \times e^{(E+M)\times t_c} \tag{14}$$

Then, the final analytical solution of Equation (11.a) providing the internal concentration of the parent compound over time during the depuration phase

$(t \geq t_c)$ writes:

$$C_p(t) = \left(C_0 - R \times \left(1 - e^{(E+M)\times t_c}\right)\right) \times e^{-(E+M)\times t} \tag{15}$$

For simplicity reasons, Equation (15) above can be written as $C_p(t) = Qe^{-(E+M)\times t}$ with Q as defined in Table 1.

Equation (11.b) is a linear first-order ODE with constant coefficients and a second member. The analytical solution of Equation (11.b) without its second member writes:

$$C_{m_\ell}(t) = K \times e^{-k_{e_\ell}\times t},\ K \in \mathbb{R}^+ \tag{16}$$

As previously, the method of the variation of a constant provides the general solution of Equation (11.b) as $C_{m_\ell}(t) = K(t)e^{-k_{e_\ell}t}$, requiring to search for function $K(t)$.

The derivative of $C_{m_\ell}(t)$ from Equation (16) writes:

$$\frac{dK(t)}{dt} = e^{-k_{e_\ell}\times t} - k_{e_\ell} \times K(t) \times e^{-k_{e_\ell}\times t} \tag{17}$$

The re-injection of derivative (17) into Equation (11.b) leads to:

$$\frac{dK(t)}{dt} = k_{m_\ell} \times Q \times e^{D_\ell \times t} \tag{18}$$

which integrates into:

$$K(t) = k_{m_\ell} \times \frac{Q}{D_\ell} \times e^{D_\ell \times t} + C,\ C \in \mathbb{R} \tag{19}$$

finally leading to the general analytical solution of Equation (11.b):

$$C_{m_\ell}(t) = k_{m_\ell} \times \frac{Q}{D_\ell} \times e^{-(E+M)\times t} + C \times e^{-k_{e_\ell}\times t},\ C \in \mathbb{R} \tag{20}$$

Constant C can be determined from the initial condition, *i.e.*, from the internal concentration of metabolite ℓ at $t = t_c$ both at the end of the accumulation phase and at the beginning of the depuration phase. From Equation (20), we get $C_{m_\ell}(t_c) = k_{m_\ell} \frac{Q}{D_\ell} e^{-(E+M)t_c} + Ce^{-k_{e_\ell}t_c}$, and from Equation (10), we get $C_{m_\ell}(t_c) = k_{m_\ell} \left(\frac{C_0 - R}{D_\ell} \left(e^{-(E+M)t_c} - e^{-k_{e_\ell}t_c} \right) + \frac{R}{k_{e_\ell}} \left(1 - e^{-k_{e_\ell}t_c} \right) \right)$. Finally, we get the following expression for constant C:

$$C = k_{m_\ell} \times \left(\frac{R}{k_{e_\ell}} \times \left(e^{k_{e_\ell}\times t_c} - 1 \right) - \frac{C_0 - R}{D_\ell} - \frac{R}{D_\ell} \times e^{k_{e_\ell}\times t_c} \right) \tag{21}$$

Replacing constant C in Equation (20) gives the final analytical solution of Equation (11.b) providing the internal concentration of metabolite ℓ for the depuration phase ($t > t_c$) as follows:

$$\begin{aligned} C_{m_\ell}(t) = k_{m_\ell} \times \Bigg(& \frac{Q}{D_\ell} \times e^{-(E+M)\times t} + \frac{R}{k_{e_\ell}} \times \left(e^{-k_{e_\ell}\times(t-t_c)} - e^{-k_{e_\ell}\times t} \right) \\ & - \frac{C_0 - R}{D_\ell} \times e^{-k_{e_\ell}\times t} - \frac{R}{D_\ell} \times e^{-k_{e_\ell}\times(t-t_c)} \Bigg) \end{aligned} \tag{22}$$

Replacing constant Q by its own expression (Table 1) leads to:

$$\begin{aligned} C_{m_\ell}(t) = k_{m_\ell} \times \Bigg(& \frac{C_0 - R}{D_\ell} \times \left(e^{-(E+M)\times t} - e^{-k_{e_\ell}\times t} \right) + \frac{R}{k_{e_\ell}} \times \left(e^{-k_{e_\ell}\times(t-t_c)} - e^{-k_{e_\ell}\times t} \right) \\ & + \frac{R}{D_\ell} \times \left(e^{-(E+M)\times(t-t_c)} - e^{-k_{e_\ell}\times(t-t_c)} \right) \Bigg) \end{aligned} \tag{23}$$

3. The generic set of solutions

Reminding the following intermediate notations $R = \frac{U}{E+M}$ and $D_\ell = k_{e_\ell} - (E+M)$ we finally obtain the full set of analytical solutions corresponding the whole one-compartment TK set of ODE describing the time-course for both the accumulation and the depuration phases of the parent compound and its potential metabolites.

- The analytical solution for the internal concentration of the parent compound during the accumulation phase, previously referred as Equation (3):

$$C_p(t) = \left(C_0 - \frac{U}{E+M}\right) \times e^{-(E+M)\times t} + \frac{U}{E+M}, \forall 0 \leqslant t \leqslant t_c$$

- The analytical solution for the internal concentration of metabolite ℓ during the accumulation phase, previously referred as Equation (10):

$$C_{m_\ell}(t) = \frac{k_{m_\ell}}{k_{e_\ell}} \times \frac{U}{E+M} \times \left(1 - e^{-k_{e_\ell}\times t}\right) + \frac{k_{m_\ell}}{k_{e_\ell} - (E+M)} \times \left(C_0 - \frac{U}{E+M}\right) \times \left(e^{-(E+M)\times t} - e^{-k_{e_\ell}\times t}\right), \forall 0 \leqslant t \leqslant t_c$$

- The analytical solution for the internal concentration of the parent compound during the depuration phase, previously referred as Equation (15):

$$C_p(t) = \left(C_0 - \frac{U}{E+M} \times \left(1 - e^{(E+M)\times t_c}\right)\right) \times e^{-(E+M)\times t}, \forall t > t_c$$

- The analytical solution for the internal concentration of metabolite ℓ during the depuration phase, previously referred as Equation (23):

$$C_{m_\ell}(t) = \frac{k_{m_\ell}}{k_{e_\ell} - (E+M)} \times \left(C_0 - \frac{U}{E+M}\right) \times \left(e^{-(E+M)\times t} - e^{-k_{e_\ell}\times t}\right) + \frac{k_{m_\ell}}{k_{e_\ell}} \times \frac{U}{E+M} \times \left(e^{-k_{e_\ell}\times(t-t_c)} - e^{-k_{e_\ell}\times t}\right) + \frac{k_{m_\ell}}{k_{e_\ell} - (E+M)} \times \frac{U}{E+M} \times \left(e^{-(E+M)\times(t-t_c)} - e^{-k_{e_\ell}\times(t-t_c)}\right), \forall t > t_c$$

We could fully finish the writing of the very final generic analytical solution of the one-compartment TK model with all the parameters to estimate from observed data using an inference process by replacing constants U, E and M by $U = \sum_{i=1}^{I} k_{u_i} \times c_i$, $E = \sum_{j=1}^{J} k_{e_j}$ and $M = \sum_{\ell=1}^{L} k_{m_\ell}$, respectively.

4. Model simulations

Model simulations of the generic set of solutions (Equations (3), (10), (15) and (23)) were performed under the R software with 500 time points in $[0; t_f]$ where t_F stands for the final time of each simulation. These simulations illustrate the toxicokinetic in three case studies where different compounds are bioaccumulated by different species. In order to proceed, the time duration of the accumulation phase (parameter t_c) is required, as well as the exposure concentrations in the media and the model parameter values (Table 2). Figures 1 to 5 show the simulations of internal concentrations over time for the three species-compound combinations considered in case studies described below. All necessary parameter values were directly picked-up from the MOSAIC$_{bioacc}$ (`https://mosaic.univ-lyon1.fr/bioacc`) exam-

ple files. For each case study, TK model parameters were varied one-at-a-time with 20, 50 and 80% of increase from the original value.

4.1. The very simplest one-compartment TK model

Equations (3) and (15) are simulated for a simple case study where fish are exposed to a highly hydrophobic chemical contaminated water. Only natural excretion is considered [2] (Figure 1 and Table 2). The corresponding inputs are the exposure concentration c_w (referring to c_i and $I = 1$), the uptake rate from water k_{u_w} (referring to k_{u_i} and $I = 1$) and the excretion rate k_{e_e} (referring to k_{e_j} and $J = 1$). When parameter k_{u_w} increases, internal concentrations are higher (*e.g.*, blue curve in Figure 1.a) than with the original value (orange curve in Figure1.a). Biologically speaking, the higher the uptake rate is for a given substance, the more it is bioaccumulated by organisms. Conversely, an increase in parameter k_{e_e} leads to a lower internal concentration (*e.g.*, blue curve in Figure 1.b), consistent with the known underlying biological mechanism: the faster a contaminant is eliminated, the quicker its concentration decreases in organisms.

4.2. A one-compartment TK model with several exposure routes, no metabolites

Equations (3) and (15) are simulated for a freshwater shrimp exposed to an organic chlorine compound by contaminated sediment and food. Only natural excretion is considered as elimination process [7] (Figure 2 and Table 2). The corresponding inputs are the exposure concentration via sediment c_s and via food c_f (referring to c_i and $I = 2$), the two uptake rates from sediment and food, k_{u_s} and k_{u_f} respectively (referring to k_{u_i} and $I = 2$)

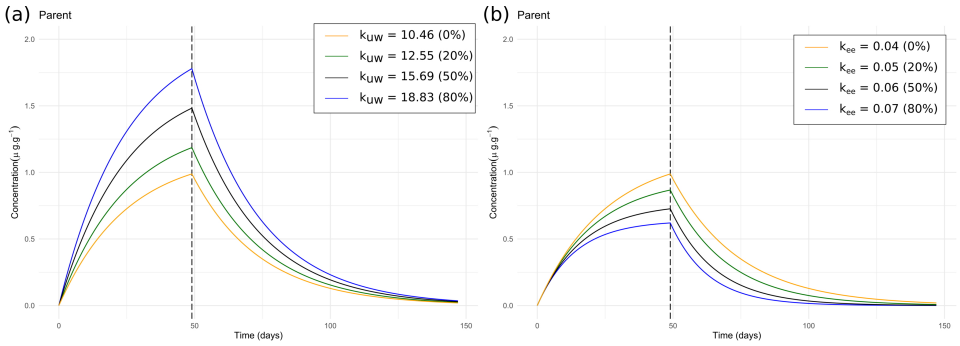

Figure 1: Example of model simulations for a simple TK model (exposure by water and elimination by excretion) and the influence of variations of parameters (a) k_{u_w} (uptake rate) and (b) k_{e_e} (excretion rate).

and the excretion rate k_{e_e} (referring to k_{e_j} and $J = 1$). When parameter k_{u_s} increases, internal concentrations are higher (*e.g.*, blue curve in Figure 2.a) than with the original value (orange curve in Figure 2.a). Biologically speaking, the higher the uptake rate from sediment is for a given substance, the stronger it is bioaccumulated by organisms. Regarding the exposure from food, as parameter k_{u_f} is low, its variation does not significantly influence the internal concentration of the contaminant (Figure 2.b). Biologically speaking, this means that the exposure via sediment is the major route of contamination for these organisms. Besides, as previously shown in section 4.1, an increase in parameter k_{e_e} leads to a faster decreasing concentration (*e.g.*, blue curve in Figure 2.c).

4.3. A one-compartment TK model with one exposure route, several metabolites

Equations (3), (10), (15) and (23) are simulated for a freshwater shrimp exposed to an organic biocide by contaminated water. Three metabolites

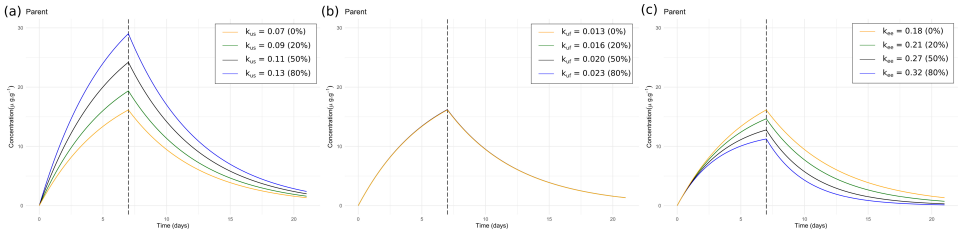

Figure 2: Example of model simulations for a TK model with multiple exposure routes (by sediment and food) and influence of variations of parameters (a) k_{u_s} (uptake rate from sediment), (b) k_{u_f} (uptake rate from food) and (c) k_{e_e} (excretion rate).

derived from the parent compound are considered [1] together with the natural excretion (Figures 3 to 5 and Table 2). The corresponding inputs are the exposure concentration via water c_w (referring to c_i and $I = 1$), the uptake rate k_{u_w} (referring to k_{u_i} and $I = 1$), the excretion rate k_{e_e} (referring to k_{e_j} and $J = 1$), the three metabolization rates k_{m_1}, k_{m_2} and k_{m_3} (referring to k_{m_ℓ} and $L = 3$) and the three elimination rates of the metabolites k_{e_1}, k_{e_2} and k_{e_3} (referring to k_{e_ℓ} and $L = 3$). When parameter k_{m_1} increases, internal concentrations are higher for metabolite 1 (*e.g.*, blue curve in Figure 3.b) than with the original value (orange curve in Figure 3.b). Conversely, internal concentrations are lower for the parent compound (*e.g.*, blue curve in Figure 3.a). Biologically speaking, the more the biotransformation rate for a given metabolite is increasing, the higher is its concentration within organisms due to the highly biotransformation of the parent compound. This leads to a lower internal concentration of the parent compound than with the original value of k_{m_1} (*e.g.*, blue curve, Figure 3.a). An increase in k_{m_1} also induces a decrease in the internal concentrations of the other metabolites (Figure 3.c and d). Besides, when parameter k_{e_1} increases, this only affects the internal concentration of metabolite 1 (Figure 4.b). In addition,

as previously viewed (sections 4.1 and 4.2), an increase in parameter k_{u_w} will induce high internal concentrations for both the parent compound and its metabolites (Figure 5). Indeed, the more the internal concentration of the parent compound is increasing, the more the biotransformation process will intensify, leading to high internal concentrations for each metabolite.

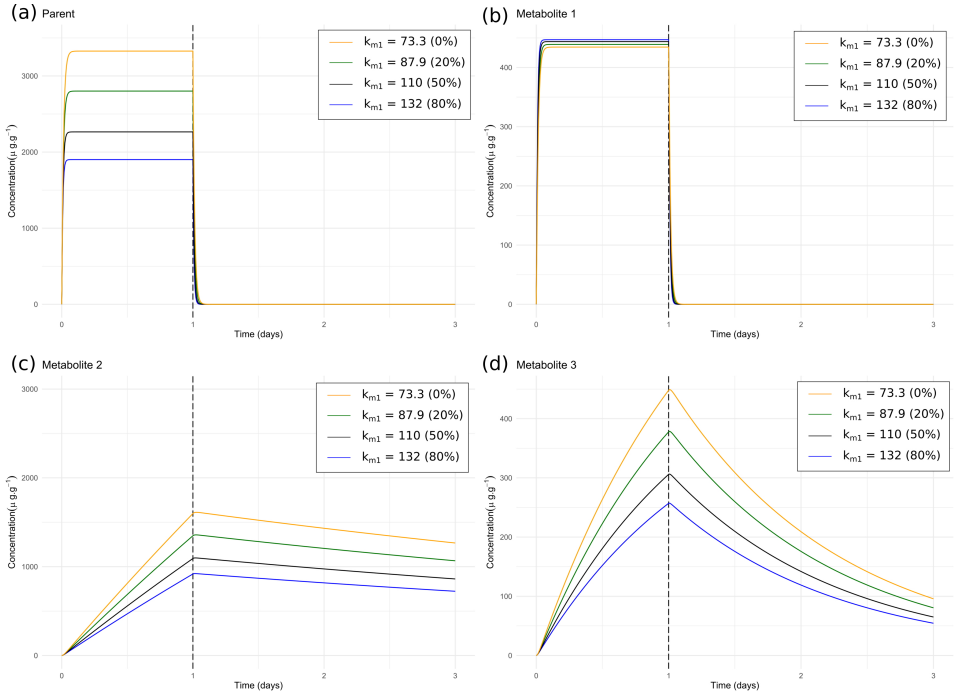

Figure 3: Example of model simulations for a TK model with biotransformation (three metabolites) and influence of the variations of parameter k_{m_1} (biotransformation rate for metabolite 1) on (a) the parent compound, (b) metabolite 1, (c) metabolite 2, and (d) metabolite 3.

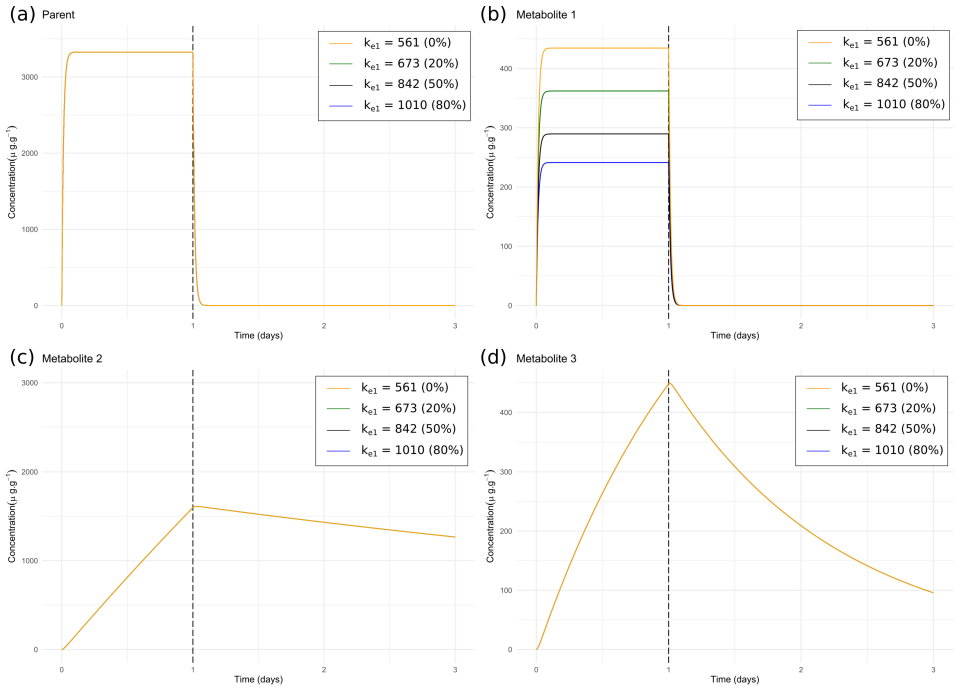

Figure 4: Example of model simulations for a TK model with biotransformation (three metabolites) and influence of the variations of parameter k_{e_1} (elimination rate of metabolite 1) on (a) the parent compound, (b) metabolite 1, (c) metabolite 2, and (d) metabolite 3.

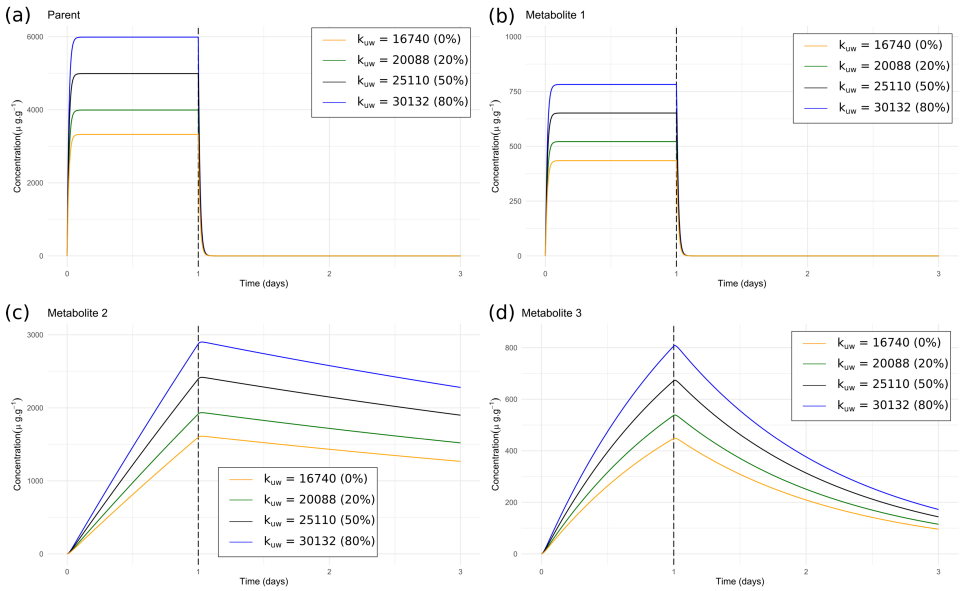

Figure 5: Example of model simulations for a TK model with biotransformation (three metabolites) and influence of the variations of parameter k_{u_w} on (a) the parent compound, (b) metabolite 1, (c) metabolite 2, and (d) metabolite 3.

5. Acknowledgments

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Symbol	Meaning and unit
t	time (in time units)
t_c	duration of the accumulation phase (in time units)
$C_p(t)$	internal concentration of the parent compound at t (in $\mu g.g^{-1}$)
$C_{m_\ell}(t)$	internal concentration of metabolite ℓ at t (in $\mu g.g^{-1}$)
$U = \sum_{i=1}^{I} k_{u_i} c_i$	sum of all uptake terms
c_i	concentration via the exposure route i (in $\mu g.mL^{-1}$)
$E = \sum_{j=1}^{J} k_{e_j}$	sum of all elimination terms for the parent compound
$M = \sum_{\ell=1}^{L} k_{m_\ell}$	sum of all elimination terms for metabolite ℓ
i	index of exposure sources, $i = 1 \dots I$
j	index of elimination processes, $j = 1 \dots J$
ℓ	index of metabolites, $\ell = 1 \dots L$
I	total number of exposure sources (#)
J	total number of elimination processes (#)
L	total number of metabolites (#)
k_{u_i}	uptake rate of exposure source i (per time units)
k_{e_j}	excretion rates of elimination process j (per time units)
k_{e_ℓ}	excretion rates of metabolite ℓ (per time units)
k_{m_ℓ}	metabolization rate of metabolite ℓ (per time units)
$R = \frac{U}{E+M}$	NA
$D_\ell = k_{e_\ell} - (E + M)$	NA $\forall \ell = 1 \dots L$
$Q = C_0 - R\left(1 - e^{(E+M)t_c}\right)$	NA

Table 1: Symbols, meaning and units for all parameters and variables involved in the full set of ordinary differential equations defining the generic one-compartment toxicokinetic model. # stands for numbers, while NA means 'Not Applicable'.

Table 2: Combinations of inputs for model simulations according to Figure 1. Hyphens stands for no required inputs.

Input	Units	Simple (section 4.1)	Multiple exposures (section 4.2)	Biotransformation (section 4.3)
c_w	$\mu g.mL^{-1}$	0.0044	-	15.53
c_s	$\mu g.g^{-1}$	-	56.6	-
c_f	$\mu g.g^{-1}$	-	1.46	-
t_c	$days$	49	7	1
k_{u_w}	$days^{-1}$	10.46	-	16740
k_{u_s}	$days^{-1}$	-	0.071	-
k_{u_f}	$days^{-1}$	-	0.013	-
k_{m_1}	$days^{-1}$	-	-	73.27
k_{m_2}	$days^{-1}$	-	-	0.5166
k_{m_3}	$days^{-1}$	-	-	0.1957
k_{e_e}	$days^{-1}$	0.04	0.178	4.164
k_{e_1}	$days^{-1}$	-	-	561
k_{e_2}	$days^{-1}$	-	-	0.123
k_{e_3}	$days^{-1}$	-	-	0.7808

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