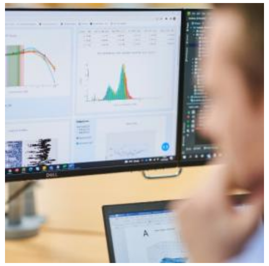
Integrating Human and Environmental Mechanistic Data to Support Safety Decisions: Identifying Synergies and Potential Challenges



Bruno Campos
(in representation of a large cross domain team…)

Unilever, Safety, Environmental & Regulatory Science,
Colworth Science Park, United Kingdom

SERS
Safety, Environmental
& Regulatory Science

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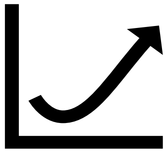
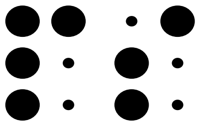
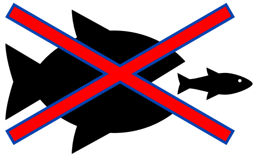
Safety science: what can we do better?



Increasing number of chemicals



Limited availability of toxicity data



Moving away from animal tests

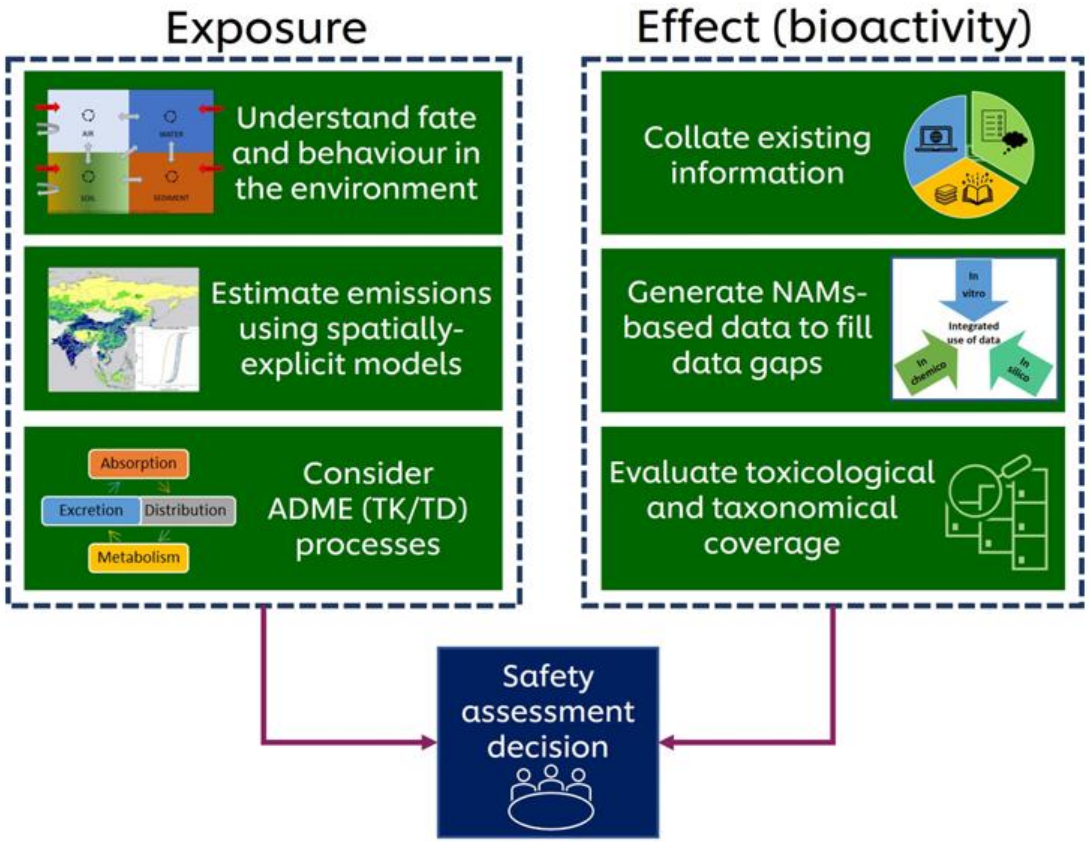
NGRA is defined as ***an exposure-led, hypothesis-driven*** *risk assessment approach that* ***integrates New Approach Methodologies (NAMs)*** *to assure* ***safety without the use of animal testing***

NAMs are NOT 1:1 replacement to animal tests

Instead 1 NAM = 1 block

different combination can address different endpoints

Establishing better 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, starting with initial assessments and refining them as more data becomes available.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Editorial

Establishing a NexGen, mechanism-based environmental risk assessment paradigm shift: Are we ready yet?

"A concerted effort and orchestration between ALL relevant stakeholders (academia, industry, civil society, regulators, and decision makers) remains the foundation for seamless science translation into fit-for-purpose tools for enhanced human and environmental protection."

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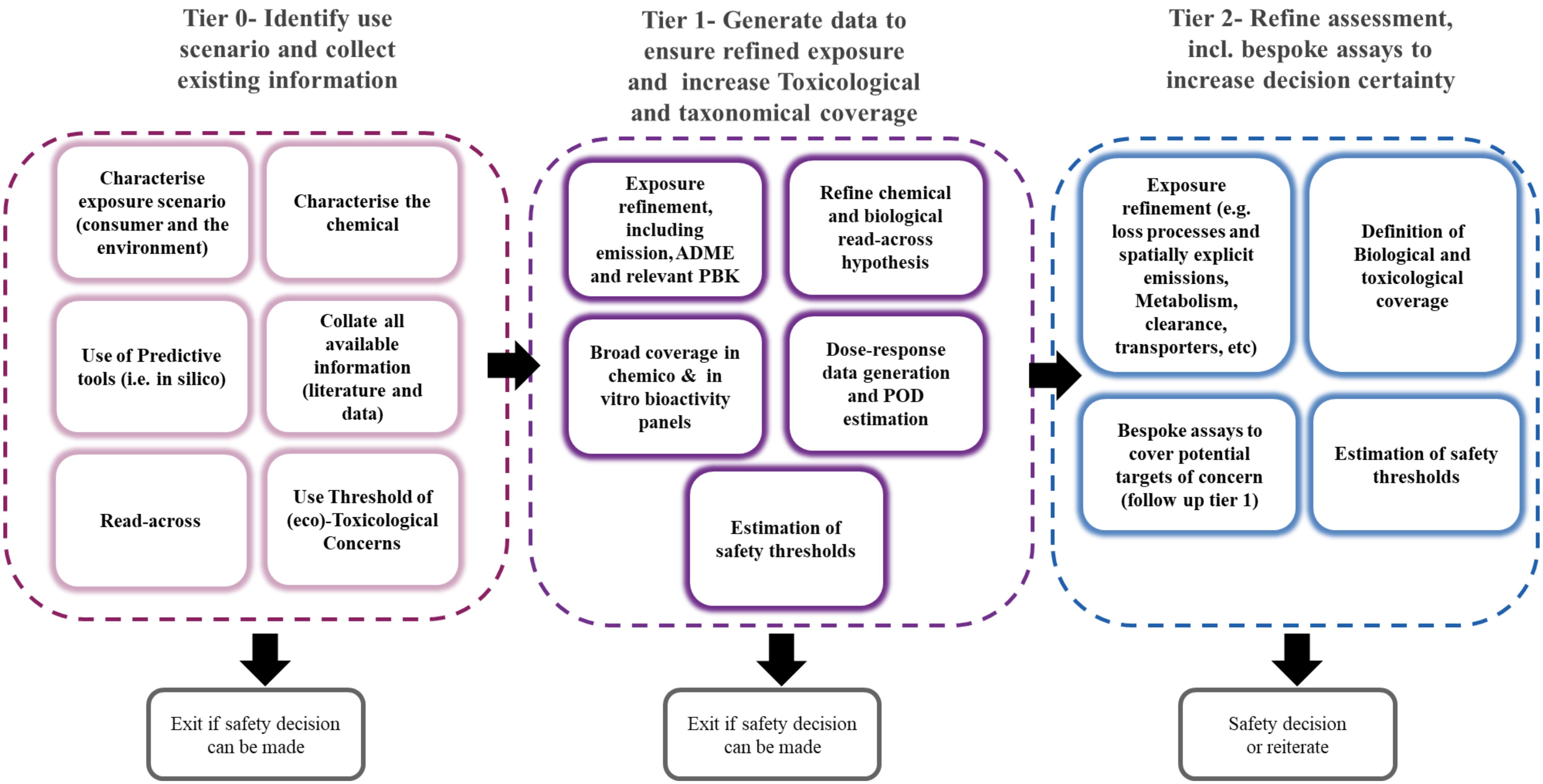
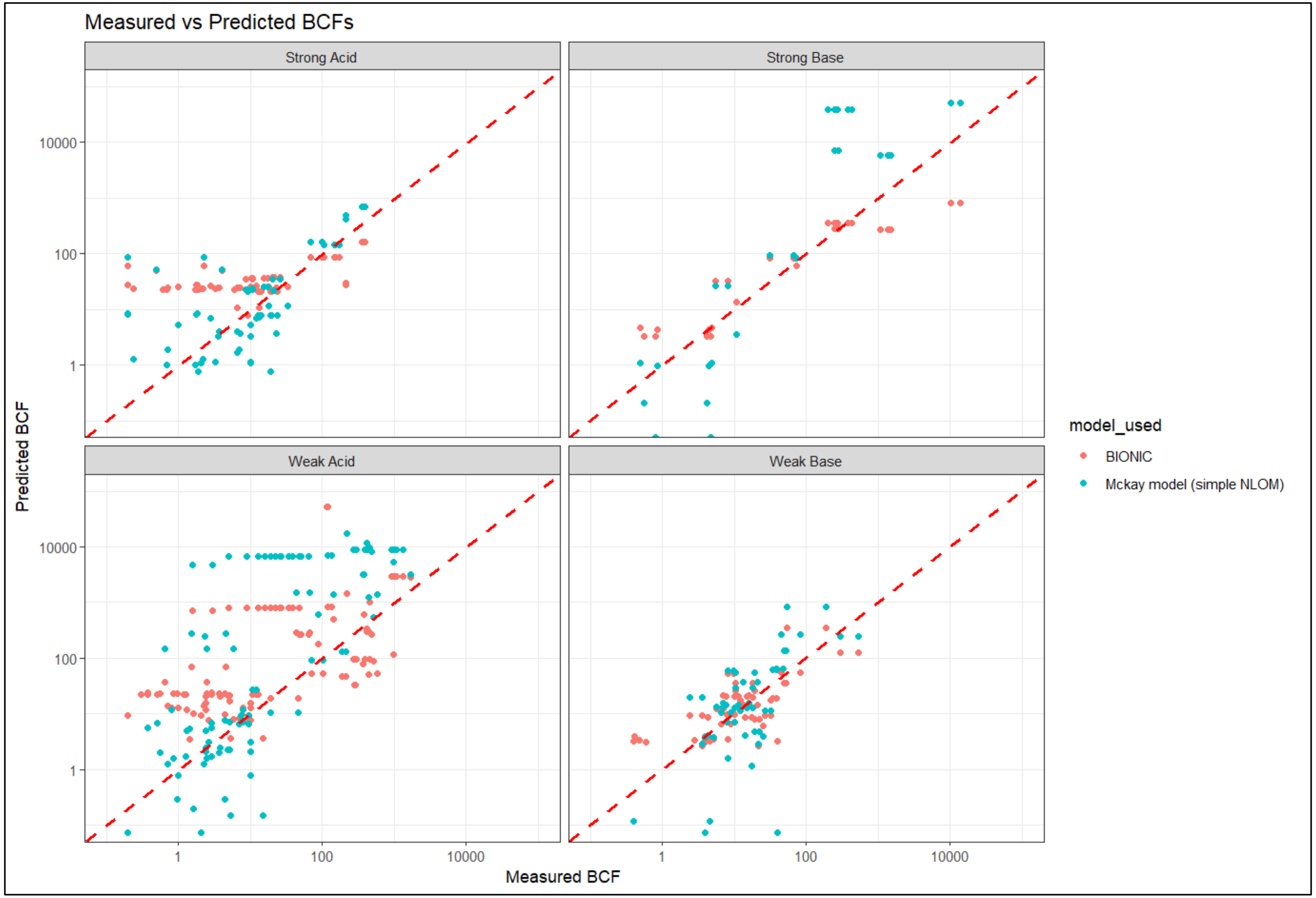
Rivetti & Campos (2023)
https://doi.org/10.1002/ieam.4763

Next generation Integrated Risk Assessment

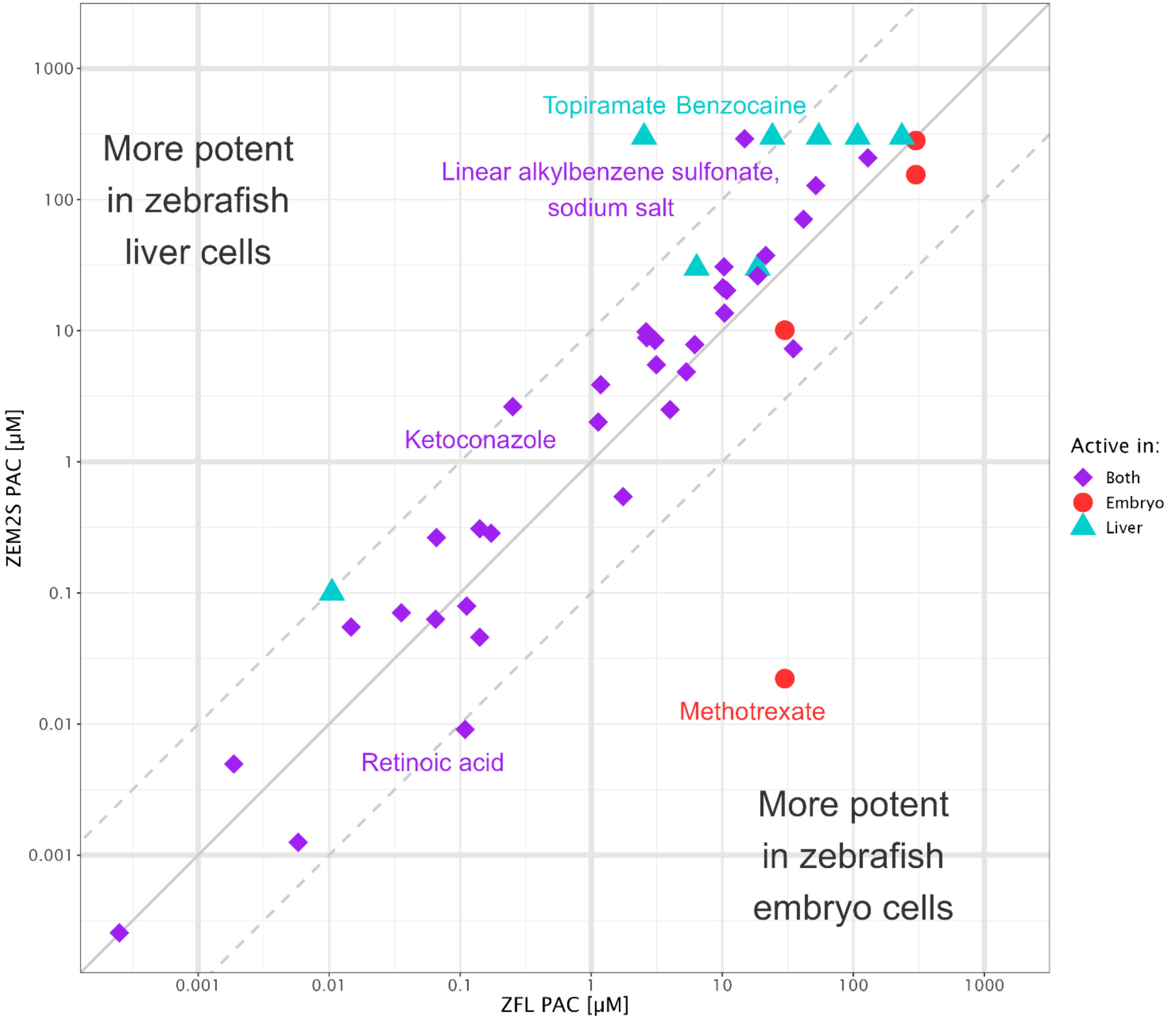


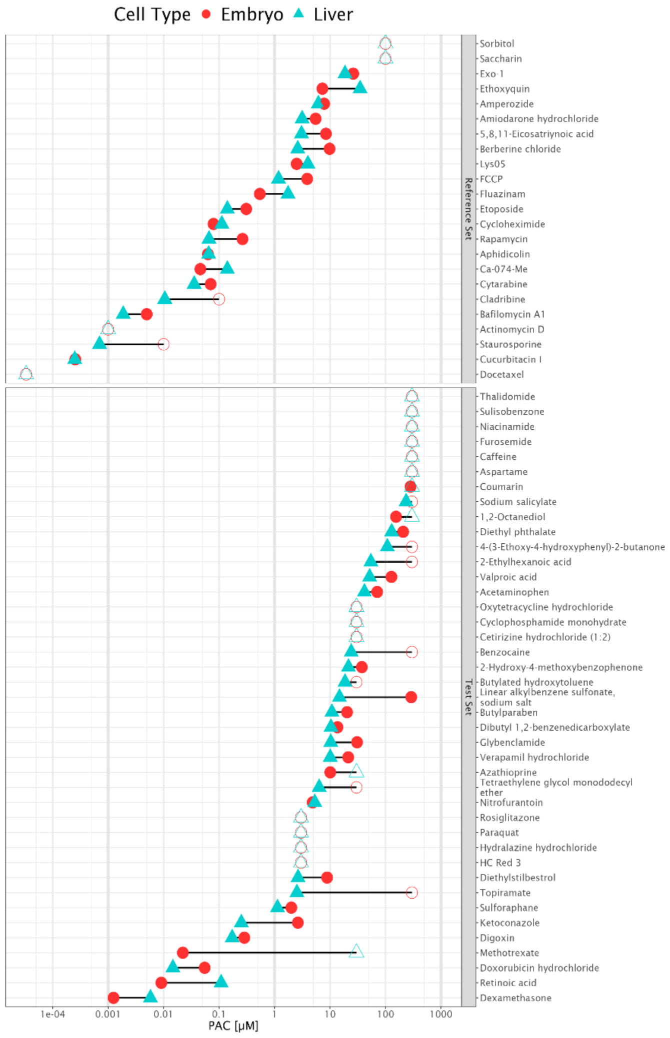
Toxicokinetics models (qIVIVE)-Evaluation



- BIONIC v3– 83% (219/263) within 10-fold (none under predicted >10 fold
- Mackay model – 67% (175/263) within 10-fold

"High-Throughput Phenotypic Profiling (HTPP) with the Cell Painting Assay to Screen Chemicals in Two Zebrafish Cell Lines."



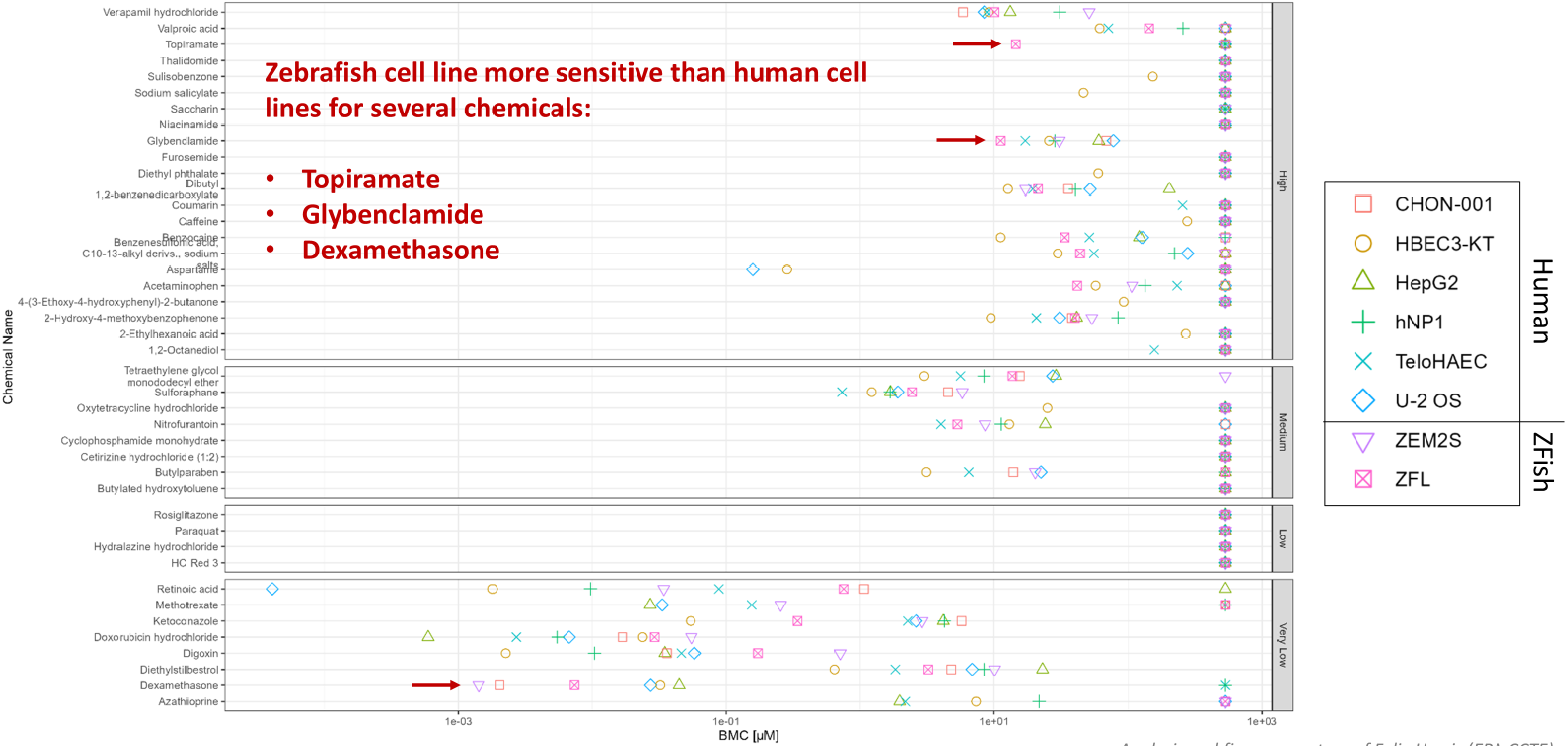


From Felix Harris, USEPA- unpublished.

Comparing HTPP Points of Departure (PoDs) from fish and human cell lines

Zebrafish cell line more sensitive than human cell lines for several chemicals:

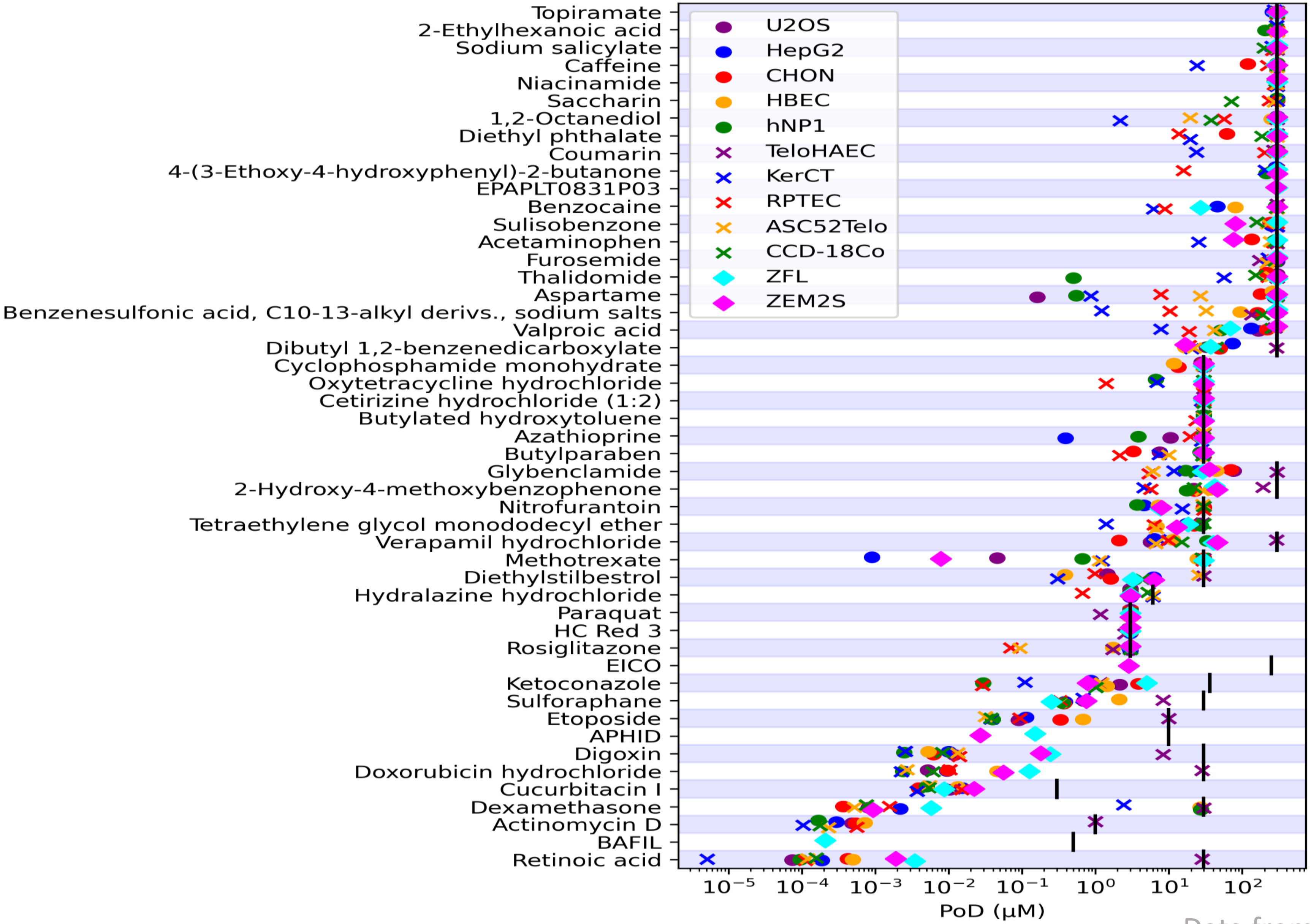
- **Topiramate**
- **Glybenclamide**
- **Dexamethasone**



Analysis and figures courtesy of Felix Harris (EPA CCTE)

!!preliminary data, do not cite!!

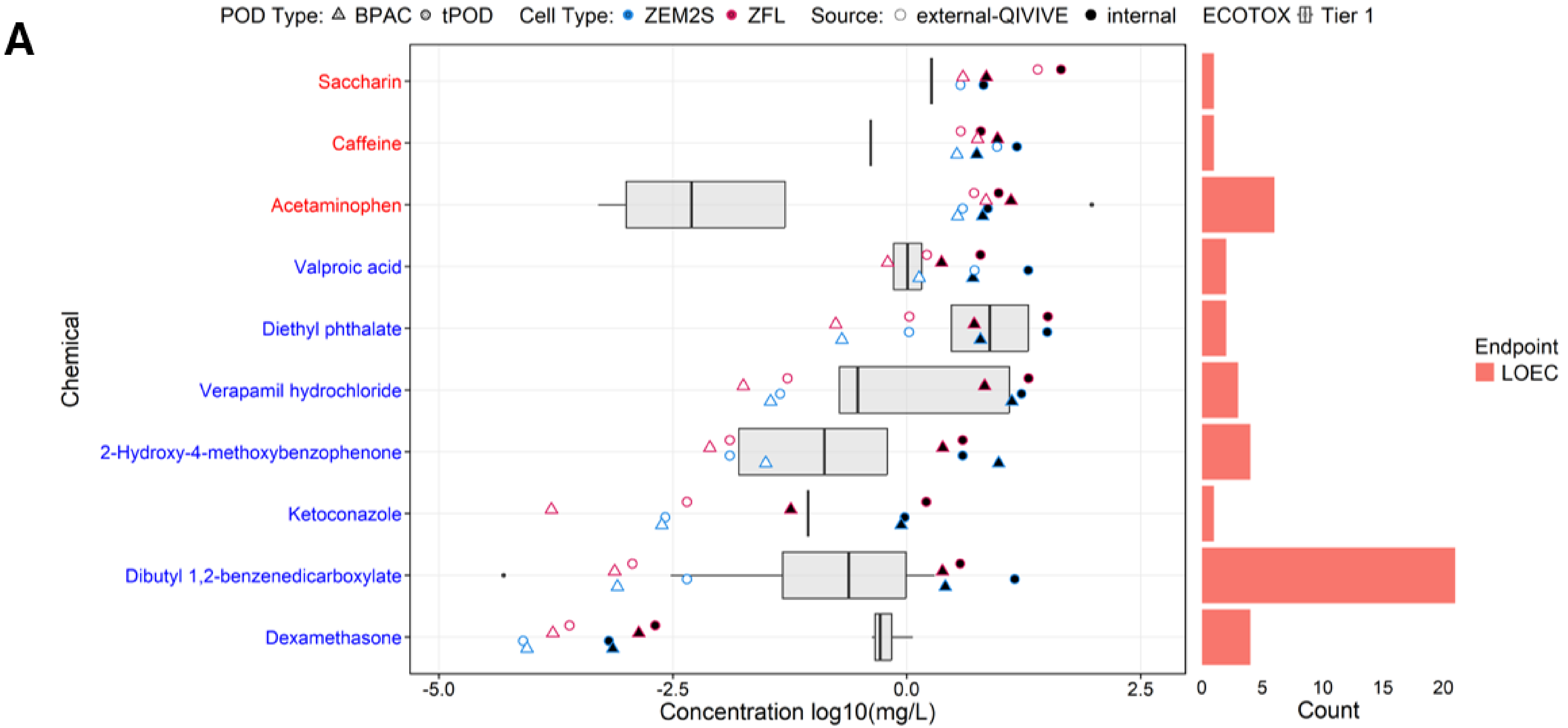
HTTr- High Throughput Transcriptomics (2 ZF +10 Human Cell lines)



Data from Harrill, Reynolds et al. unpublished

HTTr and protection levels

HTTr PoDs of 2 fish cell lines (+qIVIVE) benchmark against fish in vivo

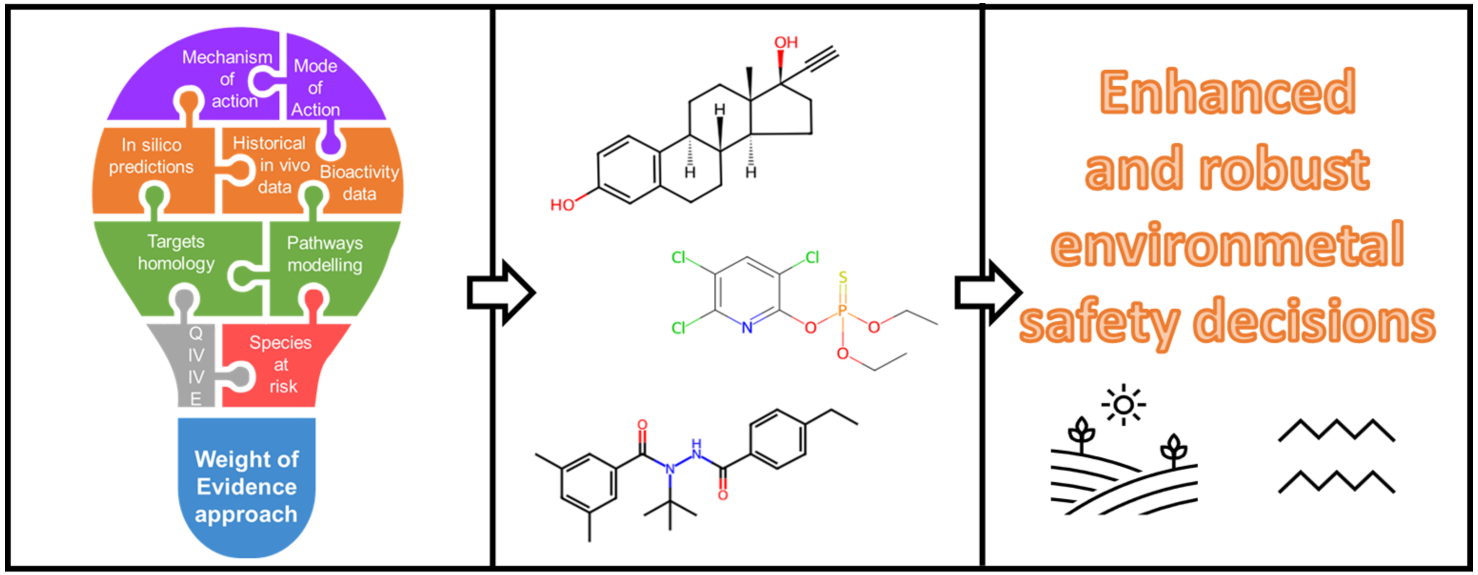


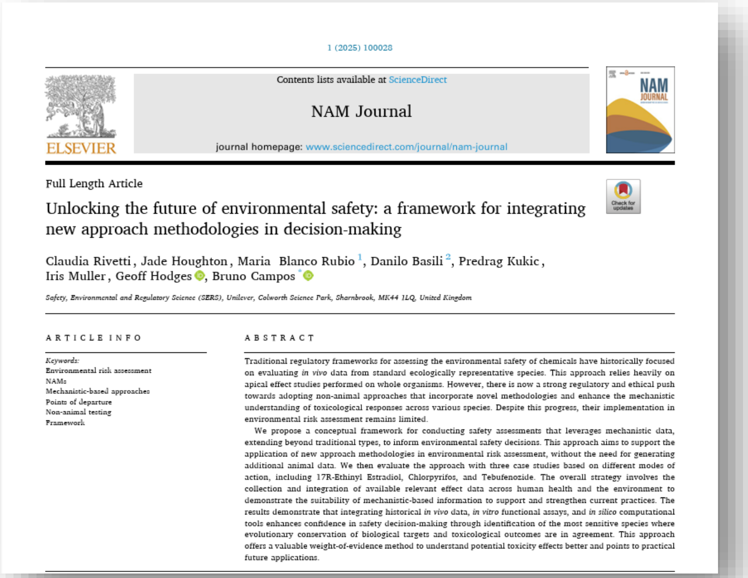
From Schumann et al., submitted

Case Studies Development

➢ 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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Full Length Article

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

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ARTICLE INFO

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Framework

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.

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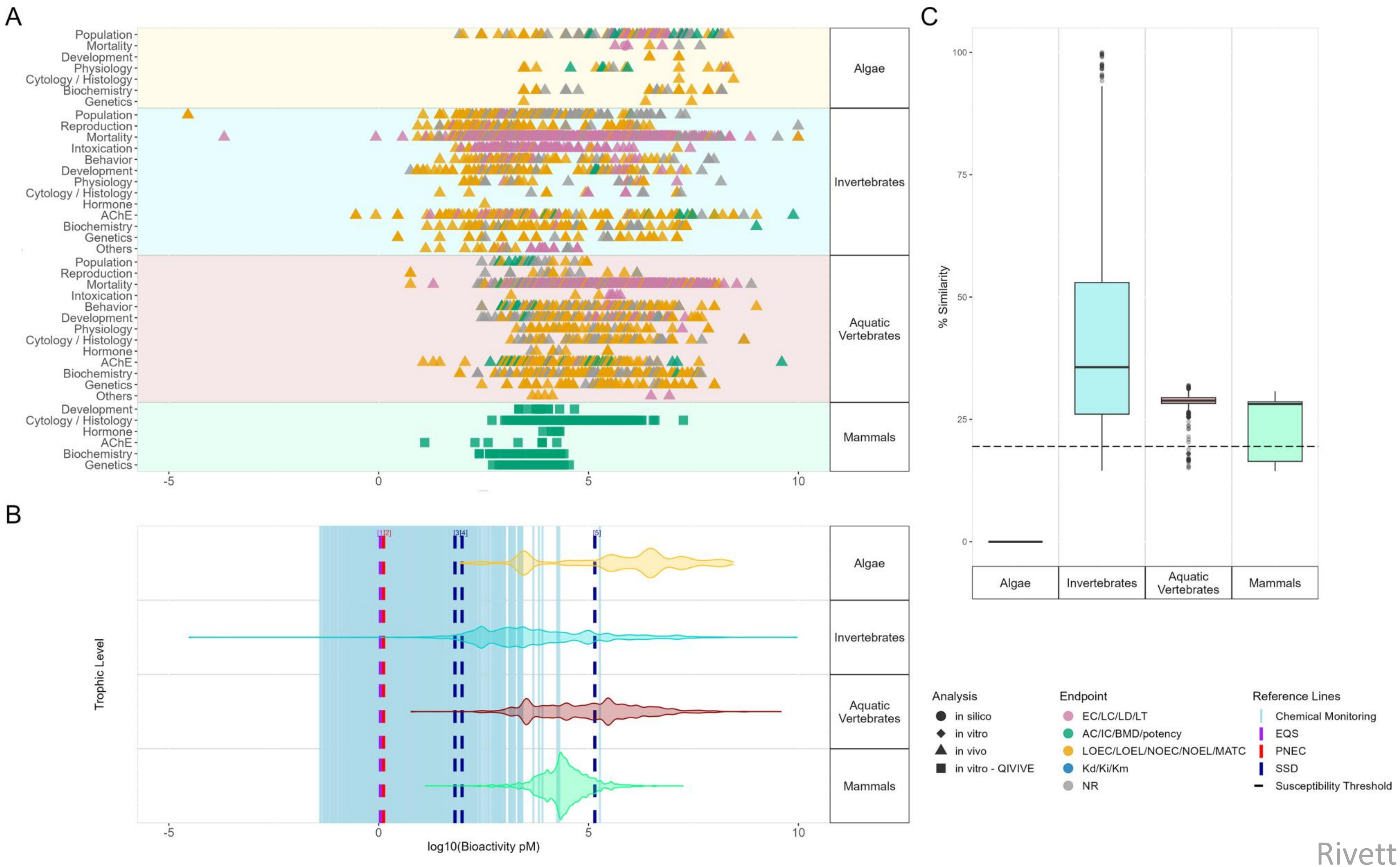
Rivetti et al. (2025)
https://doi.org/10.1016/j.namjnl.2025.100028

Chlorpyrifos

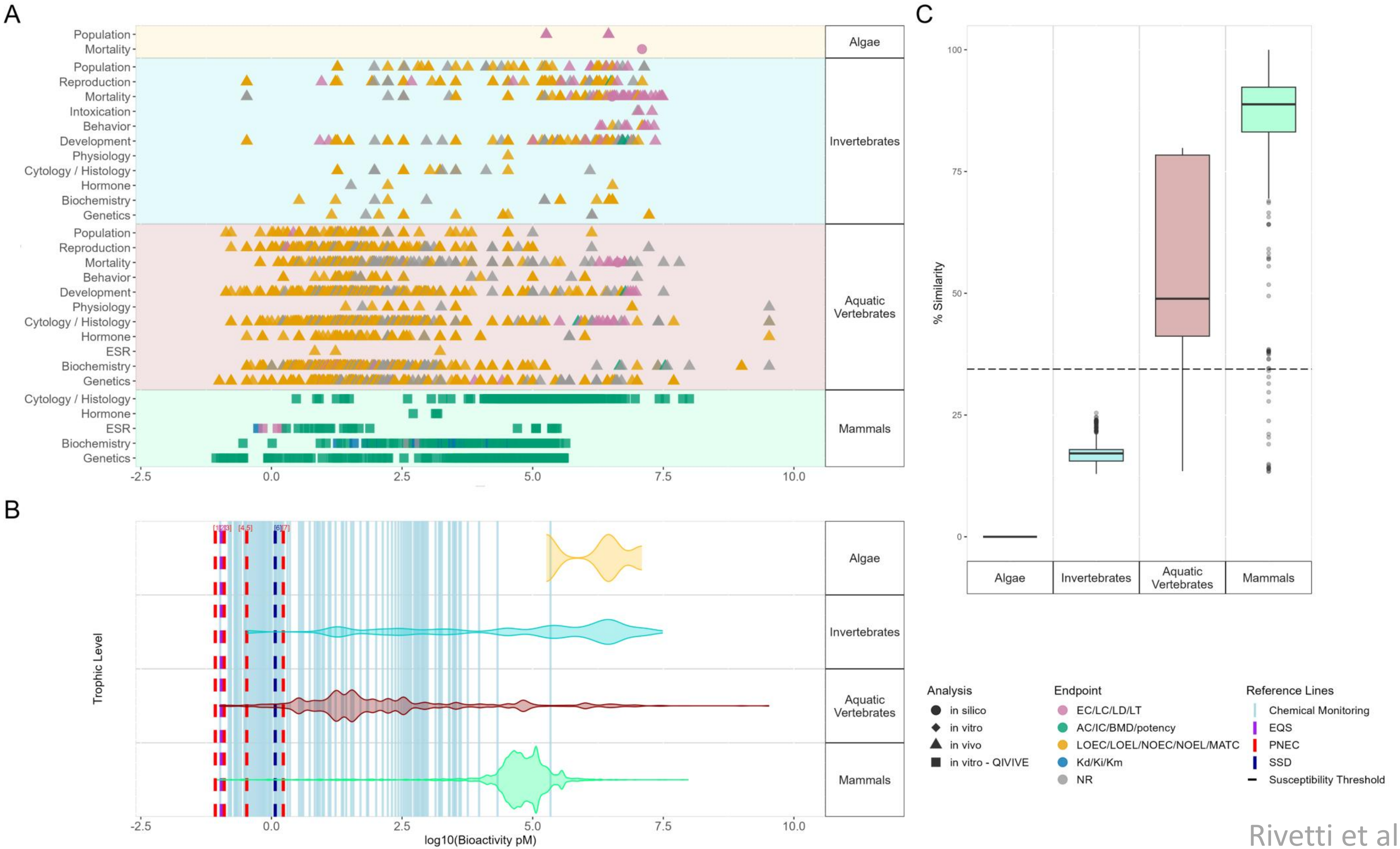
✓ A total of 10131 bioactivity data points were extracted from available sources



Rivetti et al. (2025)

Ethynyl Estradiol

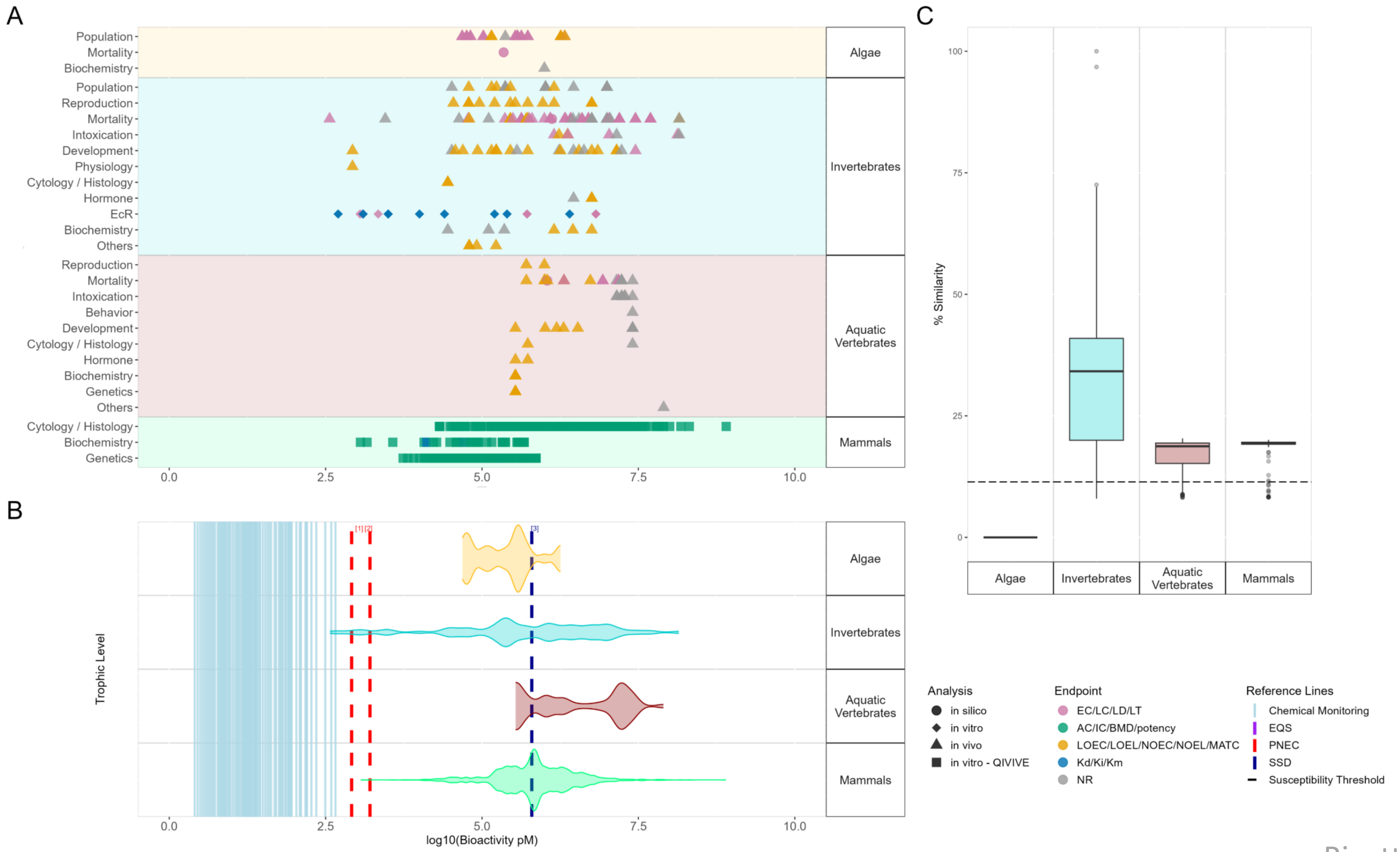
✓ A total of 8004 bioactivity data points were extracted from available sources



Rivetti et al. (2025)

Tebufenozide

✓ 2,129 bioactivity data points were extracted from various sources



Rivetti et al. (2025)

Take-home messages

- ☺ there is potential for harmonizing human health and environmental safety, encouraging synergies and cross-development of NAMs for chemical assessment and regulatory decisions.
- ☺ WOE approach combining conventional data with NAMs-based mechanistic information can be protective for environmental safety while leveraging all available information

Benefits

- ✓ reduce / replace animal testing
- ✓ increase the efficiency and reliability of chemical safety assessment
- ✓ address the complexity and diversity of environmental effects and exposures

Challenges

- ✓ ensure the relevance and applicability of NAMs to ecological endpoints and species
- ✓ validate and standardize NAMs for regulatory acceptance and harmonization
- ✓ integrate and interpret NAMs data in a weight-of-evidence approach

The team

Unilever: Claudia Rivetti, Jade Houghton, Maria Blanco Rubio, Danilo Basili, Predrag Kukic, Iris Muller, Geoff Hodges, Jacob Collins, Patrik Engi, Tym Pietrenko, Dawei Tang, Ans Punt, Maria Baltazar, Matt Dent, Gavin Maxwell and many more

US EPA: Peter G. Schumann, Joseph Bundy, Derik E. Haggard, Logan Everett, Joshua A. Harrill, Felix Harris, David Ryoo, Carlie A. LaLone

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