Source To Outcome Pathway (STOP) – Next Generation Risk Assessment (NGRA) put into practice

Tollefsen, K.E.*, Kim Leirvik, Sam A. Welch, Walter Zobl, Li Xie, Viviane Girardin

Norwegian Institute for Water Research (NIVA)

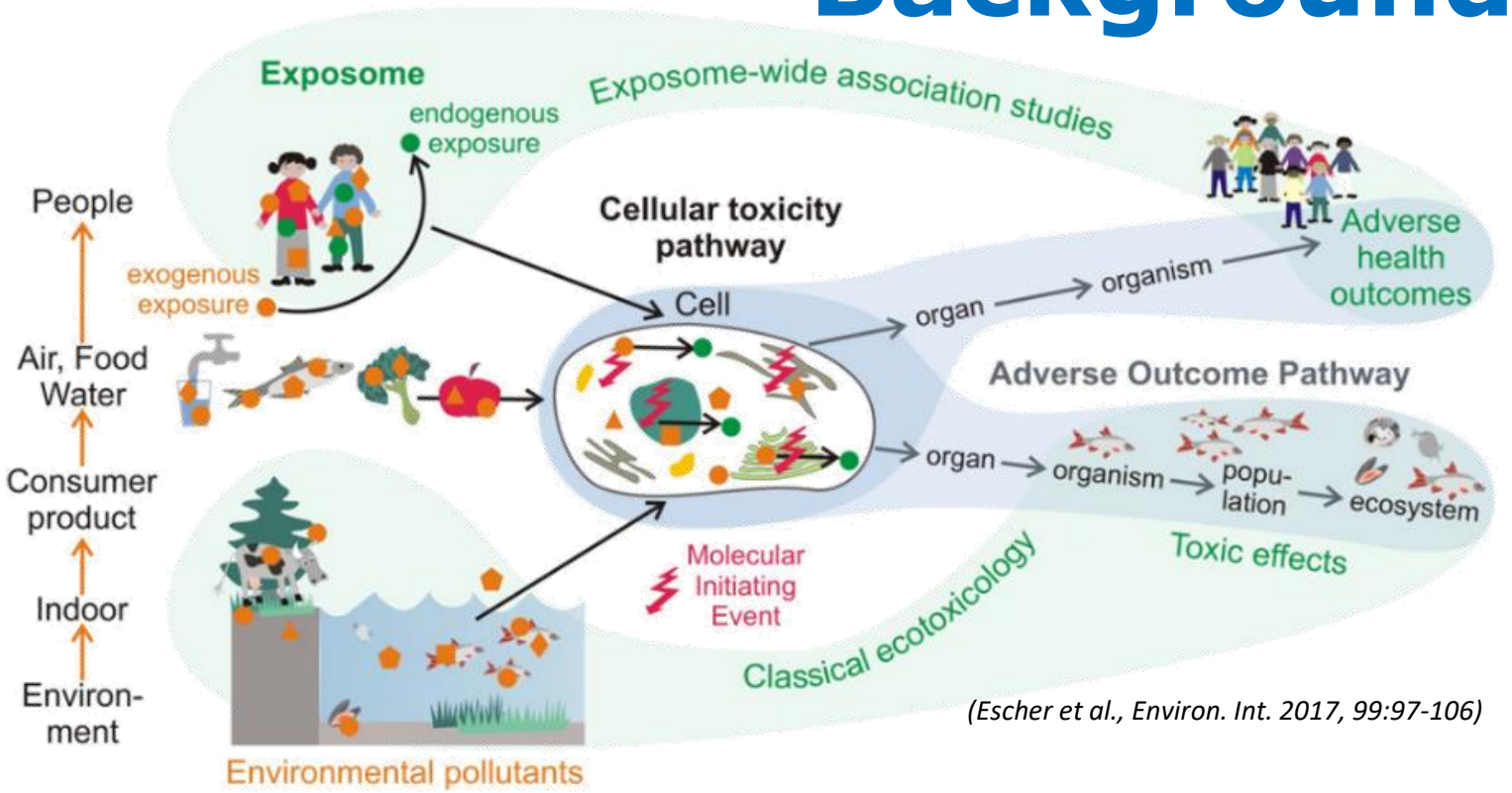
*knut.erik.tollefsen@niva.no

10th Norwegian Environmental Toxicology Symposium (NETS)

Stavanger August 28-29, 2025

NIVA PARC

Background



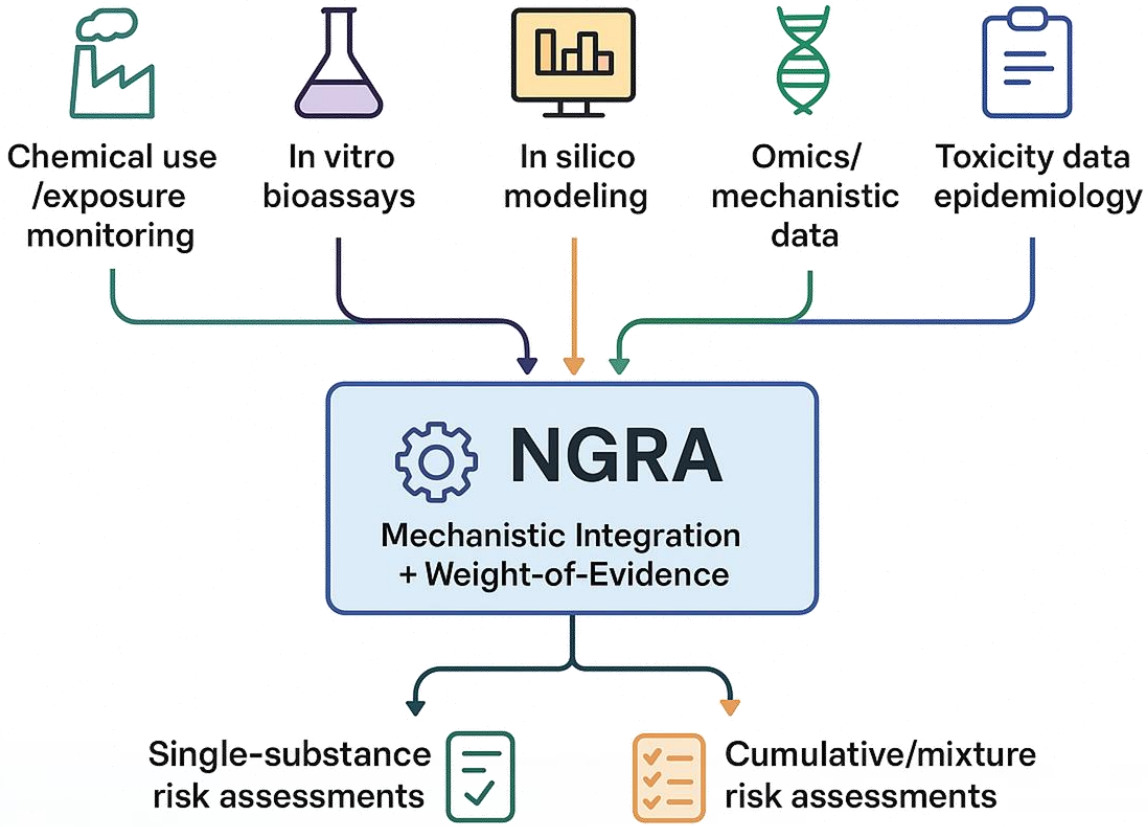
(Escher et al., Environ. Int. 2017, 99:97-106)

- **High # chemicals**
- **Multiple sources**
- **Multiple exposure pathways**
- **Multiple exposure routes**
- **High # target species**
- **Multiple Modes of Action**
- **Multiple stressors (mixtures)**

Traditional Risk Assessment

- One chemical – lack of real-life complexity
- No or little mechanistic insight – not exploiting available data
- Limit applicability to other areas of relevance

Next Generation Risk Assessment (NGRA)



OECD: structured, hypothesis-driven, and iterative approach to chemical safety evaluation that **integrates New Approach Methodologies** (NAMs), such as **in vitro assays**, **high-throughput screening**, and **computational modeling**, to assess potential risks without reliance on animal testing.

ECHA: Exposure-led, **integrative** framework that moves beyond traditional hazard-based assessments to incorporate **mechanistic data**, **probabilistic modeling**, and real-world exposure considerations.

WHO: An adaptive and evolving framework that incorporates novel scientific methods to better understand chemical risks in complex environmental and biological systems. It emphasizes the use of **alternative test methods**, **exposure science**, and **data integration** to inform public health decision-making.

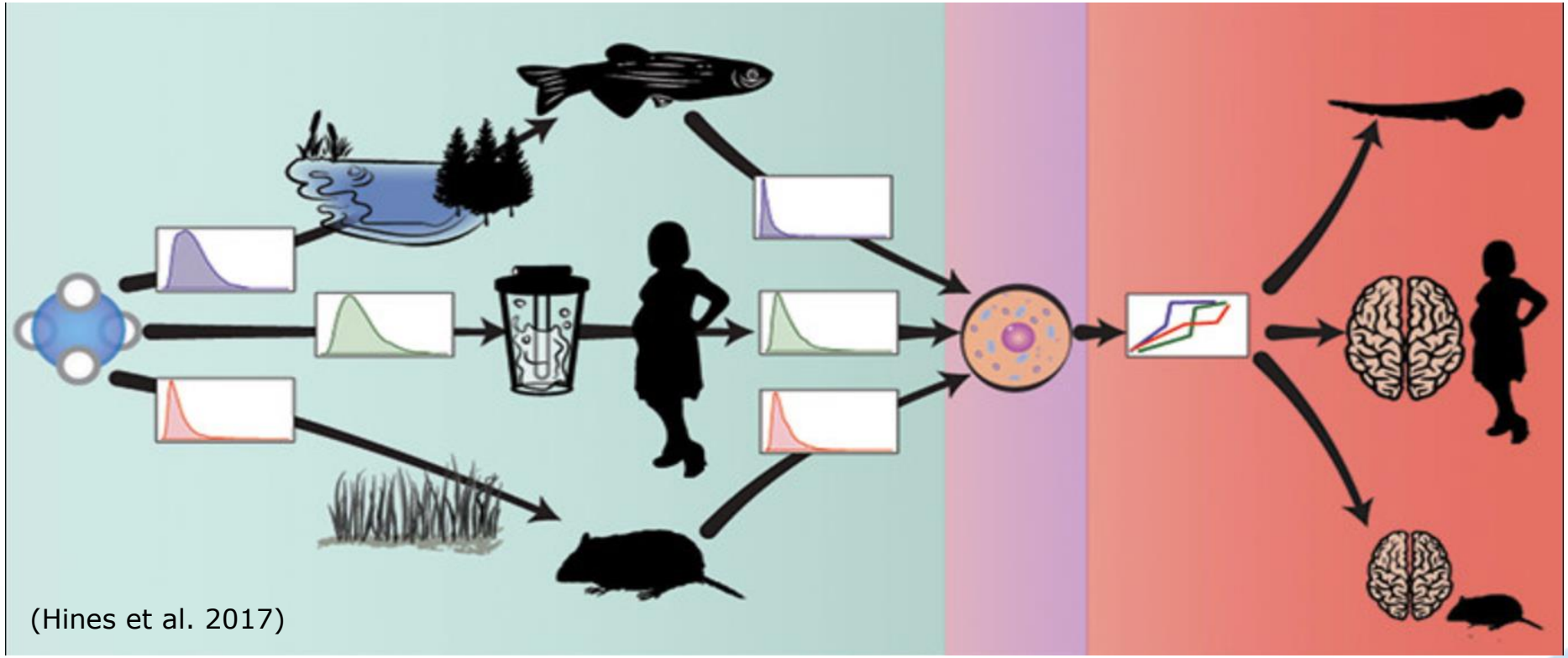
US EPA: data-driven framework that leverages **computational toxicology, machine learning, and mechanistic biological knowledge** to predict chemical hazards and exposure scenarios.

shift towards a more predictive, mechanistic, and high-throughput risk assessment for (eco)relevant exposure scenarios

NIVA PARC

Source To Outcome Pathway (STOP)

Aggregate Exposure Pathway (AEP) **Adverse Outcome Pathway (AOP)**



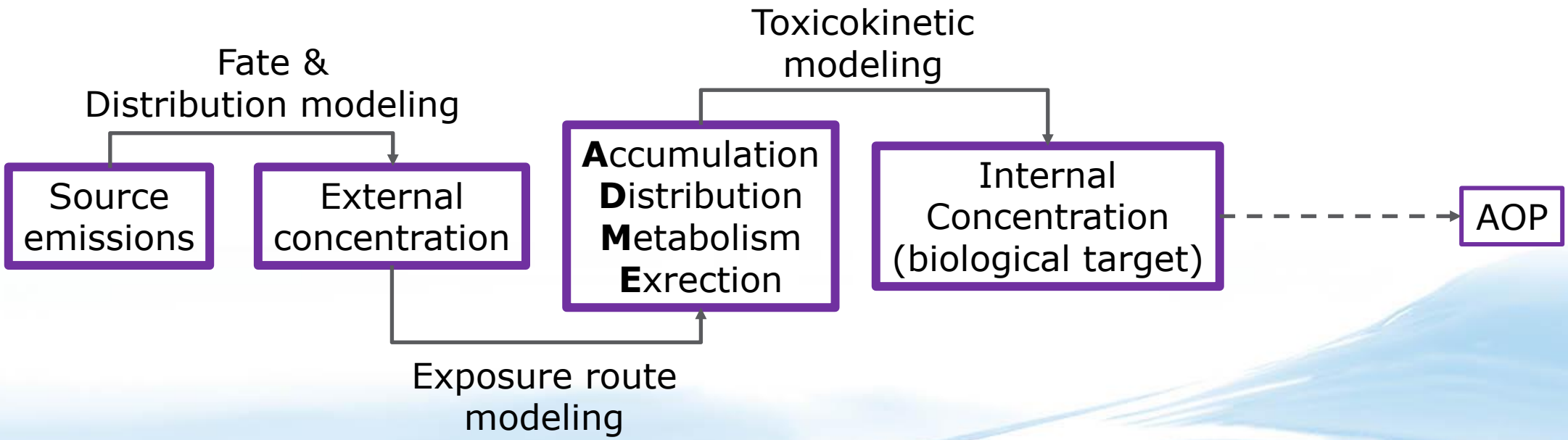
(Hines et al. 2017)

STOP combines **exposure-driven** (AEP) and **effect-driven** (AOP) frameworks into one integrated approach for mechanistic, holistic risk assessment.

NIVA PARC

Aggregate Exposure Pathway (AEP)

An **Aggregate Exposure Pathway (AEP)** is a conceptual framework that organizes and describes **the sequence of key exposure states** and **processes linking** an **external exposure** source to an **internal dose** at a biological target site relevant for risk assessment and regulatory decision-making.



(Teeguarden et al., 2016; Tan et al., 2018)

Adverse Outcome Pathway (AOP)

An Adverse Outcome Pathway (AOP) is a conceptual framework that **portrays existing knowledge** concerning the **linkage** between a direct **molecular initiating event** and an **adverse outcome**, at a level of biological organization relevant to **risk assessment**.

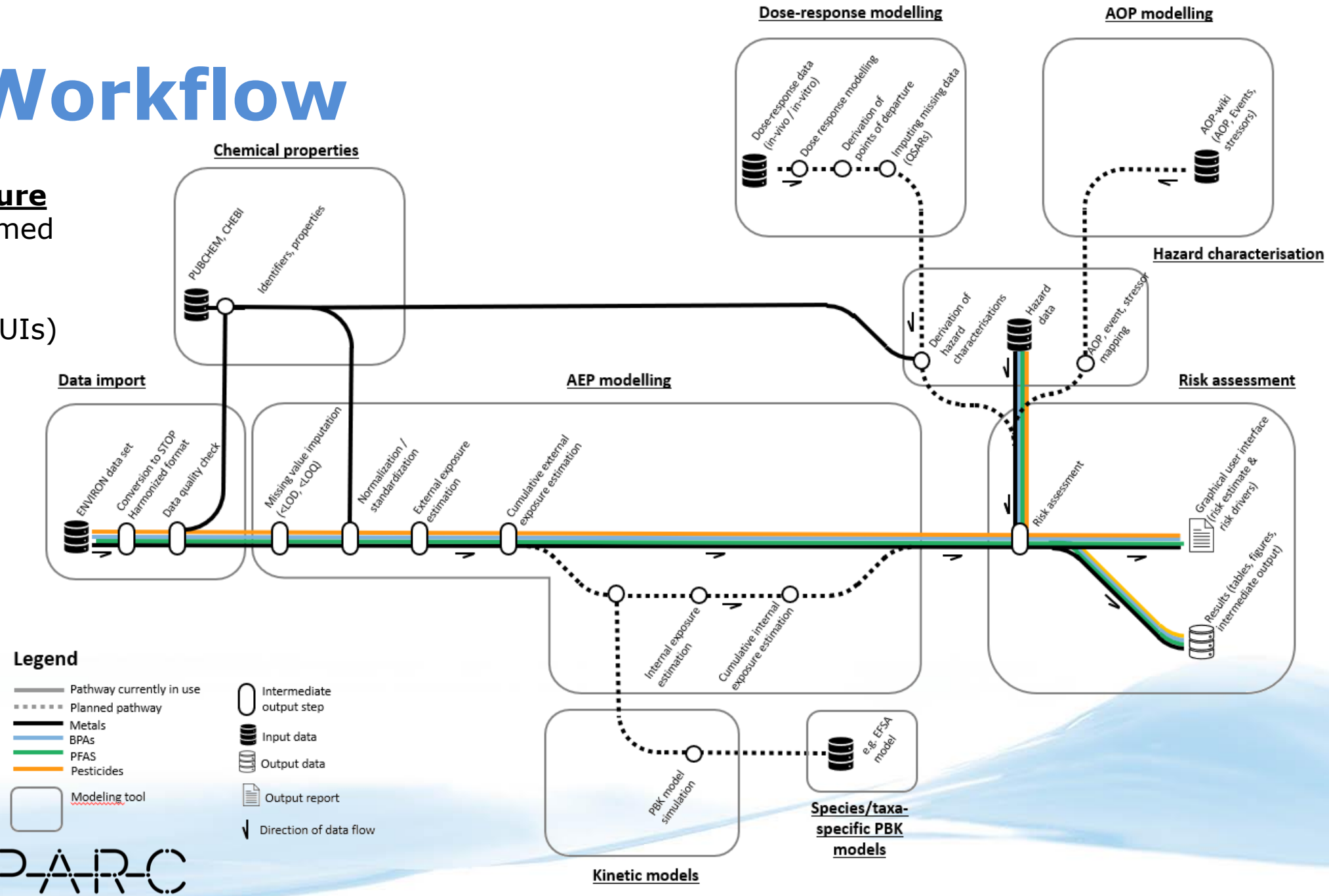
Increasing level of biological organization

(Ankley et al. 2010, Environ. Toxicol. Chem., 29(3): 730-741.)

STOP Workflow

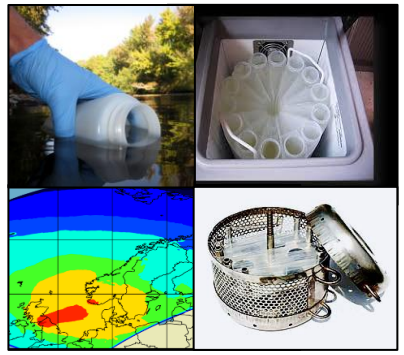
Model infrastructure

- AEP & AOP-informed
- Module-based
- Databases
- User interfaces (UIs)
- Models

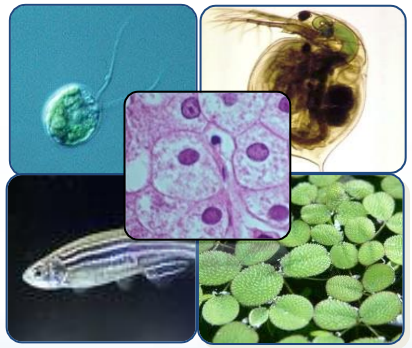


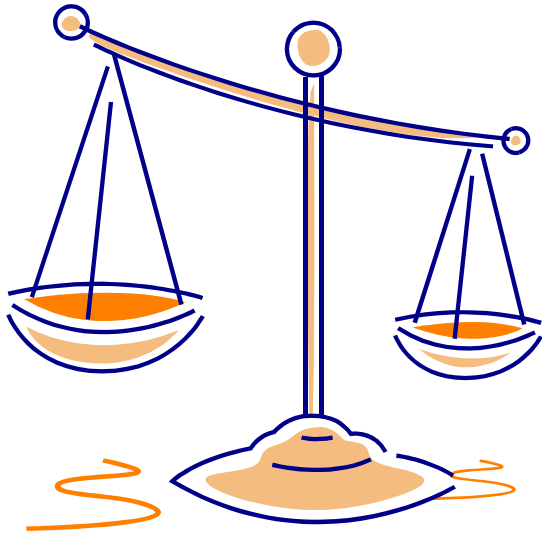
Case study – Risk prediction

Exposure



Hazard





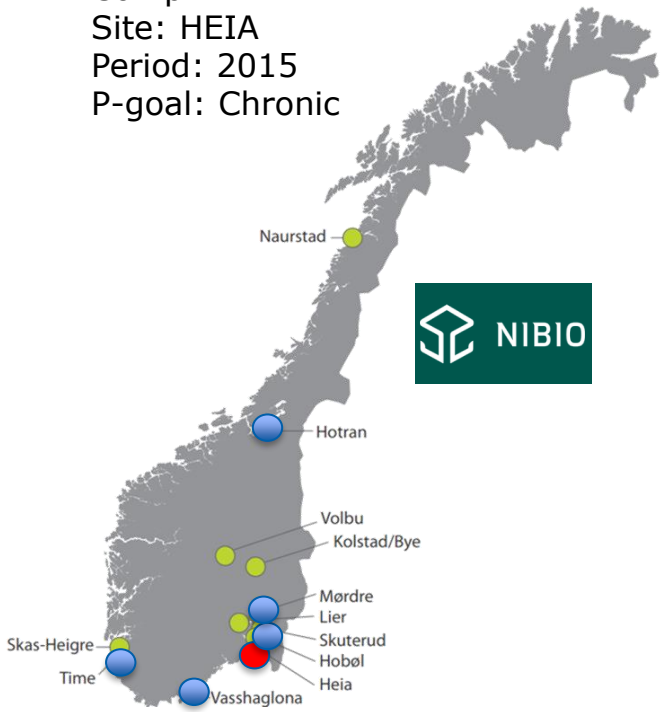
Risk Quotient (RQ) = $\sum_{n+1}^{n} C_{exposure}/C_{hazard}$
(CA assumption)

Is there a risk to non-target organisms?

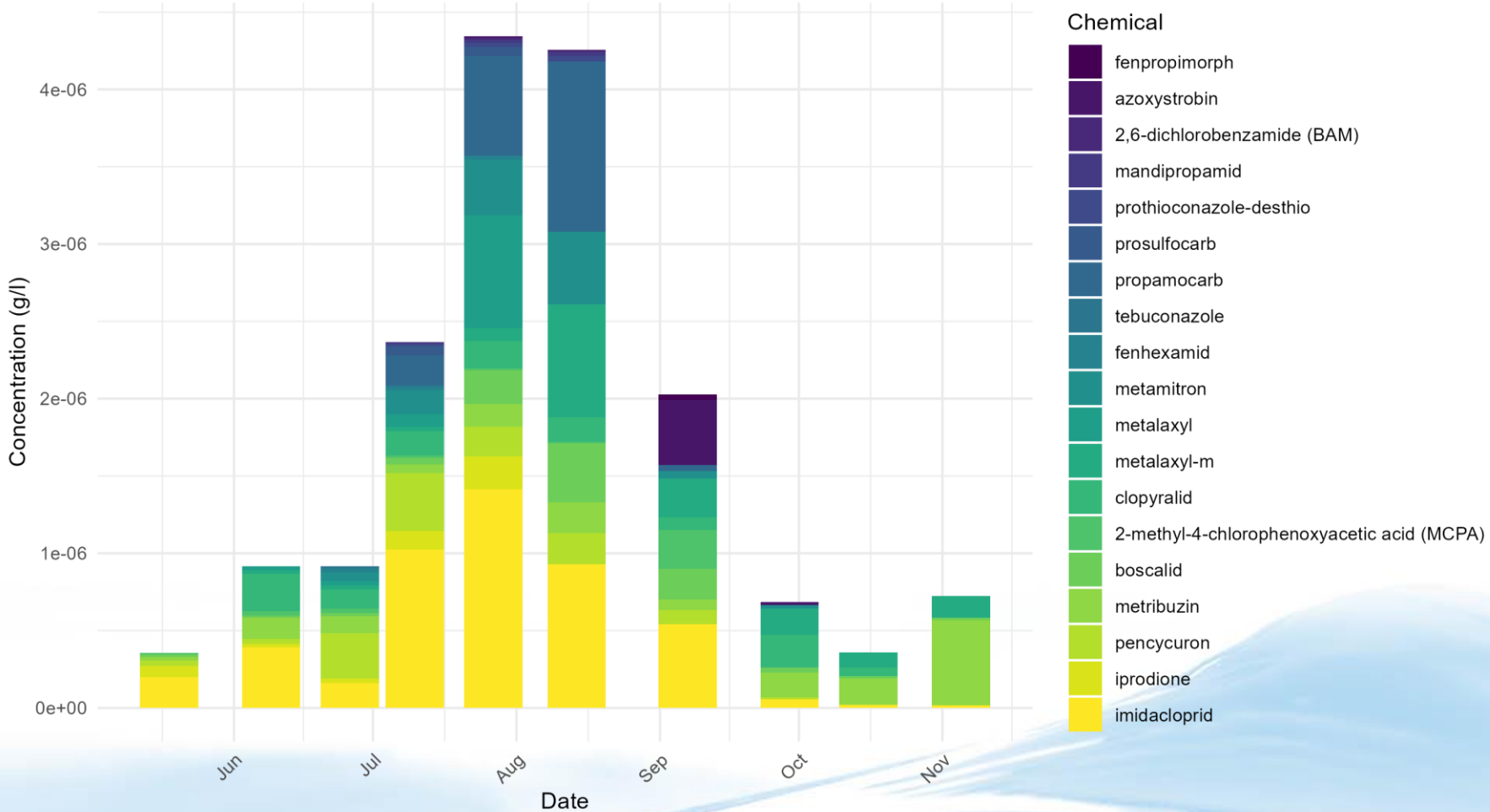
RQ>1 (Risk)
RQ<1 (No risk)

NIVA PARC

Comp: FW
Site: HEIA
Period: 2015
P-goal: Chronic



Pesticides - JOVA



Exposure data

- Water concentrations
- >115 active substances
- Multiple sites
- >20 yrs of data

Hazard data

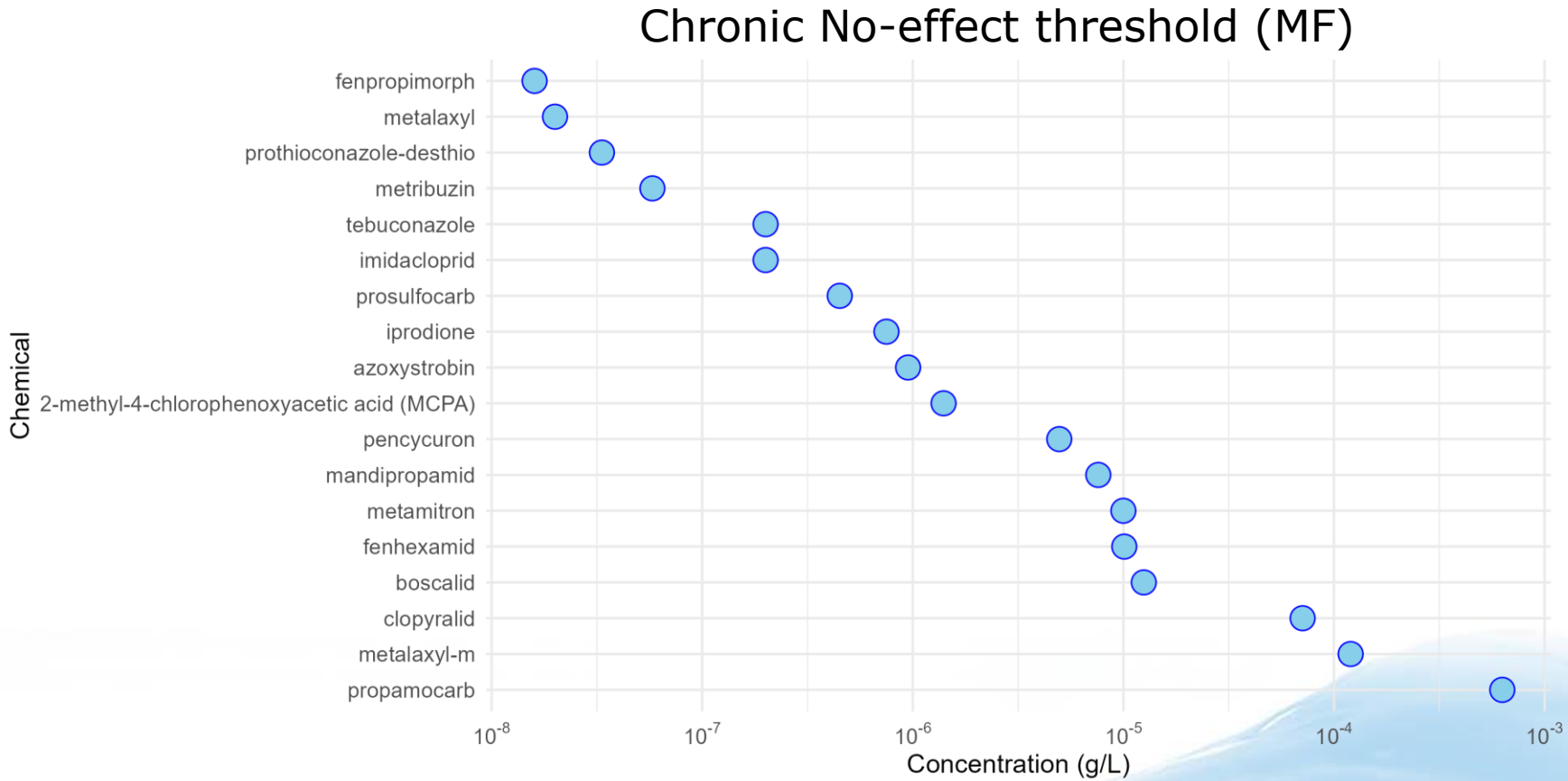
No-effect thresholds

Acute (AMF) & Chronic (MF)

- Algae
- Crustaceans
- Plants
- Fish

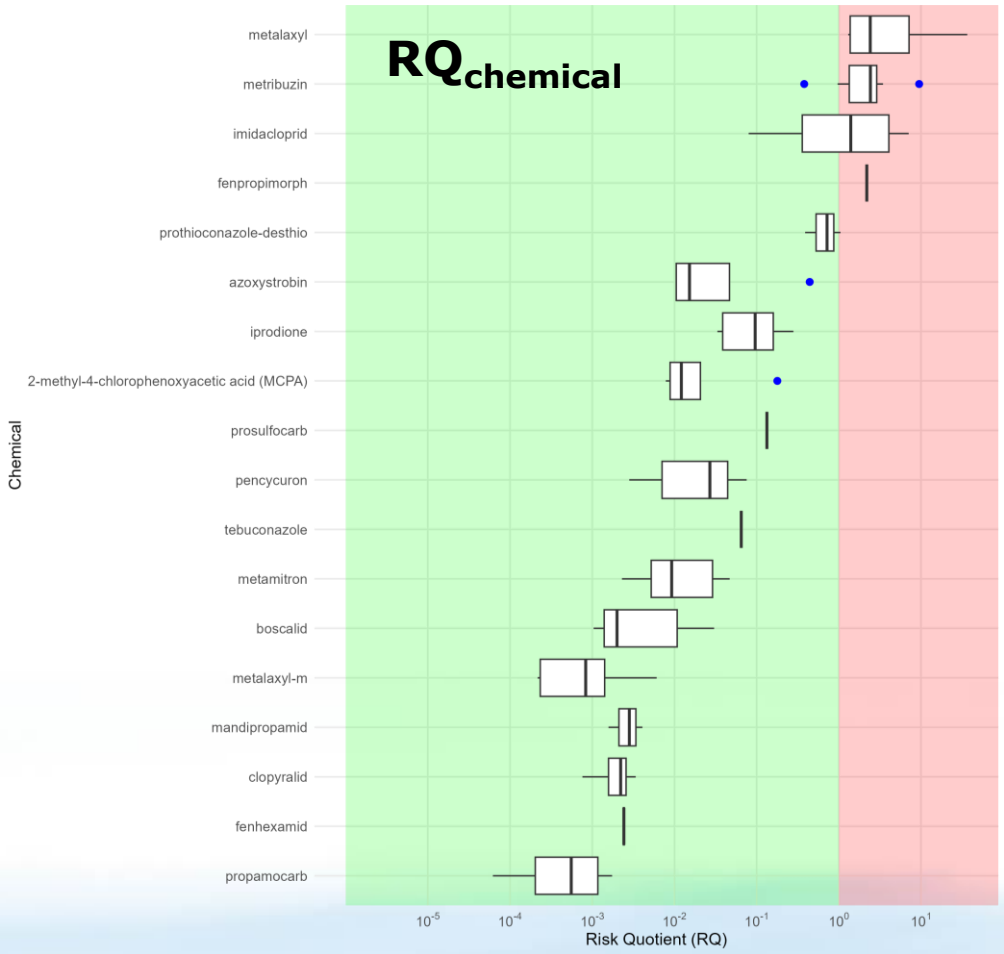
PPDB

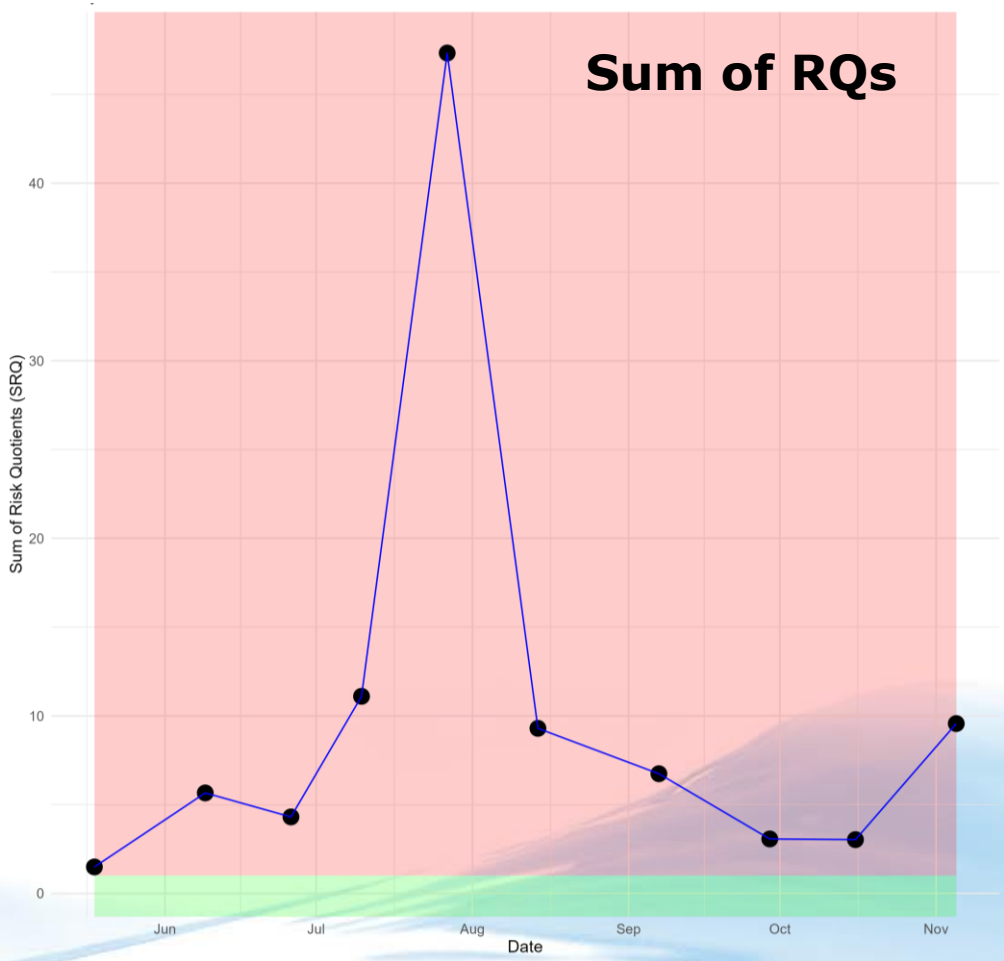
Plantevernmidler - Nibio



NIVA PARC

Risk prediction (Chronic)

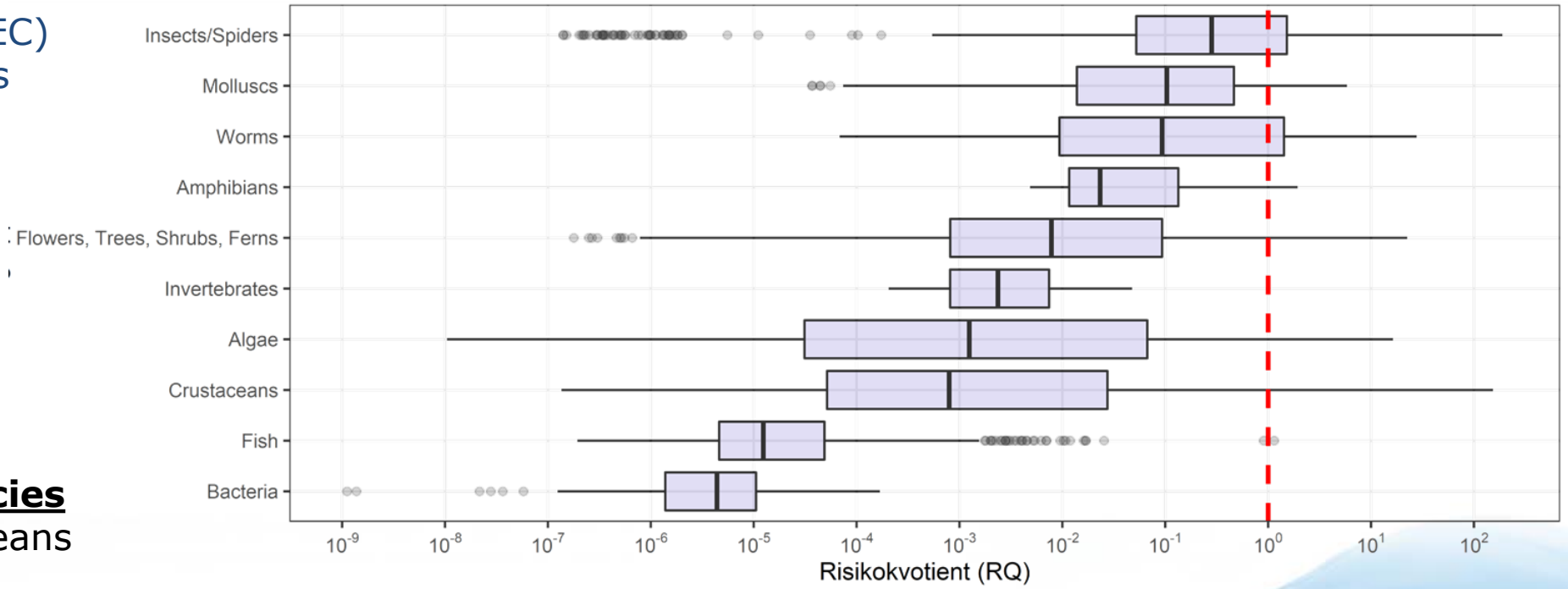




Species at risk

No-effect thresholds

- ECOTOX (Chronic, NOEC)
- Multiple species groups



Most susceptible species

Insects/spiders/crustaceans

Molluscs, worms

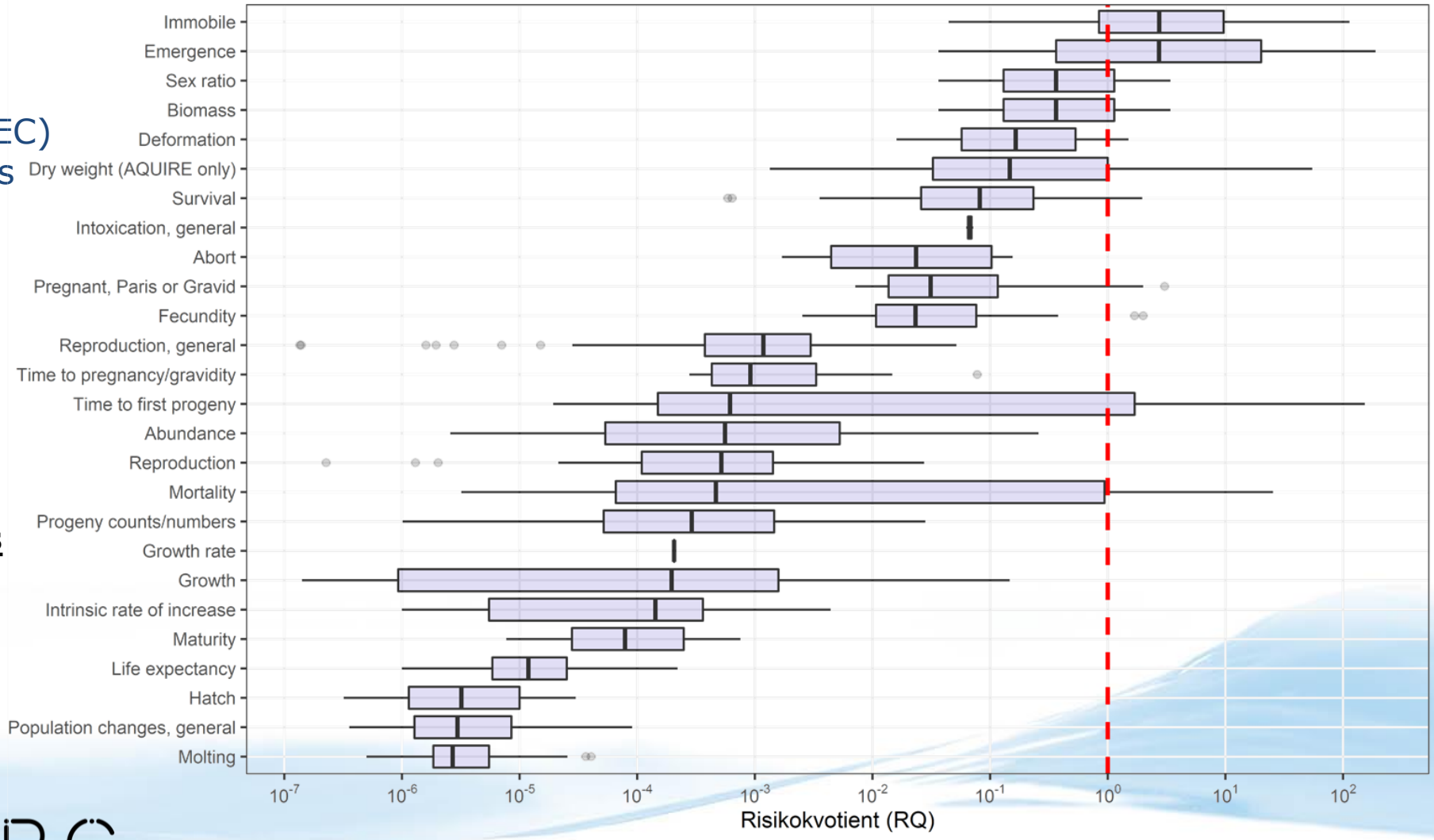
Toxicity targets (arthropods)

No-effect thresholds

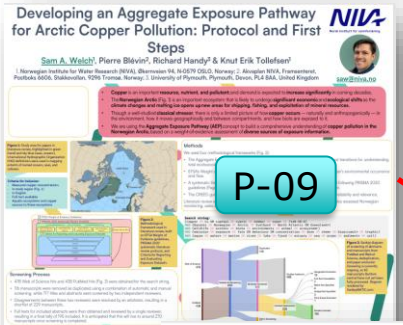
- ECOTOX (Chronic, NOEC)
- Multiple species groups

Most relevant targets

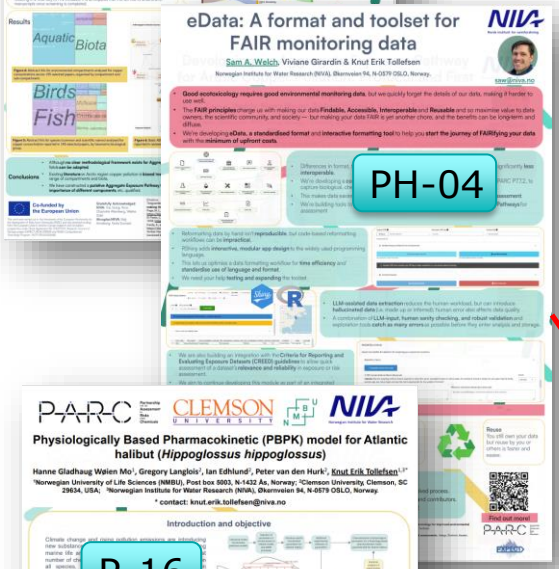
Mortality/survival
Development
Growth



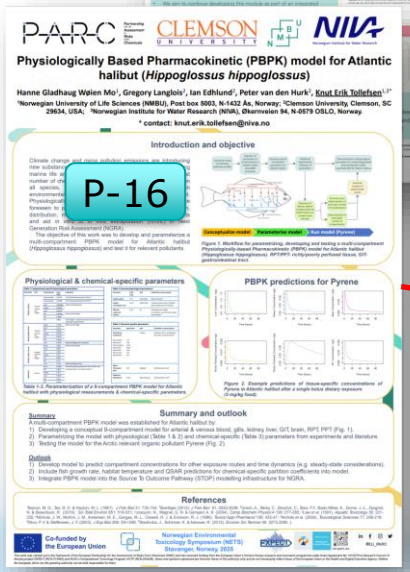
New developments



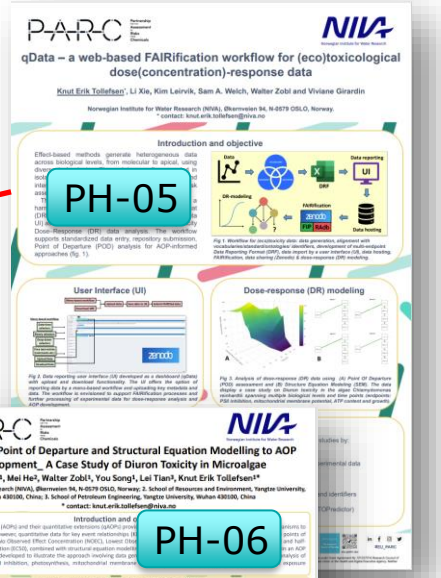
P-09



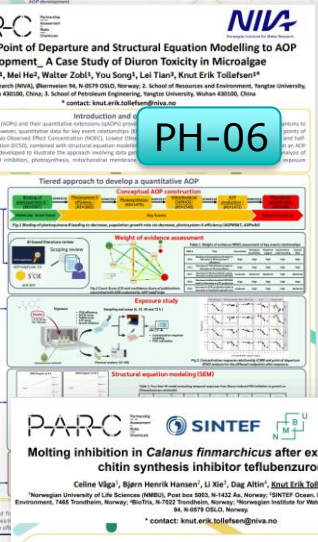
PH-04



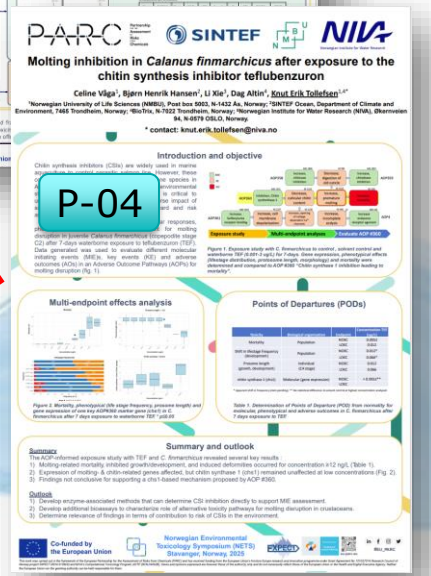
P-16



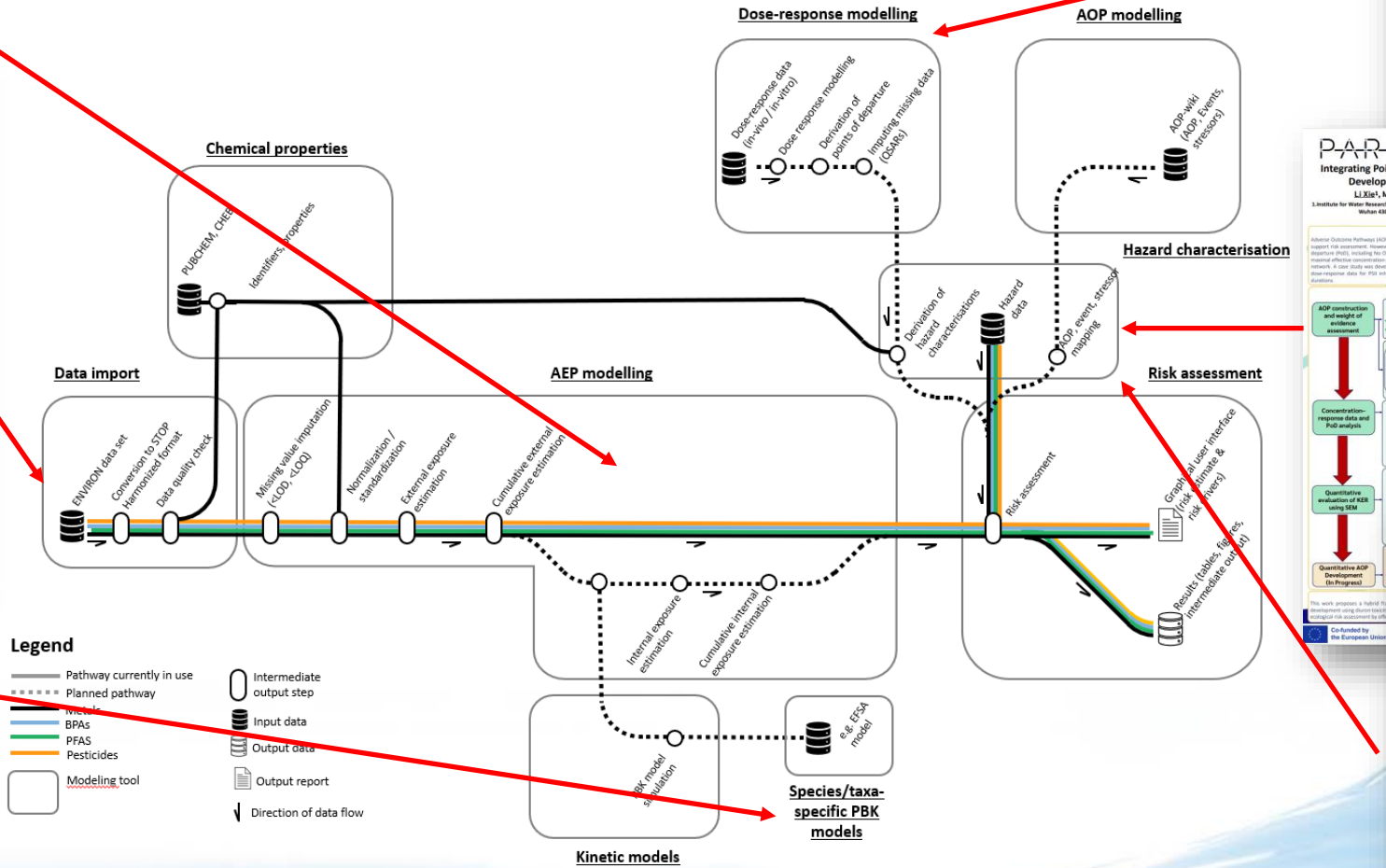
PH-05



PH-06



P-04



Summary

- **Conceptual STOP model using in-house data, databases, and models proposed**
- **Selected modules of a STOP modeling framework developed and tested**
- **Data reporting formats, User Interfaces (UI) and analysis prototyped**
- **Effects modeling (e.g. using AOPs, DR-modeling & tox thresholds) mature**
- **Exposure modeling (e.g. using AEP & monitoring data) still in the scoping**
- **Integration of the full model infrastructure pending**

NIVA PARC

Acknowledgements

NIBIO
NORSK INSTITUTT FOR BIOØKONOMI

Hans Ragnar Norli
Kathinka Lang
Marianne Stenrød
Marit Hauken
Roger Holten
Sven Roar Odenmarck

More information ?

NCTP EXPECT STOP PARC

The EXPECT team

Akvaplan niva, CLEMSON UNIVERSITY, NIVA, Newcastle University, NMBU, SINTEF

Funding

EXPECT, PARC Partnership for the Assessment of Risks from Chemicals, Norwegian Ministry of Climate and Environment, The Research Council of Norway

Contact
Knut Erik Tollefsen,
knut.erik.tollefsen@niva.no

NIVA PARC