Eawag –
Swiss Federal Institute of Aquatic
Science and Technology

Contact: Kristin.Schirmer@eawag.ch

A tiered testing strategy for rapid estimation of bioaccumulation by a combined modelling – in vitro testing approach

Project:
CEFIC-LRI
ECO 34

Kristin Schirmer[1,2], Jon Arnot[3], Nic Bury[4], Michelle Embry[5], Christer Hogstrand[4], Helmut Segner[6], Julita Stadnicka-Michalak[1,2]

[1]Eawag, Swiss Federal Institute of Aquatic Science and Technology, Switzerland; [2] École Polytechnique Fédérale de Lausanne (EPFL), Switzerland; [3]ARC Arnot Research and Consulting Inc, Canada; [4]King's College London, UK; [5]ILSI Health and Environmental Sciences Institute, USA; [6]University of Bern, Switzerland.

Background

- Bioaccumulation is the net result of competing rates of chemical uptake and elimination in an organism, i.e. toxicokinetic processes.
- The bioconcentration factor (BCF) is a common metric of regulatory interest determined from laboratory experiments commonly done with fish.
- These experiments are highly resource intensive; it is not feasible to test all chemicals requiring bioaccumulation assessment in this way.
- Alternative methods for quantifying bioaccumulation have led to the development of various predictive models but mostly lack information on biotransformation, which can significantly mitigate bioaccumulation.

The overall objective of our research is to improve alternative methods to estimate bioaccumulation of organic chemicals in fish. Based on a combination of different *in vitro* approaches to predict chemical uptake and biotransformation with toxicokinetic (TK) and quantitative structure-activity relationship (QSAR) models, we aim to develop a tiered approach, integrating modelling with testing strategies to aid in the rapid assessment of bioaccumulation potential (Figure 1, Figure 2).

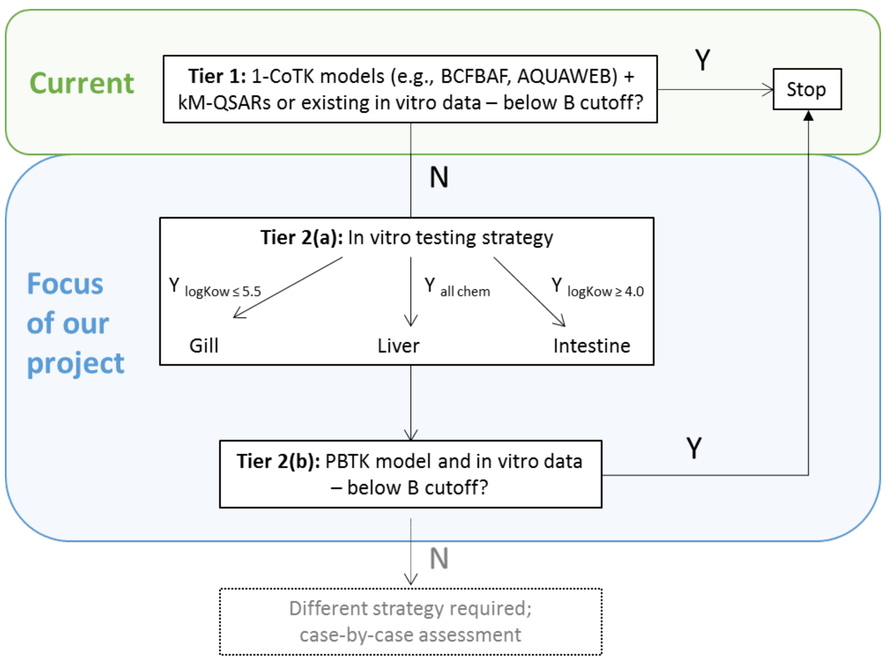


Figure 1. Current and projected tiered assessment framework for bioaccumulation prediction.

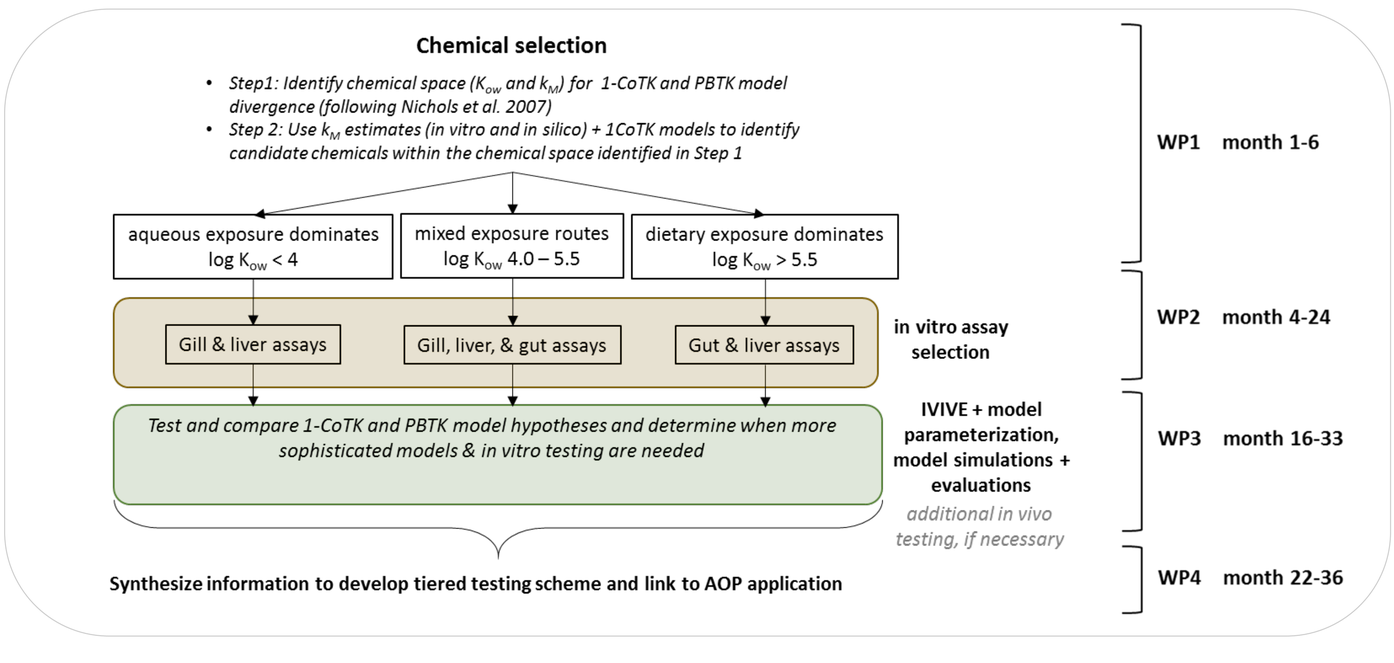


Figure 2. Project overview.

Our work is divided in four major steps (WPs)

WP1 – Chemical selection & in vitro testing strategy

Questions guiding chemical selection:

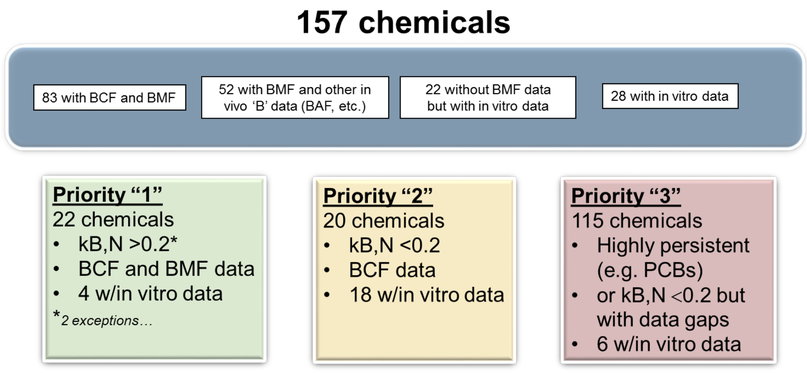
- Which types of chemicals are unsatisfactorily predicted for their bioaccumulation potential? Why? (i.e., Figure 2, WP1, Step 1)
- Which candidate chemicals for WP2 satisfy this area of "chemical space" in which there is apparent divergence between the 1-CoTK and PBTK models (i.e., Figure 1, WP1, Step 2) and for which high quality measured BCFs and BMFs are available?
- Which chemicals have already been investigated with additional tools, specifically in vitro-derived biotransformation rates?
- Which chemicals have available information on mode of action / AOP information to satisfy the objectives of Figure 2, WP4?

Currently ongoing

WP2 – In vitro biotransformation

Focus on three tissues: liver, gill and gut (Fig. 2)

WP3 – Implementation of experimental data into models



Note: kB – whole body biotransformation rate constant

Chem Name	CASNO	CANON SMILES	MW (g/mol)	ECOSAR Class	Functional class	Verhaar	Priority Filter: 1,2,3	Selected log Kow	Primary, whole body, biotransformation rate constant - 10 g fish [kM,N (/d)] - selected
Hexabromobenzene	87821	Brc1c(Br)c(Br)c(c(c1Br)Br	551.5	Neutral Organic	Br Flame retardant	4	1	6.07	2.57E-01
n-dodecane	112403	CCCCCCCCCCCC	170.3	Neutral Organic	Alkane hydocarbon	5	1	6.10	3.80E-01
Benzo[a]pyrene	50328	c1ccc2c(c1)c1ccc3c4c1c(	252.3	Neutral Organic	PAH	5	1	6.13	6.22E-01
Pentabromotoluene	87832	Brc1c(C)c(Br)c(c(c1Br)Br)(	486.6	Neutral Organic	Br Flame retardant	4	1	6.99	9.33E-01
Pentabromoethylbenzene	85223	CCc1c(Br)c(Br)c(c(c1Br)Br	500.7	Neutral Organic; Ben	Br Flame retardant	4 or 3	1	7.48	6.60E-01
Di-2-Ethylhexyl phthalate	117817	CCCCC(COC(=O)c1ccccc1C	390.6	Ester	Phthalate	5	1	7.60	2.51E-01
Decabromodiphenyl ether	1163195	Brc1c(Oc2c(Br)c(Br)c(c(c2	959.2	Neutral Organic	Br Flame retardant	4	1	8.70	4.77E-02
2,7-Dichlorodibenzo-p-dioxin	33857260	Clc1ccc2c(c1)Oc1c(O2)cc	253.1	Neutral Organic	Dioxin	1	1	5.75	4.07E-01
1,2,4-Trichlorodibenzo-p-dioxin	39227582	Clc1c(Cl)cc(c2c1Oc1cccc	287.5	Neutral Organic	Dioxin	5	1	6.35	2.57E-01

Example sheet, prepared by Jon Arnot and Michelle Embry

WP4 – Synthesize information to develop tiered scheme – link to AOP

Jon Arnot
ARC Arnot Research and Consulting Inc., Canada

Nic Bury
Christer Hogstrand
King's College, UK

Michelle Embry
ILSI HESI, USA

Helmut Segner
University of Bern, CH

Kristin Schirmer
Julita Stadnicka
Eawag, EPFL, CH