Physiologically Based Pharmacokinetic (PBPK) model for Atlantic halibut (*Hippoglossus hippoglossus*)

Hanne Gladhaug Wøien Mo[1], Gregory Langlois[2], Ian Edhlund[2], Peter van den Hurk[2], Knut Erik Tollefsen[1,3*]

[1]Norwegian University of Life Sciences (NMBU), Post box 5003, N-1432 Ås, Norway; [2]Clemson University, Clemson, SC 29634, USA; [3]Norwegian Institute for Water Research (NIVA), Økernveien 94, N-0579 OSLO, Norway.

*** contact: knut.erik.tollefsen@niva.no**

Introduction and objective

Climate change and rising pollution emissions are introducing new substances into North Sea and Arctic waters, threatening marine life and human consumption of fish. Due to the vast number of chemicals, it is not feasible to test all substances on all species, highlighting the need for predictive tools in environmental exposure, hazard and risk assessment. Physiologically based pharmacokinetic (PBPK) models are foreseen to play a key role in characterization of absorption, distribution, metabolism, and excretion (ADME) of pollutants and aid *in vitro* to *in vivo* extrapolation (IVIVE) in Next Generation Risk Assessment (NGRA).

The objective of this work was to develop and parameterize a multi-compartment PBPK model for Atlantic halibut (*Hippoglossus hippoglossus*) and test it for relevant pollutants.

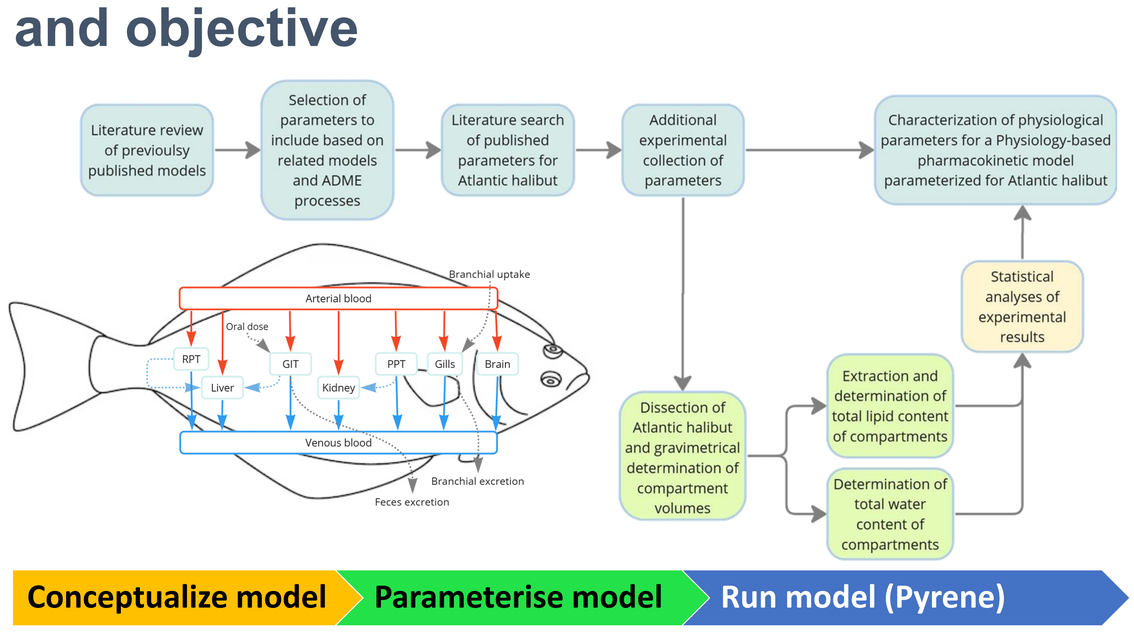

Figure 1. Workflow for parametrizing, developing and testing a multi-compartment Physiologically-based Pharmacokinetic (PBPK) model for Atlantic halibut (Hippoglossus hippoglossus). RPT/PPT- richly/poorly perfused tissue, GIT- gastrointestinal tract.

Physiological & chemical-specific parameters

Table 1 Compartment-specific physiological parameters

Parameter	Unit	Compartment	Input value	Calculation
Relative volume	Fraction of total wet weight	Venous blood	0.00171	1/3 of total blood volume (5.10 %)[6,8]
		Arterial blood	0.00340	2/3 of total blood volume (5.10 %)[6,8]
		Brain	0.000989	Measured (Regression)
		Kidney	0.00421	
		Liver	0.00747	
		RPT	0.00628	Measured (Average)
		GIT	0.0266	
		PPT	0.885	Total weight – (collective volume of the rest of the measured compartments)
Relative lipid content	Fraction of tissue wet weight	Blood	0.0164	Measured Average)
		Brain	0.123	
		GIT	0.0202	
		Kidney	0.0279	
		PPT	0.0673	
		RPT	0.0146	
		Liver	0.0555	Measured (Regression equation)
Relative water content	Fraction of tissue wet weight	Blood	0.886	Measured (Average)
		Brain	0.809	
		GIT	0.818	
		Kidney	0.791	
		PPT	0.808	
		RPT	0.717	
		Liver	0.739	Measured (Regression)
Blood flow	ml/min	Brain	0.0282	Assumed proportionality with tissue volume and calculated from % of cardiac output[1,3].
		GIT	0.366	
		Kidney	0.351	
		Liver	0.0627	
		RPT	6.910	
		PPT	0.0316	

Table 2: General physiological parameters

Parameter	Input value	Unit	Calculation or proxy species
Cardiac output	15.5	ml/min/kg	Winter flounder[4]
Oxygen consumption rate	44.74	mgO2/h/kg	Average standard value of flatfish species captured from fishbase[2]
Effective respiratory volume	3.36	l/h	Calculated from oxygen consumption rate and water oxygen concentration[9]

Table 3: Chemical specific parameters

Parameter	Input value	Unit	Calculation or proxy species
Partitioning Coefficients		Unitless	Rainbow trout or extrapolated from other compound data[5,7]
Plasma:Brain	1.71		
Plasma:GIT	1.90		
Plasma:Kidney	15.30		
Plasma:PPT	50.58		
Plasma:RPT	1.85		
Plasma:Liver	37.0		
Plasma:Gills	2.75		
Biliary Elimination Rate	0.05	mg/kg/hr	Adult Rainbow Trout[5]
Maximum Metabolism	0.255	mg/min/g liver	Adult Rainbow Trout[5]

Table 1-3. Parameterization of a 9-compartment PBPK model for Atlantic halibut with physiological measurements & chemical-specific parameters.

PBPK predictions for Pyrene

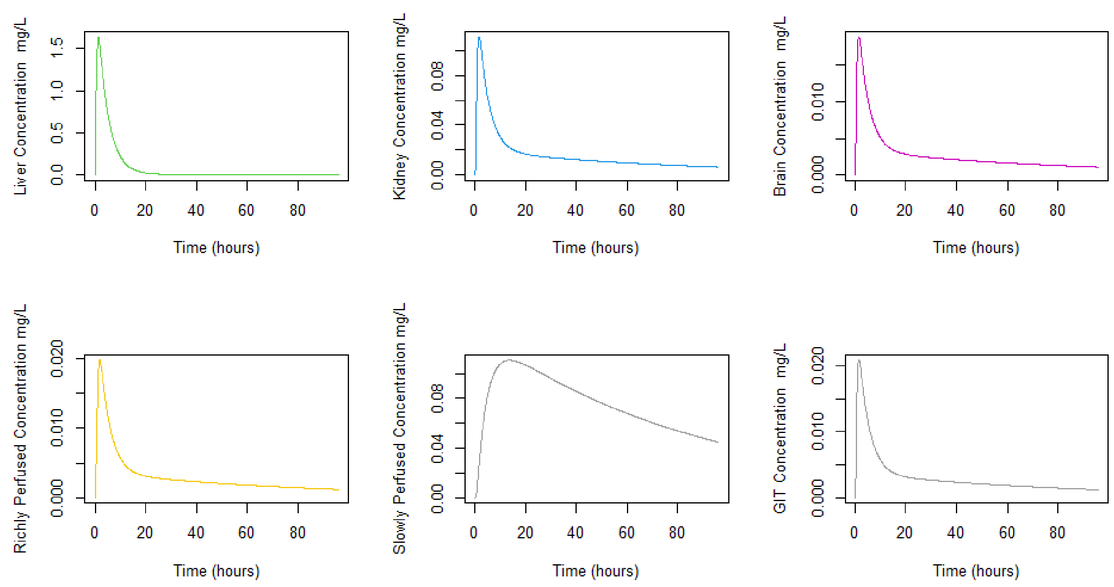

Figure 2. Example predictions of tissue-specific concentrations of Pyrene in Atlantic halibut after a single bolus dietary exposure (5 mg/kg food).

Summary and outlook

Summary

A multi-compartment PBPK model was established for Atlantic halibut by:

1) Developing a conceptual 9-compartment model for arterial & venous blood, gills, kidney, liver, GIT, brain, RPT, PPT (Fig. 1).
2) Parametrizing the model with physiological (Table 1 & 2) and chemical-specific (Table 3) parameters from experiments and literature.
3) Testing the model for the Arctic relevant organic pollutant Pyrene (Fig. 2).

Outlook

1) Develop model to predict compartment concentrations for other exposure routes and time dynamics (e.g. steady-state considerations).
2) Include fish growth rate, habitat temperature and QSAR predictions for chemical-specific partition coefficients into model.
3) Integrate PBPK model into the Source To Outcome Pathway (STOP) modelling infrastructure for NGRA.

References

[1]Barron, M. G., Tarr, B. D. & Hayton, W. L. (1987). *J Fish Biol* 31: 735-744; [2]Boettiger (2012). *J Fish Biol* 81: 2030-2039; [3]Grech, A., Tebby, C., Brochot, C., Bois, F.Y., Bado-Nilles, A., Dorne, J.-L., Quignot, N. & Beaudouin, R. (2019). *Sci Total Environ* 651: 516-531; [4]Joaquim, N., Wagner, G. N. & Gamperl, A. K. (2004). *Comp Biochem Physiol A* 138: 277-285; [5]Law et al. (1991). *Aquatic Toxicology* 35: 221-235; [6]Nichols, J. W., McKim, J. M., Andersen, M. E., Gargas, M. L., Clewell, H. J. & Erickson, R. J. (1990). *Toxicol Appl Pharmacol* 106: 433-47; [7]Nichols et al. (2004). *Toxicological Sciences* 77: 206-218; [8]Skov, P. V. & Steffensen, J. F. (2003). *J Exp Biol* 206: 591-599; [9]Stadnicka, J., Schirmer, K. & Ashauer, R. (2012). *Environ Sci Technol* 46: 3273-3280.).

Co-funded by the European Union

Norwegian Environmental Toxicology Symposium (NETS) Stavanger, Norway, 2025

With funding from The Research Council of Norway

eu-parc.eu

#EU_PARC

This work was carried out in the framework of the European Partnership for the Assessment of Risks from Chemicals (PARC) and has received funding from the European Union's Horizon Europe research and innovation programme under Grant Agreement No 101057014, Research Council of Norway project EXPECT (RCN-315969) and NIVA's Computational Toxicology Program, NCTP (RCN-342628). Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union or the Health and Digital Executive Agency. Neither the European Union nor the granting authority can be held responsible for them.