A Bayesian framework for estimating parameters of a generic toxicokinetic model for the bioaccumulation of organic chemicals by benthic invertebrates: Proof of concept with PCB153 and two freshwater species

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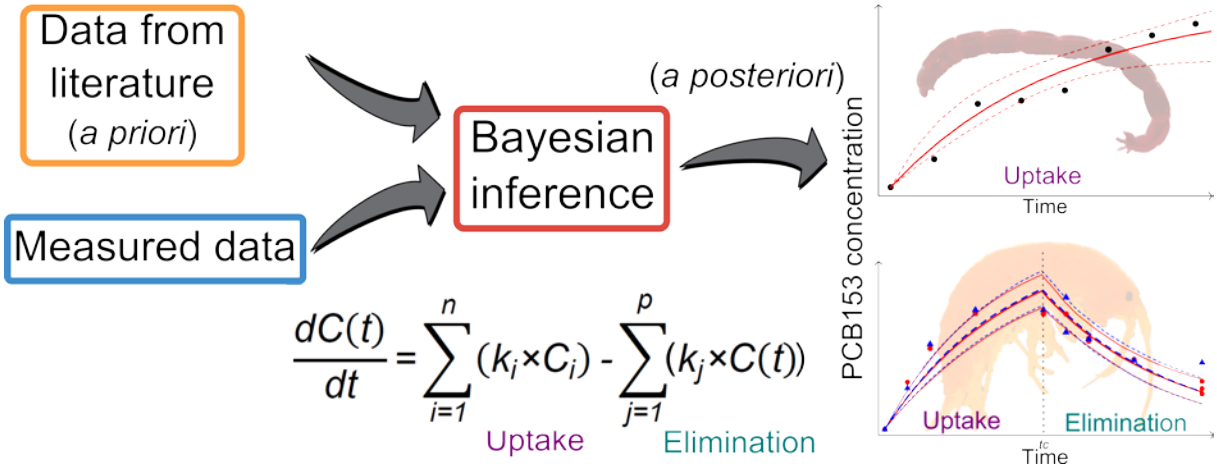
DOI: 10.1016/j.ecoenv.2019.04.080

Highlights

- A generic TK model in a Bayesian framework was proposed
- Each uptake and elimination route was considered as a module in the model
- Model parameter estimates are relevant regarding species difference

Graphical abstract



Abstract

Toxicokinetic (TK) models are relevant and widely used to predict chemical concentrations in biological organisms. The importance of dietary uptake for aquatic invertebrates has been increasingly assessed in recent years. However, the model parameters are estimated on limited specific laboratory data sets that are bounded by several uncertainties. The aim of this study was to implement a Bayesian framework for simultaneously estimating the parameters of a generic TK model for benthic invertebrate species from all data collected. We illustrate our approach on the bioaccumulation of PCB153 by two species with different life traits and therefore exposure routes: *Chironomus riparius* larvae exposed to spiked sediment for 7 days and *Gammarus fossarum* exposed to spiked sediment and/or leaves for 7 days and then transferred to a clean media for 7 more days. The TK models assuming first-order kinetics were fitted to the data using Bayesian inference. The median model predictions and their 95% credibility intervals showed that the model fit the data well. From a methodological point of view, this paper illustrates that simultaneously estimating all model parameters from all available data by Bayesian inference, while considering the correlation between parameters and different types of data, is a real added value for TK modeling. Moreover, we demonstrated the ability of a generic TK model considering uptake and elimination routes as modules to add according to the availability of the data measured. From an ecotoxicological point of view, we show differences in PCB153 bioaccumulation between chironomids and gammarids, explained by the different life traits of these two organisms.

Keywords: Bioaccumulation – Benthic invertebrates – PCB153 – Bayesian inference – Toxicokinetic model

1. Introduction

In environmental risk assessment (ERA), models based on toxicokinetic (TK) approaches are widely recognized as providing diagnostics (models for understanding) and prognostics (models for prediction), sometimes used by decision-makers (e.g., Pavan, 2006; EPA, 2006; IPCS, 2010). TK models are relevant and widely used to predict chemical concentrations in biological organisms from those to which they are exposed in their environment. This process, also called bioaccumulation, depends on environmental conditions (temperature, light, food availability), contaminant properties (octanol-water partition coefficient, water solubility, dissociation and volatilization, sorption in sediment) (Mamy, 2015) and biological characteristics of the species (life traits, diet, lifecycle). TK models describe the process of bioaccumulation as the net balance between the uptake of contaminants from different sources (water, diet) and their elimination by different processes (excretion, growth and/or biotransformation) (MacKay and Fraser, 2000). Different TK models have been proposed, such as compartmental models and physiologically based toxicokinetic (PBTK) models (Grech, 2017; Landrum, 1992). Compartmental models describe toxicant fluxes between compartments, which may or may not have a physiologic or anatomic meaning. A PBTK model subdivides the body into compartments representing real tissues or organs connected through a fluid, usually blood (Bois and Brochot, 2016). For aquatic invertebrates, compartmental models were originally developed for metals and then for some organic contaminants where the organism is often considered as a single compartment.

For soluble contaminants, it is usually assumed that the water column is the main exposure and uptake route. Nevertheless, dietary uptake is of greater importance for hydrophobic contaminants due to their high adsorption on organic matter or food (Gross-Sorokin, 2003). Moreover, it has been shown for several aquatic invertebrates, such as the insect *Chironomus riparius*, that exposure to sediment cannot be ignored (Leppänen and Kukkonen, 1998; Sidney, 2016). The importance of dietary uptake for aquatic invertebrates

has been increasingly assessed in recent years (Ashauer 2010, Carrasco-Navarro, 2015; Englert, 2017; Miller, 2017; Rösch, 2017). *Chironomus* sp. and *Gammarus* sp. are freshwater invertebrates widely used in ecotoxicology, due to their widespread presence throughout the Northern hemisphere and their capacity to accumulate various organic and inorganic contaminants (Amiard, 1987; Ashauer, 2012; Bertin, 2014; Lebrun, 2011; López-Doval, 2012; Lydy, 1999). These organisms are also an important food source for fish, amphibians and birds (Macneil, 1999), hence the transfer of contaminants within the aquatic food web.

Nowadays, TK model parameters are often determined from short-term exposures of organisms under controlled laboratory conditions (Ashauer, 2010). OECD Guideline 315 (OECD, 2008) suggests two methods to estimate the uptake and elimination rates. The most frequently used sequential method estimates the elimination rate using nonlinear regression depuration data which is then fixed to estimate the uptake rate with the uptake data. As elimination also occurs during the accumulation phase, separately estimating parameters that are linked does not allow taking into account their correlation on uncertainty. However, the precision of parameter estimates is a relevant point to strengthen environmental assessments (Lin, 2004; Richards and Chaloupka, 2009). The simultaneous method estimates both the uptake and elimination rates together, and is considered a potentially more reliable and more realistic model. Only recent studies (Ashauer, 2010; Miller, 2016, 2017) have applied simultaneous methods for parameter approximation. Sequential or simultaneous methods can be deployed in a frequentist or Bayesian approach. Apart from the problem of the correlation between all the model's parameters, the frequentist approach (sequential or simultaneous) cannot simultaneously use different kinds of data (e.g., bioaccumulation and growth data) to estimate common parameters. Bayesian inference bypasses these limits by estimating all model parameters from all kinds of data (Gelman, 1995) and thus provides a more comprehensive approach and a better quantification of uncertainty in parameter estimates as well as a better consideration of variability in model predictions (Bernillon and Bois, 2000). The

application of Bayesian inference to TK models in aquatic invertebrates remains limited (Lin, 2004).

The aim of this study was to propose a Bayesian framework to simultaneously estimate all the parameters of a generic TK model from uptake and elimination data together. As a first development step, we applied this concept to two aquatic invertebrate species. The resulting joint posterior distribution giving the probability distribution of all parameters together will enable a more accurate assessment of uncertainty around estimates and thus TK model predictions. We illustrate our approach with the bioaccumulation of the well-known contaminant PCB153 by two freshwater benthic invertebrate species with different life traits: the Diptera *C. riparius* and the amphipod crustacean *Gammarus fossarum*.

2. Model

2.1 Generic TK model

A first-order kinetic bioaccumulation model that accounts for different uptake pathways and elimination processes can be expressed as follows (Eq. (1)):

$$\frac{dC(t)}{dt} = \sum_{i=1}^{n}(k_i \times C_i(t)) - \sum_{j=1}^{p}(k_j \times C(t)) \quad (1)$$

where $C(t)$ is the contaminant concentration at time t (days) in the whole organism (ng g_{org}^{-1} where the mass of the organism is expressed in wet weight (ww)), n is the number of contamination sources, k_i the uptake rate from the contamination source i, $C_i(t)$ the contaminant concentration in the contamination source i at time t (days), p the number of elimination processes and k_j the elimination rate related to process j.

If we consider that $C_i(t)$ is constant over time, which is appropriate in laboratory conditions, Eq. (1) can be analytically integrated by distinguishing uptake (Eq. (2)) from elimination phases (Eq. (3)):

$$\begin{cases} C(t) = \frac{\sum_{i=1}^{n}(k_i \times C_i)}{\sum_{j=1}^{p} k_j} + \left(C_0 - \frac{\sum_{i=1}^{n}(k_i \times C_i)}{\sum_{j=1}^{p} k_j} \right) \times e^{-\left(\sum_{j=1}^{p} k_j\right) \times t} & \text{for } 0 < t < t_c \quad (2) \\ C(t) = \frac{\sum_{i=1}^{n}(k_i \times C_i)}{\sum_{j=1}^{p} k_j} \times e^{-\left(\sum_{j=1}^{p} k_j\right) \times (t - t_c)} + \left(C_0 - \frac{\sum_{i=1}^{n}(k_i \times C_i)}{\sum_{j=1}^{p} k_j} \right) \times e^{-\left(\sum_{j=1}^{p} k_j\right) \times t} & \text{for } t > t_c \quad (3) \end{cases}$$

where C_0 is the contaminant concentration in the whole organism at the beginning of exposure (ng g_{org}^{-1}) and t_c the time at the end of the uptake phase (days).

2.2 Application of the model to the two species studied

2.2.1 Chironomids

For chironomids, we consider that the exposure sources are water (respiration) and sediment (ingestion), while elimination occurs due to excretion and growth dilution; Eq. (1) can thus be rewritten as follows (Eq. (4)):

$$\frac{dC(t)}{dt} = k_w \times C_w + k_s \times C_s - \left(k_e + k_g\right) \times C(t) \quad (4)$$

where k_w is the uptake rate from the water (L g_{org}^{-1} d^{-1}), C_w the contaminant concentration in water (ng L^{-1}), k_s the uptake rate from the sediment (g_{sed} g_{org}^{-1} d^{-1}), C_s the contaminant concentration in sediment (ng g_{sed}^{-1} dw), k_e the elimination rate (d^{-1}) and k_g the growth rate (d^{-1}).

The chironomid growth rate is obtained from the von Bertalanffy growth equation (Eq. (5)), one of the most widely used models for describing the growth of benthic invertebrates (von Bertalanffy, 1938; K. Nakamura, 1973):

$$L(t) = L_{max} - (L_{max} - L_0) \times e^{(-k_g \times t)} \quad (5)$$

where $L(t)$ is the chironomid size (mm) at time t (d), L_{max} is the asymptotic size (mm), L_0 is the size at birth (mm) and k_g is the growth rate (d^{-1}).

Given that, for highly hydrophobic compounds, contamination from water could be restricted (k_w=0), a sub-model accounting for sediment as the only contamination source was also considered:

$$\frac{dC(t)}{dt} = k_s \times C_s - (k_e + k_g) \times C(t) \quad (6)$$

2.2.2 Gammarids

Gammarids feed on detritus such as litter (Forrow and Maltby, 2000). As a consequence, exposure to chemicals could occur from water, litter (leaves) and sediment consumption, since sediment particles deposit on the surface of leaves when gammarids forage (Bertin, 2016). Furthermore, we assumed that gammarids would not grow during the experiment, as shown by Galic and Forbes (2017), for the adult size considered here. As a result, Eq. (1) can be rewritten as follows (Eq. (7)):

$$\frac{dC(t)}{dt} = k_w \times C_w + k_s \times C_s + k_l \times C_l - k_e \times C(t) \quad (7)$$

where k_l is the uptake rate from the leaves (ng g_{org}^{-1} d^{-1}) and C_l the contaminant concentration in leaves (ng g^{-1}).

According to the experimental conditions, several sub-models could be considered and tested according to several hypotheses on the exposure routes (kw=0 and/or ks=0 and/or kl=0, Table S1).

3. Materials and methods

3.1 Chemicals, reagents and quality control

Solid 2,2′, 4,4′, 5,5′ hexachlorobiphenyl (PCB153) was purchased from Sigma-Aldrich (St Quentin-Fallavier, France). A working solution was prepared in acetone at 1.01 g L^{-1} for the contamination of sediment and leaves. The native SRM2262 solution and the internal standard PCB198 (99%) used for the quantification of PCB153 were provided by LGC Promochem (NIST) and Ultra Scientific, respectively. Native PCB153 recovery was determined using spiked samples for water (89 ± 1%), technical sand (75 ± 11%), sediment (NIST SRM1941b Organics in Marine Sediment, 64 ± 8%) and fish (NIST SRM 1947 Lake Michigan Fish Tissue, 65 ± 12%) reference materials. The limit of detection (LoD) was determined as the concentration with a signal-to-noise ratio of 3 (LoD = 0.003 ng L^{-1} for water, between 0.003 and 0.040 ng g^{-1} dw for sediment, leaves and organisms). Replicate procedural blanks (n = 13) were analyzed for each series of samples where the PCB153 concentration was always below the LoD.

3.2. Matrix spiking

3.2.1 Sediment spiking

In January and March 2017, 60 L of natural sediment was collected from a watercourse in the Miribel-Jonage nature park (Vaulx-en-Velin, eastern central France near Lyon, 4°59′27″E and 45°47′55″N for the chironomid experiment and 5°00′51″E and 45°79′71″N for the gammarid experiment). The sediment was collected using a manual dredger, sieved at 2 mm, pooled in a polypropylene (PP) jar, and stored at 4 ± 2 °C until they were used. For chironomid and gammarid experiments, respectively, the sediment was characterized by a water content of 67.9 and 51.0%, a particulate organic carbon content of 11.9 and 2.87% on dry weight matter, and 0.370 and 0.250% particulate nitrogen content. The sediment was homogenized and mixed with mechanical action (paint propeller connected to an electric drill) for 20 min.

Then 1.2 L of sediment was added in 20 and nine Pyrex bottles (2 L) for the chironomid and gammarid experiments, respectively. Each bottle was spiked with a solution of PCB153 in an acetone carrier at a nominal concentration of 100 and 50 ng g^{-1} dry weight (dw) for chironomid and gammarid experiments, respectively. The amount of carrier added to the sediment was minimal (0.07 and 0.08 $\mu L/g_{sed}$ for chironomid and gammarid experiments, respectively). Then each bottle was rotated for 24 h (chironomids) to 72 h (gammarids) at 15 revolutions per minute (rpm) at room temperature (21 °C). After 48 h storage at 4 °C, contaminated sediment in each bottle was transferred in a polypropylene jar and homogenized and restless with mechanical action for 20 min before being added to aquaria.

3.2.2 Leaf spiking

Alder leaves (*Alnus glutinosa*) were collected in November 2016 and stored in plastic boxes. Prior to exposing gammarids to PCB153, the alder leaves were placed in a bucket filled with several liters of ground water for 7 days at 21 °C. The water was renewed every 2 days to remove the exudates from the leaves. Several batches of 5 g_{dw} leaves were placed in Pyrex bottles (2 L) containing 1 L of groundwater and were spiked at a nominal concentration of wet-weight basis 50 ng_{PCB153} $kg^{-1}_{leaf,ww}$ with a solution of 5 µg L^{-1} of PCB153 in acetone. These batches were rotated for 72 h at 10 rpm at room temperature (21 °C). Then leaves were rinsed with ground water for 3 days in Pyrex bottles before being placed in aquaria.

3.3 Organism exposure to PCB153

3.3.1 Chironomid exposure

A total of seven aquaria (38-20-24.5 cm in polystyrene) were prepared with 3 L of homogenized spiked sediment and 15 L of groundwater. Each aquarium was allowed to settle for 10 days before introducing the chironomids. A control aquarium was prepared in the same way with reagent control sediment (Fig. S1).

Benthic invertebrate *C. riparius* were obtained from laboratory cultures carried out according to standard methods (OECD, 2004; AFNOR, 2010). A total of 400 fourth-instar

192 larvae (7-day-old larvae post-hatching, L4) were added to each aquarium. Chironomids were
193 exposed to spiked sediment for 7 days at 21 ± 0.2 °C in aerated and static water. A 16:8-h
194 light:dark cycle was maintained throughout the experiment. Larvae were fed every day with
195 400 mg commercial food Tetramin® per aquarium. The water quality parameters were
196 monitored and are presented in Annex S1. Chironomid survival, length and wet weight were
197 determined at each sampling time. To determine the total length, ten larvae were
198 photographed using an IEEE 1394 Digital CCD camera (F2, FOculus, Germany) mounted on
199 an Olympus BX51 light and SZX12 stereo zoom microscopes at low magnifications. The mean
200 lengths were determined using digital image analysis software (SigmaScan Pro software).

201 *3.3.2 Gammarid exposure*

202 Three weeks before the start of the experiment, about 3,000 male gammarids were
203 collected with a hand net at a reference site (Saint-Maurice de Rémens, France, 5°26′22″E -
204 45°95′79″N). Gammarids were brought to the laboratory and acclimated 3 weeks in aquaria
205 with continuously renewed groundwater under constant aeration, a 16:8-h light:dark
206 photoperiod was maintained and the temperature was kept at 12 °C. Organisms were fed *ad*
207 *libitum* with alder leaves. Only male gammarids (11.4 ± 0.9 mm) were selected, in order to
208 eliminate potential biases due to neonate release by females.

209 Gammarid experiments were composed of two phases: uptake and elimination. For the
210 uptake phase, different exposure routes were tested: gammarids were exposed to spiked
211 leaves (E1 condition) or to spiked sediment (E2 condition) for 7 days at 12 ± 0.2 °C under a
212 16:8-h light:dark cycle maintained throughout the experiment. A third condition (E3) was
213 tested, similar to E2 but without organisms, in order to determine whether there was a
214 contamination transfer from sediment to leaves (Fig. S1). The overlying water was renewed
215 daily under constant aeration. A control aquarium for E2 was prepared with homogenized
216 reagent sediment (0.08 µL of acetone/g_{sed}).

217 At the beginning of the experiment, 300 individuals were added per aquarium (test and
218 control). Gammarids exposed to the contaminated leaves (E1) were distributed in three

aquariums each containing 15 L of groundwater and one batch of previously spiked leaves per aquarium. Organisms exposed to spiked sediment (E2) were distributed in three aquariums each containing 3 L of spiked sediment, 15 L of groundwater and one batch of previously clean re-hydrated leaves. After 7 days of exposure, gammarid survival for each condition was determined and the organisms were transferred to a clean medium: 270 organisms per aquarium with groundwater for the E1 condition or with clean sediment and groundwater for the E2 condition. During depuration, gammarids were fed with clean leaves (5 g dw). The water quality parameters were monitored and are presented in Annex S1. Gammarid survival, length and wet weight were determined at the end of the uptake and elimination phases.

3.4 Sample collection

The overlying water (OW) was sampled in 1-L polyethylene (PE) bottles. Subsamples from sediment were deposited in 180-mL PE tubes. Organisms were collected in 50-mL Falcon® tubes. Every day, chironomids were collected by sieving sediment at 500 µm. The OW and sediment samples were collected at days 0, 4 and 7. The OW, sediment and organism control samples were collected at days 0 and 7. At days 0, 1, 2, 4, 7, 8, 9, 11 and 14, 90 gammarids were collected for each condition (E1 and E2). The OW, sediment, leaf and organism control samples were collected at days 0, 7 and 14. All samples were stored at −21°C and lyophilized at −65°C (Christ-Alpha 1-4LD, Bioblock Scientific) under a pressure of 0.050 mbar for 48 h for organisms, 72 h for leaves and 7 days for sediment.

3.5 PCB153 analyses

Water samples were filtered using 47 mm GF/F glass microfiber filters (Whatman®), and approximately 10 mL of filtered samples were extracted using a SPME procedure. Approximately 0.5 g of sediment samples and 0.2 g of leaves and organisms were extracted by microwave-assisted extraction (Milestone SRL, Sorisole, Italy) with 12 mL of DCM at 80 °C for 15 min. The extracts were filtered, concentrated under nitrogen flow at 40 °C and cleaned up on columns containing activated copper and acidified silica gel (40% H_2SO_4 w/w) previously

245 conditioned with 5 mL of pentane; after extract loading, PCB153 was eluted with three times 5
246 mL of a pentane/DCM (90/10, v/v). The eluate was further concentrated, solvent exchanged
247 to isooctane and taken to a final volume of 100 µL.

248 PCB153 was analyzed using 6890N Agilent Technologies gas chromatography
249 (Massy, France) connected to an electron capture detector (ECD). Analytes were injected
250 (1 µL) in pulsed splitless mode and separated with a J&W HP-5MS column (5% phenyl – 95%
251 methylpolysiloxane; 60 m × 0.25 mm × 0.1 µm). Helium (vector gas, 1.3 mL min^{-1}) and nitrogen
252 (auxiliary gas, 60.0 mL min^{-1}) were used. The injector temperature was set at 280 °C and the
253 detector temperature at 300 °C. The kiln temperature program was: 90 °C for 2 min (80 °C for
254 water samples), 15 °C min^{-1} to 178 °C (20 °C min^{-1} to 190°C), 2 °C min^{-1} to 230 °C (210 °C),
255 30 °C min^{-1} (15 °C min^{-1}) to 300 °C, 300 °C for 3.8 min (5 min). PCB153 was quantified relative
256 to internal standard (PCB198, 9.6–11.8 ng).

257 *3.6 Data analysis*

258 Significant differences were considered according to the Wilcoxon test with an α risk of 5%.
259 Graphical representations were made with the statistical software R (version 3.3.3, R Core
260 Team, 2017).

4. Link between model and data: Bayesian inference

4.1. Stochasticity

For both chironomids and gammarids, we assumed a gaussian distribution of the contaminant concentration in the organism:

$$C_{obs}(t) \sim N(C(t), 1/\sigma^2) \quad (8)$$

where N stands for the Normal law, $C_{obs}(t)$ corresponds to the contaminant concentration in the organism at time t measured during the experiments, C(t) is the contaminant concentration at time t predicted by the model and σ is the standard deviation of contaminant concentration in the organism.

For chironomid size, we also assumed a normal distribution:

$$L_{obs}(t) \sim N(L(t), 1/\sigma_L^2) \quad (9)$$

where $L_{obs}(t)$ is the length measured at time t during the experiments, L(t) is the length predicted by the von Bertalanffy model at time t, and σ_L is the standard deviation of organism size.

4.2. Graphical representation

Figure 1 represents the directed acyclic graphs (DAGs) for generic (a) chironomids (b) and gammarids (c), which symbolize the deterministic links between parameters and variables for the complete generic (Eq. (1)), chironomids (Eq. (4)) and gammarids (Eq. (7)) models and the stochastic links between the observed and predicted data.

4.3. Definition of priors

Before conducting an experimental study, a prior distribution is defined for each parameter according to information available from the literature and/or previous experiments. Depending on the source and the conditions that the information comes from, informative, semi-informative or noninformative prior distribution can be used. If a parameter was already estimated in previous studies or if previous data are available, a normal prior distribution can be used (with the mean value estimated and the precision with a standard deviation twice the

value estimated to take into account the potential differences in experimental conditions). However, if no information is available but an order of magnitude is (positive only, for example), it is possible to apply a weakly informative prior, as a uniform distribution. If any information is available on the order of magnitude of a parameter, its prior can be defined on the decimal logarithm scale in order to give the same probability to lower or higher estimates. For variance parameters, we use a noninformative (0.001, 0.001) gamma prior, as is usually done (Lambert, 2005; Richards and Chaloupka, 2009).

For chironomids, priors were defined from the values given by Schuler et al. (2003) where *Chironomus tentans* were exposed to PCB153-spiked sediment. They found a mean k_s value of 0.054 g_{sed}. g_{org}^{-1}.h^{-1} and a mean k_e value of 0.011 h^{-1}. We thus assumed a $\log_{10}$-normal (0.113, 5) prior for k_s (in g_{sed} g_{org}^{-1} d^{-1}) and a $\log_{10}$-normal (−0.578, 5) prior for k_e (in d^{-1}). For k_w, we assumed a $\log_{10}$-uniform (−5, 2) prior. We used a $\log_{10}$-normal (0.236, 2) prior for k_g (in d^{-1}) according to Péry et al. (2002), corresponding to a growth rate of 1.72 d^{-1}. Priors for L_0 and L_{max} were assumed to follow $\log_{10}$-normal distributions and were set, respectively, at (0.778, 0.64; in days) corresponding to an initial size of 6 mm, and (1.056, 0.64; in days) corresponding to a mean limit size of 11.4 mm (Péry, 2002). We assumed a non-informative (0.001, 0.001) gamma prior for the precision.

For gammarids, little information was available in the literature. As a consequence, we used a non-informative (−5, 2) $\log_{10}$-uniform prior for uptake and elimination rate constants (k_s, k_l, k_w, k_e). We also assumed a non-informative (0.001, 0.001) gamma prior for precision.

4.4. Implementation of the model – MCMC simulations

Model computation was performed with JAGS and R software (R Core Team, 2017; Plummer, 2016). The models were fitted to bioaccumulation data using Bayesian inference via Markov Chain Monte Carlo (MCMC) sampling. For each model tested, we started by running a short sampling (5,000 iterations after a burn-in phase of 10,000 iterations) using the Raftery and Lewis (1992) method to set the necessary thinning and number of iterations to reach an accurate estimation of each model parameter.

313 For chironomids, MCMC sampling was based on 150,000 iterations for three chains
314 after discarding the first 5,000 iterations. Samples from every 40th iteration were stored to
315 reduce autocorrelation. For gammarids, 26,000 iterations were done after discarding the first
316 10,000 iterations. Samples from every seventh iteration were stored to reduce autocorrelation
317 in the sample.

318 To monitor the convergence of the chains, we used a visual inspection as well as the
319 Gelman criterion (Gelman, 1995). The R codes are available in supporting information (Annex
320 S2).

321 *4.5. Posterior distributions and relevance of model predictions*

322 From the joint posterior distribution, we can obtain the marginal posterior distribution
323 for each parameter, which can be summarized by the mean or median and standard deviation.
324 The accuracy of model parameter estimation can be visualized by comparing prior and
325 posterior distributions: a thin posterior distribution reflects that the data contributed enough
326 information to precisely estimate parameters.

327 To check the relevance of model predictions, we represent, for each experiment,
328 observed data superimposed on the model simulated with the median of the posterior
329 distribution for each parameter and the 95% credibility band of the predicted data considering
330 parameter uncertainties and stochasticity. To obtain the 95% credibility band, the predicted
331 data were simulated with the model for each MCMC iteration and the stochastic model
332 considered for observed data (Eqs. (8) and (9)).

333 *4.6. Model comparisons*

334 Several hypotheses were considered and tested for chironomids (Eqs. (4) and (6)) and
335 for gammarids (Table S1) according to the experimental data available. To compare the
336 different sub-models fitted, we analyzed the precision of each parameter estimation and the
337 relevance of model predictions through the deviance information criterion (DIC), a Bayesian
338 measurement that weighs the quality of model fit with its complexity. Sub-models with lower

DIC values are expected to effectively balance between predictive capacity and complexity (Spiegelhalter, 2002).

For Bayesian inference, JAGS 4.2.0 for Windows and the *rjags* package for R software were used.

5. Results

5.1. Chironomus riparius

5.1.1. Sediment, water and chironomid contamination

The PCB153 concentrations in control and spiked sediment at day 0 were, respectively, 1.01 ± 0.25 and 83.3 ± 20.8 ng g_{sed}^{-1} versus 100 ng g_{sed}^{-1} (dw) expected. At the end of the experiment, the PCB153 concentration in spiked sediment was 89.6 ± 22.4 ng g_{sed}^{-1} (dw). No significant difference was observed for the concentrations in the sediment monitored during the experiment (*p*-value = 0.333).

At the beginning of the experiment, the PCB153 concentrations in water were 0.077 ± 0.009 ng L^{-1} and 0.230 ± 0.025 ng L^{-1} in the control and exposed aquaria, respectively, while they were 0.259 ± 0.028 ng L^{-1} and 3.85 ± 0.420 ng L^{-1}, respectively, at the end of the experiment.

PCB153 concentrations in *C. riparius* exposed to spiked sediment increased from 0.089 ± 0.031 to 142 ± 50.0 ng g_{org}^{-1} in 7 days.

5.1.2. Chironomid survival and growth

An acceptable survival rate was observed during the experiment for the test condition (88%) and for the control (76%). No adverse effect of spiked sediment on chironomid growth was observed (*p*-value = 0.248).

5.1.3. Parameter estimates

Two models were fitted to uptake data: Equation (4), which considers water and sediment exposure routes, and Equation (6), which considers sediment only. Similar marginal posterior distributions were obtained for each parameter with both models (Table S2, Fig. S2). Since the DICs for both models were similar (87.66 for Eq. (4) and 87.71 for Eq. (6)), we selected the most parsimonious one (with the fewest parameters), Eq. (6), which accounts for exposure from sediment only.

The inference process quickly converged, and thin posterior distributions were obtained for each parameter, meaning that data contribute sufficient information to accurately estimate model parameters (Fig. S2). Median values and 95% credibility intervals for each parameter were estimated and are summarized in Table 1.

5.1.4. Model predictions

The model predictions fit the bioaccumulation and growth data well (Fig. 2). For bioaccumulation (Fig. 2a), two of the eight measurements were outside the 95% credibility band of the predicted data, and for growth 23 of the 80 measurements (Fig. 2b).

5.2. Gammarus fossarum

5.2.1. Leaf, sediment, water and gammarid contamination

PCB153 concentrations in the different matrices (water, leaves and sediment) are summarized in Table 2. There was no difference among PCB153 concentrations in sediment throughout the exposure phase (*p*-value = 0.939). Leaves added to spiked sediment without gammarids (E3 condition) were significantly less contaminated than leaves in spiked sediment with gammarids (E2 condition) (*p*-value = 0.042).

As shown in Figure 3, we obtained similar PCB153 concentrations in gammarids over time for the two conditions tested (E1 and E2). PCB153 concentrations in *G. fossarum* exposed to spiked leaves (E1) and sediment (E2) increased from an initial concentration of 0.320 ± 0.110 to 10.9 ± 3.80 and 11.2 ± 3.93 ng g_{org}^{-1}, respectively, at the end of uptake phase. When gammarids were transferred into a clean media, the E1 and E2 PCB153 concentration in the organisms decreased to 4.71 ± 1.65 and 6.41 ± 2.24 ng $g_{org}^{-1,}$ respectively, at day 14.

5.2.2. Growth and survival

High survival rates were observed during the experiments. Survival after uptake and elimination periods were, respectively, 93 and 91% in control aquaria, 96 and 97% for E1 and 96 and 94% for E2.

5.2.3. Model parameters

Several models were fitted according to the exposure routes considered (Table S1). The models with similar lowest DIC values were those corresponding to hypotheses #3, 4, 6 and 7 in Table S1 (DIC values are reported in Table S2 in the SI). Similar model parameter estimations and marginal posterior distributions for each parameter were obtained for hypotheses #3, 4 and 6 (Table S2, Fig. S3). However, when the water exposure route was considered (hypothesis #7), marginal posterior distributions displayed two peaks for uptake rate constants k_l and k_s (Fig. S3), and the median values estimated for k_l and k_s considerably decreased (Table S2). We concluded accordingly that considering water as a contamination source did not contribute relevant information to accurately estimate model parameters. This conclusion is consistent with the fact that PCB153 concentrations measured in leaves and sediment were around 10,000 times higher than the concentration in water, in accordance with the hydrophobic character of this substance. Consequently, the model corresponding to hypothesis #6 was also eliminated. Between hypotheses #3 and 4, both considering contamination from leaves and sediment, we decided to keep the model corresponding to hypothesis #3. Indeed, this model is simpler than the one corresponding to hypothesis #4, in that it ignores that PCB153 transfers from sediment to leaves, while DICs are similar.

The inference process for the gammarid model corresponding to hypothesis #3 quickly converged, and thin posterior distributions were obtained for all parameters (Fig. S3). Median values and 95% credibility intervals for each parameter were estimated and are summarized in Table 1. The median estimation of k_s was around five times higher than that of k_l.

5.2.4. Model predictions

The model predictions fit well with uptake and elimination data (Fig. 3). For bioaccumulation in the E1 condition, two of the 11 measurements were out the 95% credibility band of the predicted data, and two of the 10 measures for the E2 condition.

6. Discussion

6.1. Robustness of Bayesian inference

We used Bayesian inference to simultaneously estimate all the model parameters together to enable a more accurate assessment of uncertainty around model predictions. One of the major advantages of the Bayesian analysis is the possibility of using data from different experiments simultaneously and even different types of data (e.g., uptake and elimination data, or bioaccumulation and growth data) to estimate parameters common to the different models. This was illustrated here by estimating the elimination rate from uptake and elimination data for gammarids (Fig. 3, Table 1), as well as by estimating the chironomid growth rate from bioaccumulation and growth data (Fig. 2, Table 1).

To evaluate the model performance, we used four criteria: (i) marginal posterior distributions for each model parameter, which generally provides more information compared to prior distributions; (ii) goodness of fit to experimental data; (iii) DIC value; and (iv) the principle of parsimony.

For both chironomid and gammarid models, thin posterior distributions were obtained, meaning that data provided enough information to estimate parameters precisely (Fig. S2-a and S3-a). The simultaneous estimate of model parameters assesses the uncertainty on parameters considering the correlation between them. This is an improvement compared to the common approach in TK modeling, where model parameters are often estimated sequentially, without accounting for autocorrelation or confounding factors. The existing knowledge on parameter values derived from the literature can also be accounted for, through the definition of prior distributions, which is not the case in the common approaches. Moreover, in the common framework it is not easy to consider the overall uncertainty of predictions, as recommended in the context of environmental risk assessments (Lin, 2004).

For both species, model predictions fit well with experimental data. The measurements out the 95% credibility band of the predicted data for both species could indeed be due to the

low number of data points and their proximity. For chironomids, Schuler et al. (2003) obtained a k_s mean value of 1.30 ± 0.014 g_{sed} g_{org}^{-1} d^{-1}, and a k_e mean value of 0.264 ± 0.006 d^{-1} for *Chironomus tentans* exposed to PCB153-spiked sediment. Here, we obtained lower values, especially for k_s. This could hypothetically be due to (i) the difference between the species tested, (ii) the difference in experimental conditions (shorter exposure duration and lower sediment concentration in Schuler et al. (2003)) and (iii) growth dilution, which was ignored in Schuler et al. (2003). The literature had demonstrated the importance of considering the growth rate for fourth-instar larvae of chironomids (Péry, 2002; Bertin, 2014). In the present study we estimated this model parameter at k_g = 0.123 [0.029–0.356] d^{-1}; in the literature, the values vary between 0.355 and 1.72 (Péry, 2002; Bertin, 2014). Furthermore, Watts and Pascoe (2000) observed that fourth-instar larvae of *C. tentans* were much larger than those of *C. riparius*. To our knowledge, this study is the first reporting the bioaccumulation of PCB153 from several potential food sources for gammarids. Previous studies with gammarids examined PCB uptake from water exposure (Sanders and Chandler, 1972; Lynch and Johnson, 1982), whereas accumulation through diet remains unexplored (Pinkney, 1985).

Statistical model selection is commonly based on the parsimony principle, by which hypotheses should be kept as simple as possible. The idea is that by adding parameters to a model we could improve the fit to some degree, but at the same time parameter estimates worsen because there is less information available per parameter. In addition, the computations typically require more time by adding parameters. In this study, we applied this principle when similar DICs were obtained, so the models with the least parameters were selected.

6.2. Modeling and biological implications

One advantage of the generic model developed in this study is that it allows us to consider each uptake or elimination route as a module to add according to the availability of the data measured. The different models tested can then determine which routes are the most important in the accumulation of contaminant by the organism. Sidney et al. (2016) showed

that for hydrophobic PCBs, particle ingestion was the dominant uptake route whatever species was tested (*C. riparius*, *Hyalella azteca, Lumbriculus variegatus* and *Sphaerium corneum*). This is consistent with our results for chironomids and gammarids, which confirmed that sediment is the major PCB contamination source.

The model considering the water and sediment exposure route (Eq. (4)) gave similar results to the model considering only the sediment exposure route (Eq. (6)) (i.e., similar marginal posterior distributions for k_s and k_e, predicted concentrations and DIC values). As a consequence, we concluded that not considering water exposure in the chironomid model contributes no more information and confirms that sediment is the major exposure route.

For gammarids, several hypotheses were tested, and the most parsimonious model was the one that did not account for the water exposure route (hypothesis #3). Furthermore, considering or not the transfer of PCB153 from sediment to leaves in E2 condition did not change the value and the precision of the parameters (hypothesis #4 and #3, Table S2), demonstrating that these data do not contribute additional valuable information. Indeed, previous experiments with perfluorinated alkyl compounds hypothesized that due to gammarid activity, suspended particles of contaminated sediment were deposited on the surface of leaves and were then ingested by gammarids (Bertin, 2016). These results confirm that sediment is the major contamination source.

6.3. Species comparison

Model parameter estimates are therefore consistent with the life traits of these two species: an uptake rate from sediment approximately ten times higher for chironomids (living in the sediment) than gammarids (living at the surface of sediment) and similar elimination rate constants (Fig S4).

6.4. Model limitations and implications for future use

Two limits could be highlighted in the use of the Bayesian approach in TK models: (i) the complexity of computation and (ii) the choice of prior distributions. Due to its complexity, the use of the Bayesian approach is limited in TK models. However, for invertebrates, TK models

could be considered simpler and its Bayesian computation also stem from the organism being considered a unique compartment. The majority of the problems encountered in the Bayesian approach have resulted from the choice of prior distributions. It is crucial to define prior distributions according to previous data similar to the experiment rather than to consider prior distributions selected in this paper as “generic.” Nevertheless, considering previous data (*a priori*) in the TK model could be useful to limit the cost and the number of experiments.

Further investigations will apply this Bayesian framework to more complex processes, including biotransformation or concentration dependency, where the frequentist approach could have limitations. Moreover, calculating prediction intervals has an advantage in that they can also be calculated around simulations with fluctuating input concentrations, even for scenarios that differ from the calibration experiments, and in that the correlation among parameters is accounted for (Ashauer et al., 2010). In particular for European regulations, this approach could make it possible to predict the concentration in the biota because the concentration in sediment is known, and uncertainties are thus accounted for.

7. Conclusions and perspectives

In this paper, we proposed a generic TK model in a Bayesian framework to estimate toxicokinetic parameters. This approach could be useful in order to calculate a more accurate estimation of prediction uncertainty. We demonstrated the ability of Bayesian analysis to simultaneously estimate model parameters considering several exposure routes from a PCB153 environmental exposure experiment under controlled conditions in two invertebrate species, *C. riparius* and *G. fossarum*. From a methodological point of view, this paper illustrates that considering the correlation between parameters and different types of data is a real added value for TK modeling. We demonstrated the ability of a generic TK model to consider uptake and elimination routes as modules that can be added, depending to the availability of measured data. From an ecotoxicological point of view, we showed differences in PCB153 bioaccumulation between chironomids and gammarids, which could be explained by the different life traits of these two organisms. We also confirmed that sediment is the major route of exposure for invertebrates exposed to highly hydrophobic organic contaminants. Further investigations will apply this Bayesian framework to other benthic invertebrate species, and other organic contaminants, so as to address more complex processes, including biotransformation.

Acknowledgments

This study was supported by the French Agency for Biodiversity. The authors are thankful to Grand Parc Miribel-Jonage for providing the sediment used in experiments. The authors are also grateful to Marie-Laure Delignette-Muller (LBBE, UMR CNRS 5558, France) for Bayesian inference discussions as well as Myriam Arhror and Matthieu Masson (Irstea Lyon, France) for sediment characteristic analysis. The authors are also grateful to anonymous reviewers and to Ms. L. Northrup for editing the manuscript.

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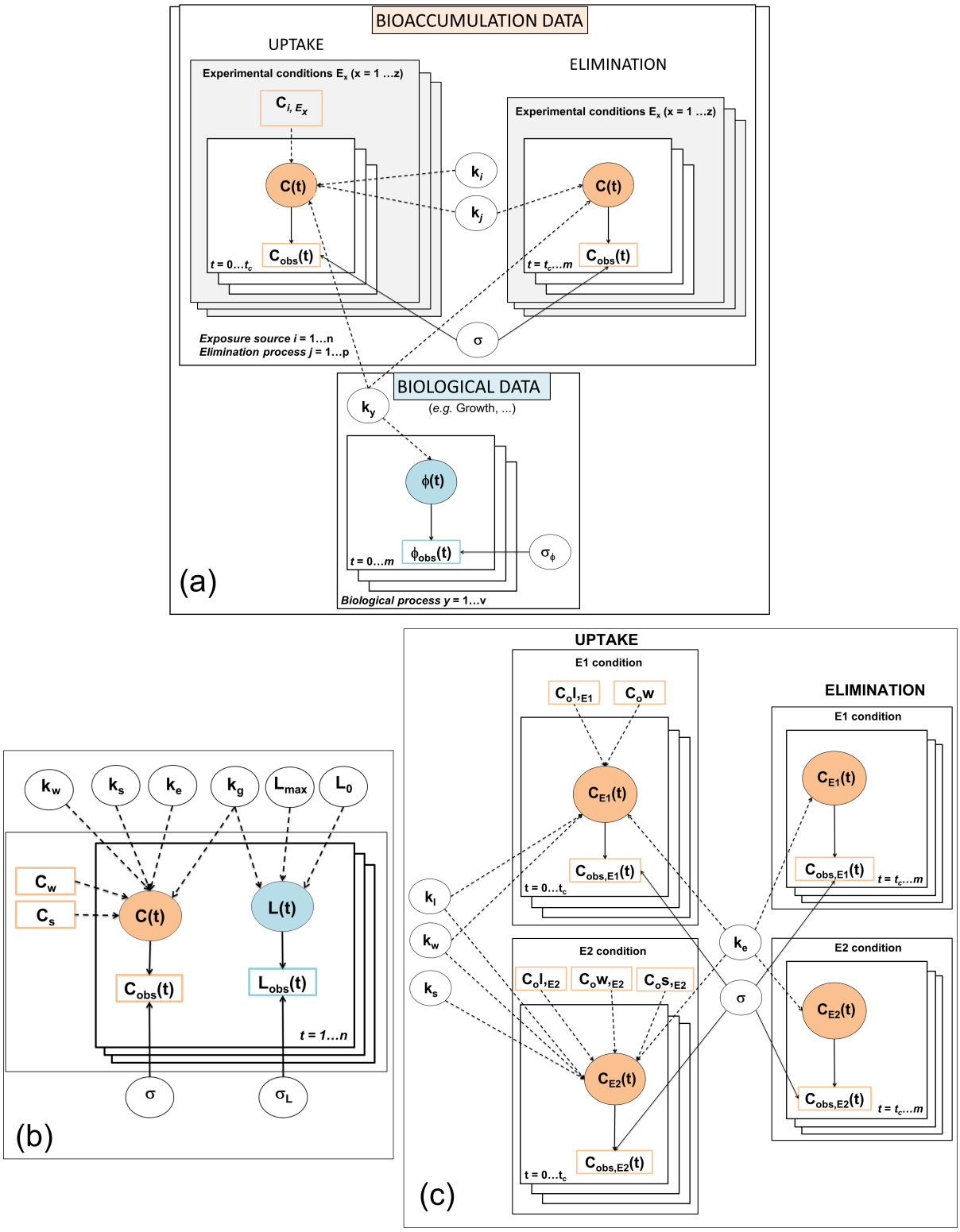

Figure 1. Directed acyclic graph (DAG) for (a) generic (b) chironomid and (c) gammarid models. Observed variables, such as the contaminant concentration in organisms, sediment and leaves, are represented by rectangle nodes. Model parameters and variables are represented by circular nodes. Dotted arrows represent deterministic links (Eqs. (1), (4) and (7)), while solid arrows represent stochastic links between predicted and observed data.

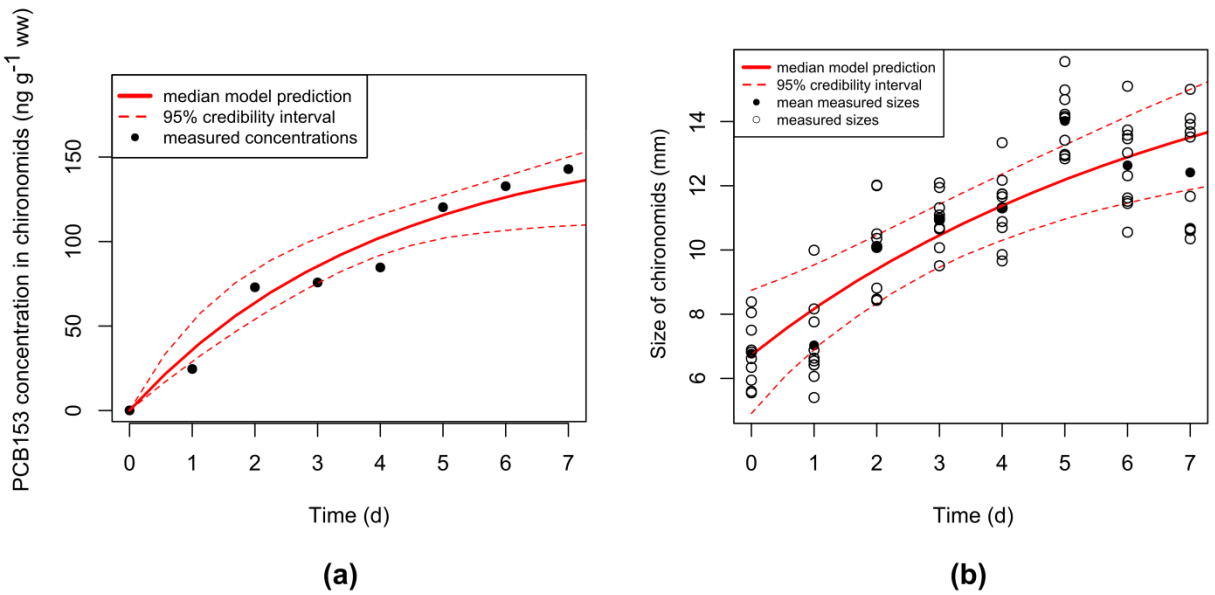

Figure 2. Observed data (dots) and model predictions (solid and dashed lines) for (a) PCB153 concentrations (ng g_{org}^{-1}) in chironomids (Eq. (6)) and (b) chironomid size (mm) (Eq. (5)) from days 0 to 7. The observed data are single values (n=1). On Figure 2-b, mean sizes at each day are symbolized by filled dots.

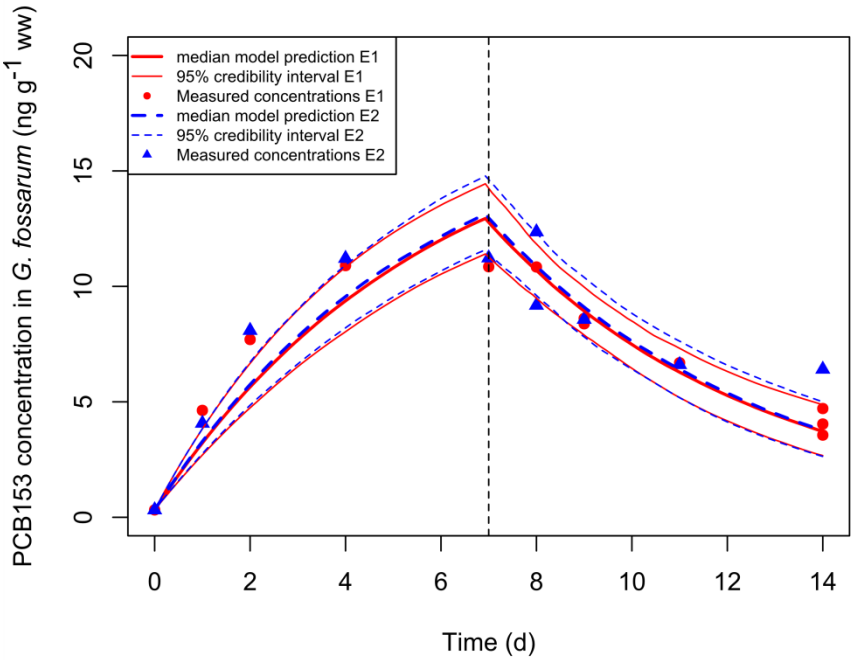

Figure 3. Measured (dots and triangles) and predicted (solid and dashed curves, from Eqs. (12) and (14)) PCB153 concentrations (ng g_{org}^{-1}) in gammarids during the uptake (days 0–7) and the elimination (days 7–14) phases (separated with the black dashed vertical line). The measured data are single values (n=1).

Table 1. Summary of the toxicokinetic model parameters: priors, median and percentile values determining the 95% credibility interval.

Organisms	Parameters	Priors	Median	Percentiles	
				2.5%	97.5%
Chironomus riparius	k_s	Log_{10}-normal (0.113, 5)	**0.473**	0.359	0.804
	k_e	Log_{10}-normal (−0.578, 5)	**0.121**	0.041	0.392
	k_g	Log_{10}-normal (0.236, 2)	**0.123**	0.029	0.356
	L_0	Log_{10}-normal (0.778, 0.64)	**6.75**	4.85	8.71
	L_{max}	Log_{10}-normal (1.056, 0.64)	**18.5**	13.3	40.7
	σ	Gamma (0.001, 0.001)	**11.8**	6.53	27.5
	σ_L	Gamma (0.001, 0.001)	**1.12**	0.672	2.18
Gammarus fossarum	k_l	Log_{10}-unif (−5, 2)	**0.013**	0.010	0.016
	k_s	Log_{10}-unif (−5, 2)	**0.071**	0.057	0.087
	k_e	Log_{10}-unif (−5, 2)	**0.178**	0.131	0.229
	σ	Gamma (0.001, 0.001)	**1.48**	1.11	2.12

Table 2. Summary of PCB153 concentrations in water, leaves and sediment according to gammarid experiments (control, E1, E2 and E3). Standard deviations (sd) are calculated on analytical replicates (n=2 when sd are given, except for leaves in E3 condition at day 7 and for sediment in E2 condition at day 0 where n=3).

	Water (ng L^{-1})			**Leaves (ng g_{leaves}^{-1})**			**Sediment (ng g_{sed}^{-1})**		
Days	**0**	**7**	**14**	**0**	**7**	**14**	**0**	**7**	**14**
Control	0.10	-	0.10	1.46 ± 0.18	1.13	1.09	0.29 ± 0.22	-	0.21 ± 0.11
E1[a]	0.30	0.10	0.10	260 ± 6.07	245 ± 30.1	3.86	-	-	-
E2[b]	0.10	0.20	0.00	1.46 ± 0.18	44.9 ± 12.7	1.72 ± 0.01	56.6 ± 8.68	30.0 ± 3.12	0.23 ± 0.12
E3[c]	0.10	0.80	-	1.46 ± 0.18	5.52 ± 0.87	-	56.6 ± 8.68	45.1 ± 1.44	-

[a] spiked leaves; [b] spiked sediment; [c] spiked sediment without gammarids