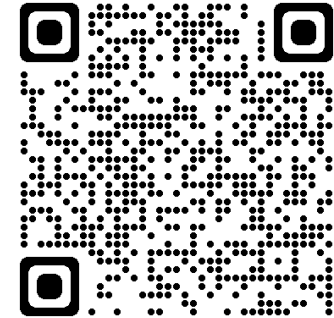
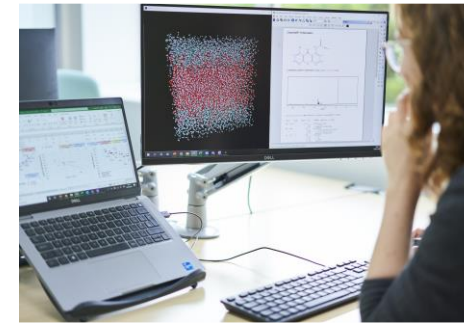


# STRATEGY TO DELIVER A MECHANISTIC BASED, NEXT GENERATION ENVIRONMENTAL SAFETY ASSESSMENT PARADIGM SHIFT

Dr Bruno Campos



## Safety and Environmental Science

We want consumers to be confident that our products are safe for them and their families, and better for the environment. The scientists at Unilever's Safety and Environmental Assurance Centre (SEAC) play a key role in ensuring that our products are safe and environmentally sustainable.



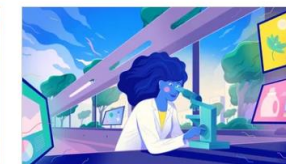
### Leading safety and environmental sustainability sciences

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

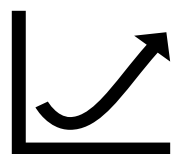
The science-based approaches we use to keep our consumers, workers and the environment safe.



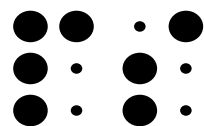
### Reducing our environmental impact

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

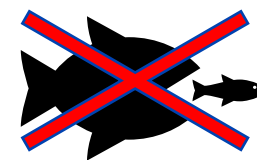
Ensuring that the use of ingredients in our products is **safe**  
for the receiving environment **YET...**



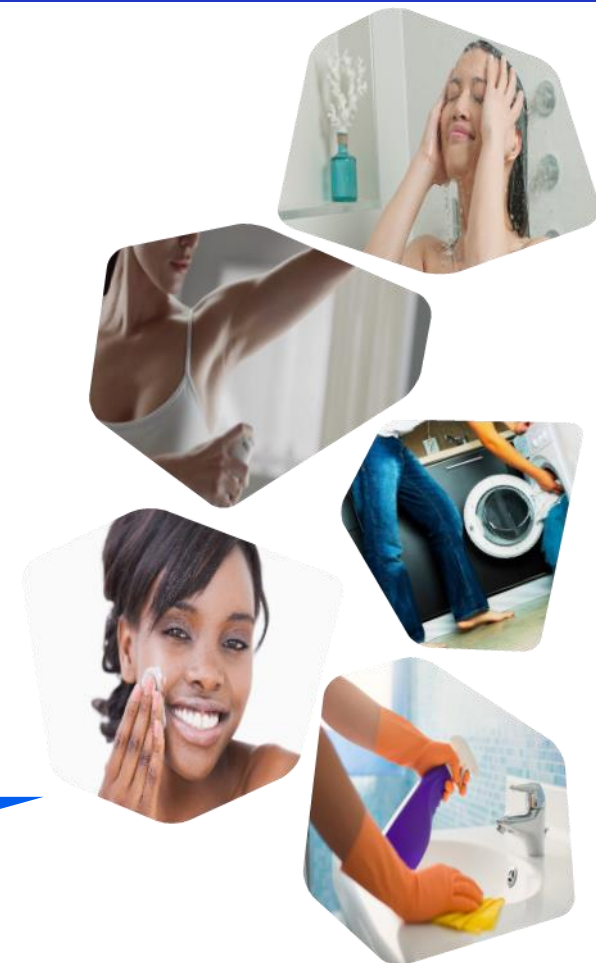
Increasing  
number of  
chemicals



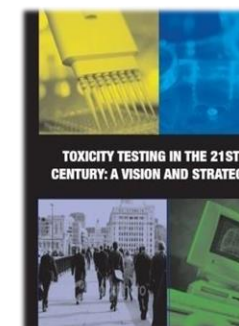
Limited  
availability of  
toxicity data



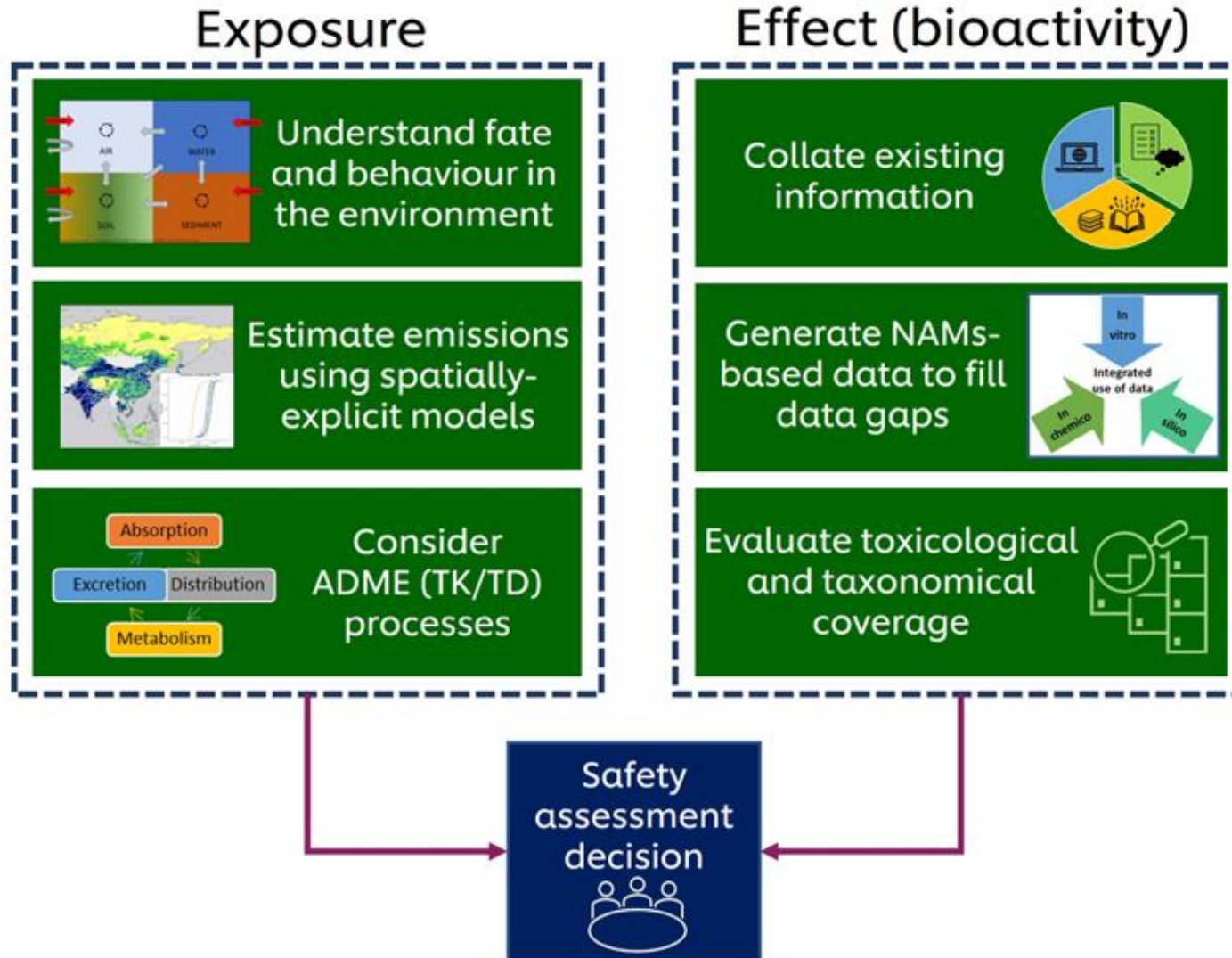
Moving  
away from  
animal tests






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***

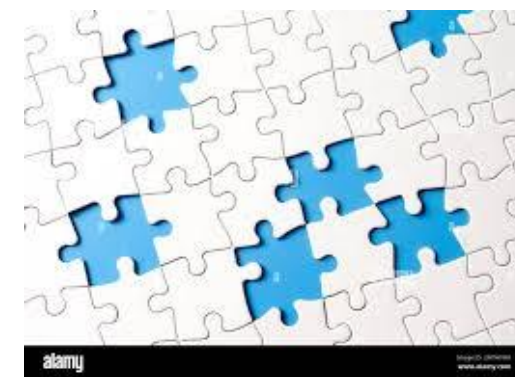


## Establishing better environmental protection through NGRA



## Examples of selected endpoints and available methods

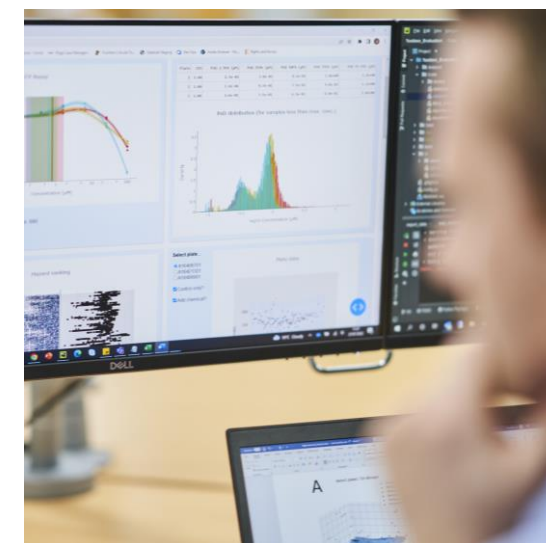
 Bioaccumulation	 Toxicity to fish	 Endocrine disruption
Bioaccumulation in fish: OECD 305	Acute toxicity to juvenile fish: OECD 203	Fish 2 generations: OECD 240
Bioaccumulation in terrestrial oligochetes: OECD 317	Chronic toxicity to fish: OECD 204, 210, 212, 229	Fish sexual development: OECD 229, 230, 234, 240, 148
In vitro clearance trout hepatocytes: OECD 319	Fish cell line acute toxicity: OECD 249	Amphibians: OECD 231, 241
Bioaccumulation in <i>Halella azteca</i> : 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 <small>Relevance?</small>
		Effects on vertebrate progeny for cosmetics: NONE
In silico models		

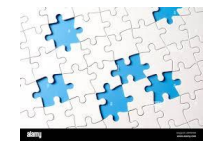


New approach methodologies (NAMs) are defined as

***“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](#)).

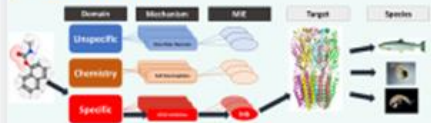
- ✓ ***in silico*** (e.g. QSAR, PBK models, machine learning models and artificial intelligence)
- ✓ ***in vitro*** (cell cultures, organoids and other micro-physiological systems)
- ✓ ***in chemico*** (i.e. abiotic methods aimed at identifying chemical reactivity)





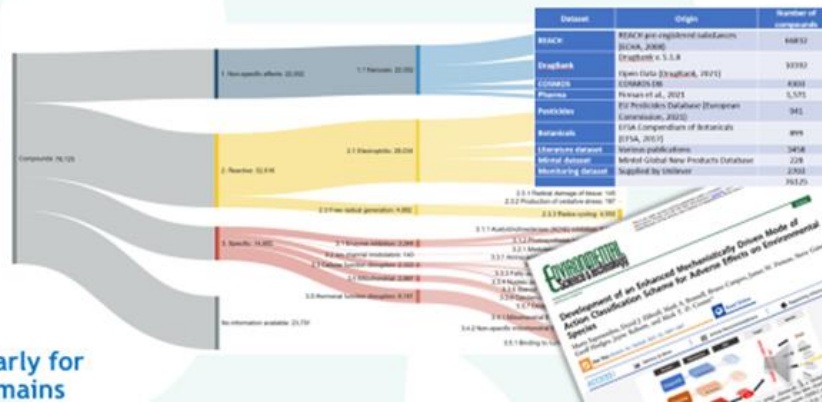
## MIE/ MechoA profiling

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



- ↑ Classified compounds
- ↑ Species coverage
- ↑ Chemical coverage
- ↑ Unique information particularly for the reactive and specific domains

Domain	Mechanistic Group	
1. Unspecific	1.0 Narcosis	1.0.1 Non-polar, 1.0.2 Polar, 1.0.3 Ester, 1.0.4 Amine
	1.1 Uncoupling	1.1.1 Other
2. Reactive / Chemistry based	2.1 Electrophilic	2.1.1 Soft, 2.1.2 Hard, 2.1.3 Pre-reactive
	2.2 Free radical generation	2.2.1 Radical damage of tissues, 2.2.2 Production of oxidative stress, 2.2.3 Redox cycling
3. Specific	3.1 Enzyme inhibition	3.1.1 AChE inhibition, 3.1.2 Photosynthesis inhibition
	3.2 Ion channel modulators	3.2.1 Modulation of ion channels
	3.3 Cellular function disruption	3.3.1 Amino acid biosynthesis disruption, 3.3.2 Cell structure disruption, 3.3.3 Fatty acid biosynthesis disruption, 3.3.4 Nucleic acid biosynthesis disruption, 3.3.5 Steroid biosynthesis disruption, 3.3.6 Carotenoid synthesis disruption, 3.3.7 Development disruption
	3.4 Mitochondrial	3.4.1 Mitochondrial ET chain inhibitors, 3.4.2 Non-specific mitochondrial ET chain inhibitors
	3.5 Hormonal function disruption	3.5.1 Nuclear receptors - ER, AR, TR etc.



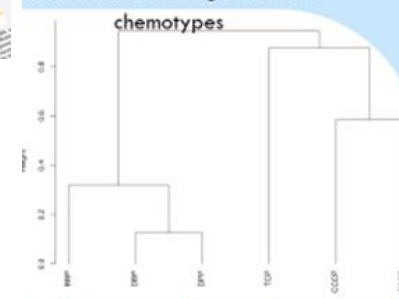
Sapounidou et al. (2021) EST

## Omics based grouping for read-across

Conventional structure-based grouping hypothesis

Omics-based chemical grouping

Hierarchical clustering of ToxPrint



Butyl phthalates

- benzyl butyl phthalate (BBP)
- dibutyl phthalate (DBP)
- diisobutyl phthalate (DiBP)

Uncouplers of oxidative phosphorylation

- 2,3,4,5-tetrachlorophenol (TCP)
- carbonyl cyanide 3- chlorophenylhydrazone (CCCP)
- carbonyl cyanide 4-(trifluoromethoxy)phenylhydrazone (FCCP)



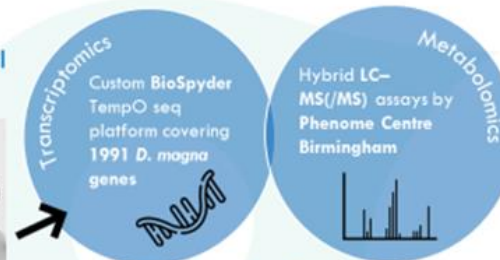
Focus Article on Omics-based grouping

Acute (48 h) exposure of juvenile (5 d) *D. magna* to 6 test compounds

Processing and statistical analysis of each omics data stream

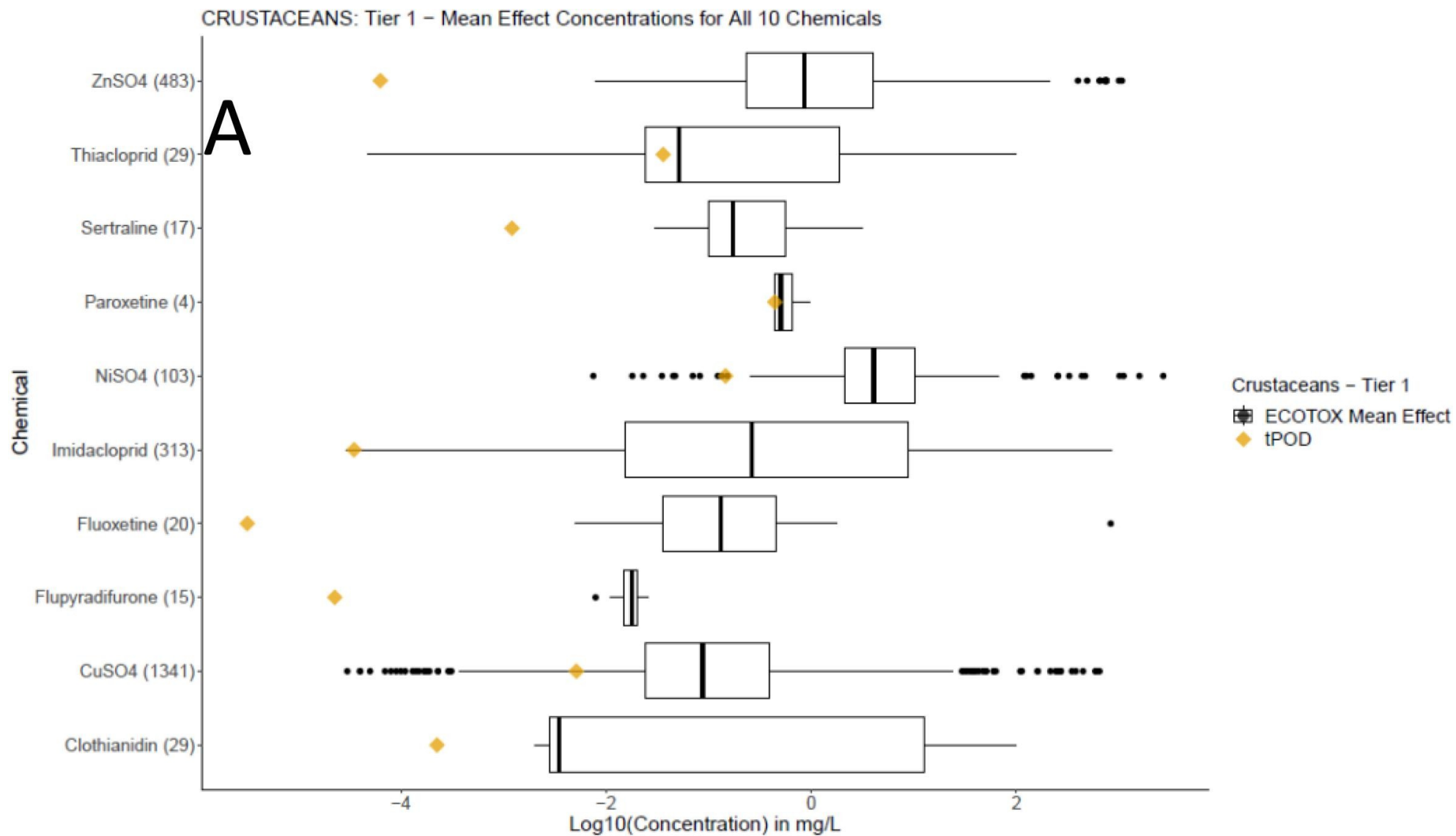
Fuse data streams and perform hierarchical cluster analysis

Multi-omics based grouping



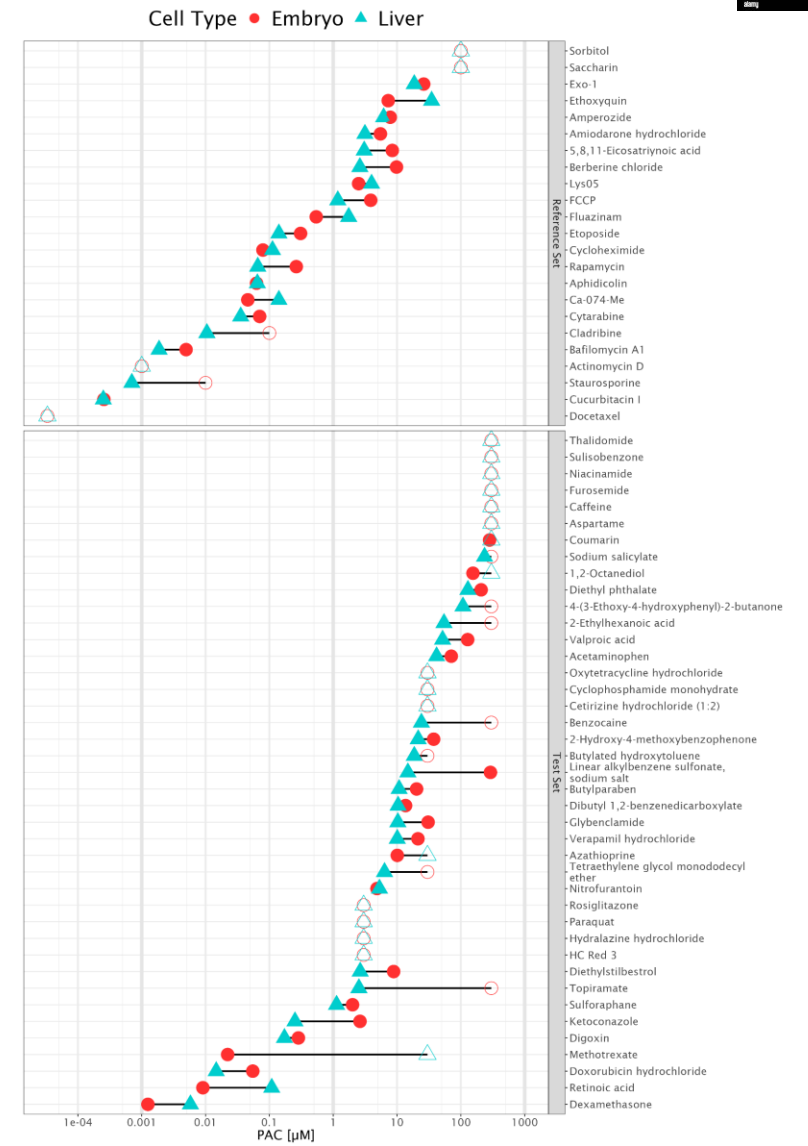
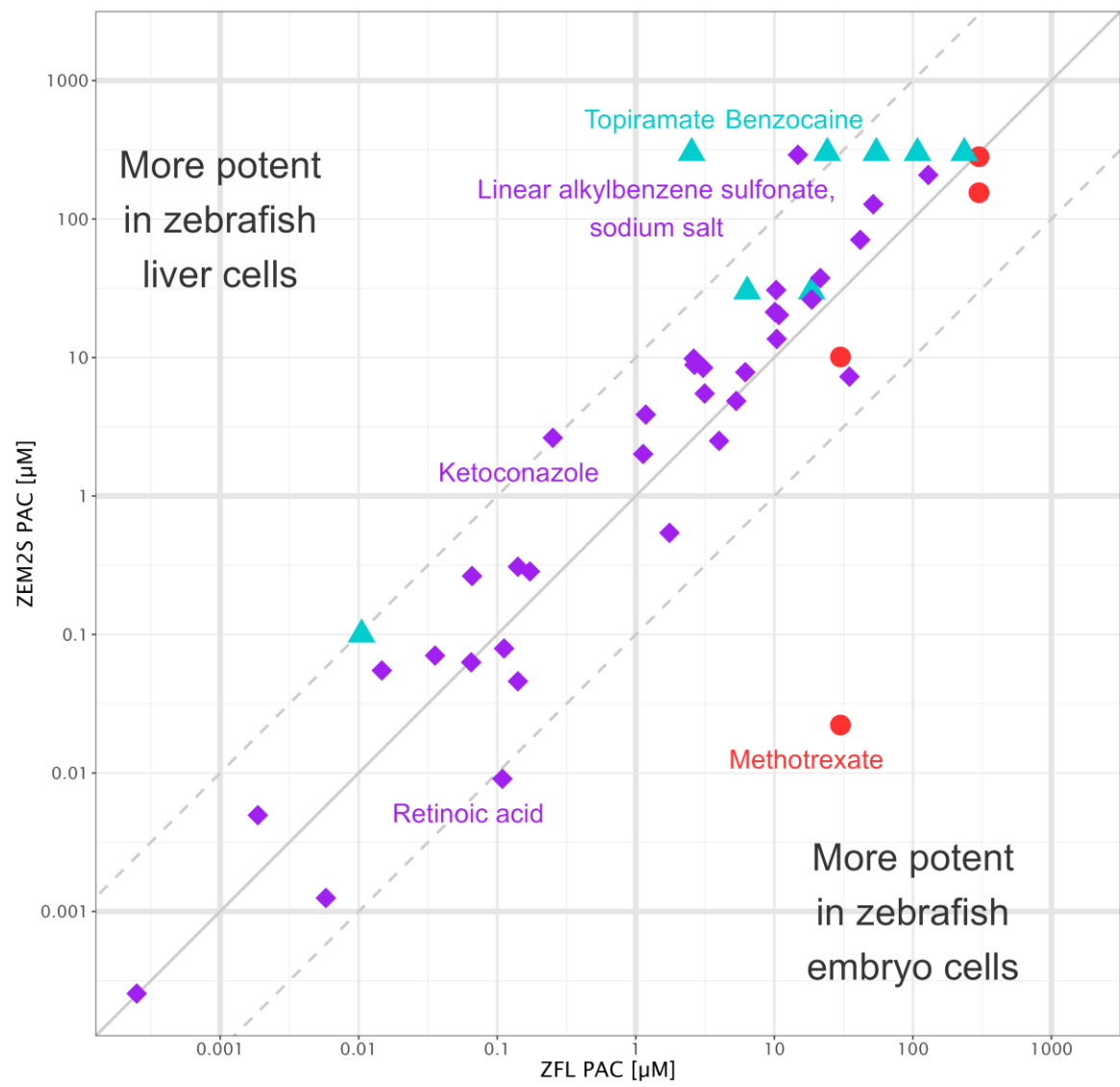
Note: This data is the property of Unilever Plc and cannot be shared without permission. It has been created for training purposes only and so may not reflect true experimental values. Unilever does not conduct fish testing including early life stage testing.



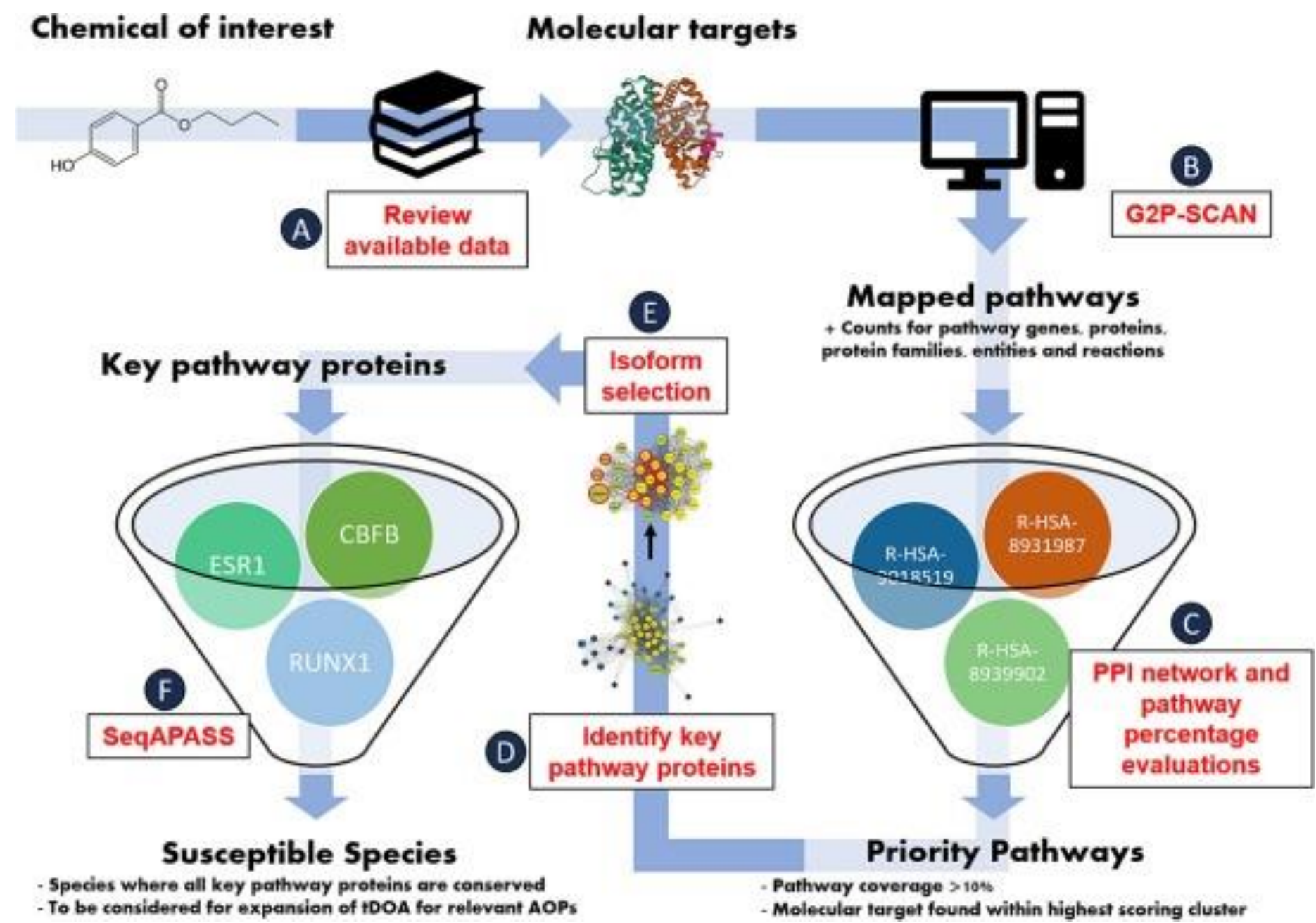




# Screening Chemicals Using High-Throughput Phenotypic Profiling (HTPP) in Two Zebrafish Cell Lines

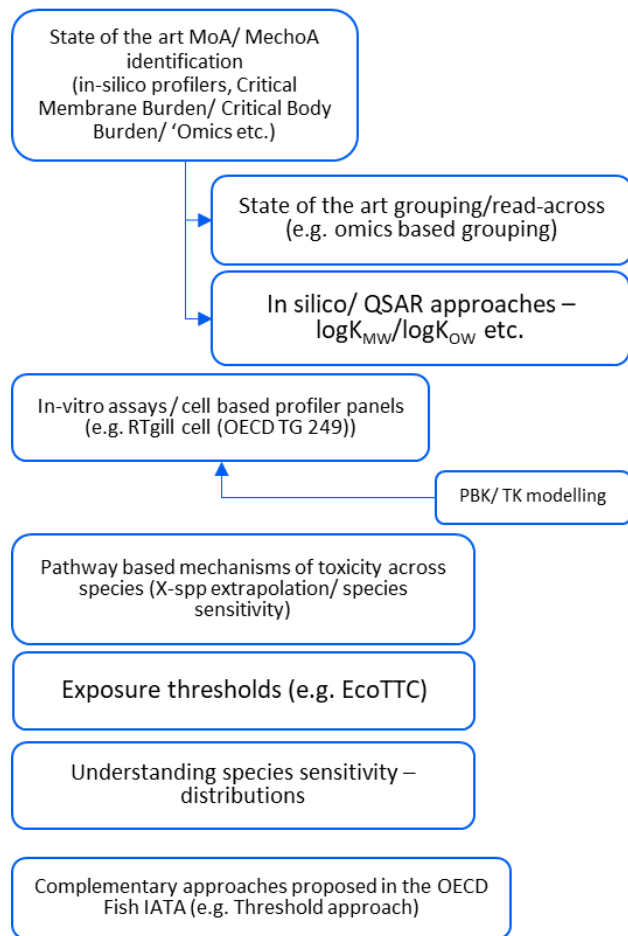




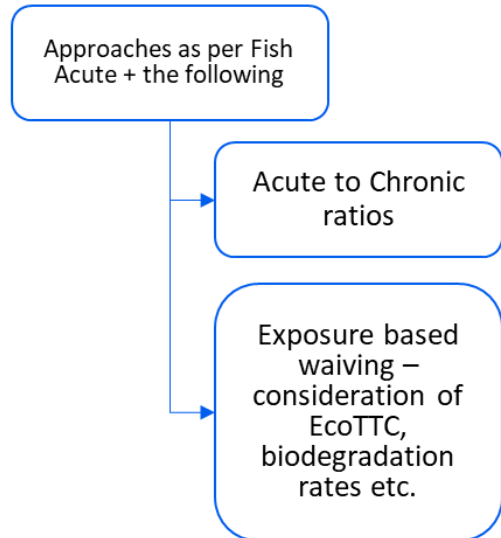




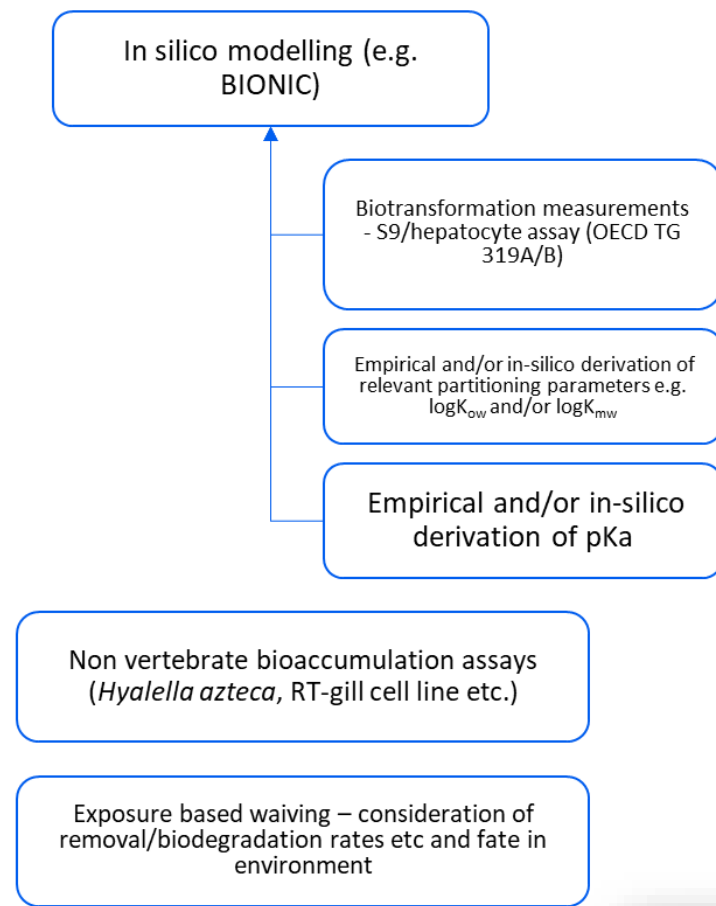
## Fish Acute



## Fish Chronic

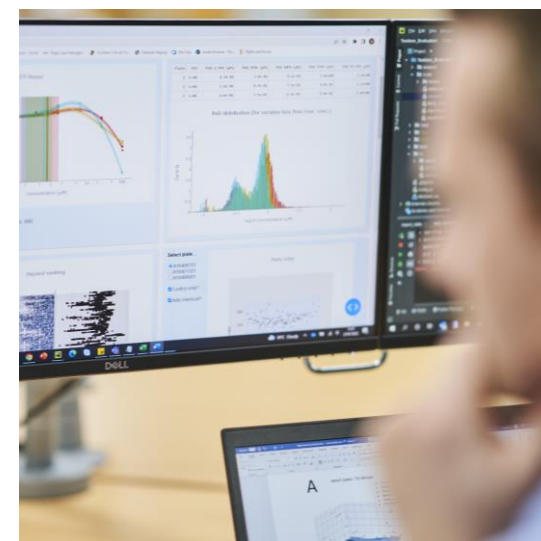


## Fish BCF



Bioaccumulation	Toxicity to fish	Endocrine disruption
Bioaccumulation in fish: OECD 305	Acute toxicity to juvenile fish: OECD 203	Fish 2 generations: OECD 248
Bioaccumulation in terrestrial organisms: OECD 311	Chronic toxicity to fish: OECD 204, 210, 211, 223	Fish sexual development: OECD 226, 230, 234, 246, 248
In vitro clearance trout hepatocytes: OECD 219	Fish cell line acute toxicity: OECD 245	Testosterone: estrogen activity (E2/E2*) : OECD 250
Bioaccumulation in <i>Hyalella azteca</i> : draft test guideline	Fish embryo acute toxicity: OECD 236	Testosterone: estrogen activity (E2/E2*) : OECD 250
TKTD models	In vitro method for chronic toxicity: NONE	Androgen: Testosterone: estrogen outcome reporter (Modaka fish) (RADAR): OCDE 251
		Investigation: OECD 251, 251, 249, 251-255, 252, 255, 255, 255
		Effects on vertebrate progeny for cosmetics: NONE

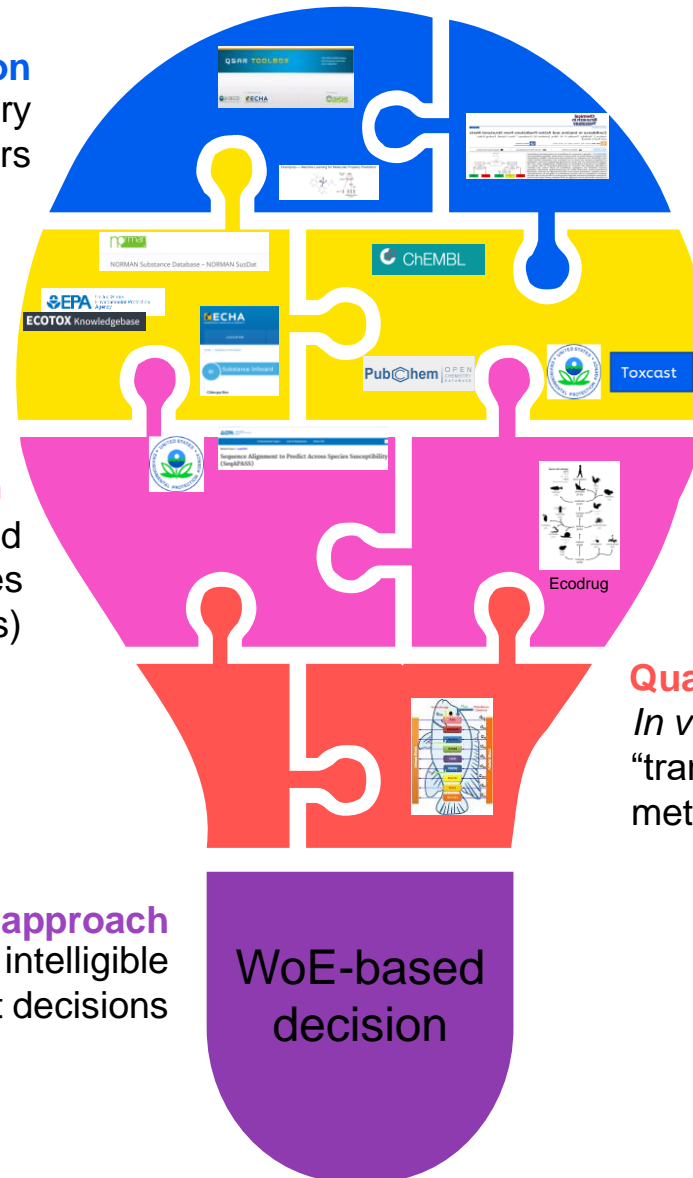
# Case study: A proof of concept to demonstrate the applicability of mechanistic info in Environmental safety assessment



**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



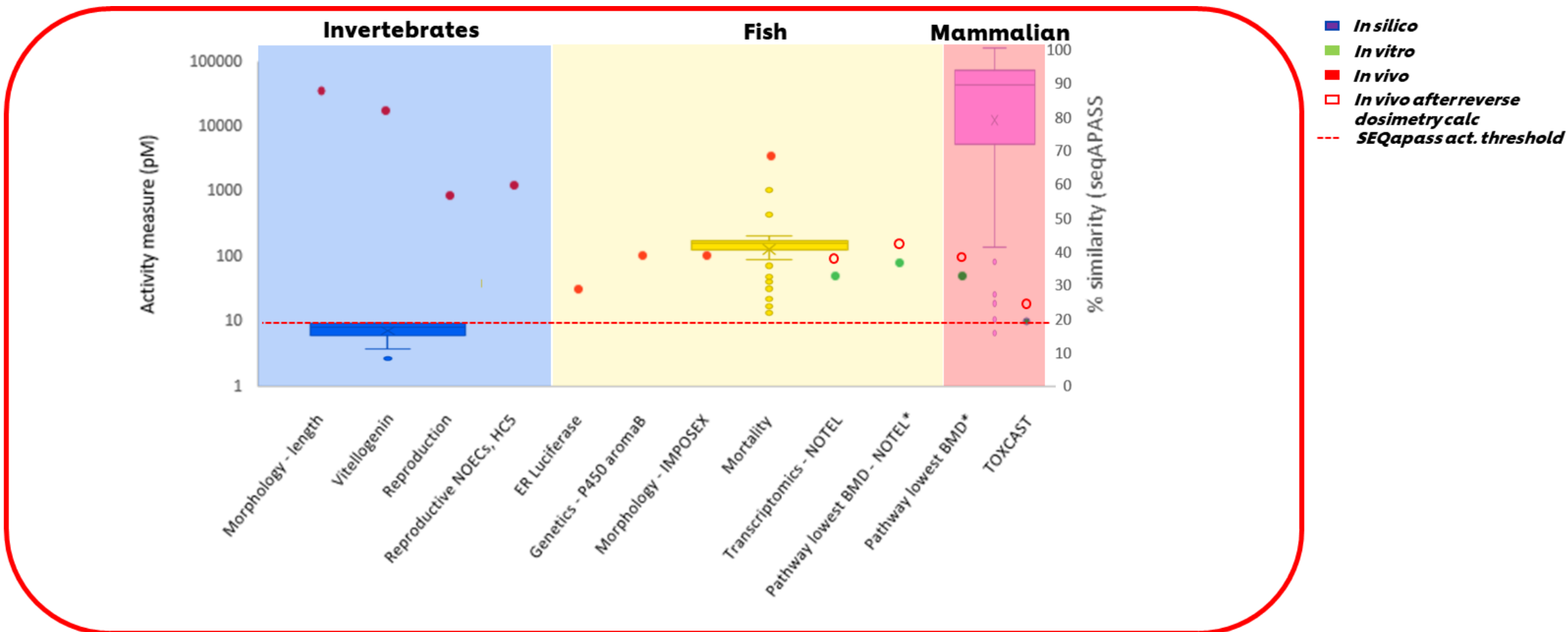
**Hazard Data**

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



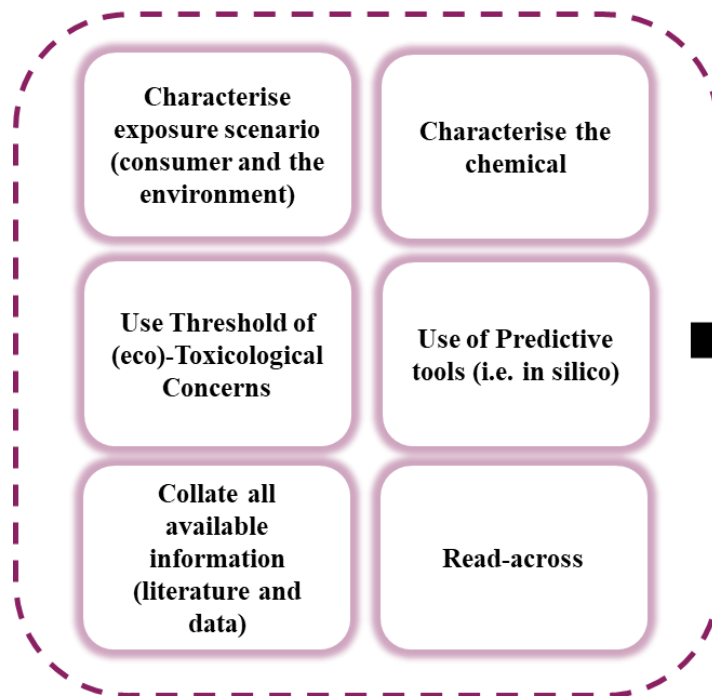
- **Understanding exposure is critical** to for Next Generation Risk Assessment.
- Tangible **opportunities** already available to improve environmental protection by applying **spatially explicit exposure, NAMs** and **weight of evidence** approaches.
- **Mechanistic understanding allows to move away 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)





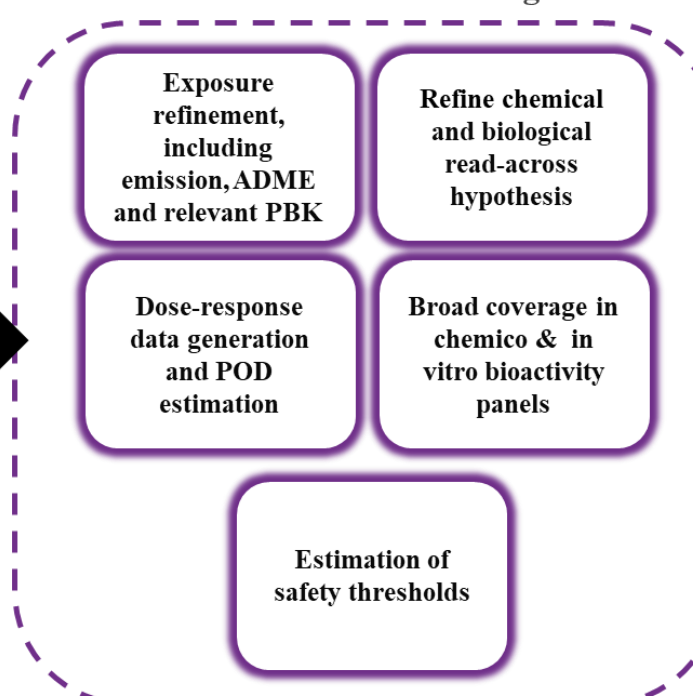
## First step- developing a common framework & language

**Tier 0- Identify use scenario and collect existing information**



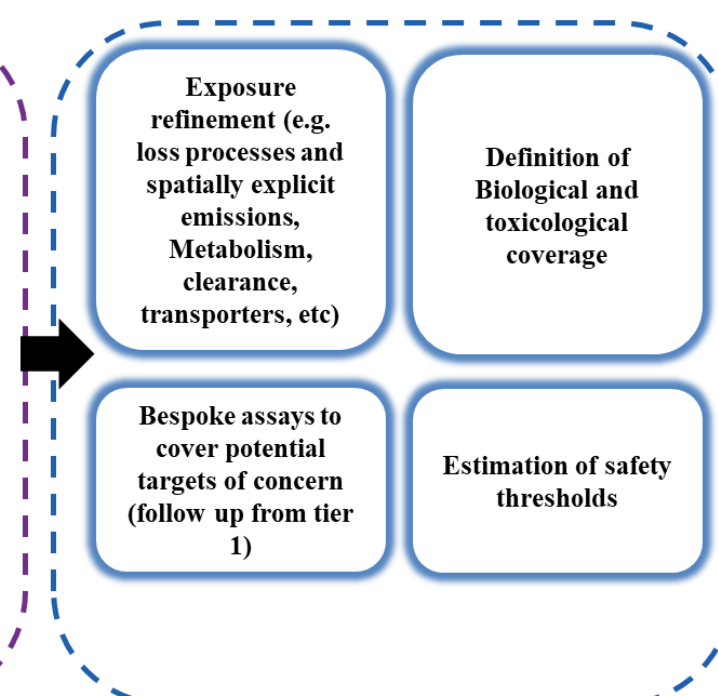
Exit if safety decision can be made

**Tier 1- Generate data to ensure refined exposure and increase Toxicological and taxonomical coverage**



Exit if safety decision can be made

**Tier 2- Refine assessment, incl. bespoke assays to increase decision certainty**



Safety decision

# 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



The collage features logos from a wide range of institutions, including: ceftic, ecefic, EPSRC, NTP, EPA, cyprotex, DelphicHSE, eawag, RISK HUNT3R, AFSA, BROWN, INDOOR Biotechnologies, BBSRC, Wageningen, DTU, UNIVERSITY OF CAMBRIDGE, Lhasa, toxys, UK Centre for Ecology & Hydrology, entronix, MANCHESTER, UNIVERSITY OF NOTTINGHAM, centex, UNIVERSITY OF BIRMINGHAM, UNIVERSITY OF LEEDS, SciBite, CARDIFF UNIVERSITY, genoskin, SOLVAY, PHARMARCO, ep, IMS, Brunel University London, XCellIRB, PHARMARCO, eurofins, ooesoLABS, OECD, UNIVERGAP, and NWO. On the right side, there is a screenshot of an EPA news release titled "EPA and Unilever Announce Major Research Collaboration to Advance Non-animal Approaches for Chemical Risk Assessment" dated August 25, 2021. Below the screenshot are the logos for ICCR (International Cooperation on Cosmetics Regulation) and the European Partnership for Alternative Approaches to Animal Testing (epaa).



[seac.unilever.com](https://seac.unilever.com)