Brief communication: new perspectives on the calculation of bioaccumulation factors for active substances in living organisms

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Abstract

Today, there are no ready-to-use convenient tools in ecotoxicology to diagnose and predict the accumulation and effects of chemical substances on living organisms, accounting for exposure situations that are known to be complex (routes of exposure, metabolization processes, cocktail effects, etc.). Regarding plant protection products in marketing authorization applications, regulation No 283/2013 (EU) defines the data requirements for active substances with a bioaccumulation test on fish according to OECD Test guideline 305. This paper presents new perspectives on the estimation of the bioaccumulation factors via an innovative ready-to-use web tool providing these factors, associated with their uncertainty to facilitate the daily work of regulators, but also of any user, by benefiting of a freely available and user-friendly on-line interface avoiding to invest into underlying mathematical and statistical technicalities. This tool, $\text{MOSAIC}_{\text{bioacc}}$, is available at https://mosaic.univ-lyon1.fr/bioacc, and can be used by any environmental scientists, ecotoxicologists or managers when accumulation-depuration data are collected and need to be easily and quickly analysed.

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1. Introduction

Nowadays, ecotoxicology has to provide relevant and effective methods and tools to diagnose and predict the accumulation and effects of chemical substances on living organisms, accounting for various exposure situations that are known to be complex (*e.g.*, routes of exposure, metabolization processes, cocktail effects, etc.). Among available methods, toxicokinetic-toxicodynamic (TKTD) models are now strongly recommended to describe the link between exposure and effects on individual life-history traits according to time from experimental data collected through standard toxicity tests (EFSA PPR Panel 2018). In particular, the TK part is used to relate the exposure concentration to the internal concentration within organisms, considering various processes such as accumulation, depuration, metabolization and excretion (ADME). Some regulations (*e.g.*, plant protection products in marketing authorization applications, regulation No 283/2013 (European Commission 2013)) require a bioaccumulation test on fish according to OECD Test guideline 305 (OECD 2012), which consists in an accumulation phase followed by a depuration phase. During the accumulation phase, individuals are exposed to the substance under interest at a range of concentrations, chosen according to the mode of action of the substance. Then, organisms are transferred to a clear medium for the depuration phase. The concentration of the substance within fishes is followed over time during both phases leading *in fine* to the estimation of the bioconcentration factor (BCF), the biota-sediment accumulation factor (BSAF) or the biomagnification factor (BMF) according to the exposure route (via water, sediment or food, respec-

tively). On a regulation point of view, such factors are key decision criteria for further estimating the concentration of active substances present in food items of vertebrates and more particularly of piscivorous birds and mammals. A test with fish according to OECD Test guideline 305 (OECD 2012) is also preferred when experimental information on bioaccumulation is needed for PBT/vPvB assessment under REACH regulation (ECHA 2017; European Commission 2006). In most cases, preference is also given to experimentally derived BCF values to be used for secondary poisoning assessment under Biocidal Products Regulation (European Commission 2012).

In the past decades, many types of methods have been proposed to estimate kinetic parameters of simple TK models, making it possible to deduce bioaccumulation factors values (especially BCF) from the separated consideration of the kinetics for both accumulation and depuration phases observed in dedicated experiments (OECD 2012). Nevertheless, TK model parameters are rarely simultaneously estimated and usually without considering together both uncertainties of parameter estimates and parameter correlations. However, it is crucial to properly estimate parameters of TK models for a better risk assessment, what thus this remains a key challenge. Besides, regulators are sceptical about the diversity and complexity of the possible methods and tools to use and run TK models, while thinking about their standardization at the same time (Tan et al. 2020). Ratier et al. (2019) recently proposed a full revisit of the approach based on a unified inference method to estimate parameters of TK models for both accumulation and depuration phases, simultaneously. This innovative framework

has been thought to make it possible to further incorporate the TK part into complete TKTD models.

The present paper presents new perspectives on the calculation of bioaccumulation factors (BCF/BSAF/BMF) via a new ready-to-use web tool, $\text{MOSAIC}_{\text{bioacc}}$, leading to the estimation of bioaccumulation factors automatically associated with their uncertainty in full compliance with the new framework from Ratier et al. (2019). The purpose is to facilitate the daily work of regulators, but also of any user, benefiting of a freely available user-friendly interface avoiding to invest into mathematical and statistical underlying technical aspects. $\text{MOSAIC}_{\text{bioacc}}$ clearly takes advantage of the new conceptual framework to deliver parameter estimates of a one-compartment TK model accounting for several exposure routes (water, pore water, sediment and food), for metabolization of the exposure chemical substance and for potential growth of organisms. The use of $\text{MOSAIC}_{\text{bioacc}}$ only requires to upload experimental data (that can be collected via standard protocols or not), then only few clicks to get all the outputs. Priority has been given to BCF/BSAF/BMF that are right away delivered as probability distributions summarized by a median and a 95% credible interval. In addition, the fitting plot and the model parameter estimates are provided, followed by a collection of goodness-of-fit criteria allowing the user to carefully check the robustness of the results. All outputs can be downloaded under different formats for further inclusion into any home-made document, while a full report can be directly downloaded.

2. Materials and Methods

MOSAIC$_{\text{bioacc}}$ is part of the web platforme MOSAIC (https://mosaic.univ-lyon1.fr/, Charles et al. 2018). It was developed as a Shiny environment (Chang et al. 2020), available at https://mosaic.univ-lyon1.fr/bioacc and hosted at the Rhône-Alpes Bioinformatics Center PRABI (PRABI, 2020). A user guide and an explanatory video are immediately available in the introductory section of the application to fully assist the user step by step in appropriating the tool and all its features. Details on underlying ordinary differential equations and their solving are also provided within a detailed user guide (see supplemental data, **Annex 1**), thus ensuring all required transparency on models behind the displayed outputs.

2.1. Data uploading

When using MOSAIC$_{\text{bioacc}}$, the first step is to upload input data (**Fig. 1-a**). MOSAIC$_{\text{bioacc}}$ expects to receive toxicity test data as a .txt file or a .csv file (comma, semicolon or tabular separator) with a specific format. Each line of the table corresponds to one time point for a given replicate and a given exposure concentration of the contaminant. The table must contain at least four columns, with the exact following headers, the order of columns not mattering (**Table 1**): 'time' (the time point of the measurement at the exposure concentration, in hours, minutes, days or weeks), 'expw', 'exppw', 'exps' or 'expf' (the concentration of the contaminant in the exposure medium: water, pore water, sediment or food, in $\mu g.mL^{-1}$ or in $\mu g.g^{-1}$), 'replicate' (a number or a character that is unique for

each replicate, dimensionless) and 'conc' (the concentration of the contaminant measured within the organisms, in $\mu g.g^{-1}$). According to the experimental design, further columns can be added in the data file: 'expw', 'exppw', 'exps' and/or 'expf' if several exposure routes are considered, 'concmℓ' (the concentration measurements of metabolite ℓ from the parent compound within the organisms (*e.g.*, concm1, concm2, ...)), 'growth' (if growth measurements of the organisms are available).

As shown on **Fig. 1-a**, the user of MOSAIC$_{\text{bioacc}}$ can either upload its own data set with a click on 'Browse' (by taking care about the format specification of its file) or try the web tool with an example data set. When the upload is complete, the user has to manually select the corresponding separator, the appropriate time unit and the duration of the accumulation phase ; please note that, when using example data sets, these fields are automatically filled in. MOSAIC$_{\text{bioacc}}$ first provides a table with the raw data which allows the user to check if the data were correctly entered. The user can also visualize a plot with the raw data (**Fig. 1-b**). In case the user uploaded a file with several exposure concentration, it has to select the one for which it wants to see the fitting results. Indeed, only one file at a time can be analysed. It should be also noted that for each new choice of exposure concentration, the duration of the accumulation phase is reset and framed in orange to invite the user to update it before to proceed to new calculations.

Some example files are provided in MOSAIC$_{\text{bioacc}}$ to illustrate the format

and help the user in running the web tool from the beginning. $\text{MOSAIC}_{\text{bioacc}}$ is presented in this paper based on a typical data set of a toxicokinetic bioassay where concentrations were collected for rainbow trout (*Oncorhynchus mykiss*) exposed via contaminated water to a highly hydrophobic chemical ($\log K_{ow}$ = 9.06) at an exposure concentration of 0.0044 $\mu g.mL^{-1}$ over 49 days, with one replicate at each time point. After 49 days, fishes were transferred in a clean medium for 98 days more (Crookes and Brooke, 2011). The data set and its HTML report can be downloaded directly from the web tool.

2.2. Model and parameters

In the TK models considered here, organisms are considered as single compartments for which a first-order kinetic bioaccumulation model accounting for several exposure and elimination routes can be expressed in a generic way as follows (Eqs. (1) to (4)):

$$\begin{cases} \frac{dC_p(t)}{dt} = U - (E+M)C_p(t) \quad (1) \\ \frac{dC_{m_\ell}(t)}{dt} = k_{m_\ell}C_p(t) - k_{e_{m\ell}}C_{m_\ell}(t) \quad (2) \end{cases} \qquad for \quad 0 \leq t \leq t_c$$

$$\begin{cases} \frac{dC_p(t)}{dt} = -(E+M)C_p(t) \quad (3) \\ \frac{dC_{m_\ell}(t)}{dt} = k_{m_\ell}C_p(t) - k_{e_{m\ell}}C_{m_\ell}(t) \quad (4) \end{cases} \qquad for \quad t > t_c$$

where $C_p(t)$ is the internal concentration of the parent compound at time t ($\mu g.g^{-1}$), $C_{m_\ell}(t)$ the internal concentration ($\mu g.g^{-1}$) of metabolite ℓ ($\forall \ell = 1 \ldots L$ with L the total number of metabolites) at time t, U the sum of all uptake terms, E the sum of all elimination terms for the parent compound, M the sum of all

metabolization terms, k_{m_ℓ} the metabolization rate of metabolite ℓ ($time^{-1}$) and $k_{e_{m\ell}}$ the elimination rate of metabolite ℓ ($time^{-1}$). A summary of the meaning of parameters and variables is provided in **Table 2**.

The above-mentionned dynamical system can explicitly be solved when exposure concentration is assumed to be constant over time (**Annex 1**).

For keeping reasonable the calculation time with $\text{MOSAIC}_{\text{bioacc}}$, only four routes of exposure are proposed ($I = 4$, namely water, pore water, sediment and food), three processes of elimination ($J = 3$, namely excretion, growth dilution and biotransformation where metabolites directly come from the parent compound (*i.e.*, phase I)). Hence, for example, if a maximum of three metabolites is considered ($L = 3$), the maximum number of parameters is 19. Thus, the user has in total 112 possible models, corresponding to the data it has (see supplemental data, **Annex 2**). The most complete model and its corresponding parameters are automatically selected according to the experimental design as given within the uploaded data set (**Fig. 1-c**). A Gaussian probability distribution was assumed for measured concentration variables of the parent compound and its metabolites within the organisms (Eqs. (5) and (6)):

$$C_{obs,p}(t) \sim \mathcal{N}(C_p(t), \sigma^2_{C_p}) \quad (5)$$

$$C_{obs,m_\ell}(t) \sim \mathcal{N}(C_{m_\ell}(t), \sigma^2_{met_\ell}) \quad (6)$$

where variables and parameters are those given in **Table 2**.

In this paper, as a proof of concept, the results will be exemplified with a data

set considering only the water exposure route (k_{uw} for the uptake route) with the corresponding elimination rate parameter (k_{ee}), that is one of the simplest models among the 112 possibilities. The corresponding first-order TK model can simply be expressed as follows (Eqs. (7) and (8)):

$$\begin{cases} \frac{dC_p(t)}{dt} = k_{uw} \times c_w - k_{ee} \times C_p(t) & \text{for } 0 \leq t \leq t_c \quad (7) \\ \frac{dC_p(t)}{dt} = -k_{ee} \times C_p(t) & \text{for } t > t_c \quad (8) \end{cases}$$

Then there are only two parameters to estimate: k_{uw}, uptake rate from water exposure and k_{ee}, excretion rate for the depuration process. An illustration of a more complex data set (with biotransformation and growth processes for a benthic invertebrate) is also given in supplemental data (**Annex 3**).

If the file has correctly been uploaded and the exposure concentration has been chosen for the analysis, a reminder of the latter is displayed on the screen and the button for launching the calculations is unlocked. When the user clicks on the 'Calculate and Display' button (**Fig. 1-c**), the calculations start running launched with a progress bar that informs about their progress. When calculations are finished, results are displayed, as plots and tables by default, and additional outputs for the goodness-of-fit checking.

2.3. Calculations

2.3.1. Bayesian inference

Model computations that underline $\text{MOSAIC}_{\text{bioacc}}$ calculations are performed with JAGS (Plummer, 2019) and the R software (R Core Team, 2020) (version 4.0.2) via the `rjags` package (Plummer, 2019). Models are fitted to bioaccumu-

lation data using Bayesian inference via Monte Carlo Markov Chain (MCMC) sampling. For each model chosen by the user, running starts with a short sampling on three MCMC chains (5,000 iterations after a burn-in phase of 10,000 iterations) using the Raftery and Lewis method (Raftery and Lewis, 1992) to set the necessary thinning and number of iterations to reach a precise and accurate estimation of each model parameter. Thanks to `rjags`, model parameters are retrieved as a joint posterior distribution from the likelihood of the observed data combined with prior distributions on parameters. All details on this approach can be found in the original research paper (Ratier et al. 2019) but also in many other papers in the field of ecotoxicology (Billoir et al. 2011; EFSA PPR Panel 2018).

2.3.2. Definition of prior distributions

For simplicity reasons, in $\text{MOSAIC}_{\text{bioacc}}$, the choice of priors is hidden to the user with no possibility to change them. To keep priors the most generic as possible, they were assumed following a non-informative (-5, 5) log10-uniform distribution for all uptake and elimination rate constants, and a non-informative (0.001, 0.001) Gamma distribution for all standard deviations, as usually done in the field of bioaccumulation studies (Lambert et al. 2005; Ratier et al. 2019; Richards and Chaloupka 2009).

2.3.3. Bioaccumulation factors

In $\text{MOSAIC}_{\text{bioacc}}$, bioaccumulation factors are calculated and provided as the first output. This paper illustrates the case of an organism exposed via

contaminated water, leading to both the kinetic bioconcentration factor (BCF_k) and the steady state bioconcentration factor (BCF_{ss}), automatically displayed by the web application. These bioaccumulation factors have exact mathematical expressions (Eqs. (9) and (10)):

$$BCF_k = \frac{k_{uw}}{k_{ee}} \qquad (9)$$

$$BCF_{ss} = \frac{C_p(t_c)}{c_w} \qquad (10)$$

where $C_p(t_c)$ is the internal parent compound concentration (in $\mu g.g^{-1}$) at the end of the accumulation phase (that is at $t = t_c$, in time) and c_w is the exposure contaminant concentration in water ($\mu g.mL^{-1}$). More details are provided in **Annex 4** about calculations at steady-state.

3. Results and Discussion

3.1. Bioaccumulation factors

When the user clicks on the 'Calculate and Display' button, some results are provided by default. First, the BCF_k is given as a probability distribution (**Fig. 2-a**) and summarized with its median and its 95% uncertainty limits (95% credible interval delimited by the 2.5% and the 97.5% quantiles of the probability distribution, **Table 3-a**). If the user asks for the BCF_{ss}, its probability distribution is also delivered (**Fig. 2-b**) also summarized with the median and the 95% uncertainty limits (**Table 3-a**). If data are available for several exposure routes (according the experimental design) and uploaded in the application, the

BCF/BSAF/BMF will be displayed in separate tabs.

3.2. Predictions

After plots and tables for bioaccumulation factors, the fitted curve and its uncertainty band superimposed to the observations is provided (**Fig. 2-c**). From the joint posterior distribution of parameters, $\text{MOSAIC}_{\text{bioacc}}$ then provides the marginal posterior distributions for each parameter, which are also summarized with quantiles in a table (**Table 3-b**). Indeed, all estimated parameters are given as medians (for point estimates) and 2.5 and 97.5% quantiles (for 95% credible intervals) of marginal posterior distributions. Credible intervals are crucial information to quantify the uncertainty on parameter estimates.

3.3. Goodness-of-fit criteria

Several goodness-of-fit criteria follow in a prioritized order chosen based on their relevance and their ease of interpretation. The fitting quality of the model can be first checked using the posterior predictive check plot: the idea is to compare each observed value to its prediction from the fitted model at the corresponding exposure concentration associated with its 95% credible interval. If the fit is correct, we expect to see 95% of the observed values falling within the 95% credible intervals of their predictions. As shown on **Fig. 3-a**, the observed values are read on the x-axis, while the y-axis reports the median predictions (black dots) and their 95% credible intervals (vertical segments).

The robustness of the inference process can be secondly checked using the comparison of prior and posterior distributions. The overall expectation is to get a

narrower posterior distribution compared to the prior one for each parameter, reflecting that data contributed enough to precisely estimate parameters (**Fig. 3-b**). The user has the possibility to select the plot for deterministic (*e.g.*, k_{uw}, k_{ee}) or stochastic (*e.g.*, σ_{C_p}) parameters.

$\text{MOSAIC}_{\text{bioacc}}$ then provides the correlation plot (**Fig. S1-a**), which allows the user to visualize correlations between parameters. This plot is obtained by projecting the joint posterior distribution in a plot matrix in planes of parameter pairs. This plot also gives marginal posterior distribution of each model parameter and Pearson correlation coefficients. Correlations between parameters are important to consider in particular when they are high (namely, greater than 0.75) what would mean that one parameter estimate could considerably influence the other. The user has the possibility to display the correlation plot for deterministic or for all parameters. Besides, $\text{MOSAIC}_{\text{bioacc}}$ automatically provides a colored matrix in order to see at a glance the most correlated or anti-correlated parameters, in order to quickly diagnose potential problems of precision due to highly correlated parameters.

The convergence of the MCMC chains is checked with the Gelman-Rubin diagnostic (Gelman and Rubin, 1992) expressed via the potential scale reduction factor (PSRF) which is expected to be close to 1.00 (**Fig. S1-b**). It can be also visually verified by the MCMC traceplot, which shows the time series of the sampling process leading to the posterior distribution ; it is expected to obtain an enough overlapping of the three chains (**Fig. S1-c**). The user has the possibility to visualize the MCMC traceplot for deterministic or stochastic

parameters.

Finally, the Deviance Information Criterion (DIC) is provided. It is a penalized deviance statistics accounting for the number of parameters that is only useful to compare several models fitted to a same data set. Models with lower DIC values will be preferred. So, the DIC could for example be used when comparing several sub-models based on different choices of parameters from all the possible combinations that the user can choose from the beginning according to the uploaded data.

3.4. Downloads

All results can be downloaded from the bottom of the web page as well as a full report with all the results. The user can also download the R code corresponding to all calculations and graphs from the uploaded data set. This guarantees the transparency and the reproducibility of all $\text{MOSAIC}_{\text{bioacc}}$ results. This R code can be used as a stepping stone to change default options and to perform further analyses directly in the R software. For example, the user can modify figures at its convenience, or make several analyses on several data sets at the same time.

4. Conclusion

Offering $\text{MOSAIC}_{\text{bioacc}}$ as a new on-line service, free, user-friendly and ready-to-use, raises important methodological issues: (1) the automatization of the inference process, in particular for Bayesian inference; (2) the default options to fix and the choices left to the discretion of the users; (3) the outputs to

primarily provide, the goodness-of-fit to show, the downloads to propose, the kind of analysis report to render. Besides its user-friendliness, this application is free of use and guarantees the privacy of the uploaded data as well as the transparency and the reproducibility of the results, together with a short response time. Thus, $\text{MOSAIC}_{\text{bioacc}}$ may be particularly useful to estimate parameters of TK models and to predict chemical concentrations bioaccumulated in organism (aquatic or terrestrial) from standard data. This tool could thus be used by risk assessors and decision makers in their daily work of assessing dossiers, *e.g.*, for the authorization of substances on the market (EFSA PPR Panel 2018), since all results provided by $\text{MOSAIC}_{\text{bioacc}}$ account for uncertainty and correlations between parameters. It could also be used by any environmental scientists, ecotoxicologists or managers when accumulation-depuration data are collected and need to be analysed. Besides, $\text{MOSAIC}_{\text{bioacc}}$ goes beyond the OECD Test guideline 305 in including biotransformation processes, thus allowing users to easily perform TK analyses accounting for metabolites, while such an approach is now recognized of strong interest in the scientific literature. $\text{MOSAIC}_{\text{bioacc}}$ is available as a new service dedicated to TK modelling approaches in the MOSAIC platform (Charles et al. 2018) making it now an all-in-one facility for many applications. $\text{MOSAIC}_{\text{bioacc}}$ will be shortly extended with a prediction tool that will allow to better design TK experiments in order to collect more relevant data for the model fitting and the estimation of bioaccumulation factors.

Supplemental Data

Supplemental data is available on-line.

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The authors declare no competing interests.

Data availability

Data are accessible directly within $\text{MOSAIC}_{\text{bioacc}}$ at https://mosaic.univ-lyon1.fr/bioacc.

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Figure 1. Data uploading and user information to enter from the $\text{MOSAIC}_{\text{bioacc}}$ homepage.

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Figure 3. Some goodness-of-fit criteria as given in $\text{MOSAIC}_{\text{bioacc}}$: (a) Posterior Predictive Check (PPC) where the observed values are read on the x-axis, while the y-axis reports the median predictions (black dots) and their 95% credible intervals (vertical segments, coloured in green if they contain the observed value, in red otherwise) ; (b) prior (gray) and posterior (orange) distributions of parameters for the simplest TK model.

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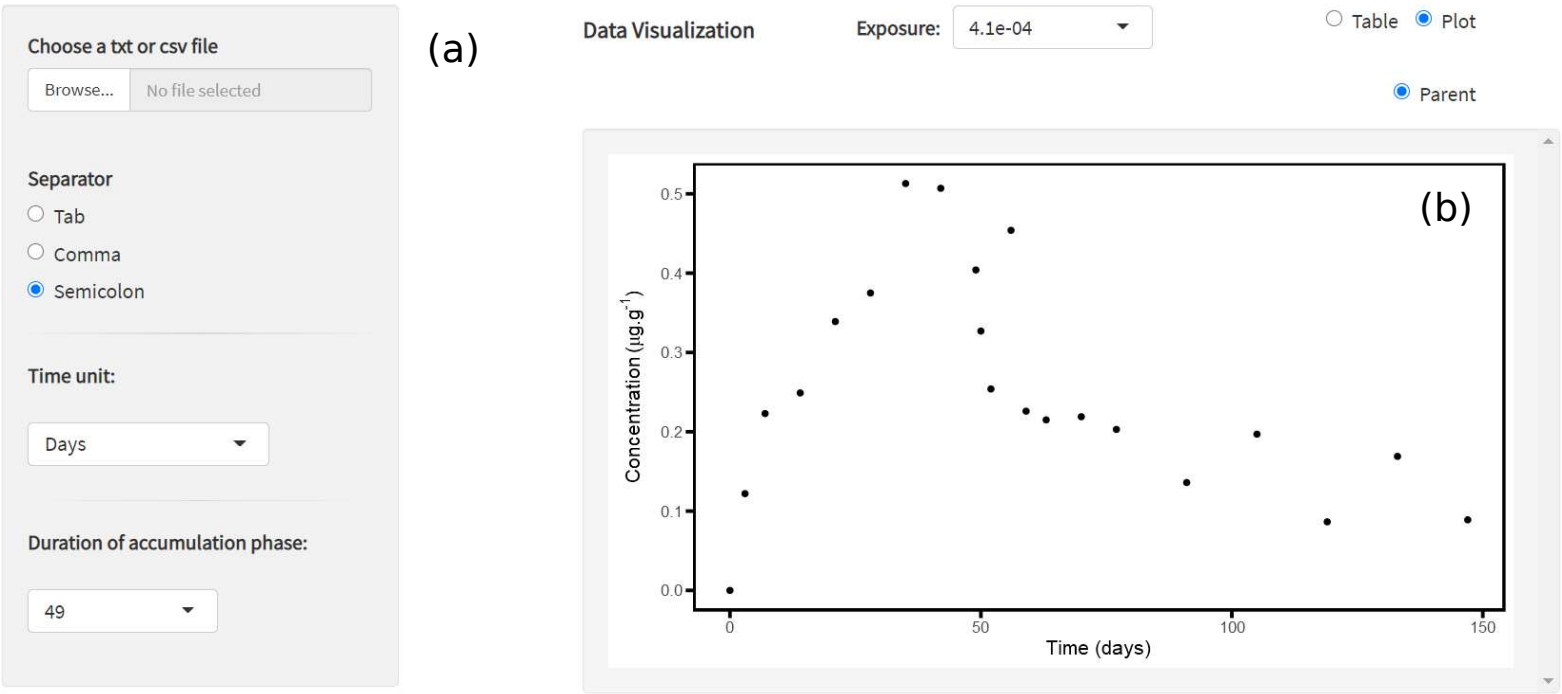

Model and parameters

All parameters are expressed in *days*$^{-1}$

(c)

Accumulation:
(Select one or several exposure media)

- [x] Water (k_{uw})
- [ ] Sediment (k_{us})
- [ ] Food (k_{uf})
- [ ] Pore water (k_{upw})

Depuration:
(Select involved processes)

- [x] Elimination (k_{ee})
- [ ] Dilution by growth (k_{eg})
- [ ] Biotransformation (k_m)

Click here for more information about parameters meaning.

$$\frac{dC_p(t)}{dt} = k_{pw} \times c_w - (k_{ee}) \times C_p(t) \quad \text{for } 0 \le t \le t_c$$

$$\frac{dC_p(t)}{dt} = -(k_{ee}) \times C_p(t) \quad \text{for } t > t_c$$

With:

$C_p(t)$ internal concentration of the parent compound at time t (in $\mu g.g^{-1}$)

c_i Exposure concentration of route i : w, s, f and pw, respectively for water, sediment, food and pore water exposure (in $\mu g.mL^{-1}$ or $\mu g.g^{-1}$). Consider that constant over time.

Click here for more information about the model and here for solving equations.

Click here for more information about the type of fitting algorithm used, the number of iterations required...

Calculations will be performed for the following exposure: $4.1.10^{-04}$ $\mu g.mL^{-1}$

Calculations can take several minutes, please be patient.

Calculate and Display

Figure 1. Data uploading and user information to enter from the MOSAIC$_{bioacc}$ homepage.

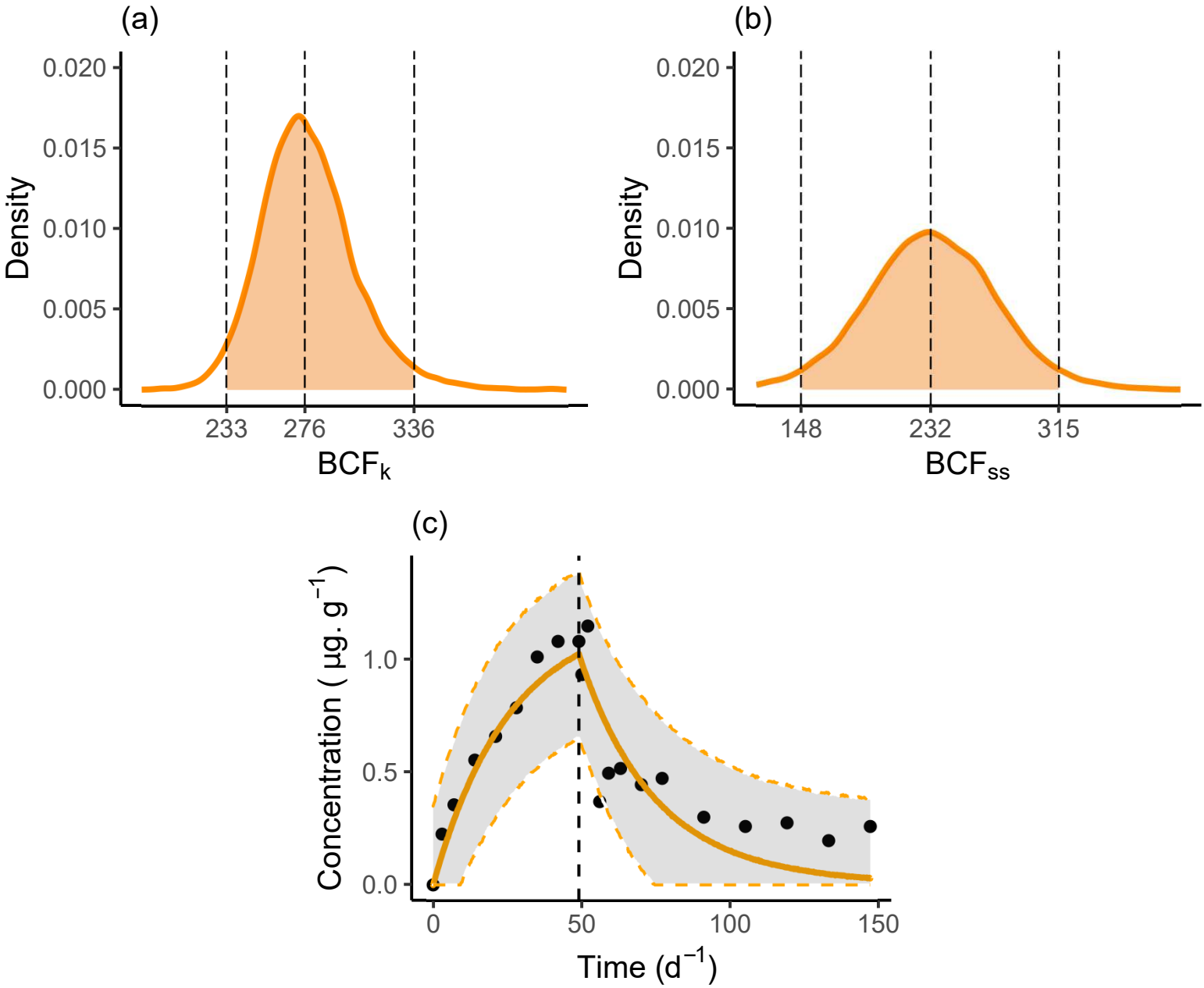

Figure 2. Probability distributions of BCF_k (a) and BCF_{ss} (b). The middle dotted line represents the median value, while left and right dotted lines are the 2.5 and 97.5% quantiles. (c): Measured (black dots) and predicted contaminant concentrations in the organisms ($\mu g.g^{-1}$), where the median curve is displayed as the orange plain line and the uncertainty band as the gray zone, delimited by the 2.5% and 97.5% quantiles in orange dotted lines.

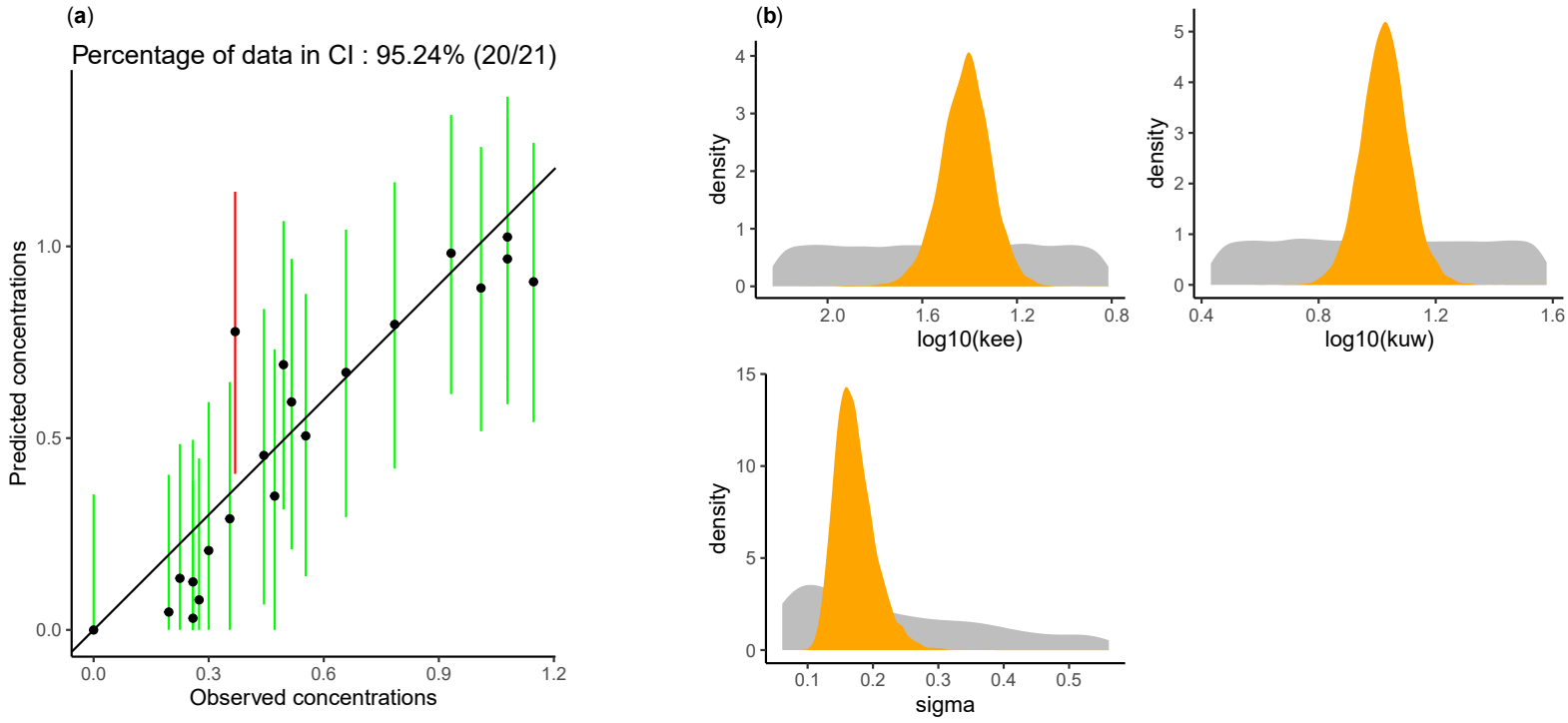

Figure 3. Some goodness-of-fit criteria as given in $MOSAIC_{bioacc}$: (a) PosteriorPredictive Check (PPC) where the observed values are read on the x-axis, whilethe y-axis reports the median predictions (black dots) and their 95% credibleintervals (vertical segments, coloured in green if they contain the observedvalue, in red otherwise) ; (b) prior (gray) and posterior (orange) distributions ofparameters for the simplest TK model.

Table 1. Example of a data set ready to be used in $MOSAIC_{bioacc}$.

time	conc	expw	replicate
0	0.000	0.0044	2
3	0.225	0.0044	2
7	0.355	0.0044	2
14	0.553	0.0044	2
21	0.658	0.0044	2
28	0.785	0.0044	2

Table 2. Meaning of parameters and variables of the TK model used in MOSAIC$_{bioacc}$.

Symbol	Meaning
i	index of exposure routes, $i = 1 \dots I$
j	index of elimination processes, $j = 1 \dots J$
ℓ	index of metabolites, $\ell = 1 \dots L$
I	total number of exposure routes
J	total number of elimination processes
L	total number of metabolites
t	time (in time unit)
c_i	exposure concentration of route i (in $\mu g.mL^{-1}$)
$C_p(t)$	internal concentration of the parent compound at time t (in $\mu g.g^{-1}$)
$C_{m_\ell}(t)$	internal concentration of metabolite ℓ (in $\mu g.g^{-1}$)
k_{u_i}	uptake rate of exposure route i (expressed in $time^{-1}$)
k_{e_j}	elimination rate of elimination process j (expressed in $time^{-1}$)
$k_{e_{m\ell}}$	elimination rate of metabolite ℓ (expressed in $time^{-1}$)
k_{m_ℓ}	biotransformation rate of metabolite ℓ (expressed in $time^{-1}$)
t_c	duration of the accumulation phase (in time unit)
$\mathcal{N}$	Gaussian probability distribution
$C_{obs,p}(t)$	internal measured concentration of the parent compound at time t (in $\mu g.g^{-1}$)
$C_{obs,m_\ell}(t)$	internal measured concentration of metabolite ℓ (in $\mu g.g^{-1}$)
σ_{Cp}	standard deviation for the internal concentration of the parent compound (in $\mu g.g^{-1}$)
σ_{met_ℓ}	standard deviation for the internal concentration of metabolite ℓ (in $\mu g.g^{-1}$)
$U = \sum_{i=1}^{I} k_{u_i} c_i$	sum of all uptake terms
$E = \sum_{j=1}^{J} k_{e_j}$	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

Table 3. Example of BCF (a) and parameters (b) estimates expressed as medians (50% quantile) and 95% credibility intervals (2.5% - 97.5% quantiles). The hyphen stands for dimensionless parameters.

	2.5%	**50%**	**97.5%**	**Units**
(a)	233	276	338	-
BCF_k	147	233	317	-
BCF_{ss}				
(b)				
k_{uw}	7.388	10.59	15.45	d^{-1}
k_{ee}	0.02307	0.03851	0.06091	d^{-1}
σ_{Cp}	0.1249	0.1684	0.2445	$\mu g.g^{-1}$