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A framework for environmental NGRA with example case studies

Claudia Rivetti

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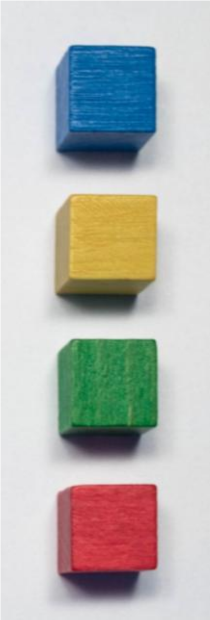
The value of New approach methodologies (NAMs)



NAMs are NOT
1:1 replacement
to animal tests

Instead
1 NAM = 1 block

different combination

can address

different endpoints

- NAMs provide **mechanistic information** on the mode of action, potency, and variability of chemical effects
- NAMs can be used **in combination with, or replace existing animal data** entirely, depending on the regulatory context and the level of confidence and validation

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modified *from Amelie Ott, ICCS*

Principles for risk assessment (ICCR - adapted)

How to conduct the risk assessment

- Considers all available information
- Uses a tiered and iterative approach
- Makes use of robust and relevant methods

Goal of the risk assessment

- Exposure led
- Hypothesis driven
- Taxonomically relevant
- Aligned to protection goals

How to document the risk assessment

- Identifies and characterizes sources of uncertainty
- Transparent and explicit about logic of overall approach

NGRA is defined as an exposure-led, hypothesis-driven risk assessment approach that integrates NAMs to assure safety without the use of animal testing

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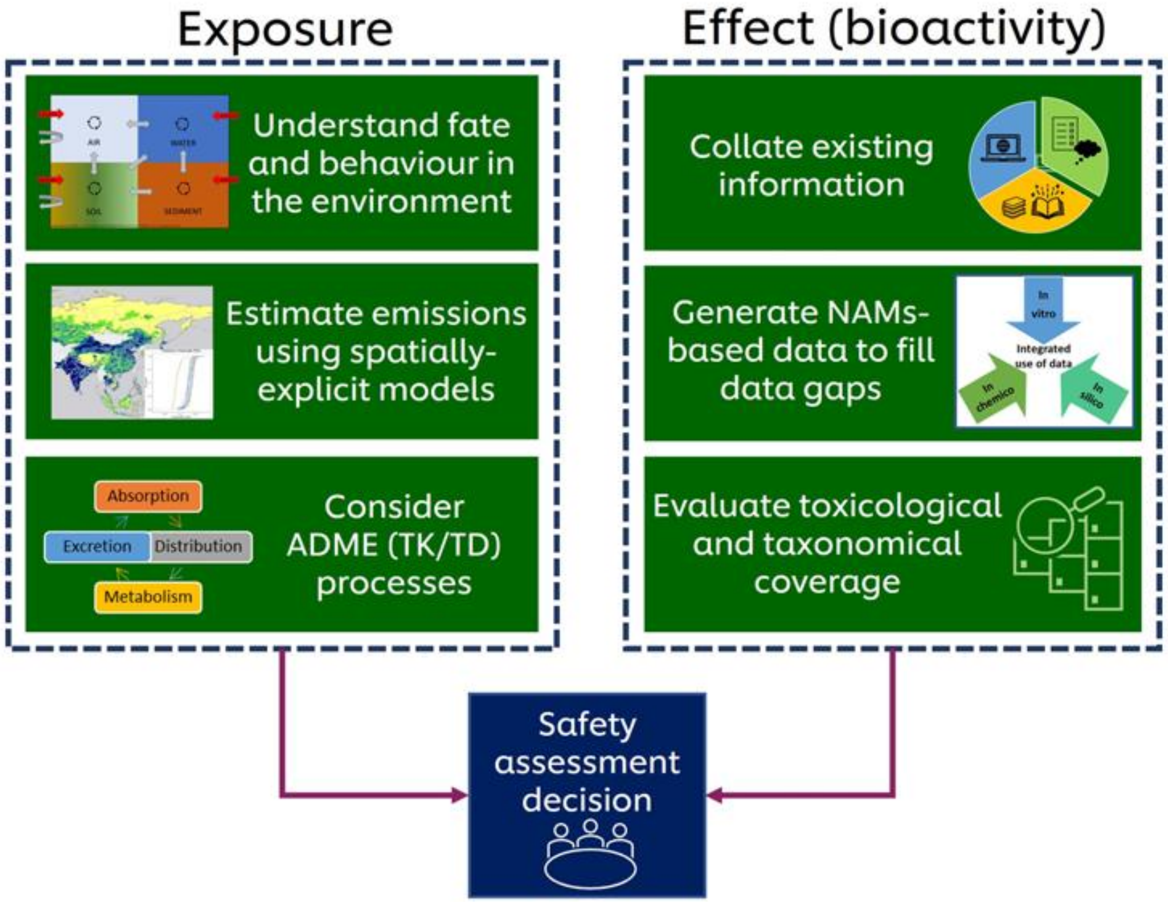
Adapted from Dent, M., et al. (2018). Comp. Tox.

The vision: Next Generation ERA

Establishing enhanced environmental protection through NexGen, mechanistic based environmental risk assessment paradigm shift

- ✓ NGRA starts with exposure and uses hypotheses to assess the potential for adverse effects
- ✓ It incorporates *in silico, in chemico,* and *in vitro* methods to gather data and assess risks, minimizing the need for animal testing.
- ✓ Iterative and Tiered Approach



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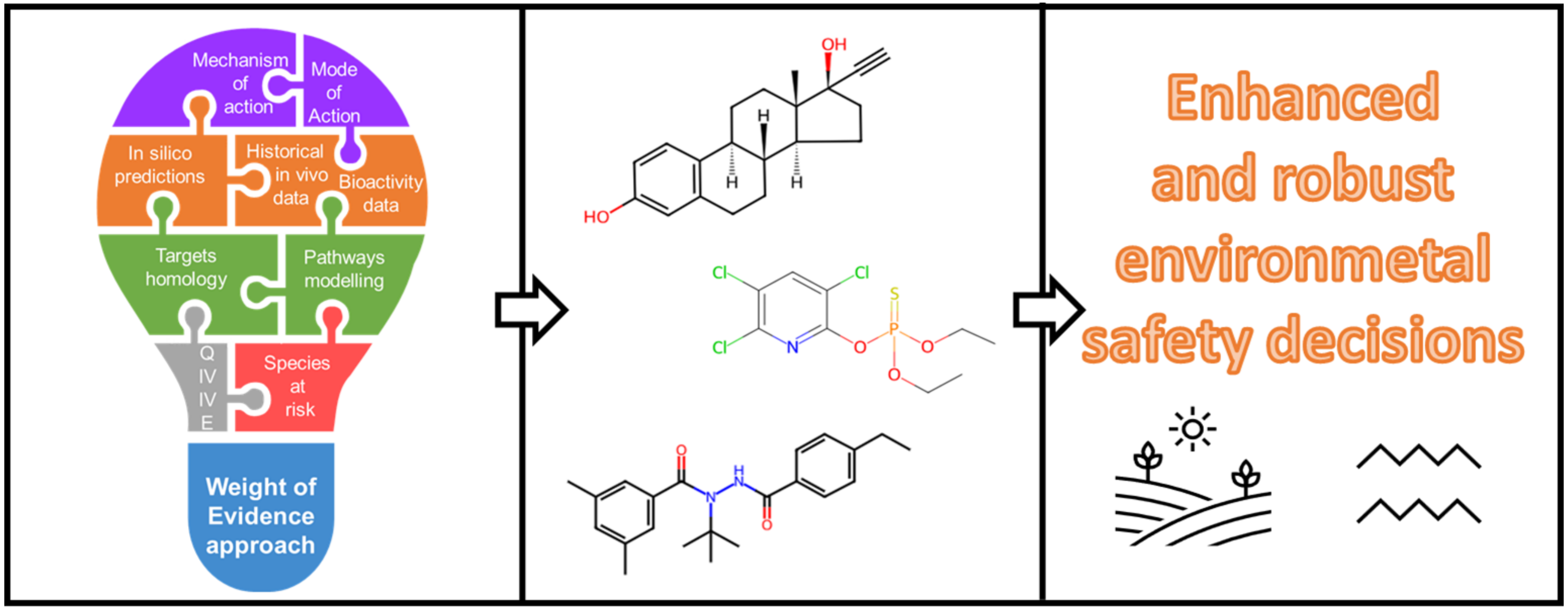
Objectives

- ❖ To develop an operating framework integrating all available information within environmental safety assessment
- ❖ To conduct case-studies to test the framework and the suitability of mechanistic-based information to support and strengthen current Environmental risk assessment practice



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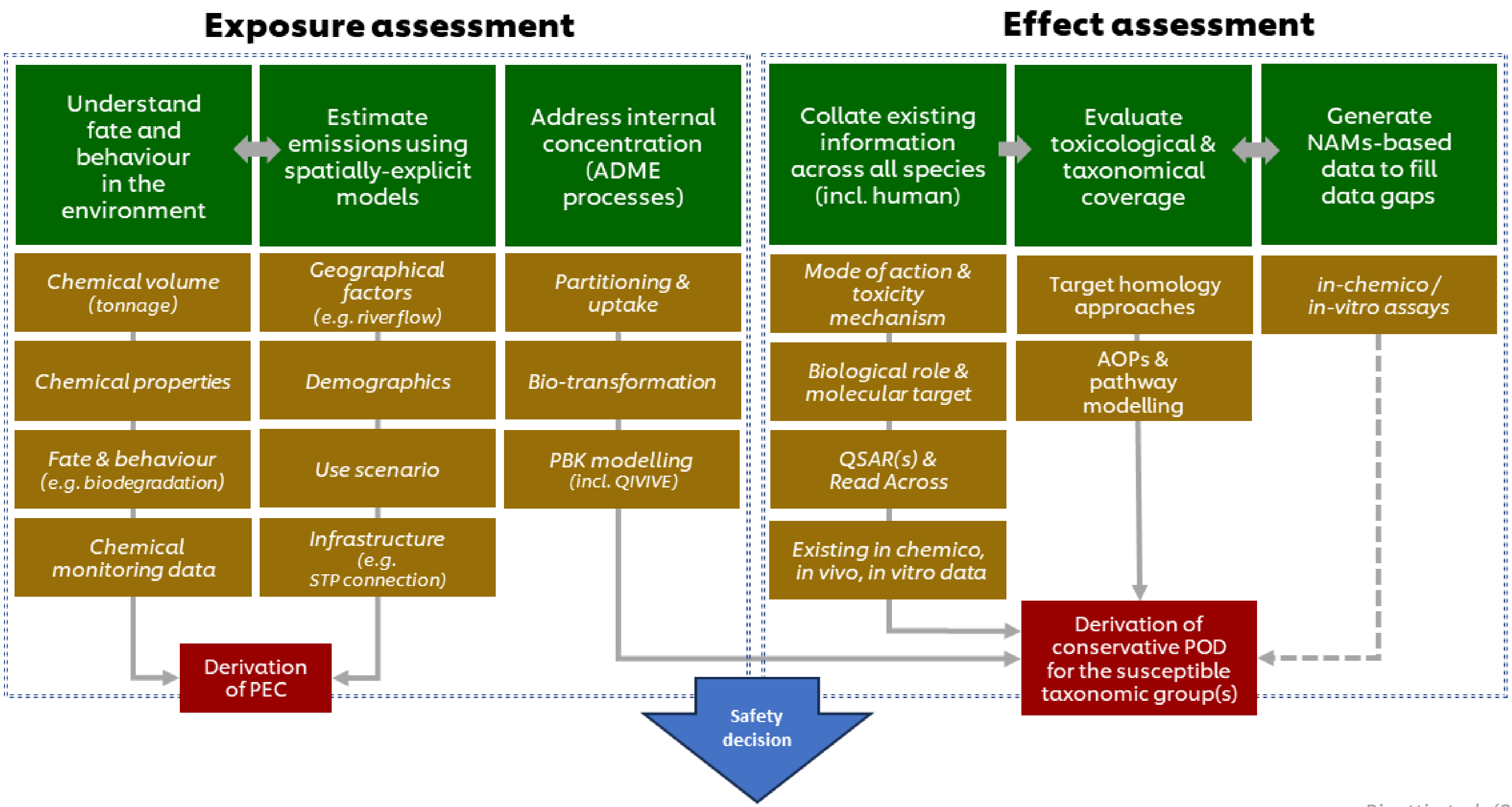
Framework for environmental NGRA

This framework aims to create a **tailored, integrated use of NA**Ms and accelerate their adoption, building confidence in their validity and utility for ERA and regulatory decision-making.



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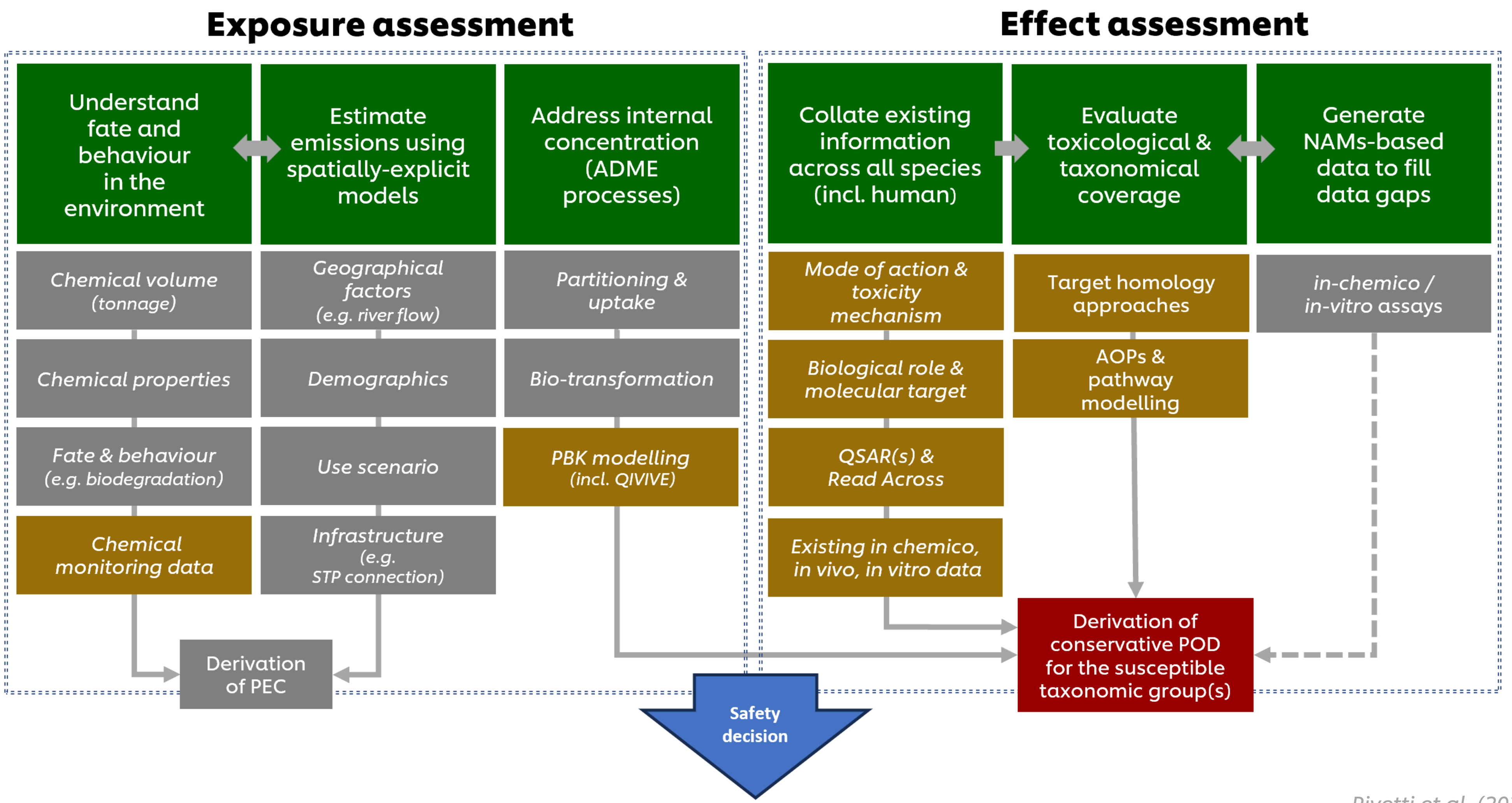

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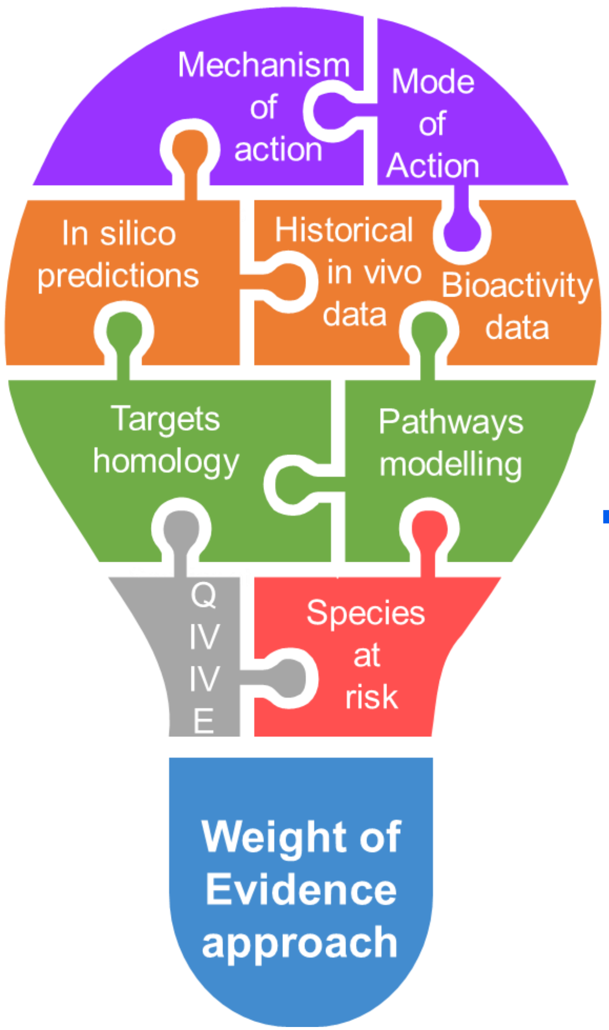
Case studies for today

- ✓ Ethynil Estradiol (EE2)
- ✓ Chlorpyrifos (CPS)
- ✓ Tebufenozide (TBZ)



Data type	Scope	Data source
In silico	Mode of Action/ Toxicity mechanism	OECD Toolbox
		ChemProp
		EnviroTox
		Sapounidou-Firmin scheme
	Biological role/ molecular target	DrugBank
		ChemSpider
		ChEBI
		PubChem
	Cross-species extrapolation	EcoDrug
		SeqAPASS
		G2P-SCAN
	Adverse Outcome Pathway	AOP-WIki
	Aquatic toxicity	EpiSUite
In vitro	Bioactivity	ToxCast / Tox21
(Historical) In vivo	Aquatic toxicity	EnviroTOX
		ECOTOX db
Exposure	Chemical monitoring	NORMAN EMPODAT db

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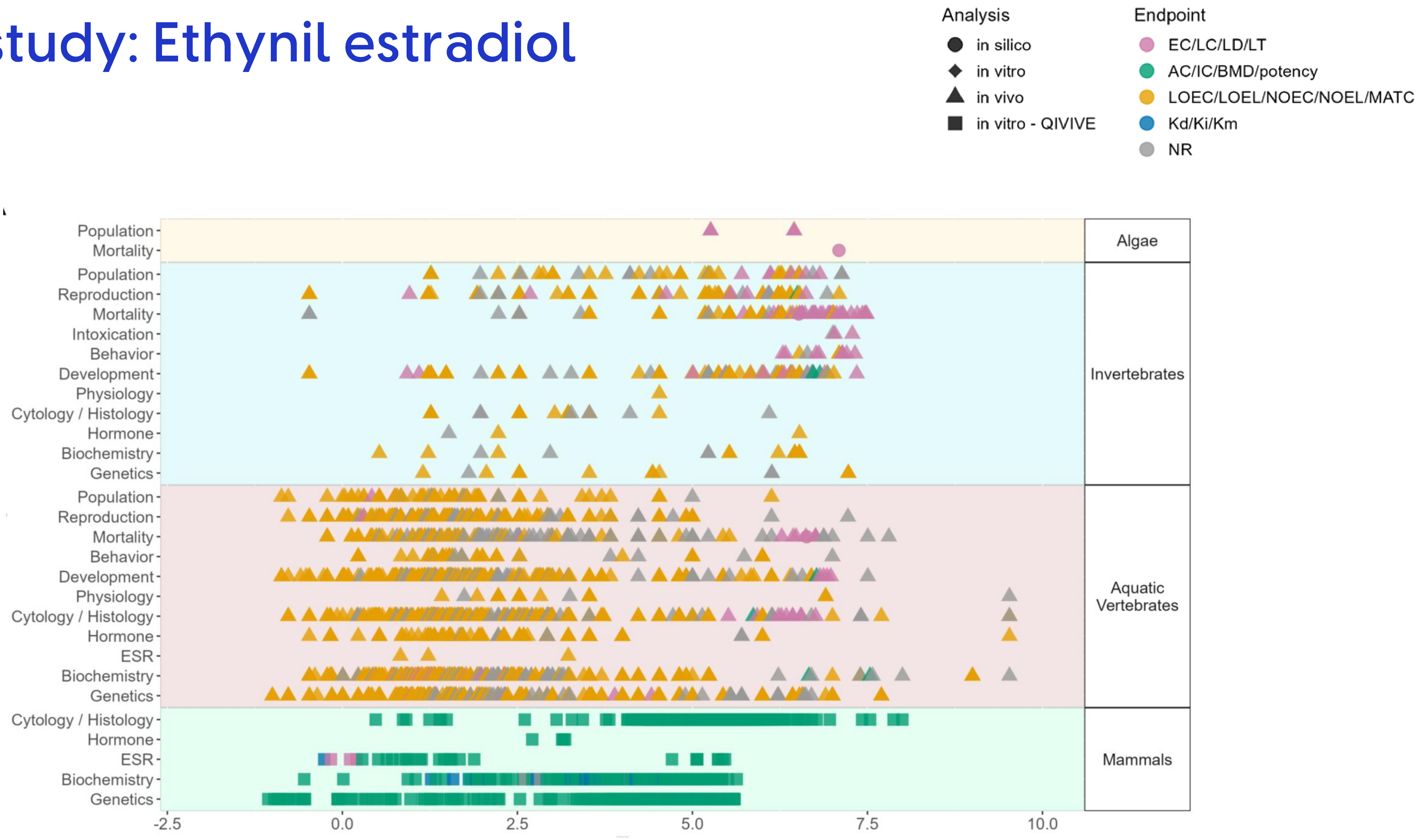
Case-study: Ethynil estradiol



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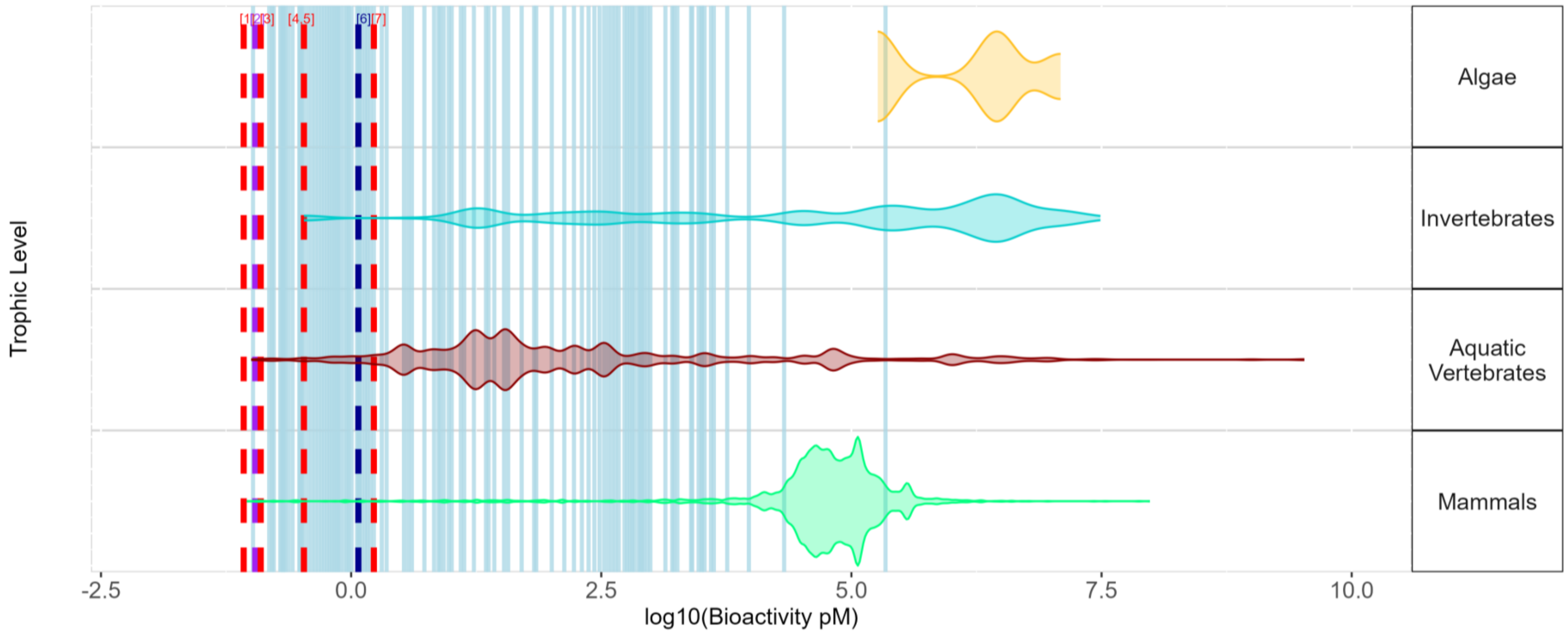
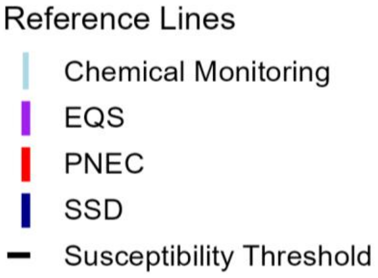
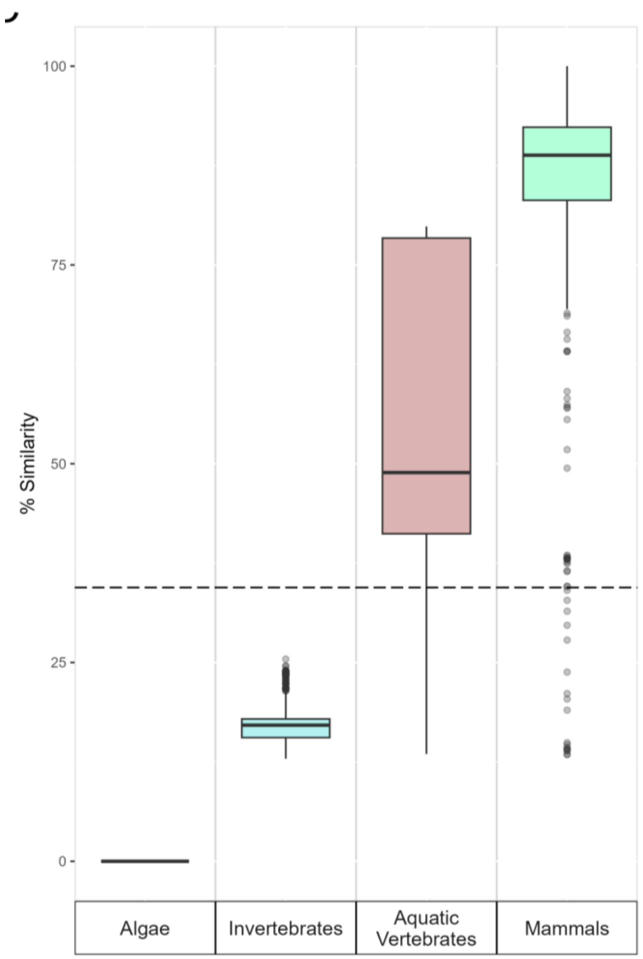




ESR conservation



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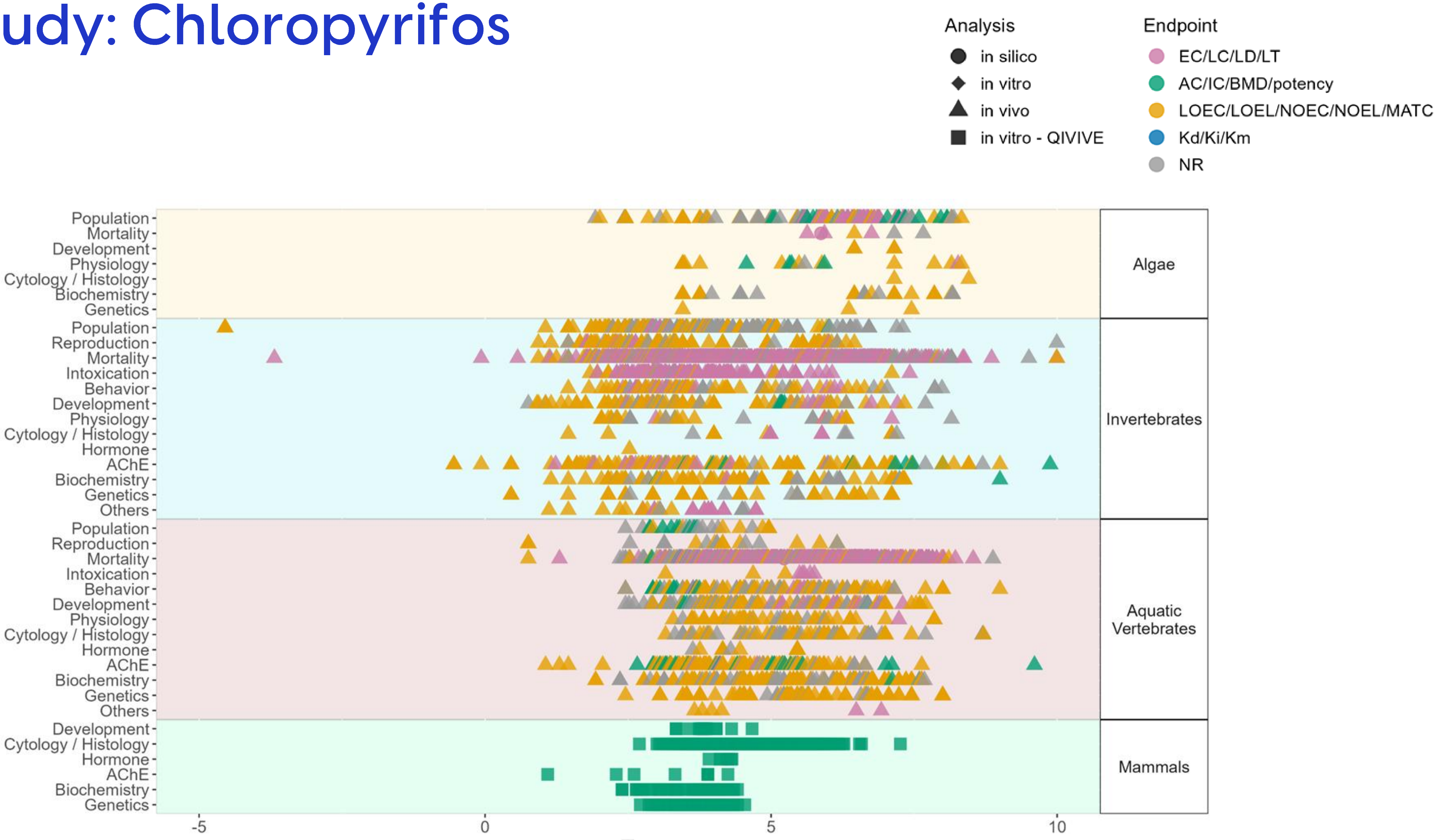
Case-study: Chloropyrifos



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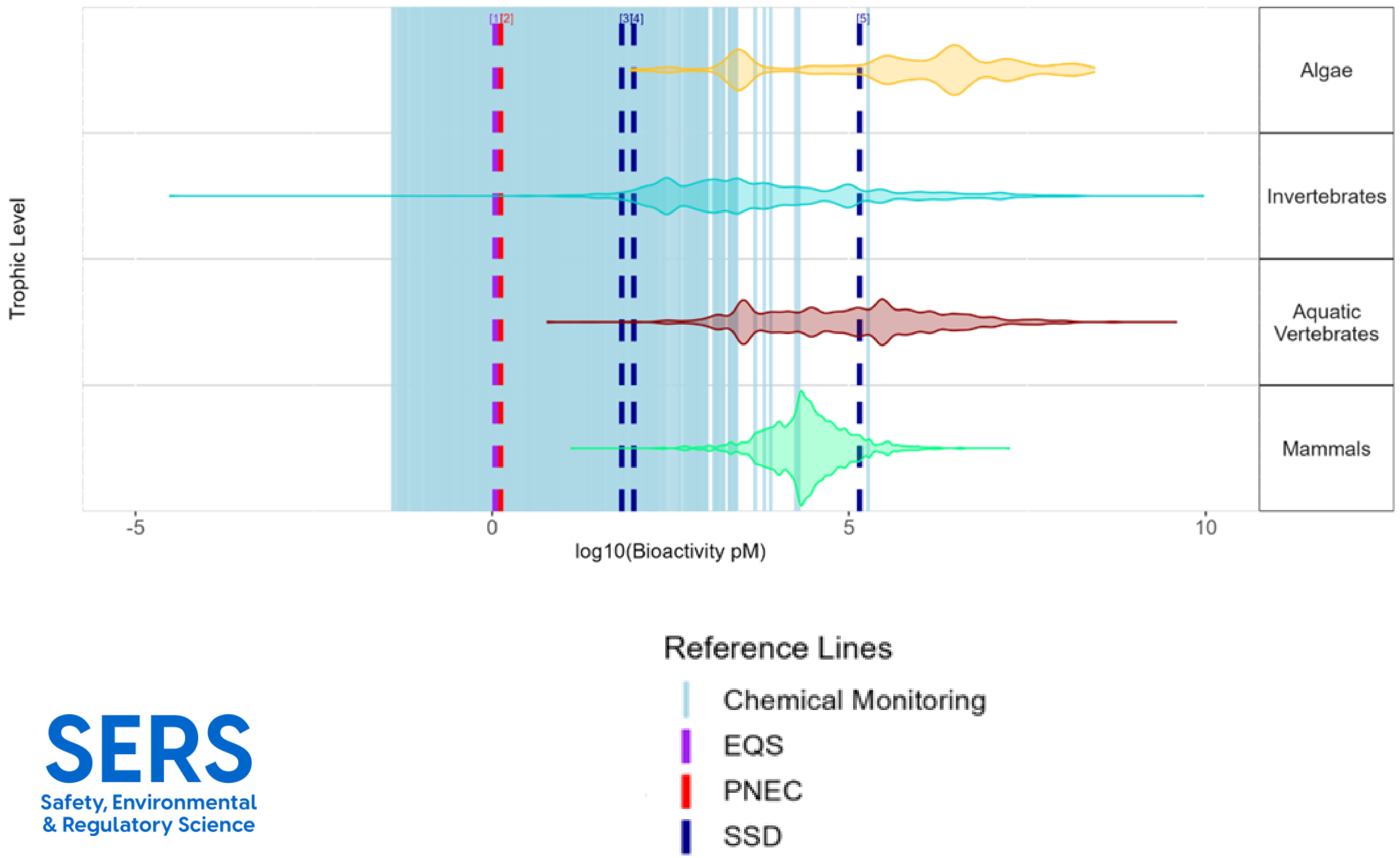
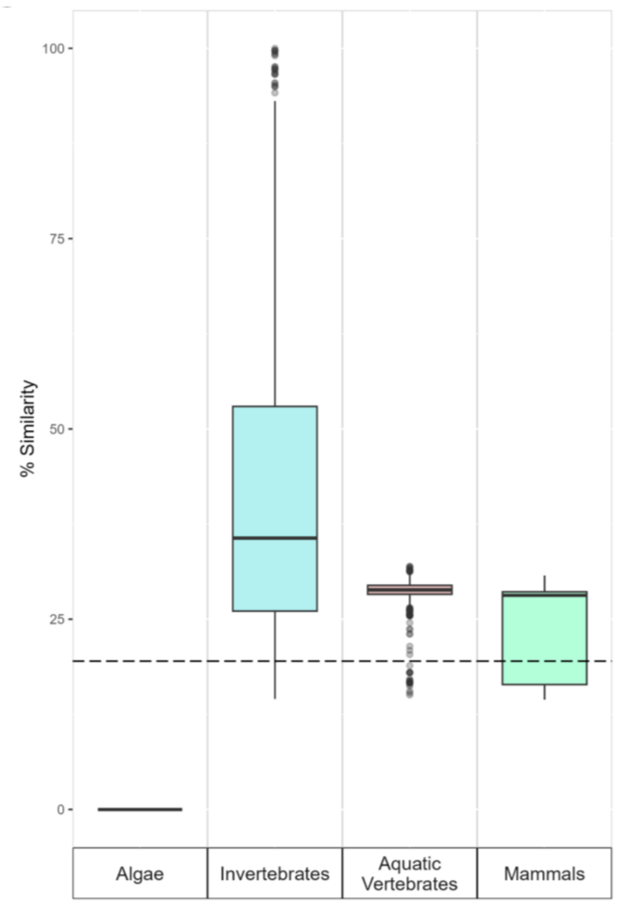
Case-study: Chloropyrifos





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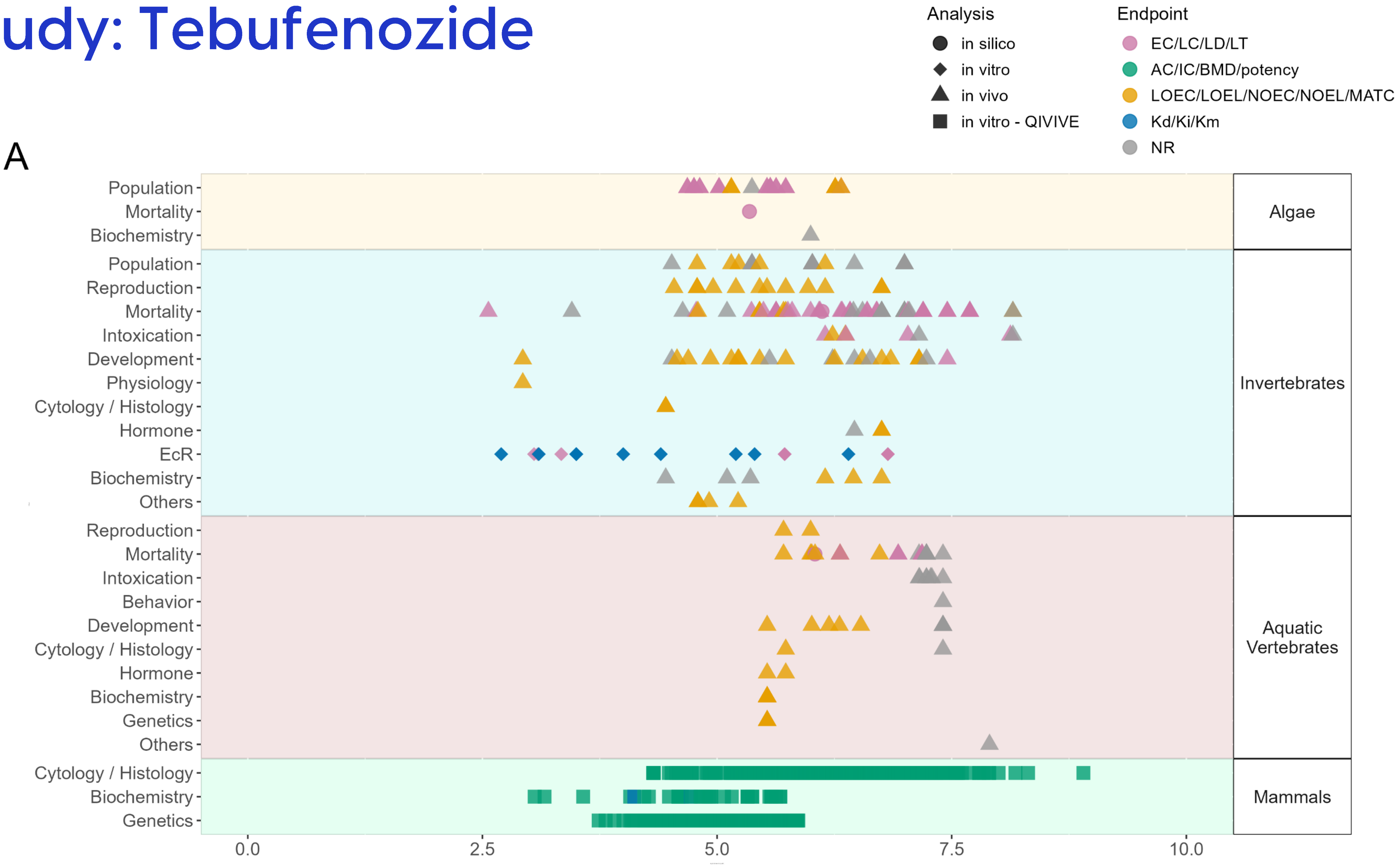
Case-study: Tebufenozide



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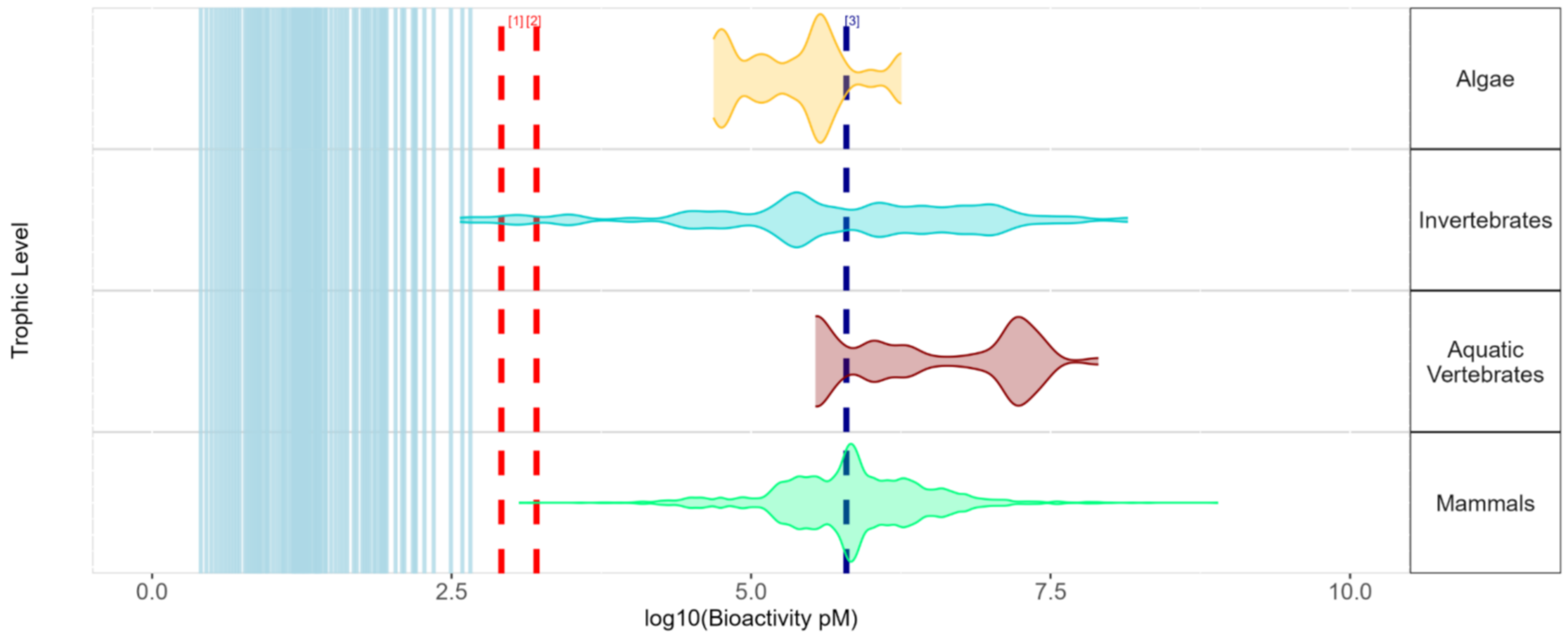
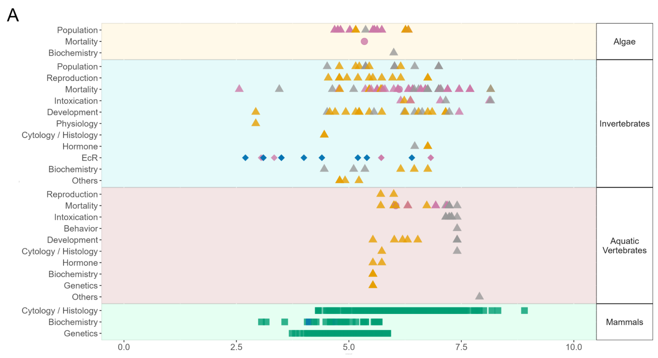
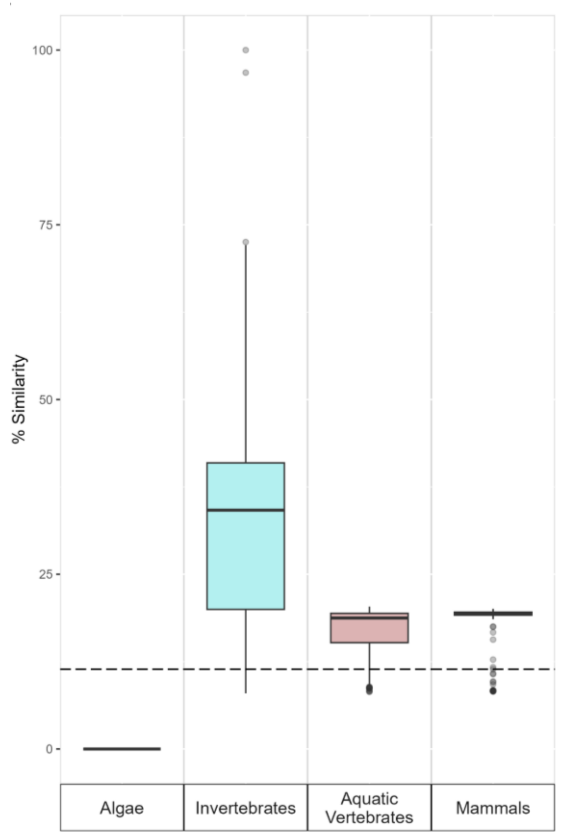


Reference Lines

- Chemical Monitoring
- EQS
- PNEC
- SSD
- Susceptibility Threshold





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Take-home messages

- ☺ **evolutionary conservation of targets and toxicological responses are aligned**, identifying the biological space at risk;
- ☺ a **WOE approach** combining conventional data with NAMs-based mechanistic information **can be protective for environmental safety**;
- ☺ there is **potential for harmonizing human health and environmental safety**, encouraging synergies and cross-development of NAMs for chemical assessment and regulatory decisions.

Benefits

- ✓ replacing animal testing
- ✓ Increasing efficiency and reliability
- ✓ addressing complexity and diversity of environmental effects and exposures

Challenges

- ? demonstrating relevance of NAMs to ecological endpoints and species
- ? validating and standardizing NAMs for regulatory acceptance
- ? structuring weight-of-evidence approach

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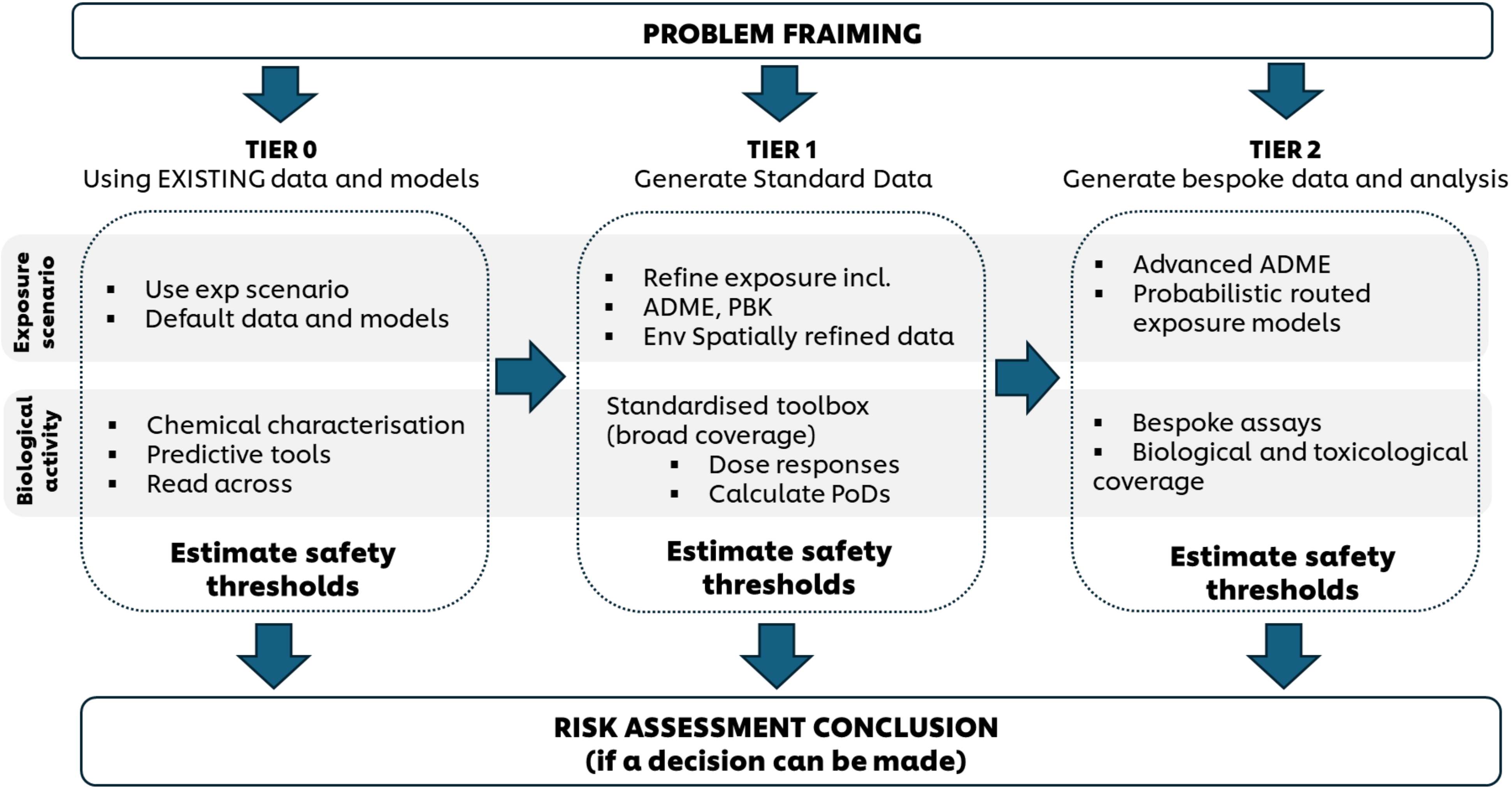
Towards integrating Human Health and Environment safety assessment



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Unlocking the future of environmental safety: a framework for integrating new approach methodologies in decision-making

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ABSTRACT

Traditional regulatory frameworks for assessing the environmental safety of chemicals have historically focused on evaluating *in vivo* data from standard ecologically representative species. This approach relies heavily on apical effect studies performed on whole organisms. However, there is now a strong regulatory and ethical push towards adopting non-animal approaches that incorporate novel methodologies and enhance the mechanistic understanding of toxicological responses across various species. Despite this progress, their implementation in environmental risk assessment remains limited.

We propose a conceptual framework for conducting safety assessments that leverages mechanistic data, extending beyond traditional types, to inform environmental safety decisions. This approach aims to support the application of new approach methodologies in environmental risk assessment, without the need for generating additional animal data. We then evaluate the approach with three case studies based on different modes of action, including 17R-Ethinyl Estradiol, Chlorpyrifos, and Tebufenozide. The overall strategy involves the collection and integration of available relevant effect data across human health and the environment to demonstrate the suitability of mechanistic-based information to support and strengthen current practices. The results demonstrate that integrating historical *in vivo* data, *in vitro* functional assays, and *in silico* computational tools enhances confidence in safety decision-making through identification of the most sensitive species where evolutionary conservation of biological targets and toxicological outcomes are in agreement. This approach offers a valuable weight-of-evidence method to understand potential toxicity effects better and points to practical future applications.

1. Introduction

Global production of chemicals is expected to double by 2030 due to the rapid increase in their use across all sectors (Alpizar et al., 2019). Ensuring the safe use of these chemicals for both humans and the environment relies on effective safety regulation grounded in robust scientific research. Conventional regulatory frameworks for assessing the environmental safety of chemicals rely on standard information requirements using a small number of model species supported by in silico determinations *e.g.* quantitative structure activity relationships (QSARs). These data are then coupled with additional safety factors to account for intra- and inter- species variability to represent the multitude of ecosystems' biodiversity, and the resulting reference values, *i.e.* predicted no effect concentrations (PNECs), are used as hazard thresholds within environmental risk assessment (ERA). Although the detail vary across geographies and chemical sectors, the aforementioned framework is regarded as the fundamental structure of ERA globally (Environment Canada, 1997, 2012; European Commission, 2003; OECD, 1995; Roast et al., 2007; USEPA, 1998).

However, the rapid scientific development observed recently has clearly outpaced the relatively slow evolution of regulatory-based requirements and frameworks (Westmoreland et al., 2022). We are now witnessing a global push towards increased protection, robustness and transparency of these assessments, aiming to deliver enhanced safety for humans and the environment (Brockmeier et al., 2017; Rivetti et al., 2020). Indeed, it could be argued whether any combination of

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Thank You

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