Perfluorooctane sulfonate toxicokinetics at different temperatures using a rainbow trout physiologically-based toxicokinetic model

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controlling risks for sustainable development

Study objectives

Project aiming to improve our understanding of the toxicokinetics of perfluoroalkyl substances (perfluorooctane sulfonate - PFOS, perfluorohexane sulfonate and perfluorononanoate - PFNA) in fish, using the rainbow trout (*Onchorynchus mykiss*) as model species.

Ultimately, the model developed should account for the influence of environmental factors, and to be predictive.

First steps (current status):

- physiologically-based toxicokinetic model (descriptive): uptake is assumed to occur through respiration and diet, elimination hypothetically occurs through feces, urine and gills.
- influence of water temperature on PFOS uptake and elimination.

Model design (developed on experimental data at 19°C)

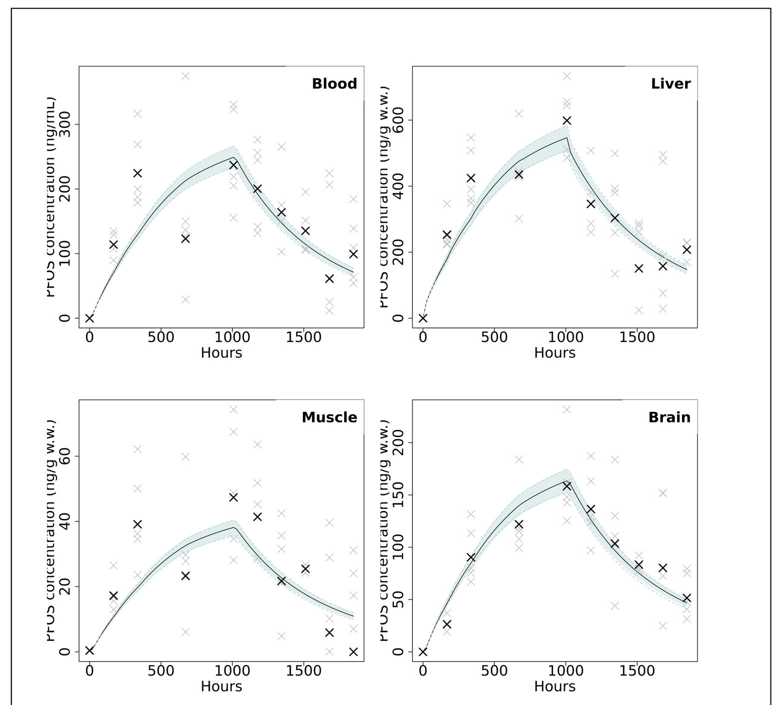
Basic model: exposure through diet only.

Additional hypotheses:

– enterohepatic cycle
– absorption / elimination through the gills

Calibration at 19°C ➡ cardiac output adjusted according to Arrhenius law.

Good fit to experimental data (below)



Predicted (line and coloured area) and observed (dots; black = means of five individuals in grey) PFOS concentrations in organs, using Model 0. Coloured areas represent the 95 % credibility intervals computed from the posterior distributions.

Vidal A, Garric J, Babut M, Beaudouin R. (2019) Elucidating the fate of perfluorooctanoate sulfonate using a rainbow trout (*Oncorhynchus mykiss*) physiologically-based toxicokinetic model. *Sci. Total Environ.* 691, 1297-1309

Approach

Combination of experiments and modelling.

Experiments at 7°C, 11°C and 19°C:

- sub-adult trout (15 months old, ≈300 g at the start of exposure)
- spiked food: PFOS, PFHxS and PFNA 500 µg kg^{-1} dw each
- water temperature 7 °C, 11°C and 19 °C
- exposure for 28 to 42 days; depuration for 28 to 35 days.

Sampling and analysis:

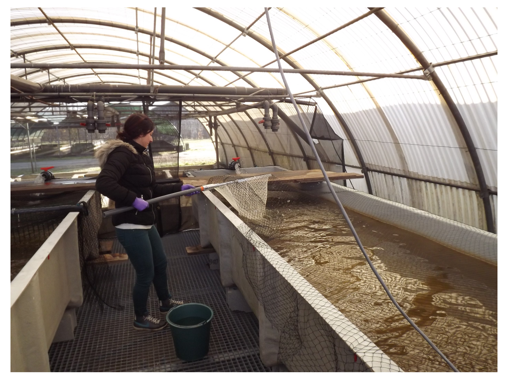
- blood, liver, kidney, viscera, brain.
- food
- water
- analysis UHPLC/ MS-MS (MRM mode)

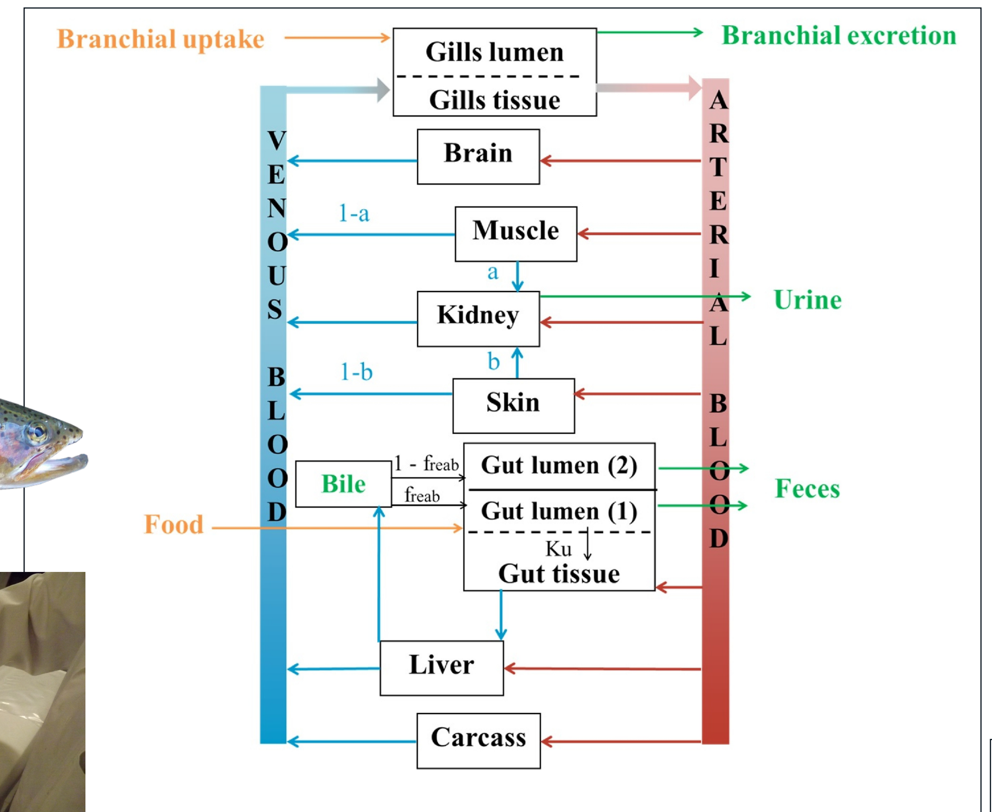
Modelling approach:

- trout physiology based on Nichols *et al*. (1990) and Grech et al. (2019);

(…/…)

Vidal A., Lafay F., Daniele G., Vulliet E., Rochard E., Garric J., Babut M. (2019) Does water temperature influence the distribution and elimination of perfluorinated substances in rainbow trout (*Oncorhynchus mykiss*)? *Environ. Sci. Pollut. Res.* 26 (16) 16355-16365





(…/…)

- growth accounted for;
- *a priori* information on plasma:tissue partition coefficients derived from Goeritz *et al*. (2013);
- PFAS TK parameters obtained by Bayesian inference using our experimental data

Influence of water temperature modelled on the basis of Arrhenius law.

Processes concerned:

- fish growth
- cardiac output and ventilation rate fitted or based on literature data.
- organ perfusion rates
- absorption rates
- clearances
- blood:tissue partition coefficients

Nichols JW, McKim JM, Andersen ME, Gargas ML, Clewell Iii HJ, Erickson RJ. 1990. A physiologically based toxicokinetic model for the uptake and disposition of waterborne organic chemicals in fish. *Toxicol. Appl. Pharm*. 106:433-447

Grech, A., Tebby, C., Brochot, C., Bois, F.Y., Bado-Nilles, A., Dorne, J.L., Quignot, N., Beaudouin, R., 2019. Generic physiologically-based toxicokinetic modelling for fish: Integration of environmental factors and species variability. *Sci. Tot. Environ.* 651, 516-531

Goeritz I, Falk S, Stahl T, Schäfers C, Schlechtriem C. 2013. Biomagnification and tissue distribution of perfluoroalkyl substances (PFASs) in market-size rainbow trout (Oncorhynchus mykiss). *Environ. Toxicol. Chem.* 32:2078-2088

Effect of water temperature on PFAS toxicokinetics

Arrhenius law

$$\dot{A}_T = exp\left(\frac{T_A}{T_r} - \frac{T_A}{T}\right)$$

T_A: Arrhenius temperature (°K)
T: water temperature (°K)
T_r: temperature at which the physiological process was originally modelled (°K)

Variation of process rate (Arrhenius S., 1889)

$$\acute{k}_T = \acute{k}_r \times \mathring{A}_T$$

$\acute{k}_T$: process rate at T °K
$\acute{k}_r$: process rate at T_r °K

Arrhenius, S. (1889) "On the reaction velocity of the inversion of cane sugar by acids" Zeitschrift für Physikalische Chemie, 4, 226

Entero-hepatic cycle: whatever the reabsorption rate, no improvement of model outputs:

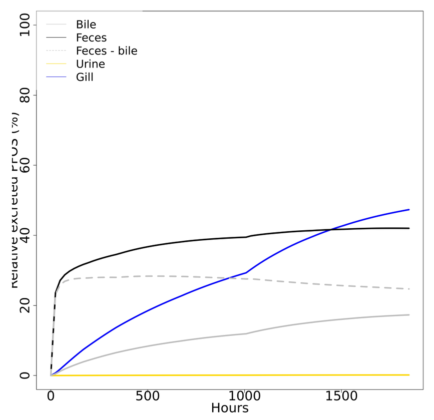
- Bayesian Information Criterion (BIC) higher for the sub-models including this cycle [782 - 803, depending on reabsorption rate] than for the basic model [777].

Considering uptake through gills (diffusion): lower overall Relative Error to the mean (RE).

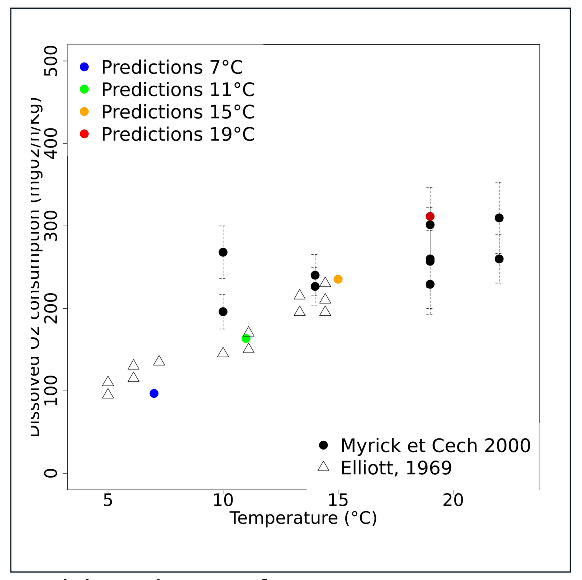
Elimination bile-feces > gills > urine (idem, lower RE).

Uptake through gills: need to acount for ionization / active transport.

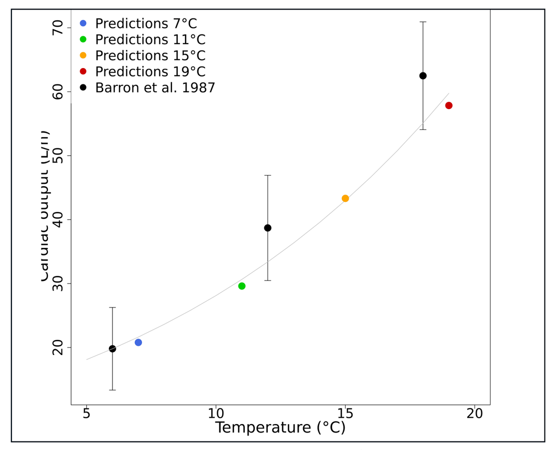
Same for elimination through gills?



PFOS elimination pathways: quantities eliminated by each route relative to the administered dose



Model predictions for oxygen consumption (coloured dots) compared to measurements from Myrick and Cech (2000) (black dots) and Elliott (1969) (open triangles)



Predicted cardiac outputs (coloured dots) compared to measured cardiac outputs from Barron et al. (1987)

Basic model ⇨ influence of temperature on fish growth:

- model output depends of T°C, food quantity (***α***), growth rate (***k***), and maximal size (***L_m***);
- calibration on experimental data from Goeritz et al. (2013) assuming ***α*** =1.0
- respective ***α*** values at 7°C and 19 °C equal 0.56 and 0.58

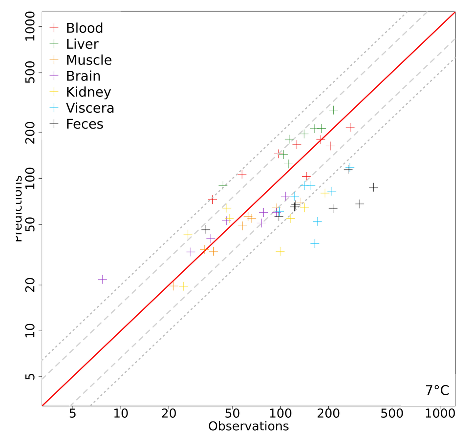
Hypotheses: each process considered separately; additionally, all processes together.

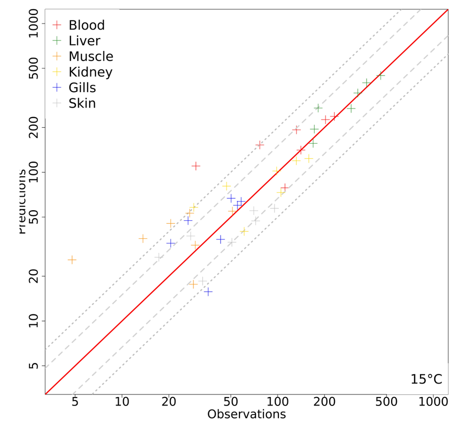
Bayesian inference: adjustment to all experimental data (4 temperatures) simultaneously.

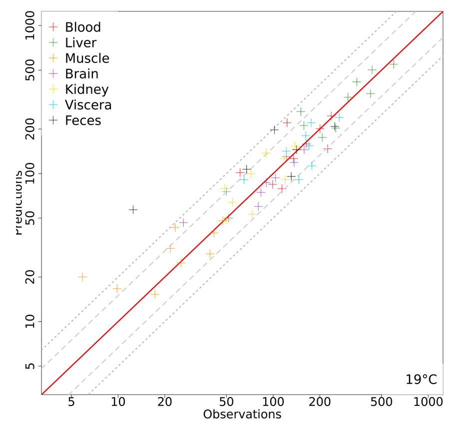
Bayesian Information Criterion (BIC) allows determining the best model.

Lower BIC values obtained when all processes (cardiac output, organ perfusion rates, partition coefficients, absorption rates, clearances) included.

Good agreement between observed and predicted concentrations in most organs at 7°C, 15° and 19°C.







- Predicted cardiac outputs and oxygen consumption in agreement with available experimental data.
- Predicted PFOS concentrations farther from observations in viscera and kidney than in muscle, blood and liver

Barron, M.G., Tarr, B.D., Hayton, W.L., 1987. Temperature-dependence of cardiac output and regional blood flow in rainbow trout, Salmo gairdneri Richardson. *J. Fish Biol.* 31, 735–744

Myrick, C.A., Cech Jr, J.J., 2000. Temperature influences on California rainbow trout physiological performance. *Fish Physiol. Biochem.* 22, 245-254

Elliot, J.W. 1969 The oxygen requirements of Chinook salmon. *The Progressive Fish-Culturist* 31, 67-73

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