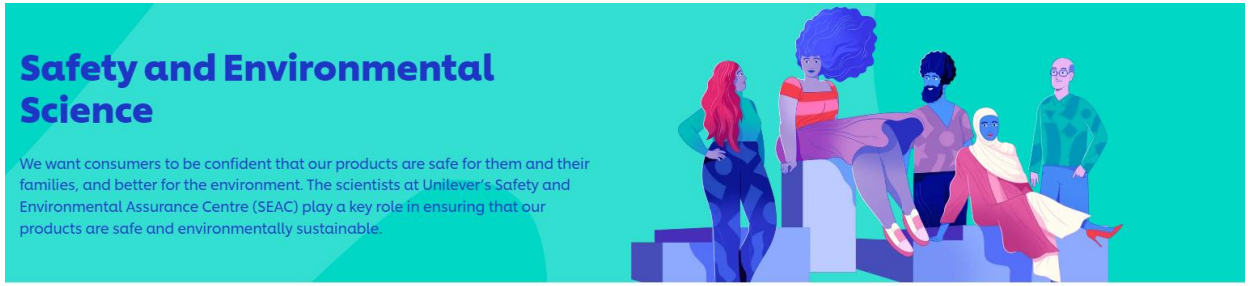
STRATEGY TO DELIVER A MECHANISTIC BASED, NEXT GENERATION ENVIRONMENTAL SAFETY ASSESSMENT PARADIGM SHIFT

Dr Bruno Campos



Leading safety and environmental sustainability sciences
The scientists behind our safe and sustainable products

Safe and sustainable by design
How we build safety and sustainability into every product innovation.

Keeping people and the environment safe
The science-based approaches we use to keep our consumers, workers and the environment safe.

Reducing our environmental impact
How we harness the latest science to minimise our environmental footprint.

Unilever

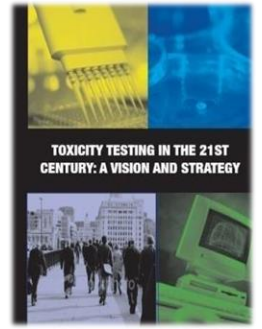
Ensuring that the use of ingredients in our products is **safe** for the receiving environment **YET...**

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)** and **spatially explicit modelling** to assure **safety without the use of animal testing***



Unilever

Establishing better environmental protection through NGRA

Exposure

Understand fate and behaviour in the environment

Estimate emissions using spatially-explicit models

Consider ADME (TK/TD) processes

Effect (bioactivity)

Collate existing information

Generate NAMs-based data to fill data gaps

Evaluate toxicological and taxonomical coverage

Safety assessment decision

Rivetti & Campos, IEAM 2023

Examples of selected endpoints and available methods

Bioaccumulation	Toxicity to fish	Endocrine disruption
Bioaccumulation in fish: OECD 305	Acute toxicity to juvenile fish: OECD 203	Fish 2 generations: OECD 240
Bioaccumulation in terrestrial oligochetes: OECD 317	Chronic toxicity to fish: OECD 204, 210, 212, 229	Fish sexual development: OECD 229, 230, 234, 240, 148
In vitro clearance trout hepatocytes: OECD 319	Fish cell line acute toxicity: OECD 249	Amphibians: OECD 231, 241
Bioaccumulation in *Halella azteca*: draft test guideline	Fish embryo acute toxicity: OECD 236	Fish embryo estrogen activity (EASZY): OECD 250
TKTD models	In vitro method for chronic toxicity: NONE	Xenopus Eleutheroembryo Thyroid Assay (XETA): OECD 248
		Androgen Disruption Adverse outcome Reporter (Medaka fish) (RADAR): OCDE 251
		Invertebrates: OECD 201, 211, 242, 243 218-219, 222, 220, 225, 226, 232 Relevance?
		Effects on vertebrate progeny for cosmetics: NONE

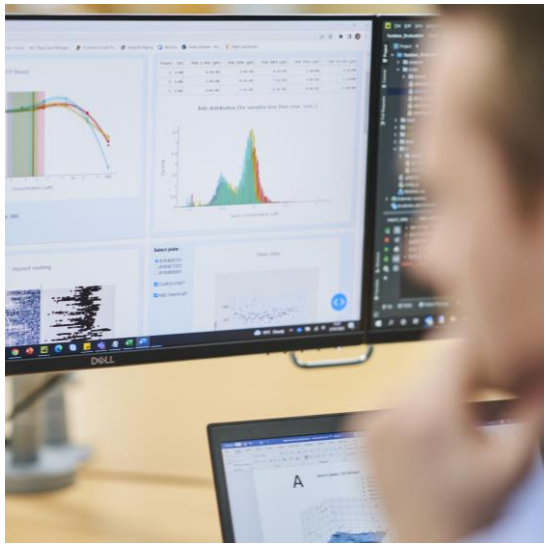
In silico models

Adapted from Veronique Poulsen 2023

Hazard characterization – the future

New approach methodologies (NAMs) are defined as

" any non-animal technology, methodology, approach or combination thereof that can be used to provide information on chemical hazard and human risk assessment" (Dent et al., 2018).



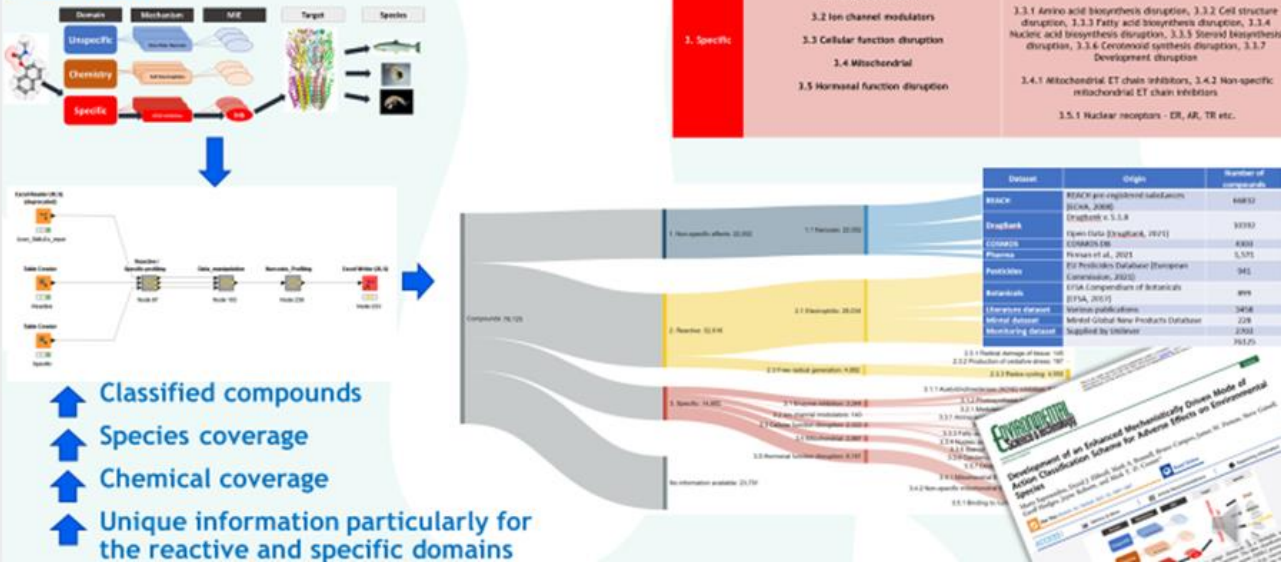
- ✓ ***in silico*** (e.g. QSAR, PBK models, machine learning models and artificial intelligence)
- ✓ ***in vitro*** (cell cultures, organoids and other micro-physiological systems)
- ✓ ***in chemico*** (i.e. abiotic methods aimed at identifying chemical reactivity)

Adapted from Miccoli et al. (2022) EFSA Journal

Some examples: Grouping and read-across: chemical and biological based

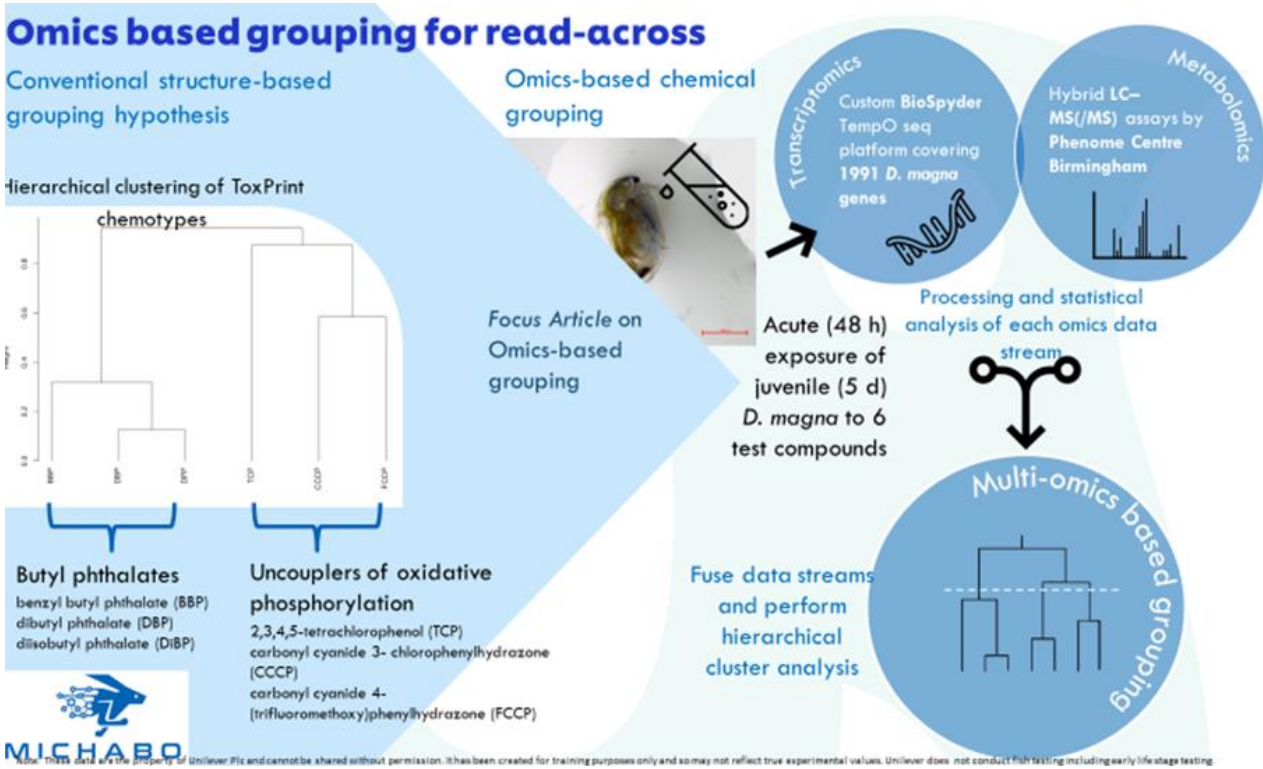
MIE/ MechoA profiling

To reduce the proportion of compounds that receive an "unclassified" by current schemes enabling more robust grouping/ read-across/ prioritisation



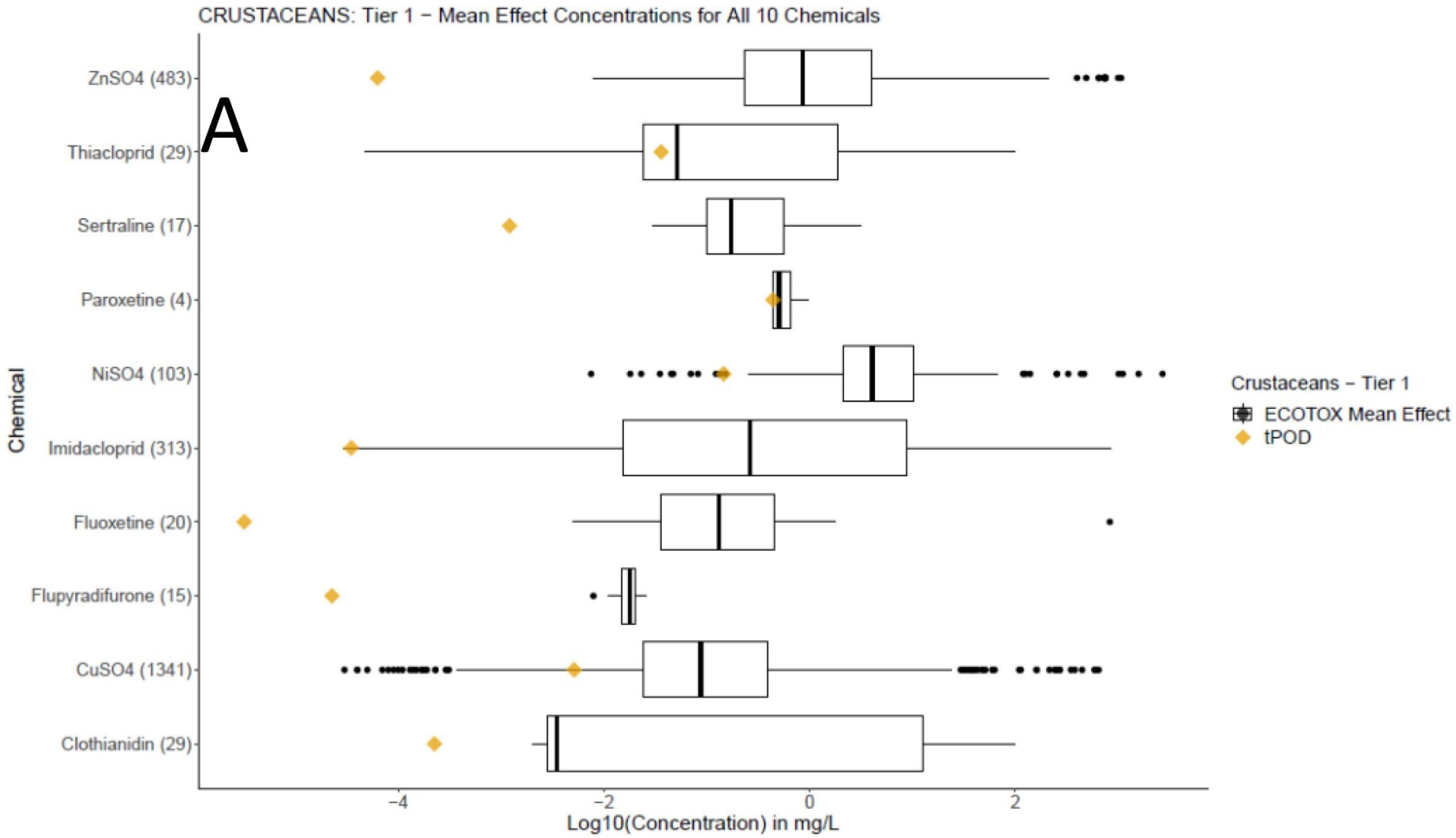
Sapounidou et al. (2021) EST

Omics based grouping for read-across



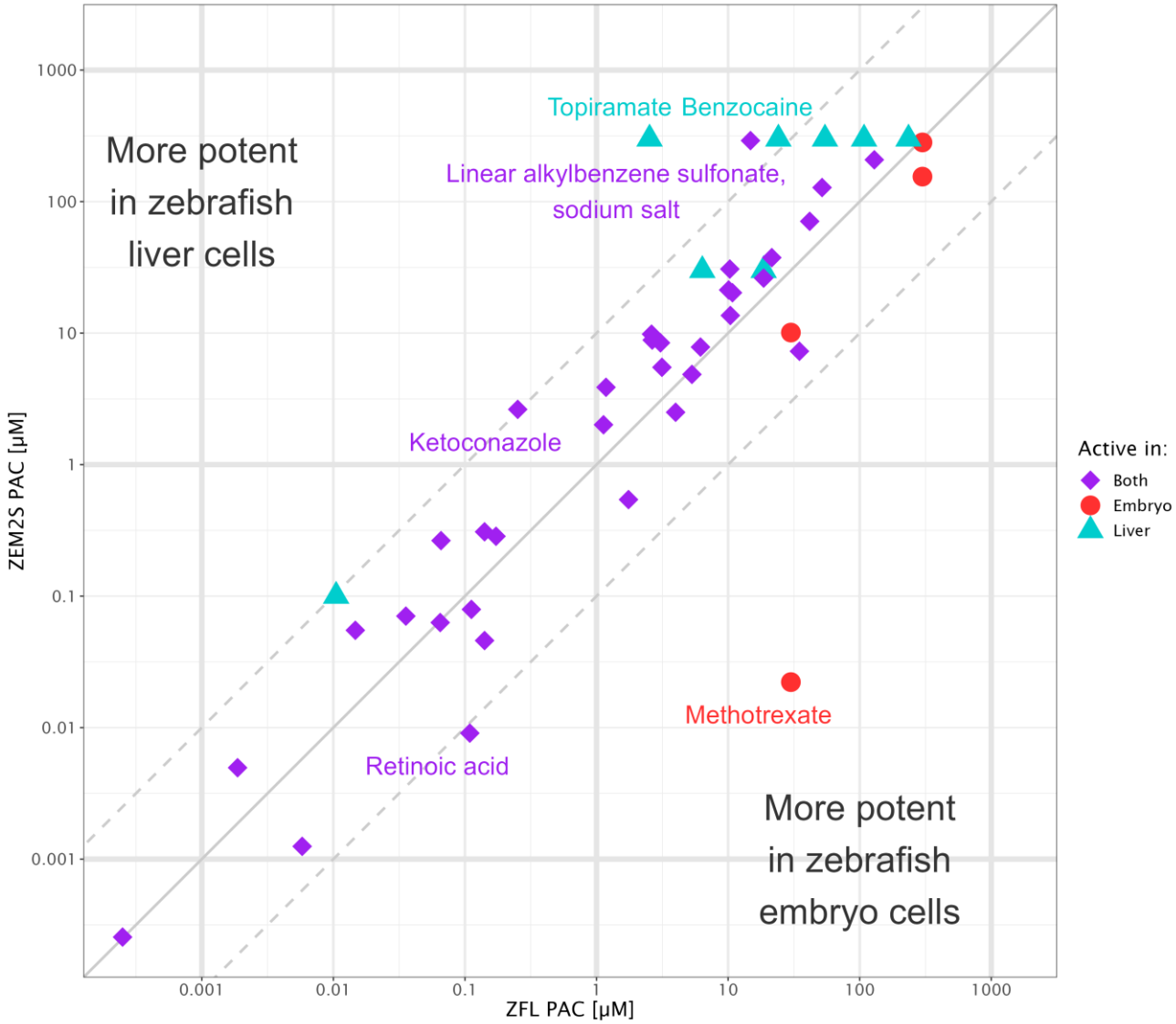
Viant et al. (2024) ET&C

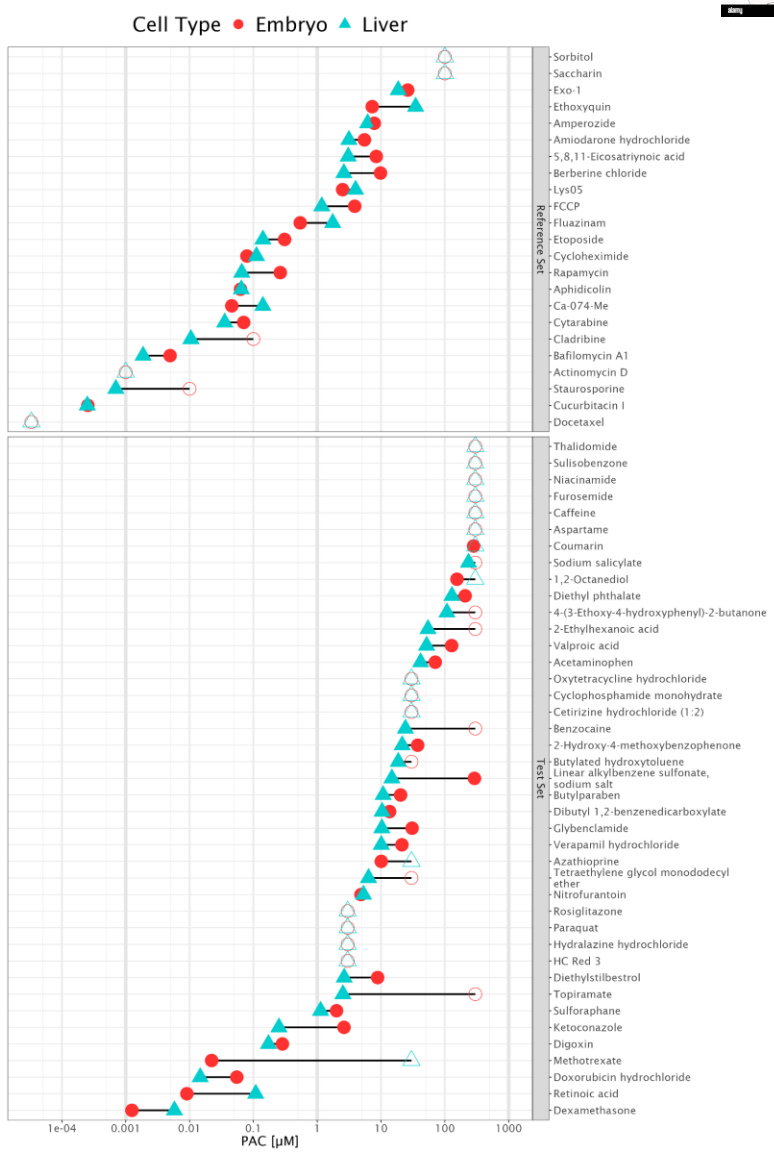
Some examples: OMICs and protectiveness



From Villeneuve et al. (2023) Curr. Res. Tox.

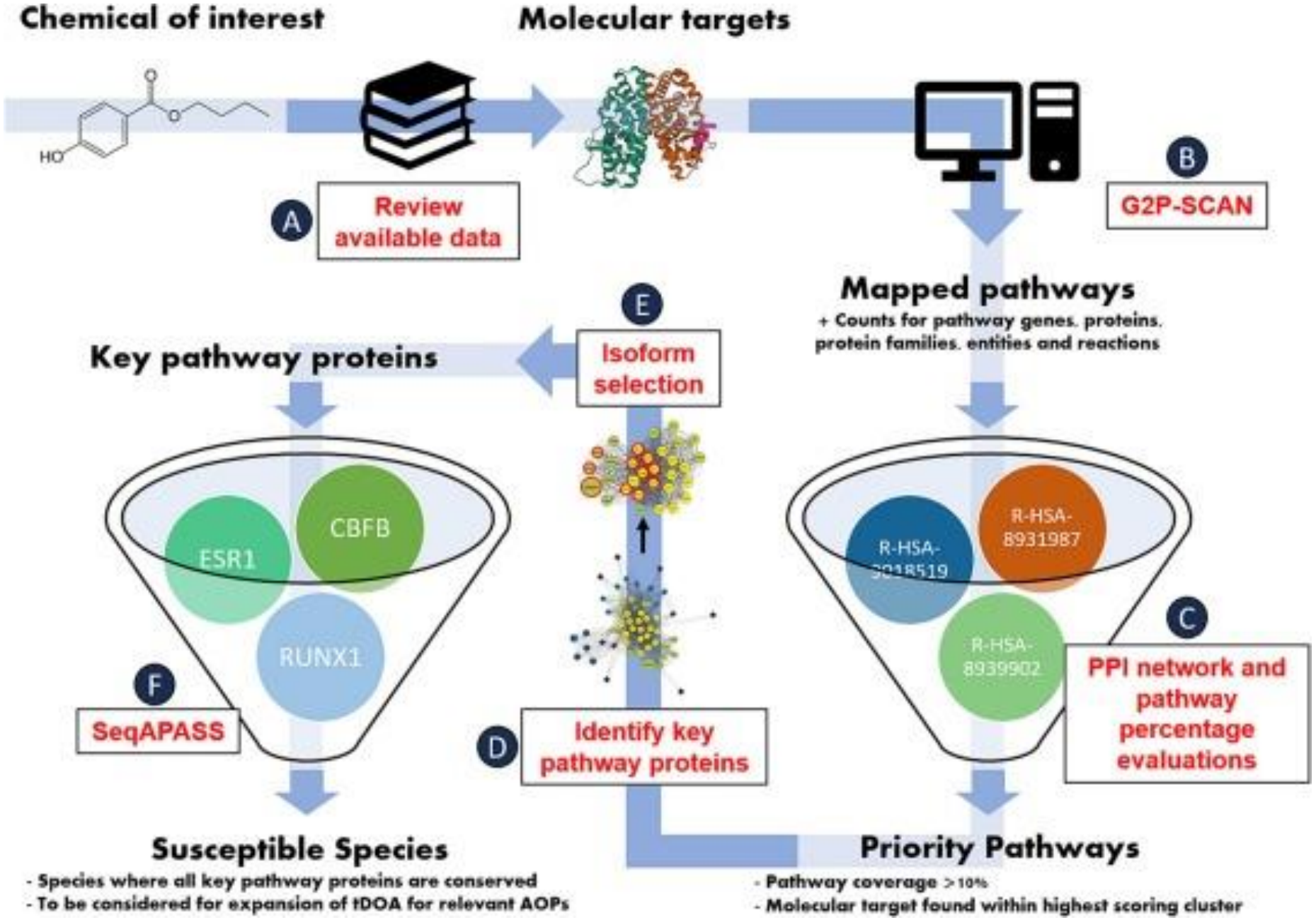
Screening Chemicals Using High-Throughput Phenotypic Profiling (HTPP) in Two Zebrafish Cell Lines





From Villeneuve et al. (2023) Curr. Res. Tox.

Some examples: Defining the taxonomical applicability domain



Schuman et al. (2024) STOTEN

Some examples: Weight of Evidence

Fish Acute

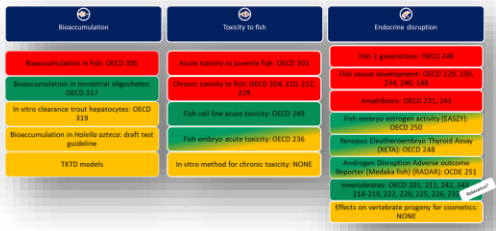
- State of the art MoA/ MechoA identification (in-silico profilers, Critical Membrane Burden/ Critical Body Burden/ 'Omics etc.)
  - State of the art grouping/read-across (e.g. omics based grouping)
  - In silico/ QSAR approaches – $logK_{MW}$/$logK_{OW}$ etc.
- In-vitro assays / cell based profiler panels (e.g. RTgill cell (OECD TG 249))
  - PBK/ TK modelling
- Pathway based mechanisms of toxicity across species (X-spp extrapolation/ species sensitivity)
- Exposure thresholds (e.g. EcoTTC)
- Understanding species sensitivity – distributions
- Complementary approaches proposed in the OECD Fish IATA (e.g. Threshold approach)

Fish Chronic

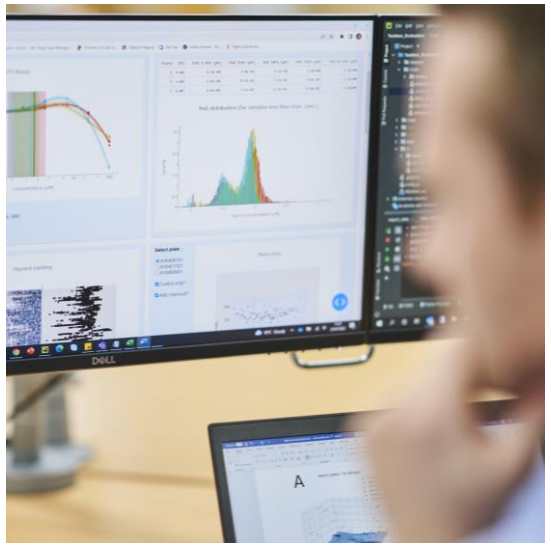
- Approaches as per Fish Acute + the following
  - Acute to Chronic ratios
  - Exposure based waiving – consideration of EcoTTC, biodegradation rates etc.

Fish BCF

- In silico modelling (e.g. BIONIC)
  - Biotransformation measurements - S9/hepatocyte assay (OECD TG 319A/B)
  - Empirical and/or in-silico derivation of relevant partitioning parameters e.g. $logK_{ow}$ and/or $logK_{mw}$
  - Empirical and/or in-silico derivation of pKa
- Non vertebrate bioaccumulation assays (*Hyalella azteca*, RT-gill cell line etc.)
- Exposure based waiving – consideration of removal/biodegradation rates etc and fate in environment



Case study: A proof of concept to demonstrate the applicability of mechanistic info in Environmental safety assessment



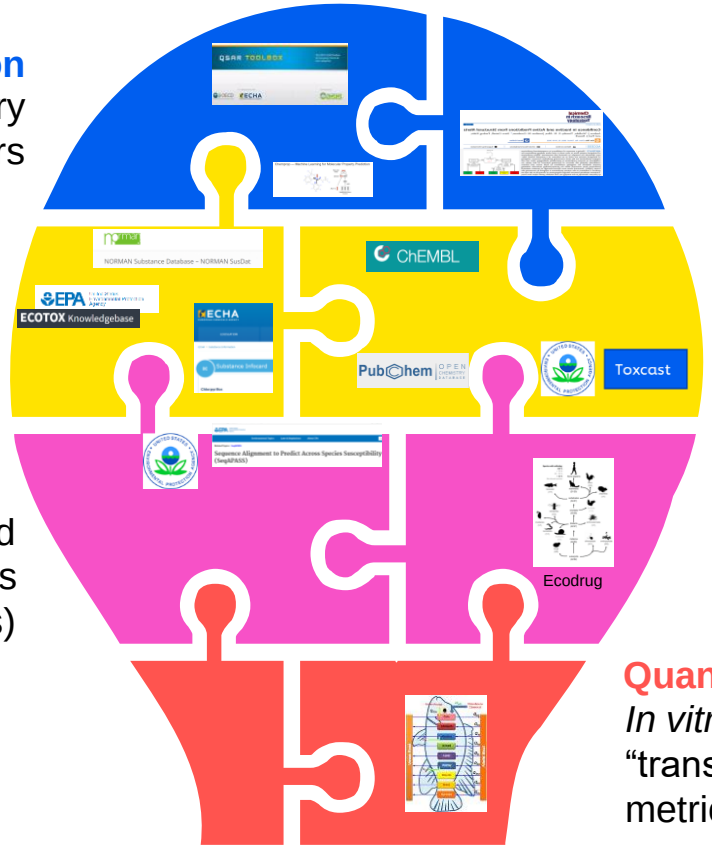
Unilever

Information collection process

Mode of Action identification
Using available scientific and regulatory information and in silico profilers

Species at risk identification
Use of publicly available tools and databases to identify susceptible species (based on targets and processes)

Weight Of Evidence approach
Collate all the information in an intelligible way to guide and support decisions

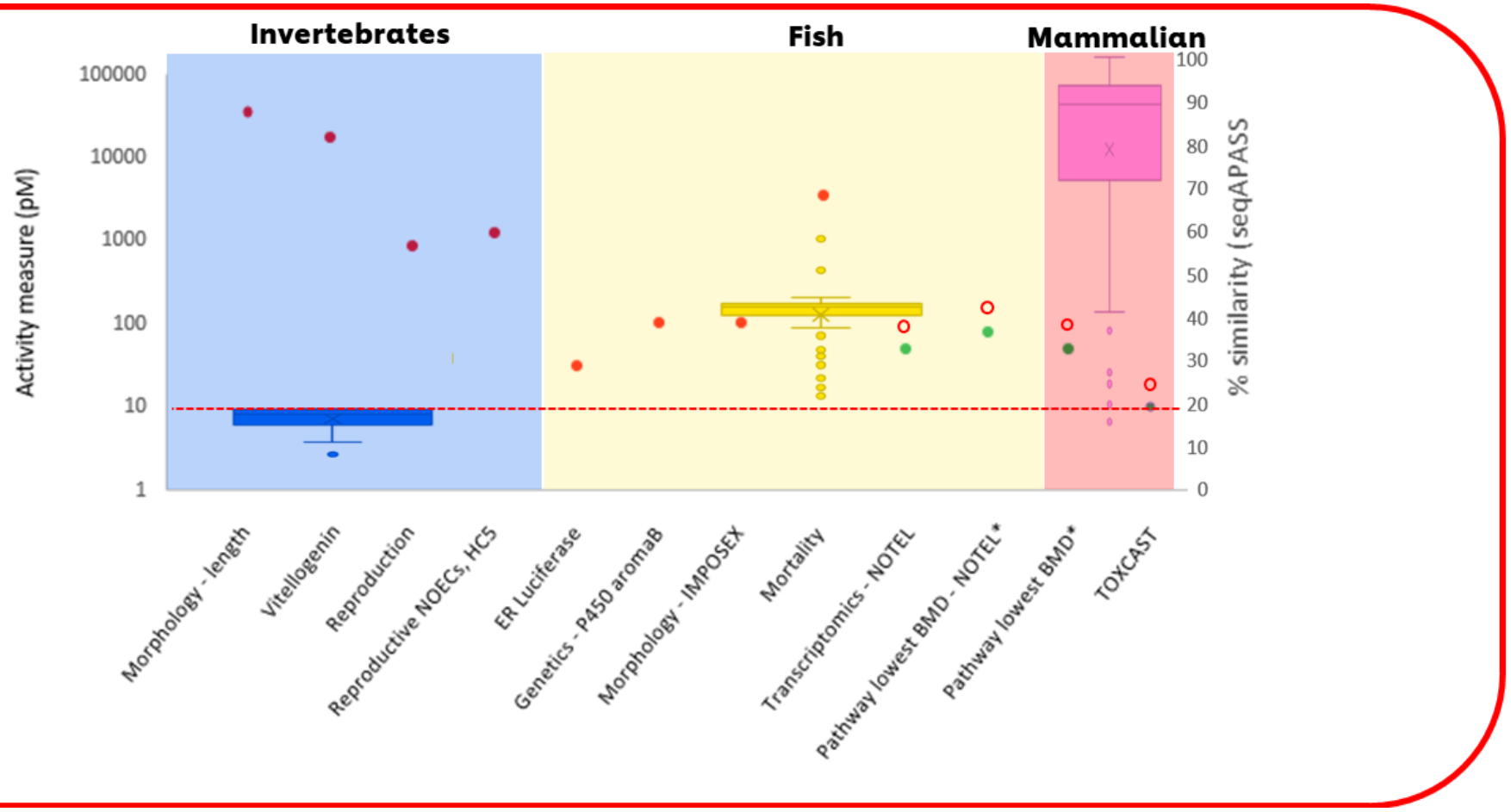


Hazard Data
Including historical *in vivo* as well as *in vitro* data and *in silico* predictions to generate relevant PoD

Quantitative In Vitro to In Vivo Extrapolation
In vitro and *in vivo* exposures must be "transformed" into comparable exposure metrics requiring robust qIVIVE models

WoE-based decision

Case study- Ethinylestradiol



Rivetti et al. (2024) in preparation

Take-home messages

- **Understanding exposure is critical** to for Next Generation Risk Assessment.

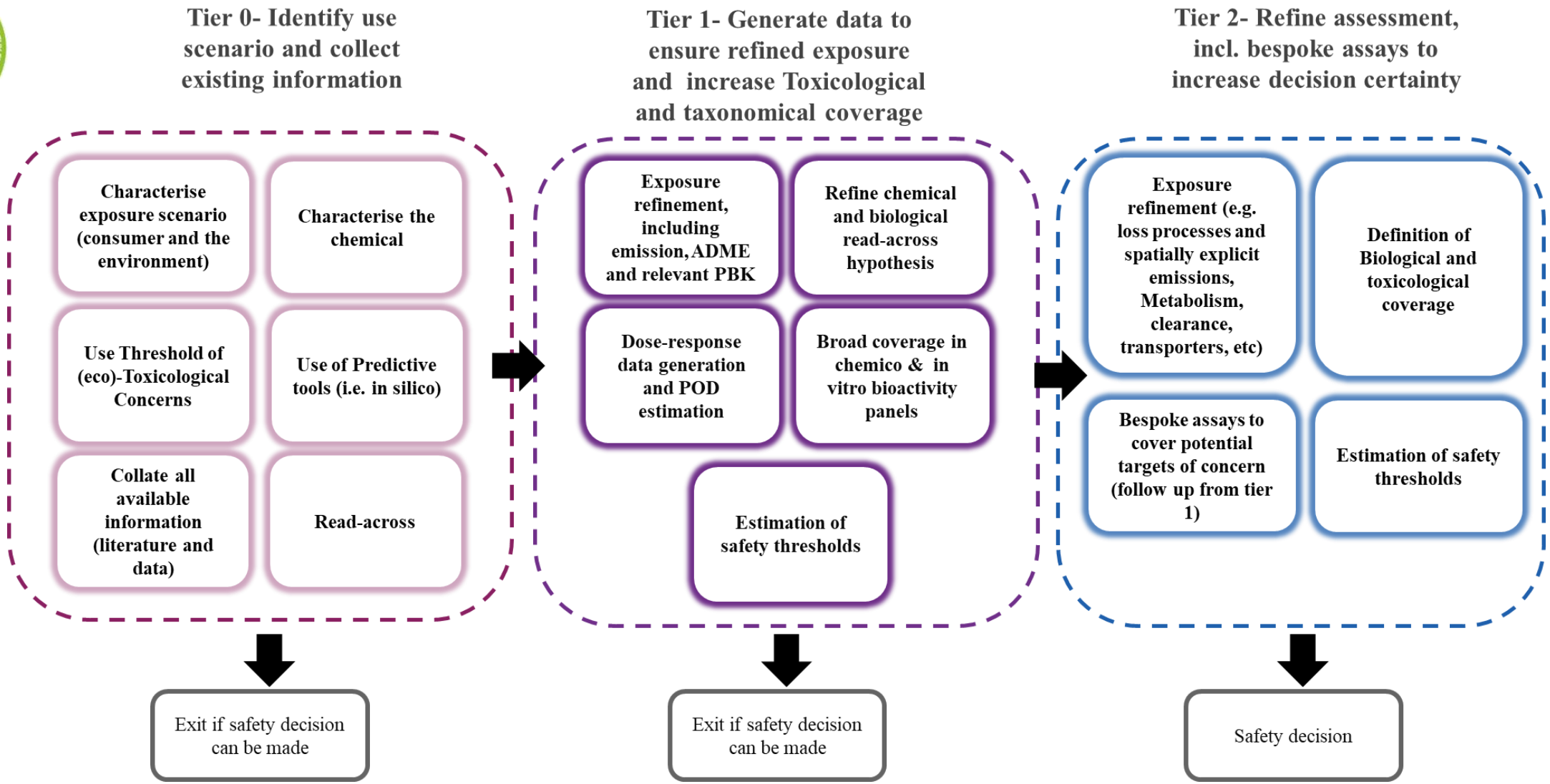
- Tangible **opportunities** already available to improve environmental protection by applying **spatially explicit exposure**, **NAMs** and **weight of evidence** approaches.

- **Mechanistic understanding allows to move away from black box studies / models** to better understand **fate and distribution of chemicals** and their potential **impacts on organisms and ecosystem's**.

- There are **challenges** to address particularly in **standardisation and training** needs within user communities (Risk Assessors and Regulatory bodies)

Unilever

First step– developing a common framework & language



adapted from *Baltazar et al.* 2020

Thank You

"the team"

- Emilia Gattas
- Nicola Furmanski
- Jayne Roberts
- Claudia Rivetti
- Alexandre Teixeira
- Chris Finnegan
- Ian Malcomber
- Juliet Hodges
- David Gore
- Jade Houghton
- Katie Endersby
- Predrag Kukic
- Iris Muller
- Simran Sandhu
- Baile Xu
- Matt Dent
- Maria Baltazar
- Paul Carmichael
- and many more...

All underpinned by SEAC science, its scientists and our scientific partners

seac.unilever.com