

Supporting Information for *Benchmarking the persistence of active pharmaceutical ingredients in river systems* by Mark Honti, Márton Zsugyel, Carolin Seller, and Kathrin Fenner

with 38 pages, 21 figures, and 2 tables.

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S1 Compounds

Table S1: Compounds used from the different measurement campaigns. ●: measured in that campaign, –: not measured or not present in sufficient quantities.

Compound	Abbr.	Usage	Rhine			Danube	
			Ruff et al. 2015	SMPC P1	SMPC P3	ICPDR JDS3	ICPDR JDS4
5-Methyl-Benzotriazole*	5MB	corrosion inhibitor	–	●	●	●	●
Acesulfame	ACE	artificial sweetener	●	●	●	●	●
Aliskiren	ALI	pharmaceutical	–	●	●	–	–
Amisulpride	AMI	pharmaceutical	●	●	●	●	–
Atazanavir	ATA	pharmaceutical	–	●	●	–	–
Atenolol	ATE	pharmaceutical	●	●	●	–	●
Benzotriazole	BEN	corrosion inhibitor	–	●	●	–	–
Bezafibrat	BEZ	pharmaceutical	–	●	●	–	–
Bicalutamid	BIC	pharmaceutical	–	●	●	–	–
Carbamazepine	CAR	pharmaceutical	●	●	●	●	●
Citalopram	CIT	pharmaceutical	–	●	●	–	●
Clarithromycin	CLA	pharmaceutical	●	●	●	–	–
Clopidogrel carbox. acid	CLO	pharm. metabolite	●	●	●	–	–
Cyclamate	CYC	artificial sweetener	●	●	●	–	●
Diclofenac	DIC	pharmaceutical	●	●	●	●	●
Ephedrin	EPH	pharmaceutical	●	–	●	–	–
Fexofenadine	FEX	pharmaceutical	–	●	●	–	–
Gabapentin	GAB	pharmaceutical	●	●	●	●	–
Hydrochlorothiazide	HYD	pharmaceutical	●	●	●	–	–
Irbesartan	IRB	pharmaceutical	●	●	●	●	–
Ketoprofen	KET	pharmaceutical	–	●	●	–	–
Lamotrigine	LAM	pharmaceutical	●	●	●	●	●
Levetiracetam	LEV	pharmaceutical	●	●	●	–	–
Lidocaine	LID	pharmaceutical	●	●	●	●	●
Mefenamic acid	MEF	pharmaceutical	–	●	●	–	–
Metformin	MET	pharmaceutical	●	–	–	●	–
Moclobemide	MOC	pharmaceutical	–	●	●	–	–
Metoprolol	MTO	pharmaceutical	●	●	●	–	●
Olmisartan	OLM	pharmaceutical	–	●	●	–	–
Oxcarbazepine	OXC	pharmaceutical	–	●	●	–	–
Oxypurinol	OXY	pharm. metabolite	–	●	●	–	–
Phenazone	PHE	pharmaceutical	●	●	●	●	●
Pregabalin	PRE	pharmaceutical	–	●	●	–	–
Propranolol	PRO	pharmaceutical	●	●	●	–	–
Ranitidine	RAN	pharmaceutical	–	●	●	–	–
Saccharin	SAC	artificial sweetener	●	●	●	–	–
Sitagliptin	SIT	pharmaceutical	●	●	●	–	–
Sulfamethoxazole	SUL	pharmaceutical	●	●	●	●	●
Trimethoprim	TRI	pharmaceutical	●	●	●	–	–
Valsartan	VAL	pharmaceutical	●	●	●	●	●
Venlafaxine	VEN	pharmaceutical	●	●	●	●	–

* In the Rhine the sum of 5MB and the conservative 4-Methyl-Benzotriazole due to analytical limitations.

S2 A Benchmarking Method for Rivers

S2.1 Benchmarking with a single pollution source

Benchmarking equations derive from the relative behaviour of mass-balance models (??). Here we derive simple benchmarks for cases when pollutants originate from a single source. Assume that pollutants emitted into a surface water body degrade with first-order kinetics at a non-negative rate. Then, for each pollutant S , the following general equation applies:

$$\frac{dM_S(t)}{dt} = -k_S M_S(t) \quad (S1)$$

where $M_S(t)$ is the mass of S at time t , and k_S is the degradation rate constant (which can be 0 for non-degrading compounds).

S2.1.1 Solution for a lake

Hydraulic steady state with constant volume (V) and thus similar incoming and outgoing discharge:

$$\frac{dM_S(t)}{dt} = V \frac{dC_S}{dt} = QC_{S,in} - QC_S - k_S C_S V \quad (S2)$$

which by division by V becomes:

$$\frac{dC_S}{dt} = \frac{1}{\tau} (C_{S,in} - C_S) - k_S C_S \quad (S3)$$

where τ is the hydraulic residence time in the system. In a permanent scenario with constant $C_{S,in}$ the following equilibrium concentration develops (where the above equation is equal to 0):

$$C_{S,eq} = \frac{C_{S,in}}{1 + k_S \tau} \quad (S4)$$

The benchmark ratio between two compounds named S and B in terms of steady state concentrations:

$$\frac{C_{S,eq}}{C_{B,eq}} = \frac{C_{S,in} (1 + k_B \tau)}{C_{B,in} (1 + k_S \tau)} \quad (S5)$$

From this one can express k_S from observed concentrations and k_B :

$$k_S = \frac{1}{\tau} \left(\frac{C_{B,eq} C_{S,in}}{C_{S,eq} C_{B,in}} (1 + k_B \tau) - 1 \right) \quad (S6)$$

When B is conservative ($k_B = 0$), this simplifies into:

$$k_S = \frac{1}{\tau} \left(\frac{C_{B,eq} C_{S,in}}{C_{S,eq} C_{B,in}} - 1 \right) \quad (S7)$$

S2.1.2 Solution for a river section

Downstream of the emission point, steady-state concentrations depend on the travel time (t):

$$\frac{dC_S(t)}{dt} = -k_S C_S \quad (S8)$$

Utilizing that for a steady flow with a constant flow velocity v there is a simple relation between travel time and downstream distance ($t = \frac{x}{v}$):

$$\frac{dC_S(x)}{dx} = -\frac{k_S}{v} C_S \quad (S9)$$

Solving with a known initial concentration ($C_{S,in}$) yields:

$$C_S(x) = C_{S,in} \exp \left(-k_S \frac{x}{v} \right) \quad (S10)$$

The benchmark ratio for compounds S and B is:

$$\frac{C_S(x)}{C_B(x)} = \frac{C_{S,in} \exp \left(-k_S \frac{x}{v} \right)}{C_{B,in} \exp \left(-k_B \frac{x}{v} \right)} \quad (S11)$$

Leading to

$$k_S = k_B + \frac{v}{x} \log \left(\frac{C_B(x) C_{S,in}}{C_S(x) C_{B,in}} \right) \quad (S12)$$

which can be solved at various distances (or travel times) downstream of the emission point based on the value of the $C_B(x)/C_S(x)$ ratio, thereby yielding multiple estimates for k_S .

S2.2 Benchmarking in rivers with many unknown polluting sources

The approach behind equation (S12) is not well suited for multiple emission sources, as the relation between k_S and k_B quickly gets complicated as the number of sources increases, and solving the corresponding equations require the exact knowledge of source locations and the $C_{S,in} : C_{B,in}$ ratios at each source. Thus, for the scale of long rivers a different approach is needed that (i) can handle lots of emission sources, and (ii) does not require the specifications for each source, as these are seldom available.

Equation (S12) demonstrates that it would be enough to know the concentration ratio at a single location to calculate k_S from k_B , so an entire longitudinal concentration ratio profile contains plentiful information that can be presumably used to develop a catchment-scale benchmarking algorithm that can cope with incomplete emission information and lots of emission points.

S2.2.1 Emission and transport model

Assume that the actual emissions (\mathcal{E}) of B and S by direct inputs and tributaries are (i) numerous, discrete and equidistantly placed along the river, (ii) are independent from neighbouring sources, (iii) and follow statistical distributions that apply to the entire length of the river. Furthermore, assume that B is conservative ($k_B = 0$). Let $q(x)$ denote the lateral incoming discharges along the river, also coming from a single distribution. Then the emissions of S and B can be calculated from multiplying q with the concentrations of S and B in the influents (c_S and c_B , respectively). Assuming that q , c_S , and c_B follow the same three distributions everywhere, the emission amounts $\mathcal{E}_S = q c_S$ and $\mathcal{E}_B = q c_B$ will be homoscedastic too, that is their distributions will not change along the river. There is no need to require dependence between c_S and c_B , which would be anyway weak considering the usual variability of directly emitted concentrations and the varying extent of degradation in the differently-sized tributaries. However, due to the common role of q , \mathcal{E}_S and \mathcal{E}_B will be correlated.

From the assumption that emission at each emission point is a stochastic variable and therefore the emission profile along the river is a discrete stochastic process, the transported fluxes of S and B , and accordingly the benchmark ratio will all be stochastic processes too. In the following we derive the statistical properties of these processes.

The transported flux $F_S(x)$ [g d^{-1}] will approach to a certain value downstream (in finite time if $k_S > 0$, see Figure S1). Due to the large assumed number of emission points, at a certain river cross-section the expected value of the transported flux $E[F_S(x)]$ is determined by the average emission rate and not by the difference between individual emissions. Then $E[F_S(x)]$ comes from the integral of equation (S10):

$$E[F_S(x)] = \int_{\chi=0}^x E[\mathcal{E}_S] \cdot \exp\left(-k_S \frac{\chi}{v}\right) d\chi \quad (\text{S13})$$

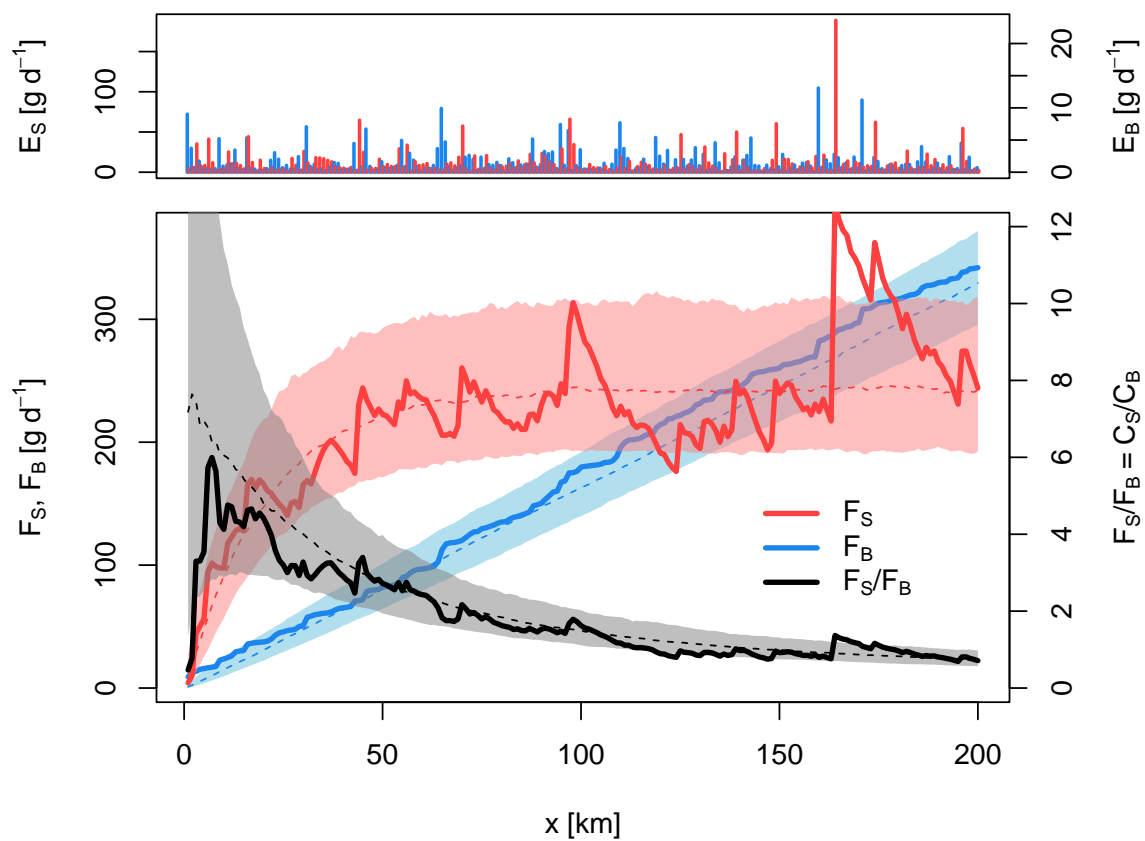


Figure S1: A synthetic example of strongly varying equidistant emissions along an upstream river section and the corresponding flux profiles and the concentration ratio profile. Compound S degrades fast with a half-life length of 15 km, while B is conservative. Thick lines show a specific realization, shaded areas indicate uncertainty intervals at 80% confidence level.

where $E[\mathcal{E}_S]$ is the mean distance-specific emission rate [$\text{g m}^{-1} \text{d}^{-1}$] along the river.

The solution of this integral equation is:

$$E[F_S(x)] = \frac{E[\mathcal{E}_S]v}{k_S} \left(1 - \exp\left(-k_S \frac{x}{v}\right) \right) \quad (\text{S14})$$

For conservative compounds, the limit solution is (logically) the product of distance-specific emission rate and the river length for any x and v :

$$\lim_{k_S \rightarrow 0} E[F_S(x)] = E[\mathcal{E}_S] x \quad (\text{S15})$$

Proof: It is known that

$$\lim_{h \rightarrow 0} \frac{\exp h - 1}{h} = 1 \quad (\text{S16})$$

Let h be $-k_S \frac{x}{v}$, so by considering that x and v can be both nonzero:

$$\lim_{k_S \rightarrow 0} \frac{1 - \exp\left(-k_S \frac{x}{v}\right)}{k_S \frac{x}{v}} = 1 \quad (\text{S17})$$

and then

$$\lim_{k_S \rightarrow 0} \frac{v}{k_S} \left(1 - \exp\left(-k_S \frac{x}{v}\right) \right) = x \quad (\text{S18})$$

leading to

$$\lim_{k_S \rightarrow 0} \frac{E[\mathcal{E}_S]v}{k_S} \left(1 - \exp\left(-k_S \frac{x}{v}\right) \right) = E[\mathcal{E}_S] x \quad (\text{S19})$$

– Q.E.D.

So assuming that B is conservative:

$$E[F_B(x)] = E[\mathcal{E}_B]x \quad (\text{S20})$$

To estimate the variance of F_S (and F_B) at a certain location x use the ξ distance between two subsequent sources. The variance of the accumulated flux at a specific x declines with the square of k_S , but it can be summed up along the river in a similar way as the mean:

$$\text{Var}[F_S(x)] = \frac{\text{Var}[\mathcal{E}_S]v}{2k_S\xi} \left(1 - \exp\left(-2\frac{k_S x}{v}\right) \right) \quad (\text{S21})$$

$$\text{Var}[F_B(x)] = \text{Var}[\mathcal{E}_B] \frac{x}{\xi} \quad (\text{S22})$$

S2.2.2 Approximation for the mean and variance of the benchmark ratio along the river

The expected value and the variance of a ratio of two random variables does not have closed equation except cases with certain assumptions on the distribution and covariance of the components. To avoid having to make specific assumptions on the distributions of concentrations and the emissions, we apply the delta-method, that is a Taylor-series expansion around the means to estimate the selected statistical moments (??):

$$\mathbb{E} \left[\frac{X}{Y} \right] \approx \frac{\mathbb{E}[X]}{\mathbb{E}[Y]} - \frac{\text{Cov}[X, Y]}{\mathbb{E}[Y]^2} + \frac{\mathbb{E}[X]}{\mathbb{E}[Y]^3} \text{Var}[Y] \quad (\text{S23})$$

and

$$\text{Var} \left[\frac{X}{Y} \right] \approx \frac{\text{Var}[X]}{\mathbb{E}[Y]^2} - 2 \frac{\mathbb{E}[X]}{\mathbb{E}[Y]^3} \text{Cov}[X, Y] + \frac{\mathbb{E}[X]^2}{\mathbb{E}[Y]^4} \text{Var}[Y] \quad (\text{S24})$$

To assemble the mean and variance of the benchmark ratio, we substitute $F_S(x)$ for X and $F_B(x)$ for Y . As $\mathbb{E}[F_S(x)]$, $\mathbb{E}[F_B(x)]$, $\text{Var}[F_S(x)]$, and $\text{Var}[F_B(x)]$ are already known, the only open question is $\text{Cov}[F_S(x), F_B(x)]$.

It is known that $\text{Cov}[ZV, ZW] = \mathbb{E}[V]\mathbb{E}[W]\text{Var}[Z]$ for independent Z , V , and W (?). Thus, considering that it is mostly $q (= Z)$ that can create covariance between $F_S (= ZV)$ and $F_B (= ZW)$, we get:

$$\text{Cov}[F_B, F_S] = \frac{\mathbb{E}[F_S]}{\mathbb{E}[q]} \mathbb{E}[c_B] \text{Var}[q] \quad (\text{S25})$$

Having all components, the expected value of the benchmark ratio can be expressed:

$$\mathbb{E} \left[\frac{F_S}{F_B} \right] \approx \frac{\mathbb{E}[F_S]}{\mathbb{E}[F_B]} - \frac{\text{Cov}[F_S, F_B]}{\mathbb{E}[F_B]^2} + \frac{\mathbb{E}[F_S]}{\mathbb{E}[F_B]^3} \text{Var}[F_B] \quad (\text{S26})$$

which leads to

$$\mathbb{E} \left[\frac{F_S}{F_B} \right] \approx \frac{v}{k_S} \left(1 - \exp \left(-\frac{k_S}{v} x \right) \right) \left(\frac{1}{x} \frac{\mathbb{E}[\mathcal{E}_S]}{\mathbb{E}[\mathcal{E}_B]} + \frac{1}{x^2} \left(\frac{\mathbb{E}[\mathcal{E}_S] \text{Var}[\mathcal{E}_B]}{\xi \mathbb{E}[\mathcal{E}_B]^3} - \frac{\mathbb{E}[\mathcal{E}_S] \mathbb{E}[c_B] \text{Var}[q]}{\mathbb{E}[q] \mathbb{E}[\mathcal{E}_B]^2} \right) \right) \quad (\text{S27})$$

The unknown statistical properties of emissions can be merged into aggregate parameters:

$$\mathbb{E} \left[\frac{F_S}{F_B} \right] \approx \frac{v}{k_S} \left(1 - \exp \left(-\frac{k_S}{v} x \right) \right) \left(\frac{\alpha}{x} + \frac{\beta}{x^2} \right) \quad (\text{S28})$$

where $\alpha = \frac{E[\mathcal{E}_S]}{E[\mathcal{E}_B]}$ and $\beta = \frac{E[\mathcal{E}_S]}{E[\mathcal{E}_B]^2} \left(\frac{\text{Var}[\mathcal{E}_B]}{\xi E[\mathcal{E}_B]} - \frac{E[c_B]\text{Var}[q]}{E[q]} \right)$.

For large x , the effect of β/x^2 is losing its relative importance for most possible values of β . Thus, in an analogy to Taylor-series approximations, it can be assumed that $\beta = 0$ for $x \gg 0$.

Similarly, the variance of the bechmark ratio is:

$$\text{Var} \left[\frac{F_S}{F_B} \right] \approx \frac{\text{Var}[F_S]}{E[F_B]^2} - 2 \frac{E[F_S]}{E[F_B]^3} \text{Cov}[F_S, F_B] + \frac{E[F_S]^2}{E[F_B]^4} \text{Var}[F_B] \quad (\text{S29})$$

which leads to

$$\text{Var} \left[\frac{F_S}{F_B} \right] \approx \frac{v}{k_S} \left(1 - \exp \left(-\frac{k_S}{v} x \right) \right) \left(\frac{\gamma}{x^2} \left(1 + \exp \left(-\frac{k_S}{v} x \right) \right) - \frac{\delta}{x^3} \right) \quad (\text{S30})$$

with $\gamma = \frac{\text{Var}[\mathcal{E}_S]}{2\xi E[\mathcal{E}_B]^2}$ and $\delta = 2 \frac{E[\mathcal{E}_S]E[c_B]\text{Var}[q]}{E[\mathcal{E}_B]^3} - \frac{\text{Var}[\mathcal{E}_B]}{\xi E[\mathcal{E}_B]^4}$

Outside the initial range, the effect of the cubic term can be neglected ($\delta = 0$ for $x \gg 0$).

S2.2.3 Heteroscedastic emissions

Large rivers may flow through regions with different distributions of c_S and c_B . Such differences should only be considered when they are systematic and affect longer sections of the river. Such a case is an international river that has significantly different emission patterns in its upstream and downstream countries. To calculate the statistical properties of the benchmark ratio along the river, the locations of turning points between the distinct emission regimes must be known.

Let's assume that a river flows through different emission regimes that are labelled with roman numerals and that it is long enough to neglect β/x^2 from equation (S28). In this case, the expected value of the benchmark ratio for a single section would be:

$$E \left[\frac{F_S}{F_B} \right] \approx \alpha \frac{v}{k_S x} \left(1 - \exp \left(-\frac{k_S}{v} x \right) \right) \quad (\text{S31})$$

Each regime has its own, different $\alpha = \frac{E[\mathcal{E}_S]}{E[\mathcal{E}_B]}$ and its downstream limit coordinate X . Starting from upstream, the first regime is thus characterised by $\alpha_I = \left(\frac{E[\mathcal{E}_S]}{E[\mathcal{E}_B]} \right)_I$ and X_I , the following is by $\alpha_{II} = \left(\frac{E[\mathcal{E}_S]}{E[\mathcal{E}_B]} \right)_{II}$ and X_{II} , and so on.

At each regime boundary, the course of $E \left[\frac{F_S}{F_B}(x) \right]$ changes. In regime j (where $x \in [X_{j-1}, X_j]$) the course must be calculated considering the actual regime and all upstream regimes too:

$$\begin{aligned}
E \left[\frac{F_S}{F_B}(x) \right]_j &= \sum_{l=1}^{j-1} \left\{ \left(\frac{E[\mathcal{E}_S]}{E[\mathcal{E}_B]} \right)_l \frac{\exp(-k'_S(x - X_l)) - \exp(-k'_S x)}{k'_S x} \right\} + \\
&+ \left(\frac{E[\mathcal{E}_S]}{E[\mathcal{E}_B]} \right)_j \frac{1 - \exp(-k'_S(x - X_{j-1}))}{k'_S x}
\end{aligned} \tag{S32}$$

where $X_0 = 0$ and $k'_S = \frac{k_S}{v}$. This equation assumes that $E[\mathcal{E}_B]$ is the same in all sections and thus that $F_B(x)$ is a linear function of x . For carbamazepine, this condition was fulfilled in the Danube (Figure S2).

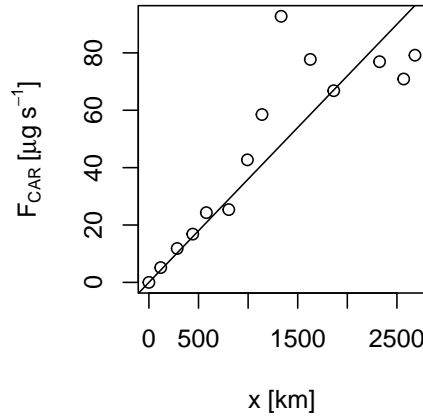


Figure S2: Carbamazepine flux along the Danube River in the JDS3 campaign. Dots indicate measurements, line is a linear fit to the data.

Remark: When $\frac{E[\mathcal{E}_S]}{E[\mathcal{E}_B]}$ is the same everywhere in equation (S32), regardless of the placement of X limits, we arrive at equation (S31).

As equation (S30) demonstrates for homoscedastic emissions, the variance of benchmark ratio depends on intricate properties of the emission statistics. This makes the variance under heteroscedastic emissions extremely complicated. Generally, according to numerical simulations, the same decaying pattern applies as for the homoscedastic case, yet the section boundaries are all breaking points and variance may even locally increase downstream. As a workaround, one can utilise the fact that total variance is likely to be dominated by measurement variance except the most upstream part of long rivers. Thus, benchmark variance can be calculated based on the most upstream section alone, thereby neglecting smaller changes downstream.

S2.2.4 Calculation algorithm

Here we describe the step-by-step procedure of fitting the homoscedastic benchmark model to API data.

1. Select the conservative benchmark compound B and the compound of interest (S).
2. Obtain concentration (or flux) data for compounds S and B along the main channel of the river. The two compounds must have been measured in the same cross-sections.
3. Assign a downstream distance coordinate to each sampling site. The starting point should be just upstream of where emissions are likely to start. The benchmarking method assumes that the flux of both S and B is 0 at $x = 0$.
4. Calculate the C_S/C_B ratios at each cross-section. If one of the compounds is missing at a certain cross-section, remove that section from the fitting data.
5. Fit the model to the data
 - (a) Assign prior parameter distributions to k'_S , α , β , γ , δ , and σ . It has to be noted that k'_S can be slightly negative if the benchmark compound is not completely resistant to removal, so there the prior should allow such values, while preventing too high absolute numbers. It is recommended to restrict the prior distributions of the other parameters to the non-negative domain as otherwise their assigned meaning would be violated. An exponential prior distribution helps to keep a parameter value positive while strongly favouring smaller numbers. If you don't want to use parameter priors, just assume that all of them are uniform distributions over a wide domain or discard them from the rest of the calculation algorithm. Doing so will increase parameter uncertainty and the risk of getting meaningless parameter values.
 - (b) Calibrate the model by maximising model posterior probability of parameters. Perform the following calculation steps in a desired optimiser function/framework (as the simplest solution, you can use `optim()` with `method = "Nelder-Mead"` in R):
 - i. Guess a set of values for k'_S , α , β , γ , δ , and σ .
 - ii. Calculate the prior probability of the parameter set by multiplying the probability density values of each parameter value and the corresponding prior distribution.
 - iii. For each cross-section calculate the expected value of the benchmark ratio with equation (S28) and the variance of the benchmark ratio with equation (S30) using the previously guessed parameter values. Then calculate the likelihood of parameters at each cross-section from the observed benchmark ratio and the probability density function of a normal distribution with the given expected value (mean) and variance.
 - iv. The total likelihood of the parameter set is the product of the cross-section likelihoods. To ease calculation, use log-likelihoods and sum them up instead of multiplying.

- v. The posterior probability is the product of prior probability and the total likelihood. When using log-likelihood, add the logarithm of the prior probability.
 - vi. Based on the posterior probability, guess a new set of values and start a new iteration in point ii.
6. Perform MCMC to assess parameter uncertainty. MCMC sampling is based on the posterior probability of parameters and produces a quasi-random sample of model parameters that – when enough iterations are available – is statistically representative of the posterior parameter probability distribution. MCMC starts from an arbitrary parameter combination, then in each iteration a random but close parameter combination is proposed, which is either accepted or rejected by the jump algorithm. When the new parameter combination belongs to a better posterior probability as the old one, it is accepted. Otherwise, it is accepted randomly, with a probability depending on the difference in posterior (more worse posteriors are accepted with less probability). Upon accept, the new parameter combination will replace the old one as the base for further jumps. MCMC requires thousands of model runs and posterior evaluations, and can be done with several alternative R packages, such as `mcmc`, `rjags`, `rstan`, etc. MCMC samples are typically pre-processed before interpreting. Subsequent parameter samples are normally correlated as the jump distance between subsequent rounds is bounded by the acceptance rule. That's why it is common to apply a thinning factor, which simply keeps every n^{th} step and discards the others. Efficient MCMC algorithms adjust the size and correlation structure of the jump distribution to keep acceptance rates optimal. This interferes with the convergence of the MCMC chain to the posterior, so the normal procedure is to restrict jump distribution adjustments to a first n iterations (called as the *burn-in* period), which are later discarded from processing. We used the Metropolis-Hastings algorithm of MCMC, thinned the chain by a factor of 5 to reduce correlation in the sample and dedicated the first 100 000 rounds of the 110 000 total rounds to burn-in.
7. Compare campaigns
- (a) Select the two campaigns (A and B) to be compared.
 - (b) Select the subset of compounds that is present in both campaign A and B.
 - (c) For each compound in the subset
 - i. Load the MCMC samples of k'_S from the two campaigns, neglecting the first iterations belonging to burn-in.
 - ii. Calculate the median values of k'_S from both samples.
 - (d) Rank the compounds in the subset based on their median k'_S values in campaigns A and

B separately.

- (e) Compare the ranks from the two campaigns to each other. Kendall's τ and the corresponding p value can be calculated with `cor.test(ranks.a, ranks.b, method="kendall")` in R, where `ranks.a` and `ranks.b` are the rankings of the subset compounds in the two campaigns.
- (f) Outliers can be detected by robust linear regression, using `MASS::rlm(ranks.b ~ ranks.a + 0, psi = psi.bisquare)` in R. Weights are obtained by taking the `w` property of the result of the `rlm` call. We used a weight threshold of $w < 0.5$ to label a point as an outlier.

S3 Parameter priors used in model calibration

Table S2: Prior parameter distributions used to fit observed C_S/C_B profiles

Parameter	Prior type	Distribution properties
α_i	lognormal	mean=most upstream C_S/C_B reading, relative standard deviation=20% for the uppermost (Rhine, Danube), 100% for other sections (Danube)
γ	exponential	mean=1
k'_S	uniform	minimum=-0.1, maximum=+0.1 [km ⁻¹], negative values allowed to describe back transformation of conjugates, where applicable
σ	exponential	mean=10% of observed mean C_S/C_B
X_i (Danube)	uniform	limits=real boundaries of DE-AT, AT-SK, SK-HU, HU-RS ± 30 [km]

S4 Ranking of uncertain quantities

S4.1 Calculating optimal ranks for uncertain quantities

Assigning ranks to highly uncertain quantities is itself uncertain and for a larger set of quantities it is combinatorically difficult. ranking 40 different samples of k'_S has $40! \approx 10^{48}$ possible solutions, while most of the combinations are obviously far from reasonable. To find the optimal ranking, we use Thurstone's model, which relies on probabilities of inequality relations between neighbouring elements of the ranking (?). In such a case the likelihood of the ranking is:

$$L(R) = \prod_{i=2}^n P(k'_{S_{i-1}} < k'_{S_i}) \quad (\text{S33})$$

where n is the number of compounds to be ranked.

The independent MCMC samples provide an empirical estimate for $P(k'_{S_i} < k'_{S_j}) = \sum [k'_{S_i} < k'_{S_j}] / m$ for compounds i and j , where $[...]$ is the Iverson bracket and m is the size of the MCMC

samples. From such pairwise relations a full probability matrix \mathcal{P} can be composed, showing all possible relations.

Our hypothesis is that sorting the compounds based on the medians of their k'_S samples yields an optimal ranking in the above defined likelihood model. When a sample is compared to itself, $P(k'_{S_i} < k'_{S_i}) = \frac{1}{2}$. We show that the same applies for non-identical samples having continuous symmetric unimodal distributions when their median is the same. The consequence of this hypothesis is that ranking by medians can determine an order where $P(k'_{S_i} < k'_{S_{i+1}}) > \frac{1}{2}$. For the sake of brevity, from this point on we denote the two samples of k'_S with X and Y , their means by \bar{X} , and \bar{Y} , their medians by \tilde{X} , and \tilde{Y} , respectively.

Getting the probability for the $X < Y$ inequality would generally require calculating the following integral:

$$p(X < Y) = \int_{-\infty}^{\infty} \int_{-\infty}^y f_X(x) f_Y(y) dx dy \quad (\text{S34})$$

where f_X and f_Y are the probability density functions of X , and Y , respectively.

Luckily, the relation can be translated into a univariate form by using the difference variable $D = X - Y$:

$$P(X < Y) = P(D < 0) \quad (\text{S35})$$

The distribution of D has the following property due to the additive behaviour of mean

$$E(D) = E(X) - E(Y) \quad (\text{S36})$$

then

$$P(D < 0) = \int_{-\infty}^0 f_D(\xi) d\xi = F_D(0) \quad (\text{S37})$$

where f_D is the probability density function of D and F_D is the cumulative distribution function of D . \tilde{D} is defined as:

$$P(D \leq \tilde{D}) = \int_{-\infty}^{\tilde{D}} f_D(\xi) d\xi = \frac{1}{2} = \int_{\tilde{D}}^{\infty} f_D(\xi) d\xi = P(D \geq \tilde{D}) \quad (\text{S38})$$

$F_D(0) = \frac{1}{2}$ means that $\tilde{D} = 0$. When X and Y are independent and have symmetrical distributions then the median is equal to the mean: $\tilde{D} = \bar{D}$. According to the additivity of independent means, the mean of D can be calculated from the means of X and Y : $\bar{D} = \bar{X} - \bar{Y}$.

When $\bar{X} - \bar{Y} = 0$ then it follows that:

$$\bar{X} = \bar{Y} \quad (\text{S39})$$

and due to the symmetry of distributions of X and Y :

$$\boxed{\tilde{X} = \tilde{Y}} \quad (\text{S40})$$

–Q.E.D.

From the proven hypothesis it follows that when $P(X < Y) \neq \frac{1}{2}$ then the then the medians and means of X and Y are not the same. When $\tilde{X} < \tilde{Y}$ then $P(X < Y) > \frac{1}{2}$. Thus, one can sort X and Y according to their medians. For symmetrically distributed X and Y sorting by the mean would be sufficient too, as $\bar{X} = \tilde{X}$. However, sorting by the median works for asymmetrically distributed samples too, given that both f_X and f_Y can be made symmetrical with the same transformation. The reason for this is that common transformations $t(\dots)$ do not change the order of elements, so

$$\widetilde{t(X)} = t(\tilde{X}) \quad (\text{S41})$$

Samples of k'_S are typically not symmetrical, but get closely normal after a log-transformation (see Box-plots in Fig. ??). Thus, rankings obtained by order of medians are presumably not optimal, but good approximations of the most likely solution.

The above defined likelihood of a ranking depends on the number of ranked items. To define a comparable metric for the quality of rankings, we define the unambiguity of an (optimal) ranking ($U(R)$) from the geometric mean of $P(k'_{S_{i-1}} < k'_{S_i})$ probabilities as:

$$U(R) = 2 \exp \left(\frac{\log L(R)}{n-1} \right) - 1 \quad (\text{S42})$$

$U(R)$ takes its maximum (1) when $P(k'_{S_{i-1}} < k'_{S_i}) = 100\%$ for all i , and is at its minimum (0%) for a totally undecidable ranking (where $P(k'_{S_{i-1}} < k'_{S_i}) = \frac{1}{2}$ for all i , e.g. because we try to rank exact copies of the same sample).

The similarity of two rankings of the same set of compounds is expressed by Kendall's rank correlation coefficient (τ). Compounds behaving differently in compared campaigns are detected by robust linear regression, using Tukey's score function (ψ). The weight threshold for outliers was 50%.

S4.2 An approximate uncertainty range for ranks

The uncertainty range for the rank of a certain compound can be estimated with an algorithm that resembles local sensitivity analysis. The likelihood of a specific ranking is approximated from the compound's relation to the others, ignoring relations unrelated to the compound in question. Relations are determined based on the \mathcal{P} matrix containing all possible $P(k_{S_j} < k_{S_i})$ values.

We assume that in a ranking that has the i^{th} compound at rank $R_i = r$ the other compounds are assigned to ranks $r_j < r_i$ if they have a $P(k_{S_j} < k_{S_i}) < 0.5$. The others are ranked above the compound ($r_i < r_j$).

Let P' be the ordered list of $P(k_{S_j} < k_{S_i})$ for all j . Then the left-sided estimate for the likelihood:

$$P(R_i = r)_{\text{left}} \propto \prod_{k=1}^{i-1} (1 - P'_k) \prod_{l=i}^n P'_l$$

The right-sided estimate is:

$$P(R_i = r)_{\text{right}} \propto \prod_{k=1}^i (1 - P'_k) \prod_{l=i+1}^n P'_l$$

Harmonising the two estimates:

$$P(R_i = r) \propto \min(P(R_i = r)_{\text{left}}, P(R_i = r)_{\text{right}})$$

The approximate confidence interval for the ranking can be extracted from the discrete probabilities by using a cut-off limit.

S5 Calculating total system half-lives from in the Rhine

For a given stream reach and compound, first-order total system degradation rate constants can be calculated from compound properties and reach characteristics (??). We used typical values for the Rhine main channel, and posterior estimates for compound properties from (?).

Param.	Meaning	Unit	Value
SSC	suspended solids concentration	kg m^{-3}	0.030
Z_w	water depth	m	4.0
Z_a	depth of active sediment layer	m	0.025
$f_{oc, sed}$	sediment organic carbon content	kg kg^{-1}	0.005
S	fine sediment dry mass in active layer	kg m^{-2}	3.0
K_{oc}	sediment adsorption coefficient	$\text{m}^3 \text{kg}^{-1}$	by compound
k'_{bio}	second-order biotransformation rate constant	$\text{m}^3 (\text{kg OC d})^{-1}$	by compound
$k_{photo, surf}$	surface phototransformation rate constant	d^{-1}	by compound
k_{hydr}	hydrolysis rate constant	d^{-1}	by compound

The fraction of time spent in settled sediment is

$$\phi_{\text{settled}} = \frac{\frac{S}{SSC \cdot Z_w}}{\frac{1}{K_{oc} \cdot f_{oc, sed} \cdot SSC} + 1 + \frac{S}{SSC \cdot Z_w}} \quad (\text{S43})$$

The aqueous fraction in the water column ($f_{aq, w}$ [-]) is

$$f_{aq, w} = \frac{1}{1 + K_{oc} \cdot f_{oc, sed} \cdot SSC} \quad (\text{S44})$$

The aqueous fraction in the sediment ($f_{aq, sed}$ [-]) is

$$f_{aq, sed} = \frac{1}{1 + \frac{S \cdot K_{oc} \cdot f_{oc, sed}}{Z_a}} \quad (\text{S45})$$

The total system first-order biotransformation rate ($k_{biotransf}$ [d^{-1}]) is

$$k_{biotransf} = k'_{bio} \cdot f_{oc, sed} \left(SSC \cdot f_{aq, w} (1 - \phi_{\text{settled}}) + \frac{S}{Z_a} \cdot f_{aq, sed} \cdot \phi_{\text{settled}} \right) \quad (\text{S46})$$

The first-order water column phototransformation rate (k_{photo} [d^{-1}]) is

$$k_{photo, w} = k_{photo, surf} \cdot \exp \left(-(11 \cdot SSC + 0.22) \frac{Z_w}{2} \right) \cdot f_{aq, w} \quad (\text{S47})$$

The first-order total system hydrolysis rate ($k_{\text{hydr,ts}}$ [d^{-1}]) is

$$k_{\text{hydr,ts}} = k_{\text{hydr}} (f_{\text{aq,w}} (1 - \phi_{\text{settled}}) + f_{\text{aq,sed}} \cdot \phi_{\text{settled}}) \quad (\text{S48})$$

Then finally the total system attenuation rate (k_{ts} [d^{-1}]) is

$$k_{\text{ts}} = k_{\text{biotransf}} + k_{\text{photo,w}} + k_{\text{hydr,ts}} \quad (\text{S49})$$

which can be converted into a half-life ($DT_{50,\text{ts}}$ [d]) as

$$DT_{50,\text{ts}} = \frac{\ln(2)}{k_{\text{ts}}} \quad (\text{S50})$$

S6 Fits of the benchmark model to measured data

Model fits are first ordered by campaign and then by compound. Campaigns are in their time order, compounds are in alphabetical order of their abbreviations,

S6.1 Rhine campaigns

S6.1.1 Ruff et al. (2015)

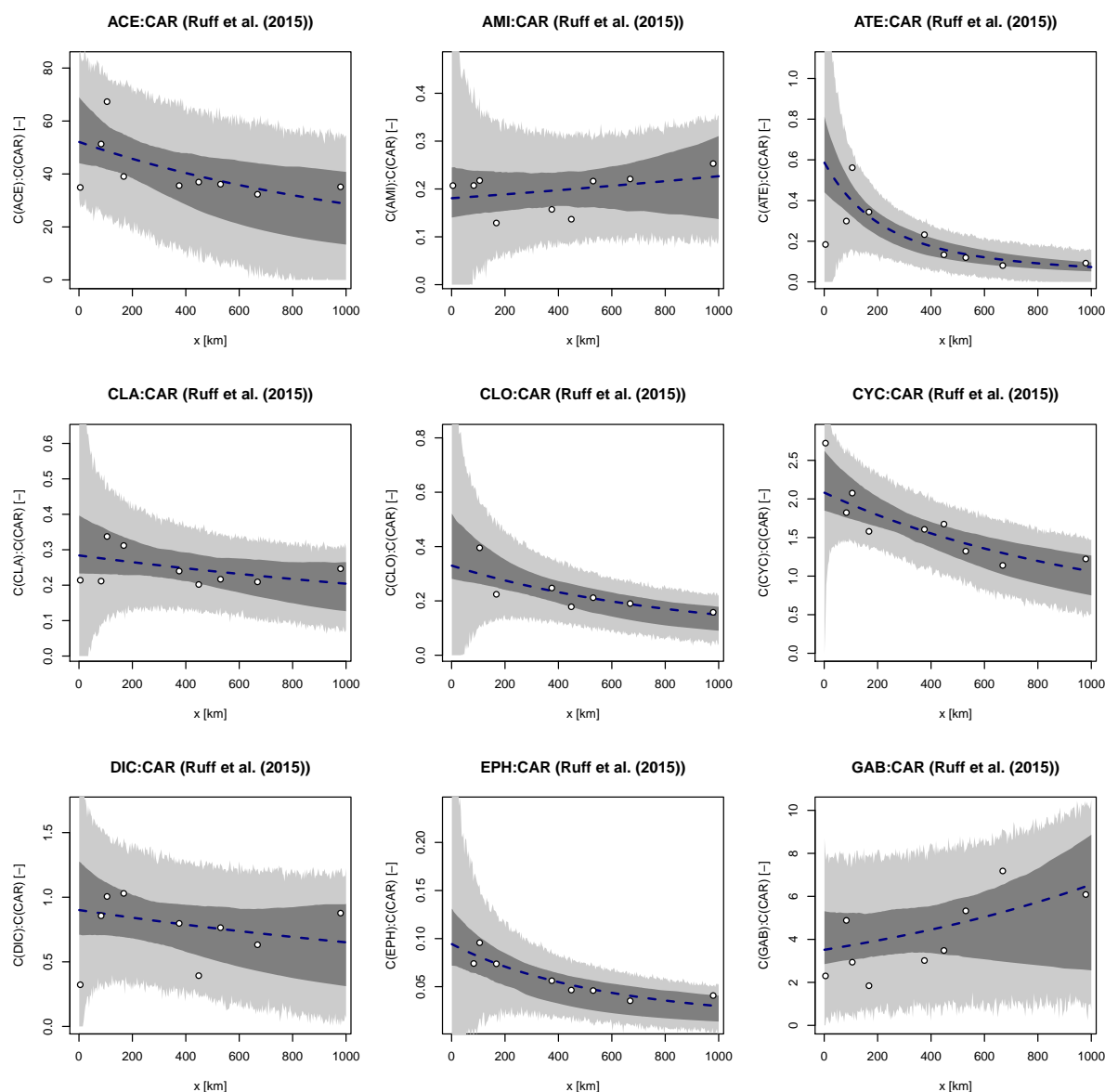


Figure S3: Model fits on benchmark ratios in the Ruff et al. (2015) campaign. Dots indicate observations, dashed line is the best model fit. Shaded areas indicate uncertainty at 95% confidence level, the darker is the parametric uncertainty, while the lighter includes observation uncertainty too.

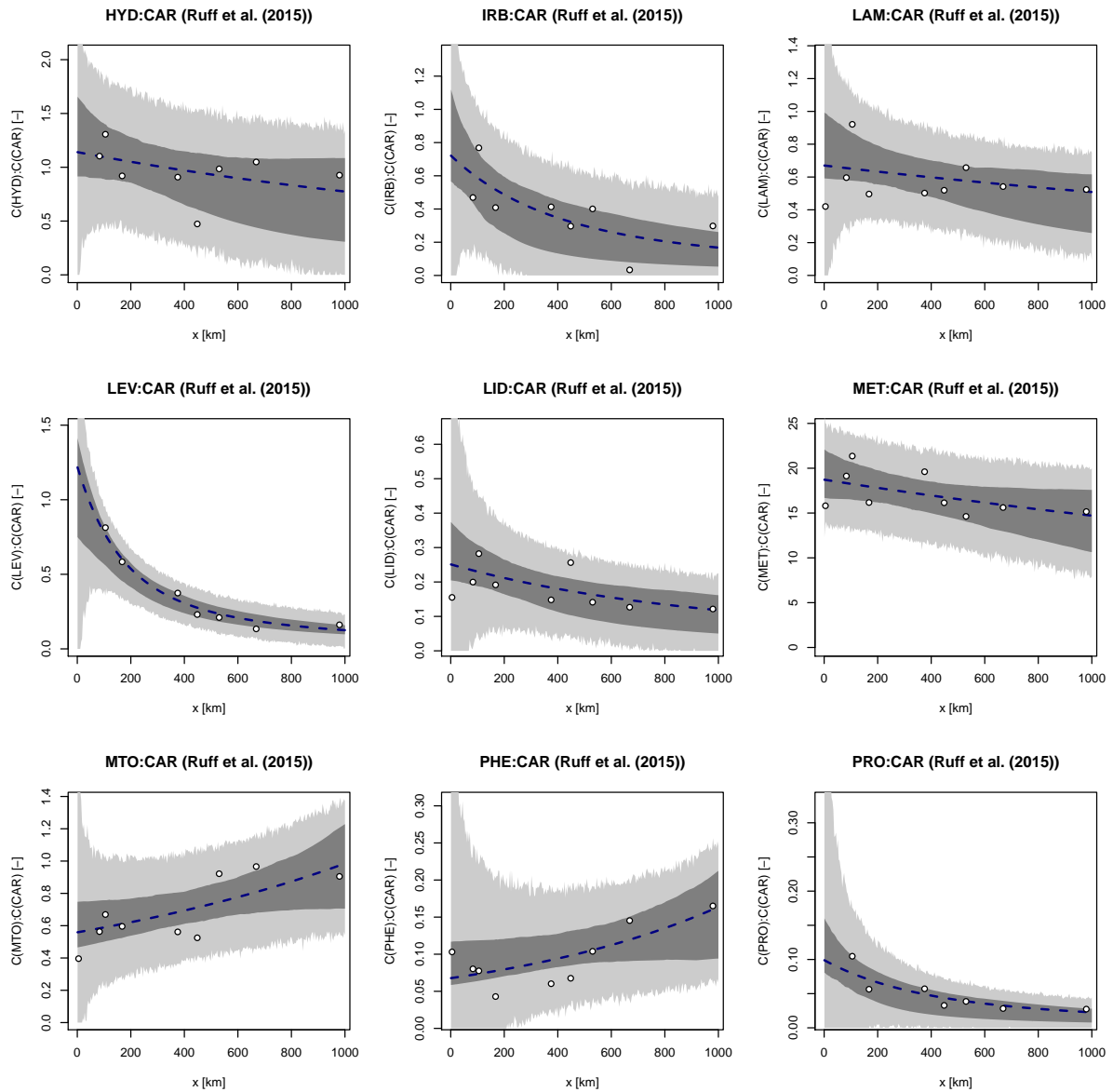


Figure S4: Model fits on benchmark ratios in the Ruff et al. (2015) campaign. Dots indicate observations, dashed line is the best model fit. Shaded areas indicate uncertainty at 95% confidence level, the darker is the parametric uncertainty, while the lighter includes observation uncertainty too.

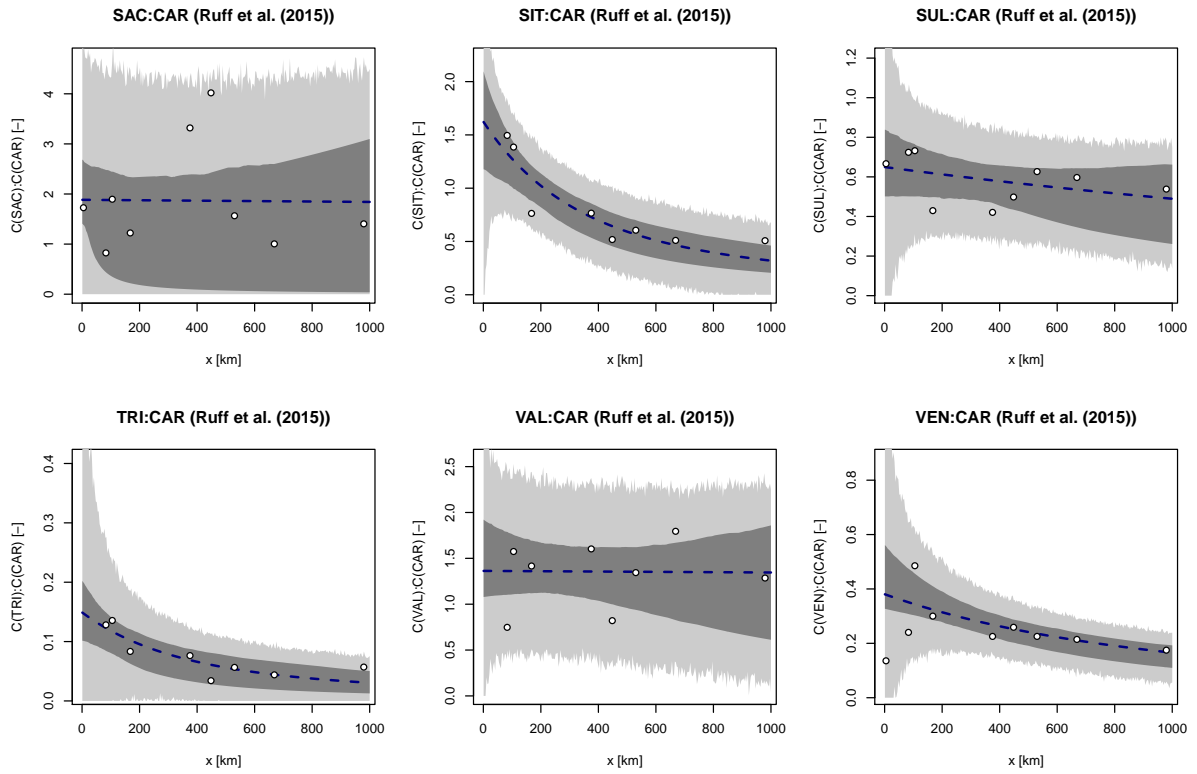


Figure S5: Model fits on benchmark ratios in the Ruff et al. (2015) campaign. Dots indicate observations, dashed line is the best model fit. Shaded areas indicate uncertainty at 95% confidence level, the darker is the parametric uncertainty, while the lighter includes observation uncertainty too.

S6.1.2 SMPC P1

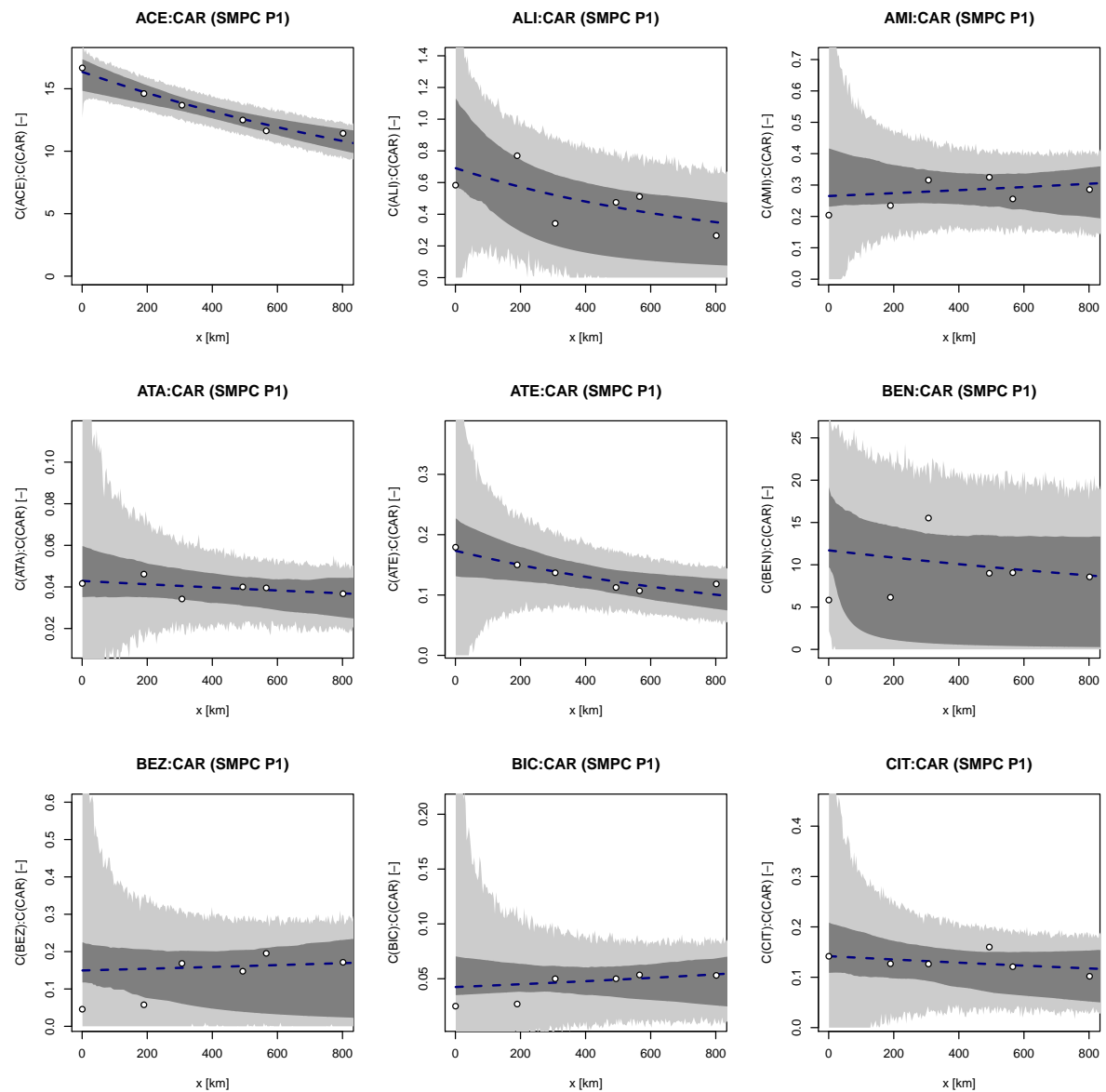


Figure S6: Model fits on benchmark ratios in the SMPC P1 campaign. Dots indicate observations, dashed line is the best model fit. Shaded areas indicate uncertainty at 95% confidence level, the darker is the parametric uncertainty, while the lighter includes observation uncertainty too.

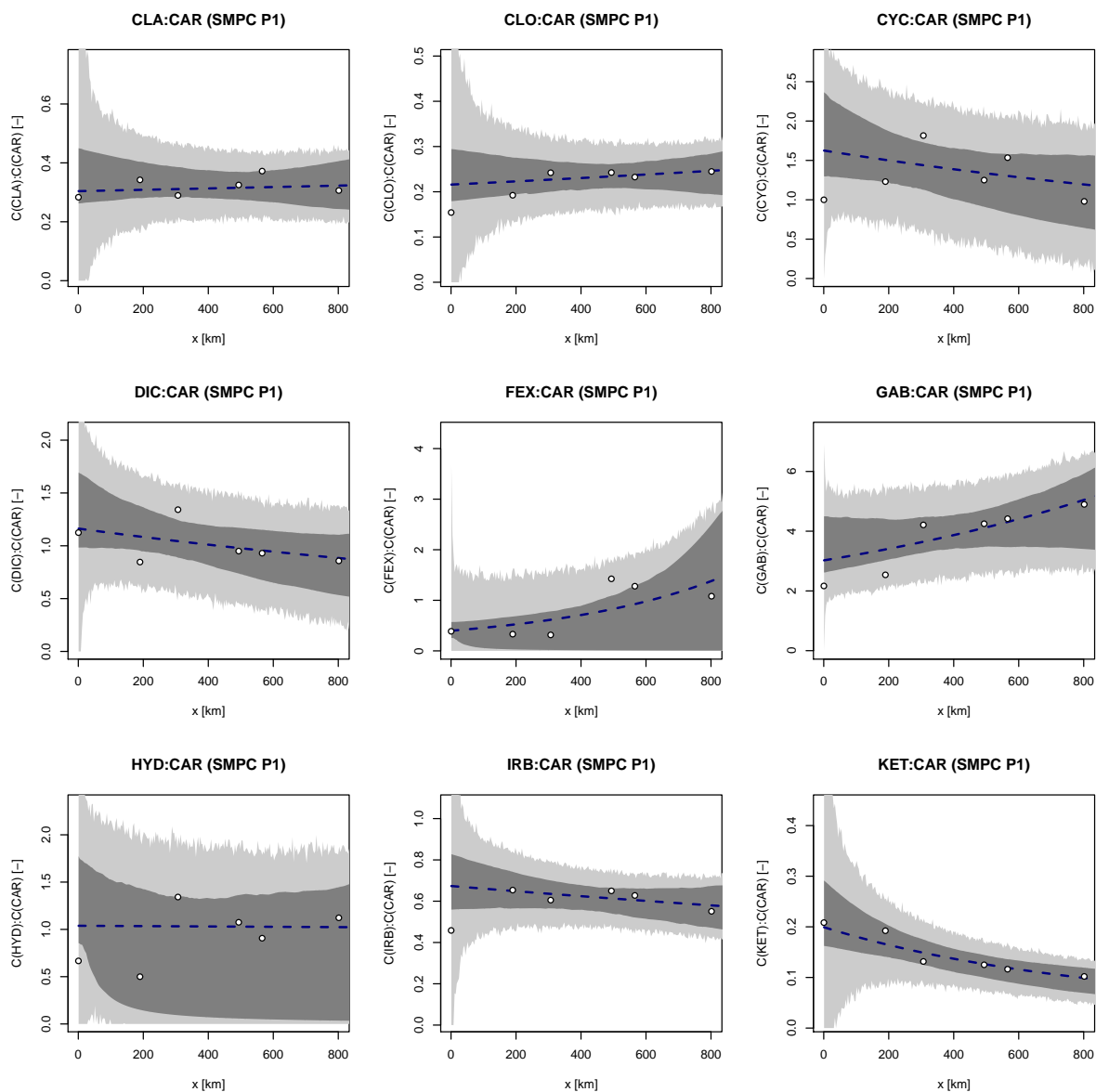


Figure S7: Model fits on benchmark ratios in the SMPC P1 campaign. Dots indicate observations, dashed line is the best model fit. Shaded areas indicate uncertainty at 95% confidence level, the darker is the parametric uncertainty, while the lighter includes observation uncertainty too.

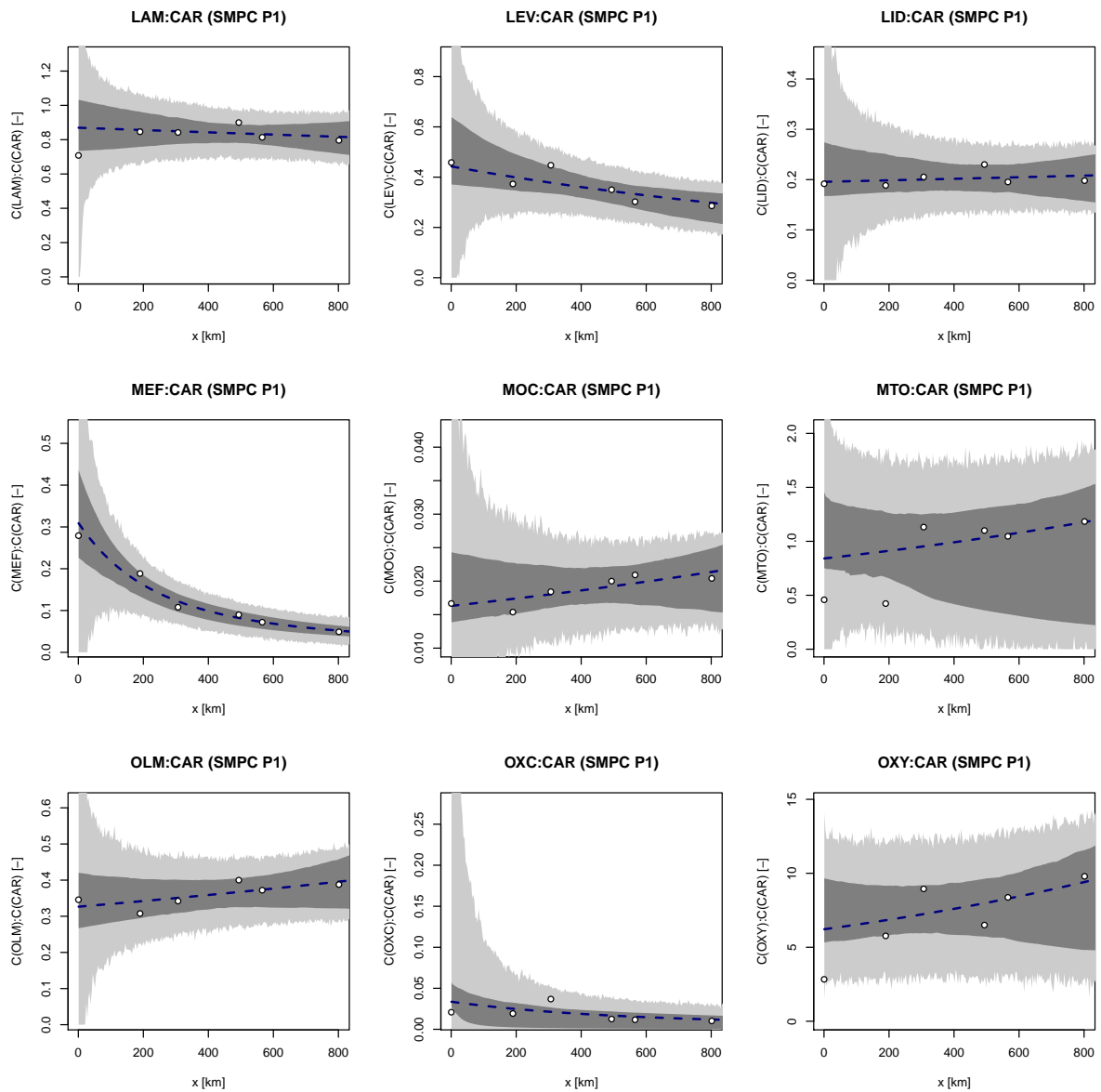


Figure S8: Model fits on benchmark ratios in the SMPC P1 campaign. Dots indicate observations, dashed line is the best model fit. Shaded areas indicate uncertainty at 95% confidence level, the darker is the parametric uncertainty, while the lighter includes observation uncertainty too.

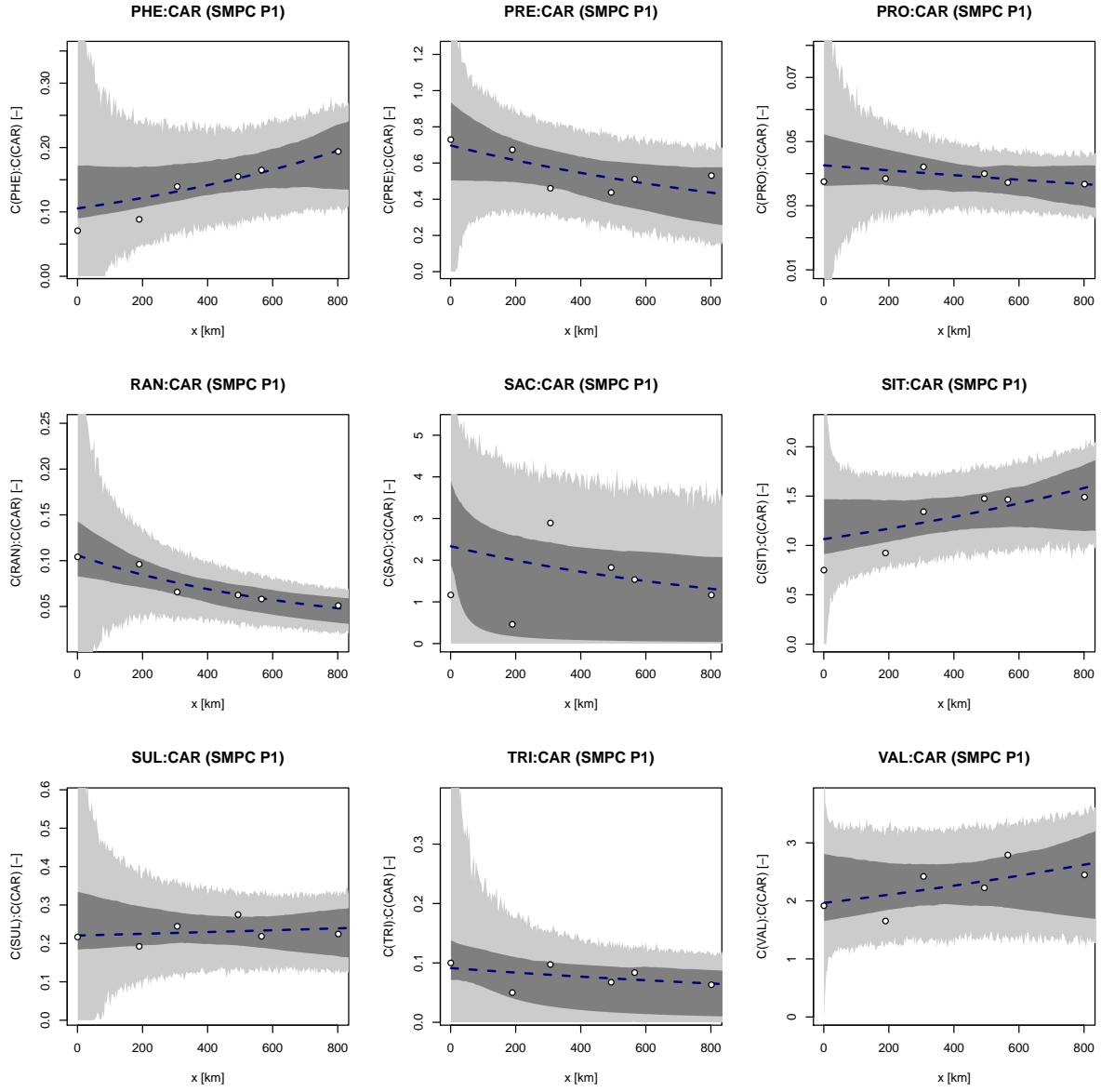


Figure S9: Model fits on benchmark ratios in the SMPC P1 campaign. Dots indicate observations, dashed line is the best model fit. Shaded areas indicate uncertainty at 95% confidence level, the darker is the parametric uncertainty, while the lighter includes observation uncertainty too.

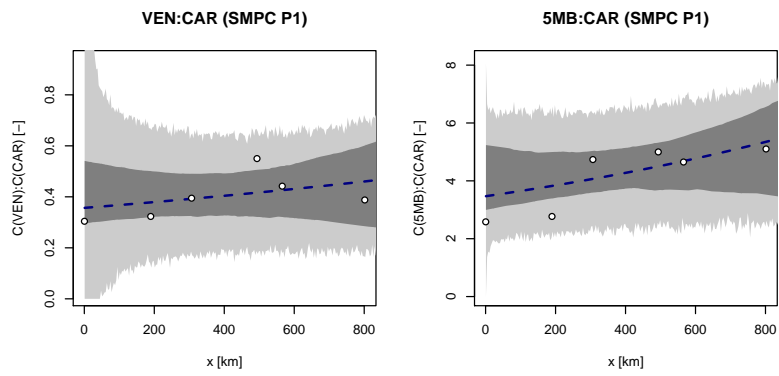


Figure S10: Model fits on benchmark ratios in the SMPC P1 campaign. Dots indicate observations, dashed line is the best model fit. Shaded areas indicate uncertainty at 95% confidence level, the darker is the parametric uncertainty, while the lighter includes observation uncertainty too.

S6.1.3 SMPC P3

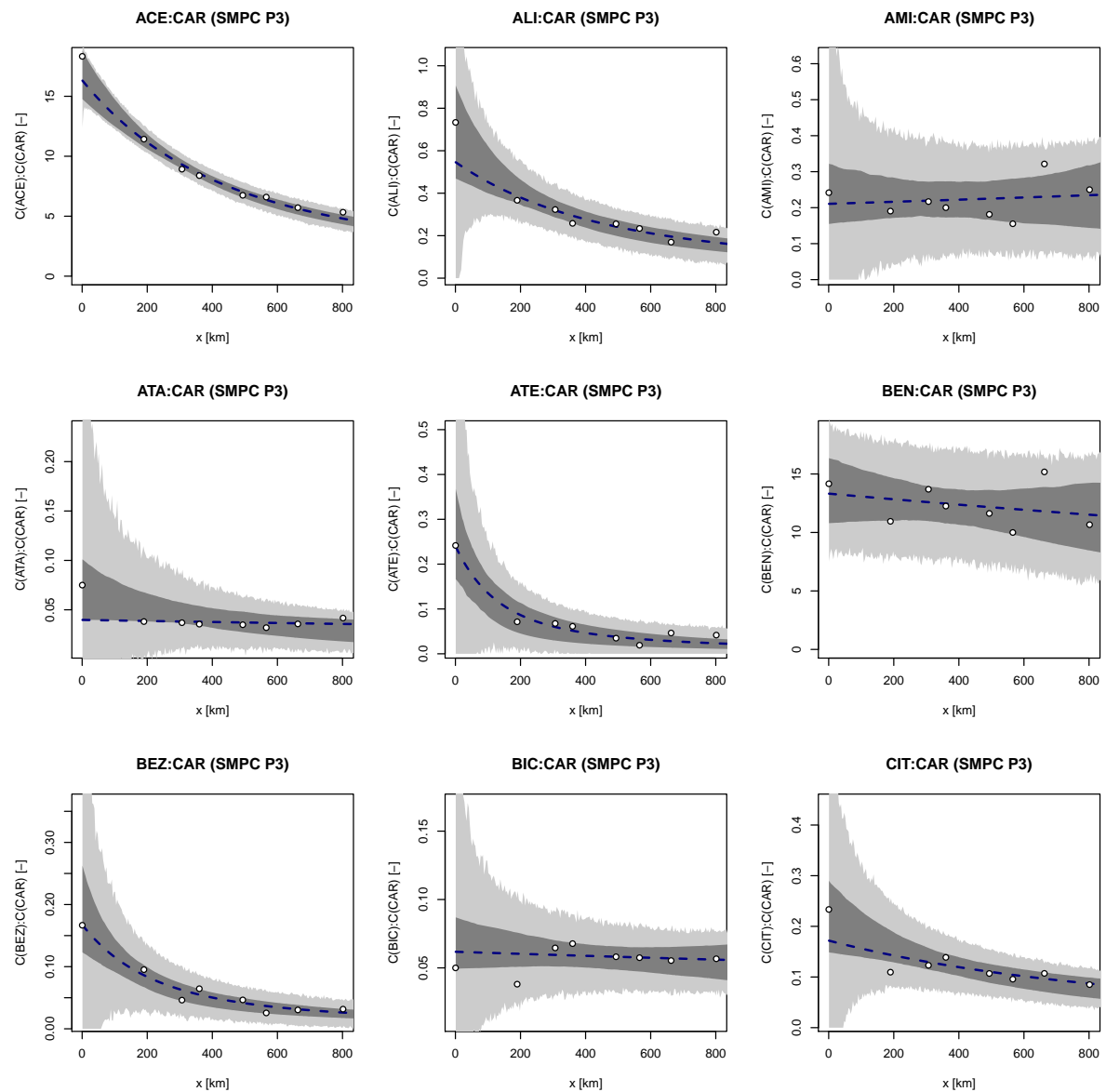


Figure S11: Model fits on benchmark ratios in the SMPC P3 campaign. Dots indicate observations, dashed line is the best model fit. Shaded areas indicate uncertainty at 95% confidence level, the darker is the parametric uncertainty, while the lighter includes observation uncertainty too.

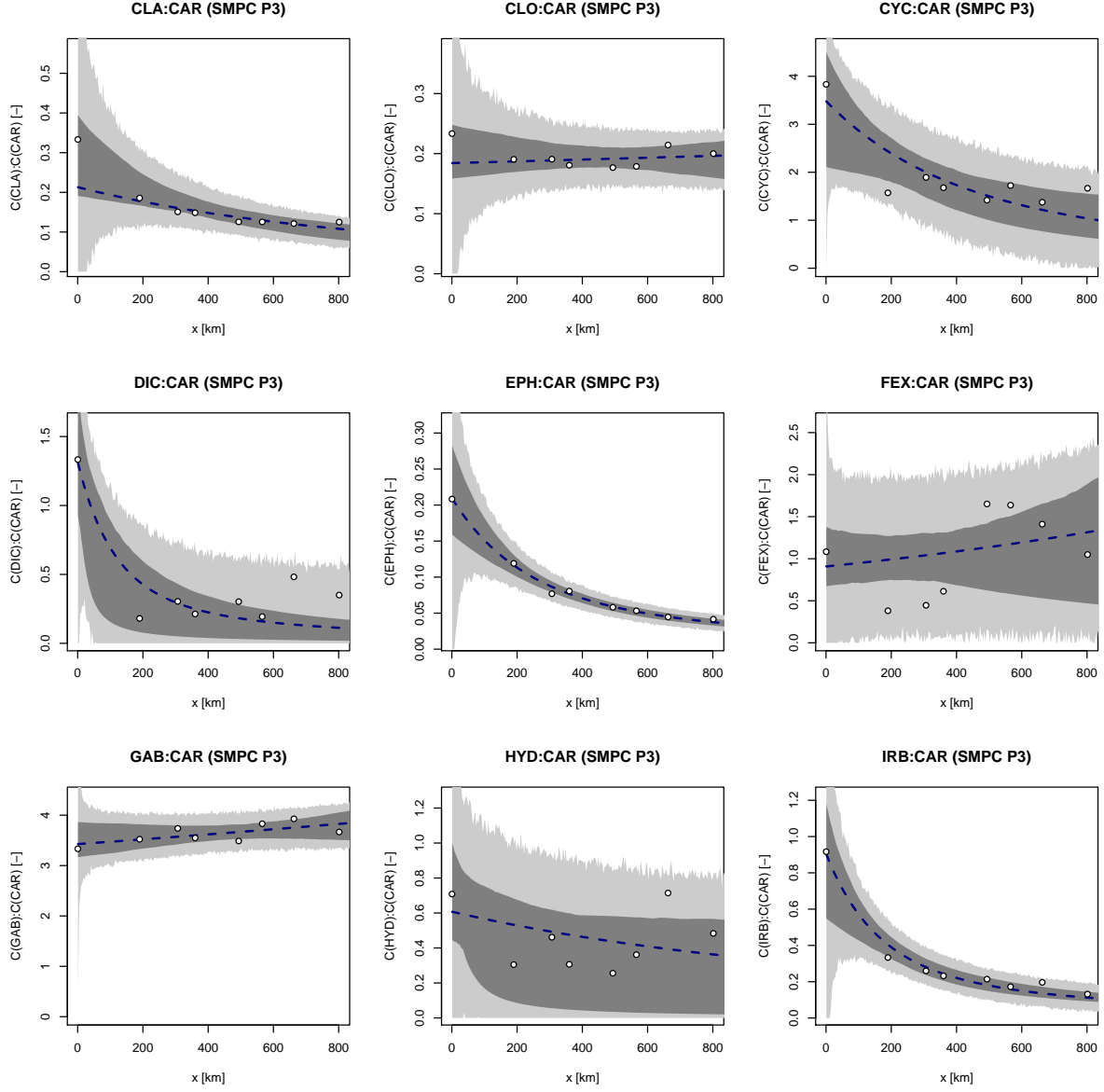


Figure S12: Model fits on benchmark ratios in the SMPC P3 campaign. Dots indicate observations, dashed line is the best model fit. Shaded areas indicate uncertainty at 95% confidence level, the darker is the parametric uncertainty, while the lighter includes observation uncertainty too.

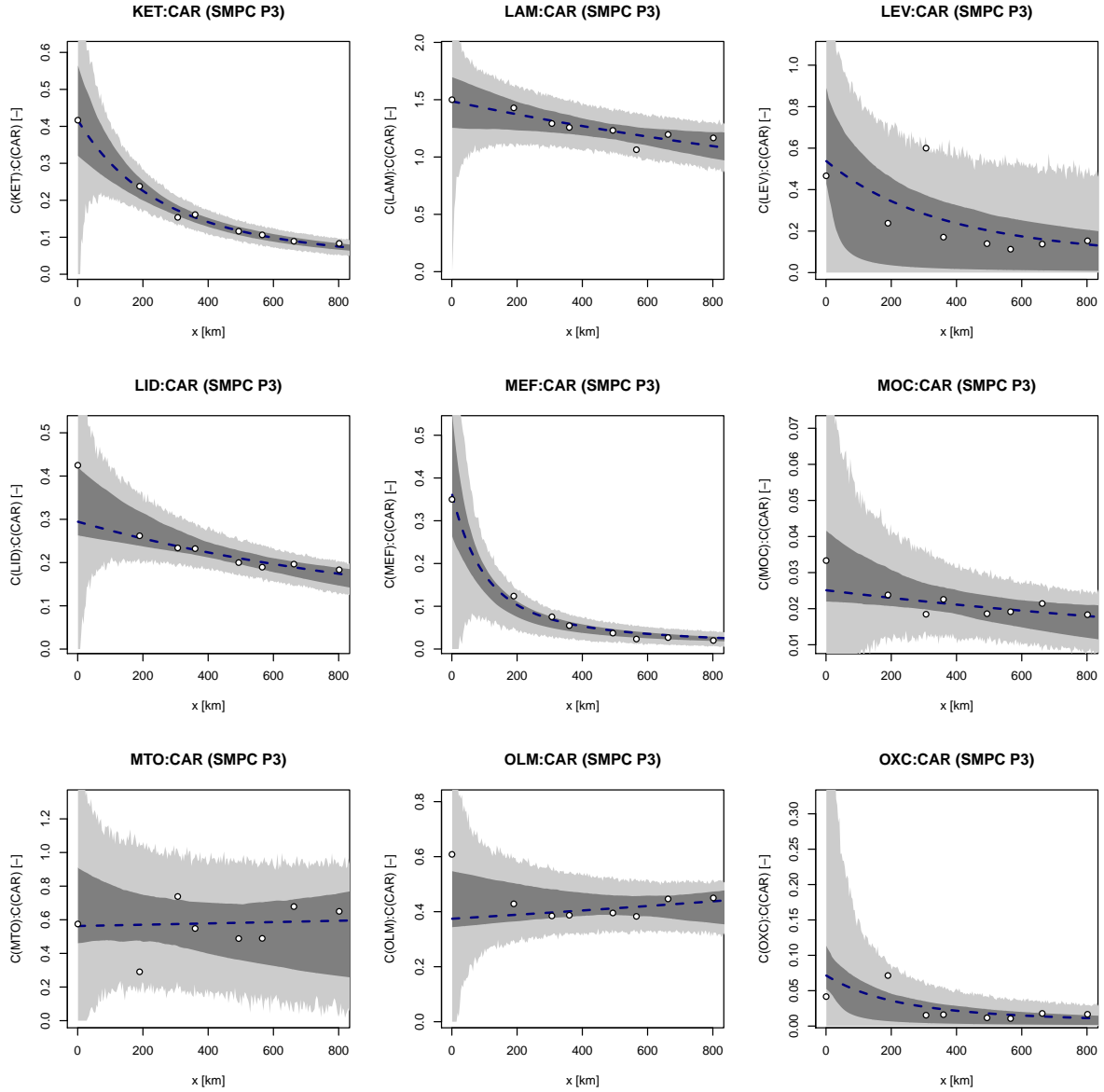


Figure S13: Model fits on benchmark ratios in the SMPC P3 campaign. Dots indicate observations, dashed line is the best model fit. Shaded areas indicate uncertainty at 95% confidence level, the darker is the parametric uncertainty, while the lighter includes observation uncertainty too.

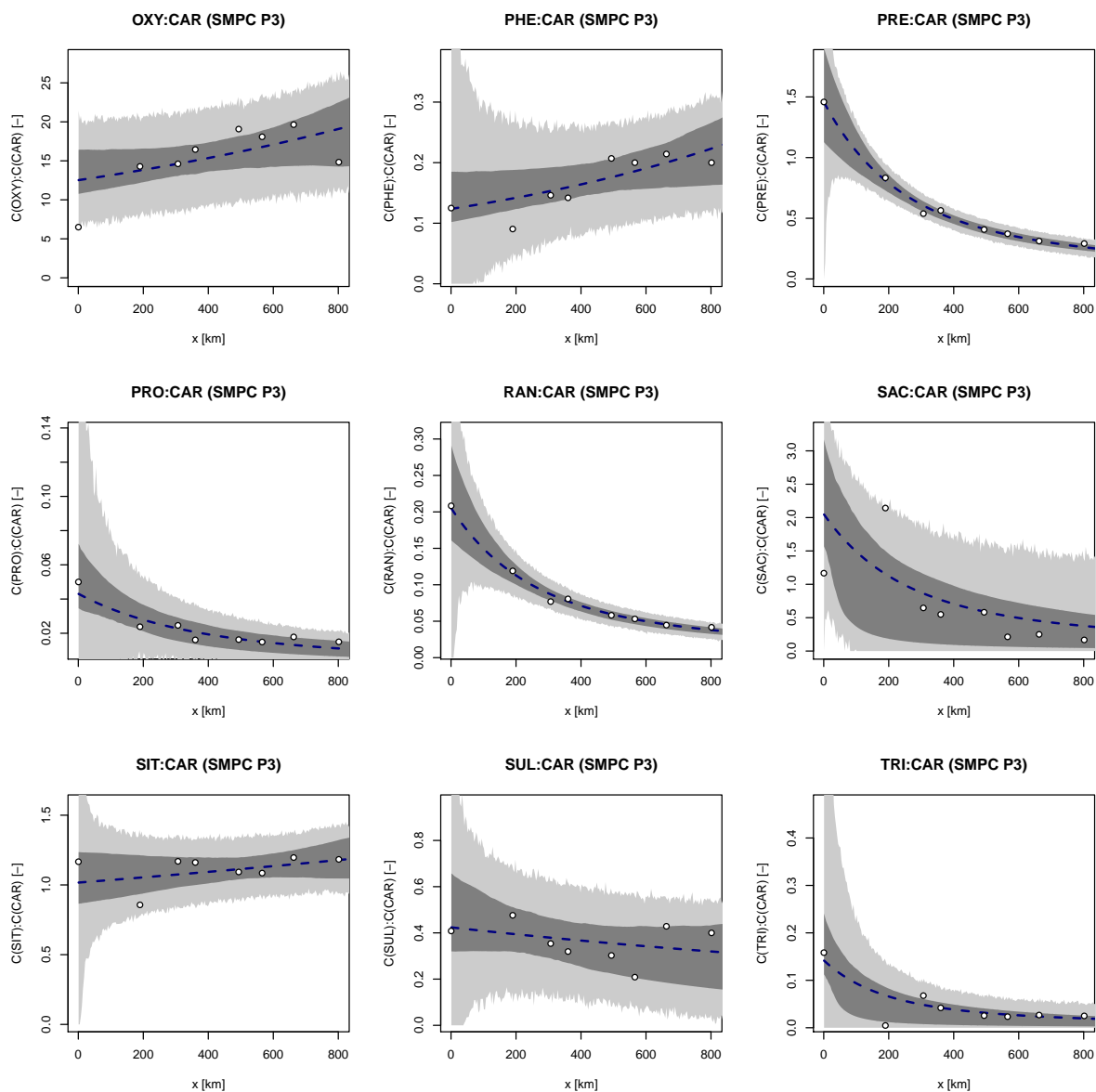


Figure S14: Model fits on benchmark ratios in the SMPC P3 campaign. Dots indicate observations, dashed line is the best model fit. Shaded areas indicate uncertainty at 95% confidence level, the darker is the parametric uncertainty, while the lighter includes observation uncertainty too.

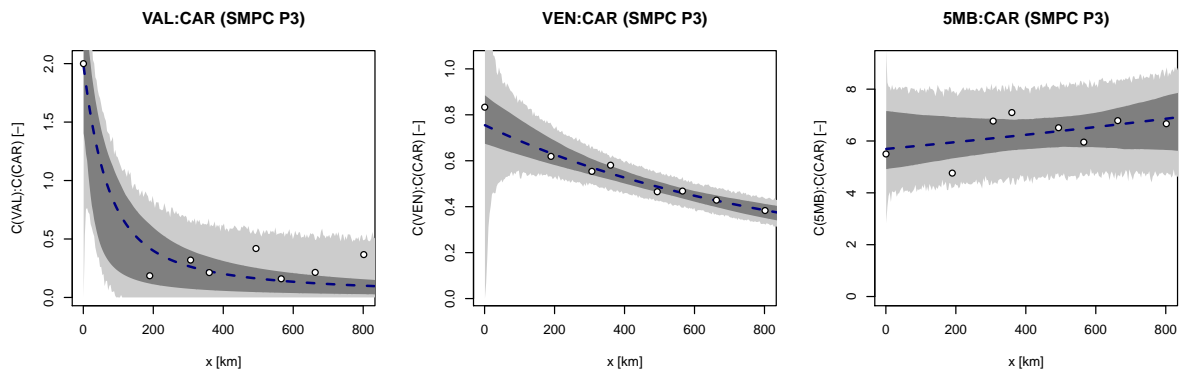


Figure S15: Model fits on benchmark ratios in the SMPC P3 campaign. Dots indicate observations, dashed line is the best model fit. Shaded areas indicate uncertainty at 95% confidence level, the darker is the parametric uncertainty, while the lighter includes observation uncertainty too.

S6.2 Danube campaigns

S6.2.1 JDS3

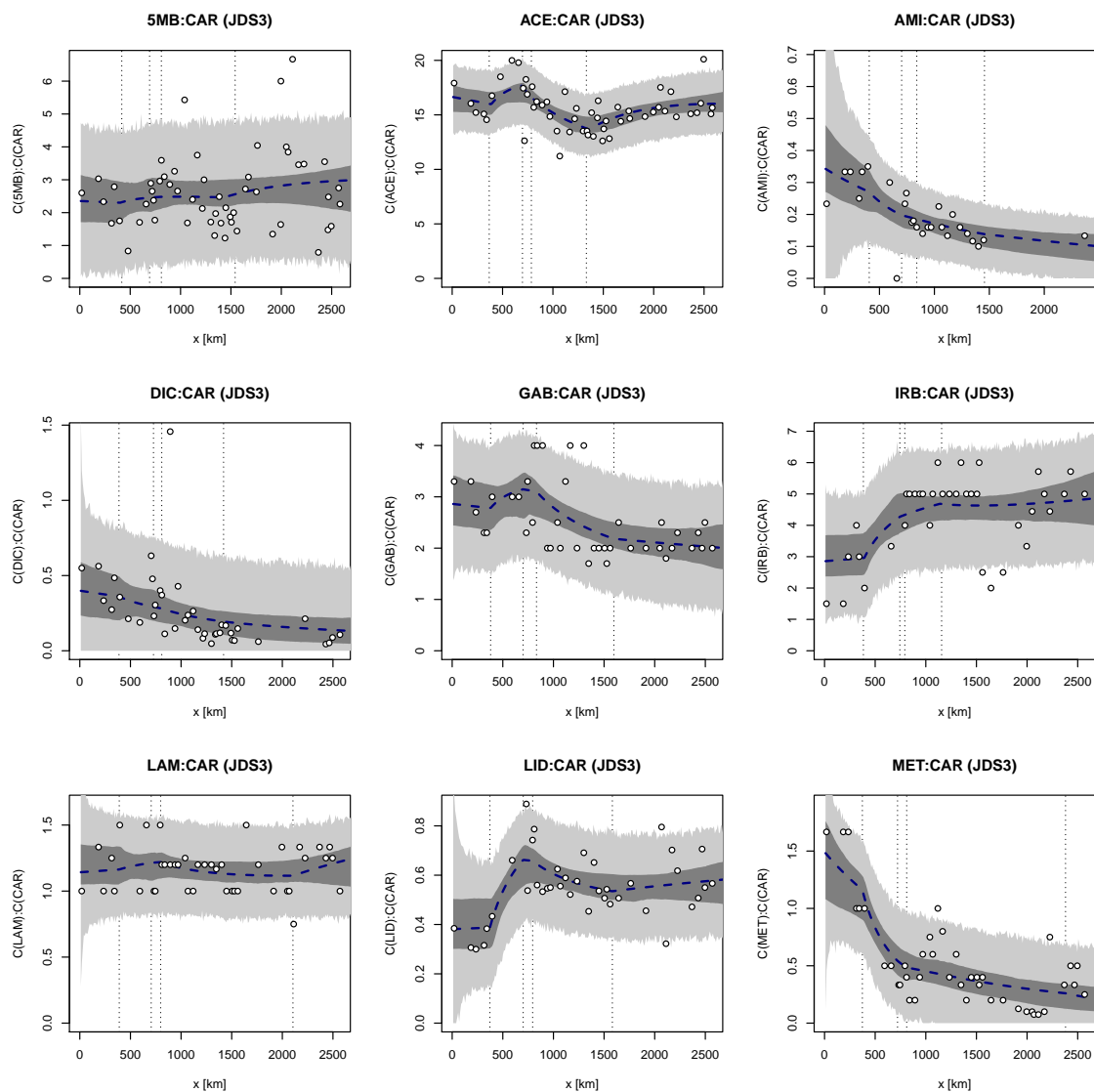


Figure S16: Model fits on benchmark ratios in the JDS3 campaign. Dots indicate observations, dashed line is the best model fit. Shaded areas indicate uncertainty at 95% confidence level, the darker is the parametric uncertainty, while the lighter includes observation uncertainty too. Dotted vertical lines indicate the posterior position of emission boundaries.

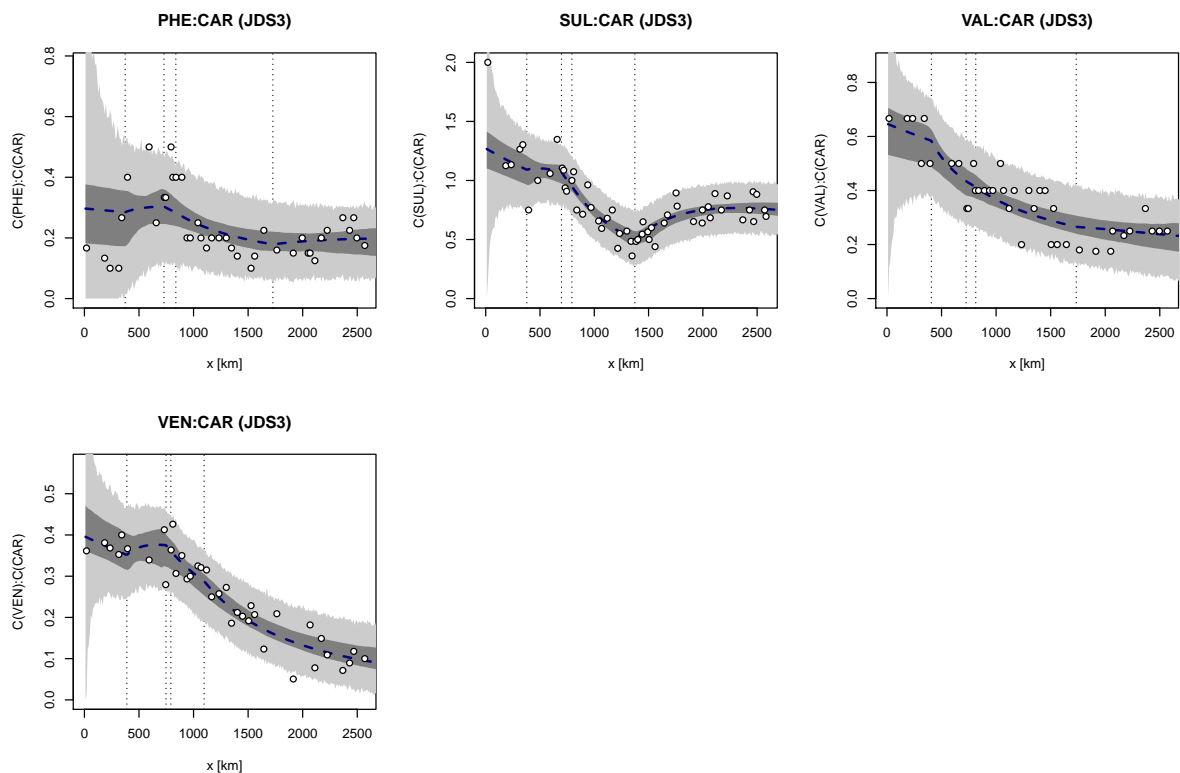


Figure S17: Model fits on benchmark ratios in the JDS3 campaign. Dots indicate observations, dashed line is the best model fit. Shaded areas indicate uncertainty at 95% confidence level, the darker is the parametric uncertainty, while the lighter includes observation uncertainty too. Dotted vertical lines indicate the posterior position of emission boundaries.

S6.2.2 JDS4

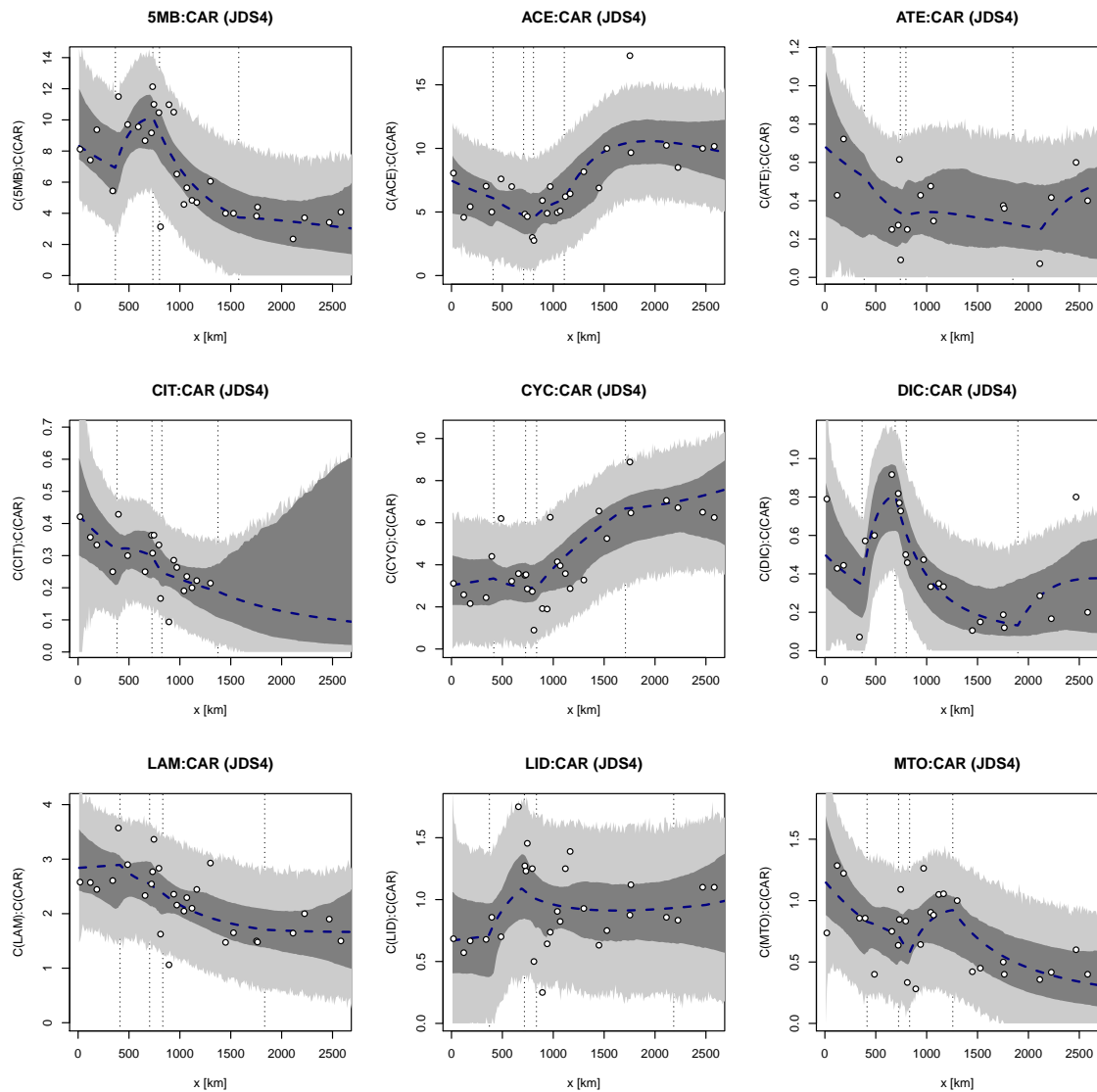


Figure S18: Model fits on benchmark ratios in the JDS4 campaign. Dots indicate observations, dashed line is the best model fit. Shaded areas indicate uncertainty at 95% confidence level, the darker is the parametric uncertainty, while the lighter includes observation uncertainty too. Dotted vertical lines indicate the posterior position of emission boundaries.

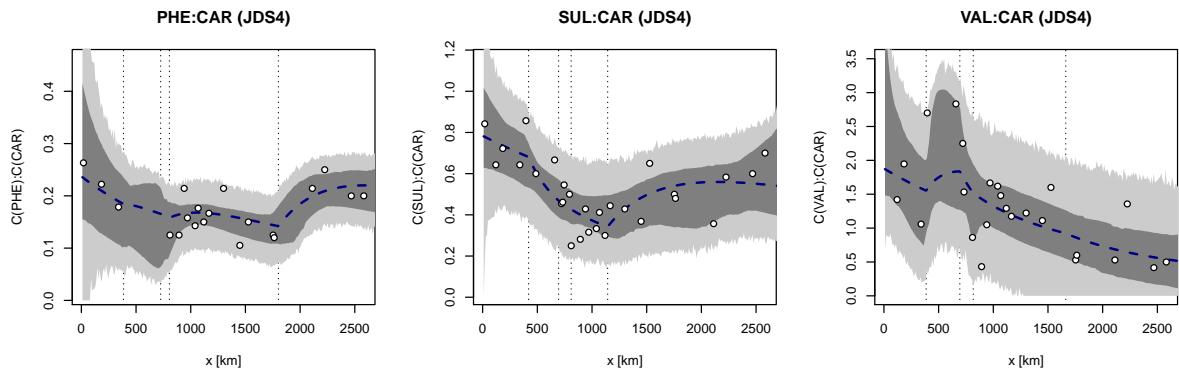


Figure S19: Model fits on benchmark ratios in the JDS4 campaign. Dots indicate observations, dashed line is the best model fit. Shaded areas indicate uncertainty at 95% confidence level, the darker is the parametric uncertainty, while the lighter includes observation uncertainty too. Dotted vertical lines indicate the posterior position of emission boundaries.

S6.3 Relative fit error by campaign

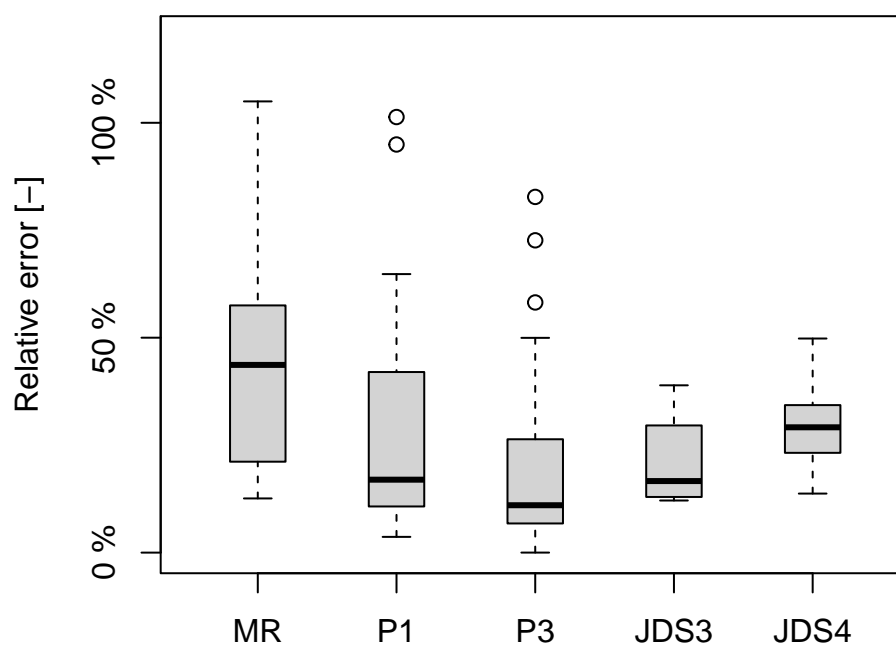


Figure S20: Relative fit error (σ divided by the mean benchmark ratio) by campaign.

S7 Carbamazepine profiles in the two rivers

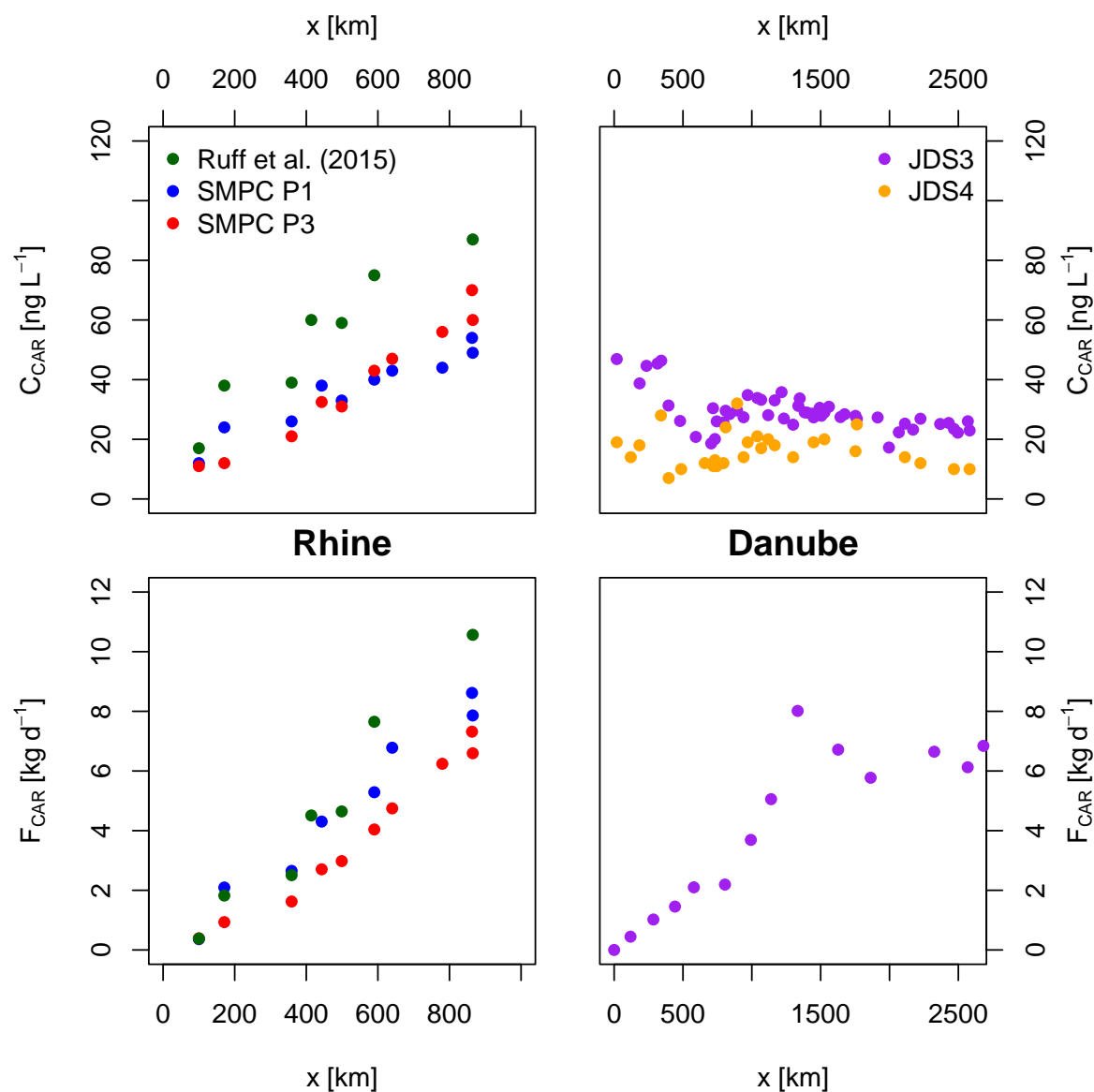


Figure S21: Carbamazepine concentration (upper row) and flux profiles (lower row) in the two rivers. Left panels show the Rhine, right panels show the Danube. Flux was calculated where concentration data had associated flow or it could be assigned based on measurement location and time.

S8 Glossary

Abbreviations, symbols and acronyms (except compound codes):

API: Active pharmaceutical ingredient

B: The benchmark compound

C_B: Concentration of *B*

C_S: Concentration of *S*

DT₅₀: Dissipation half-life

ICPDR: International Commission for the Protection of the Danube River

ICPR: International Commission for the Protection of the Rhine

JDS: Joint Danube Survey of ICPDR

k_S: First-order dissipation rate constant

k'_S: Longitudinal first-order dissipation rate constant

MCMC: Markov chain Monte Carlo

OECD 308: Laboratory simulation test guideline for aerobic and anaerobic transformation in aquatic sediment systems

R: A specific ranking

REACH: European Regulation framework for Registration, Evaluation, Authorisation and Restriction of Chemicals

S: The substance of interest

SMPC: Sondermessprogramm Chemie, Special Chemical Monitoring Programme of ICPR

U(R): The unambiguity of an (optimal) ranking

v: Flow velocity

WWTP: Wastewater treatment plant

α: Empirical model coefficient

β: Empirical model coefficient

γ: Empirical model coefficient

δ: Empirical model coefficient

σ: Observation error

τ: Kendall's rank correlation coefficient