New Approach Methodologies in Environmental Safety: opportunities and roadblocks ahead

Dr Bruno Campos
bruno.campos@unilever.com

Safety and Environmental Assurance Centre, Unilever, United Kingdom


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.

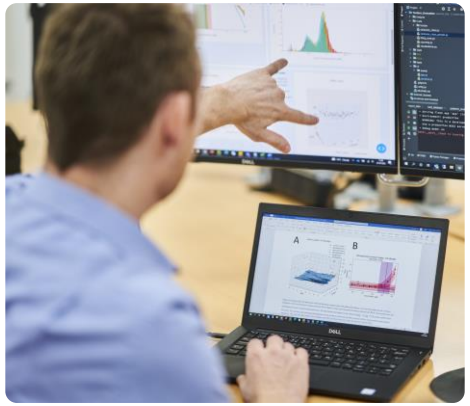
Reducing our environmental impact

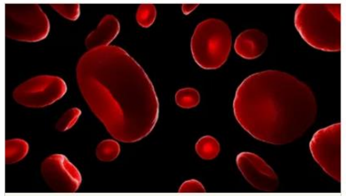
How we harness the latest science to minimise our environmental footprint.

Unilever

Safety without Animal Testing:

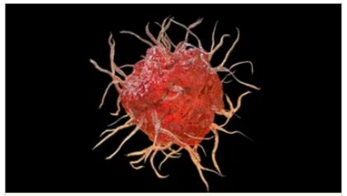
- **Unilever is committed to ending animal testing globally**. We believe in using science, not animals, to assure the safety of our products and their ingredients.
- **Non-animal safety approaches are applied by our leading-edge scientists** in collaboration with world-class researchers & experts.
- These partnerships, combined with our multi-disciplinary expertise **enable us to protect people and the environment without animal testing**.





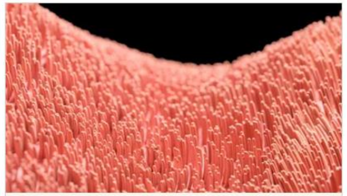
Systemic Safety

To understand the safety of ingredients if they are absorbed into the body (systemic safety), we do not use an animal study to...



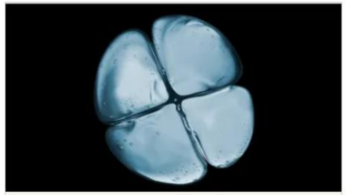
Skin Allergy Safety

Some ingredients used in consumer products have the potential to cause allergic contact dermatitis (ACD), a type of skin allergy. To...



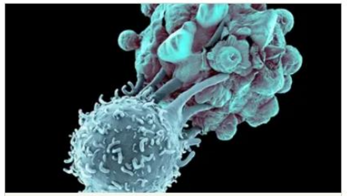
Inhalation Safety

A significant proportion of Unilever's products are aerosols and sprays which include underarm antiperspirants, hair sprays...



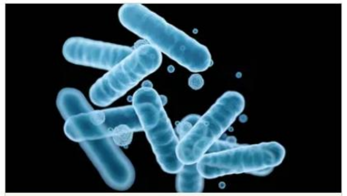
DART Safety

Developmental and reproductive toxicity (DART) refers to potential adverse effects that exposure to an ingredient may have on ...



Immune Effects Safety

We consider all potential adverse impacts on the human immune system resulting from exposure to an ingredient. These include...

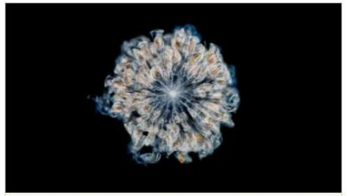


Microbiological Safety

Some of our consumer products have the potential to change the human microbiome or raise microbiological concerns...

Environmental Safety

Unilever ingredients are often disposed of down the drain after use, so it is important for us to assess the environmental safety of...



Biodegradation

Biodegradation is the process in which an ingredient is broken down through natural processes by microorganisms into simple substances...

https://seac.unilever.com/our-science/safety-without-animal-testing/

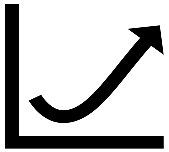
Unilever

Next Generation Risk Assessment (NGRA)

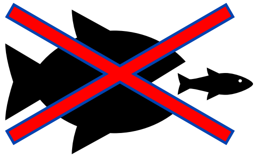
NGRA is defined as ***an exposure-led, hypothesis-driven*** risk assessment approach that ***integrates New Approach Methodologies (NAMs)*** to assure ***safety without the use of animal testing***

Safety science: what can we do better?

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



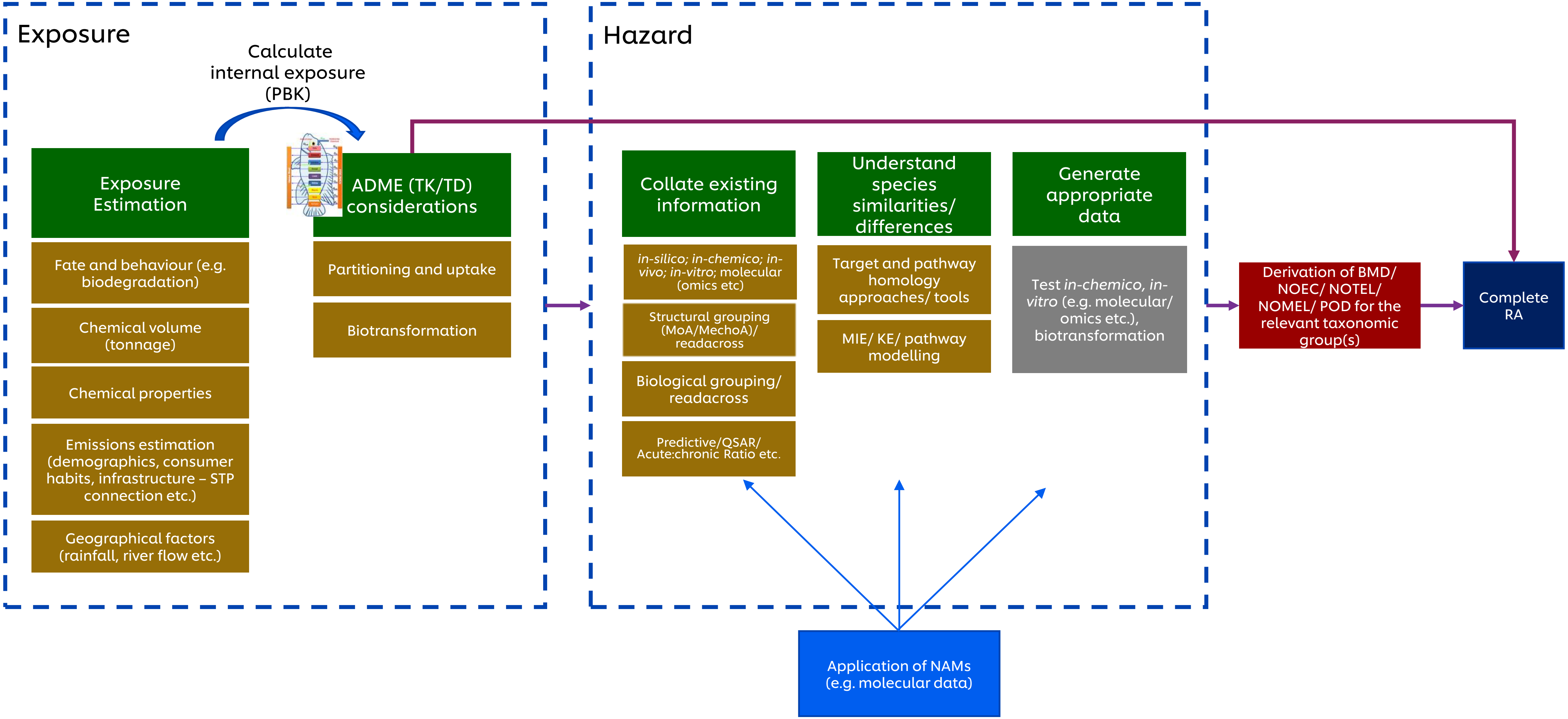
Better, more sustainable chemicals



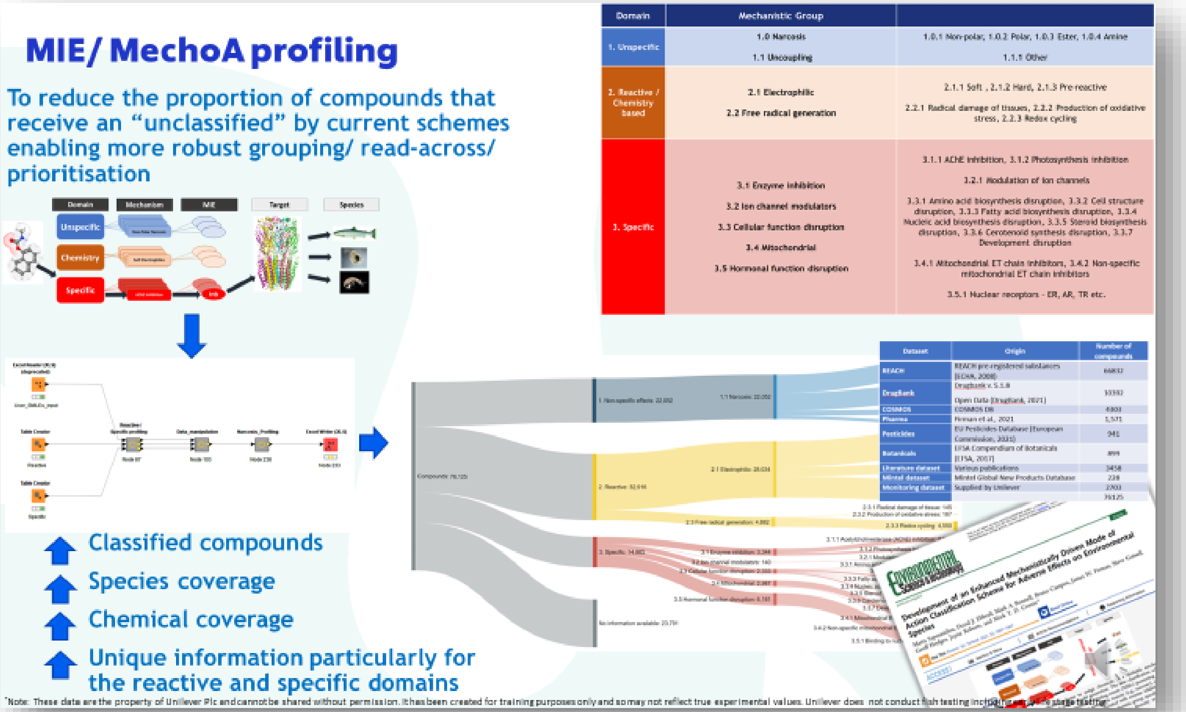
Moving away from animal tests

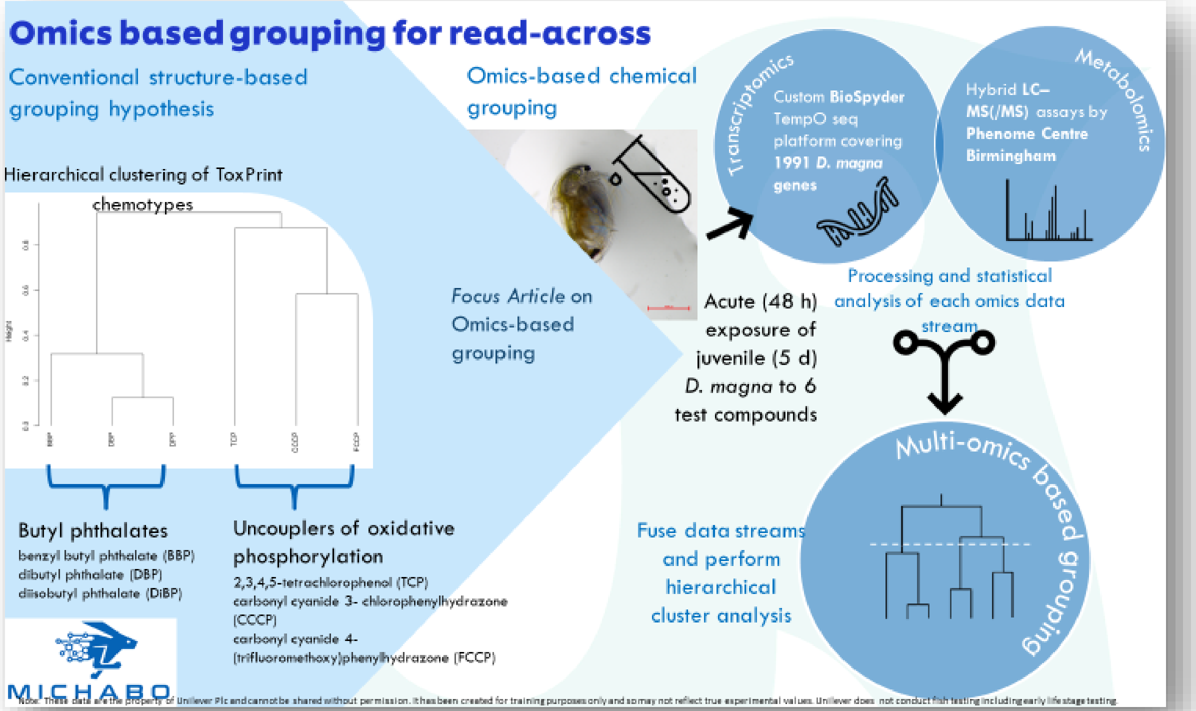
...THUS NAMs provide the opportunity for more mechanistic, higher throughput and animal-free ERA

NAMs in environmental safety assessments



Grouping: chemical and biological based





Note: These data are 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.

Genes-to-Pathways Species Conservation ANalysis (G2P-SCAN)

What?

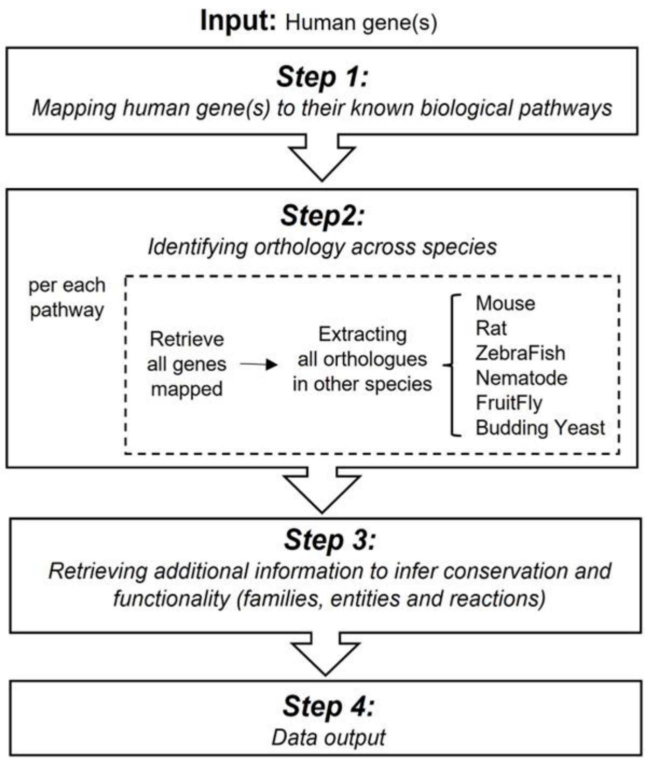
A workflow to integrate and socialize a number of existing software and databases to help data gathering and structuring for subsequent analysis.

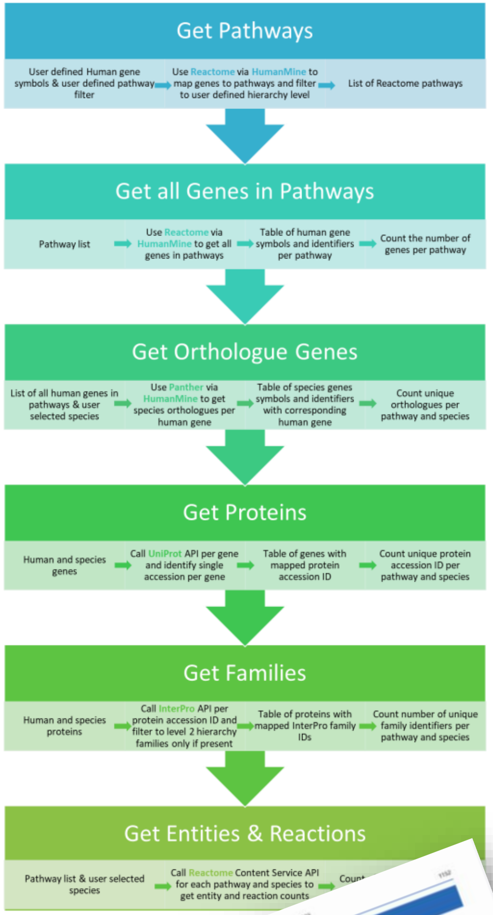
How?

Leveraging on the integrated use of available data in a WoE approach to serve as a scaffold for a mechanistically-driven testing strategy and hazard characterization.

Why?

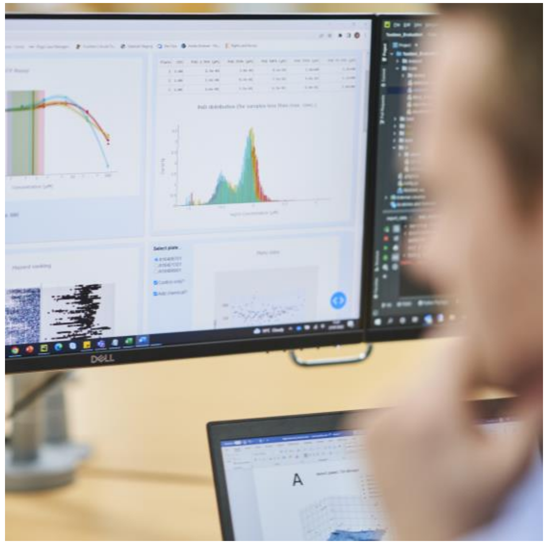
Providing the evidence of the conservation and functional coverage across species is critical to discern the conservation in physiological processes and predict response patterns and toxicity outcomes in the environment.





Rivetti, C., et al. (2023). ET&C

Case study: A framework to demonstrate the applicability of NAMs in Environmental Risk Assessment (ERA)



Objectives:

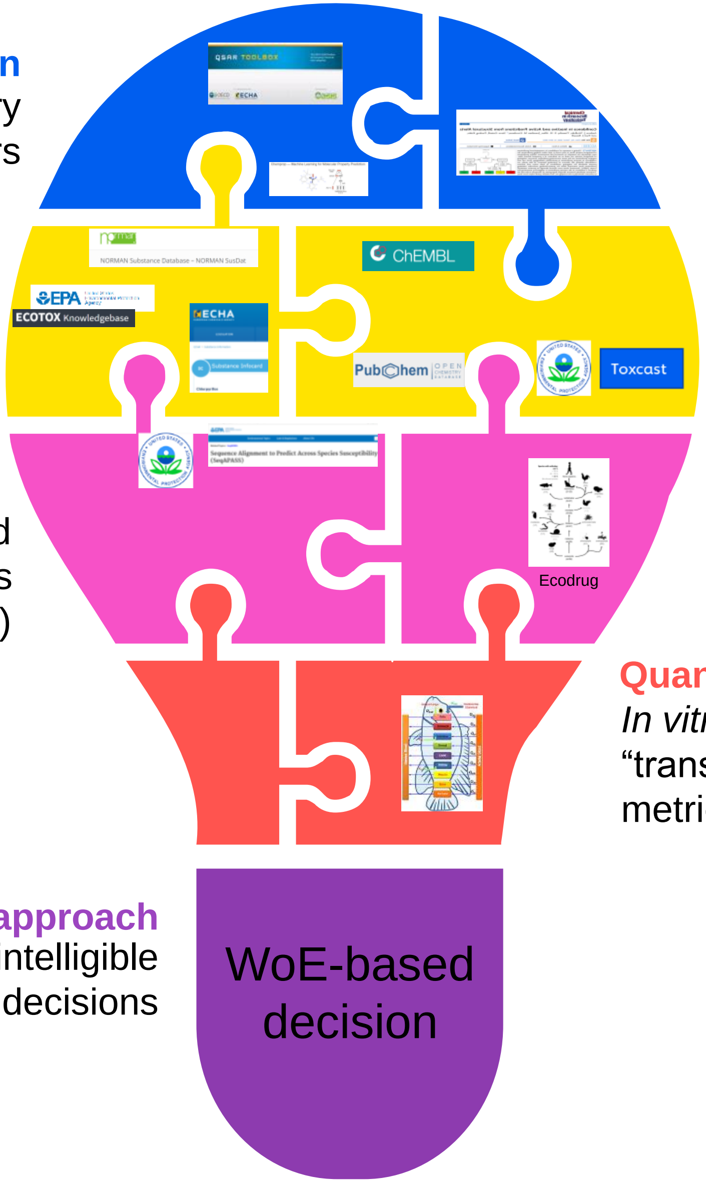
Evaluate the utility and the applicability of mechanistic-based information to complement and strengthen current ERA practices without the need for generating new animal data

- ✓ **Assessing the availability, suitability and power of NAMs-based data**
- ✓ **Benchmark mechanistically-derived Points of Departure (PoD) to complement current ERA practices**
- ✓ **Use all data as part of a weight of evidence approach to provide increased confidence in decisions**

The integration of historical *in vivo* data and NAMs can build confidence in safety decision making

Insights will help gain better mechanistic understanding of potential expected toxicity effects

Information gathering process:



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

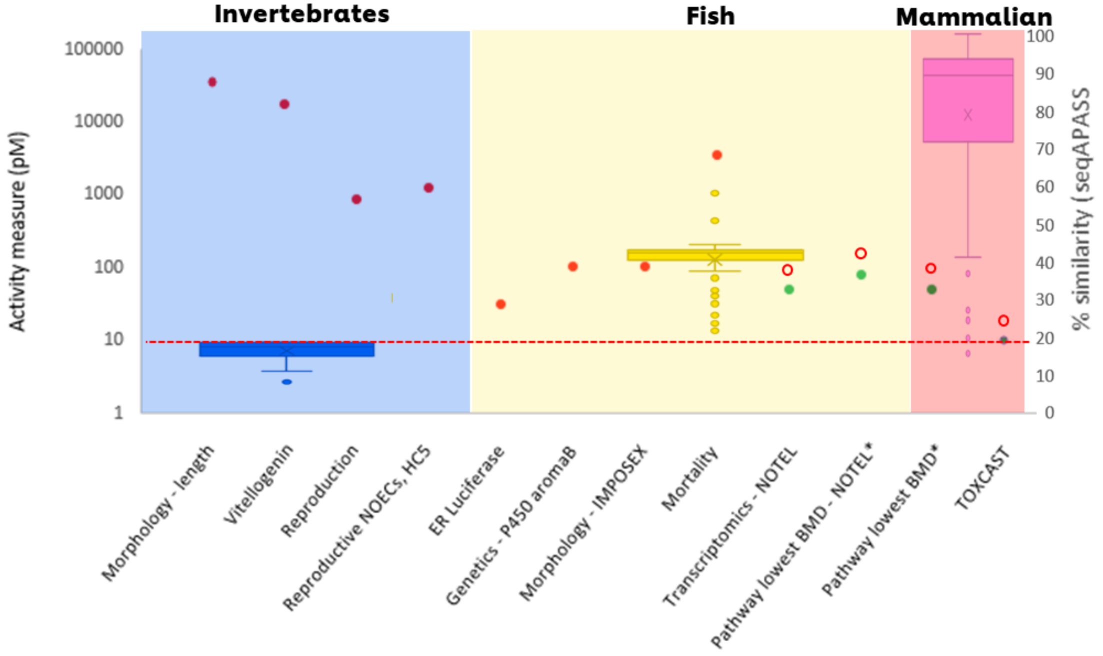
Hazard Data
Including historical *in vivo* as well as *in vitro* data and *in silico* predictions to generate relevant PoD

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

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

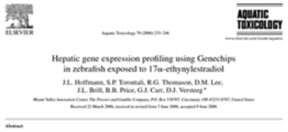
Weight Of Evidence approach
Collate all the information in an intelligible way to guide and support decisions

Case-study 1: ethinylestradiol



In silico
In vitro
In vivo
In vivo after reverse dosimetry calc
SEQapass act. threshold

Microarray analysis


Hepatic gene expression profiling using Genechips in zebrafish exposed to 17α-ethynylestradiol
J.L. Hoffmann, S.P. Torontali, R.G. Thomason, D.M. Lee, J.L. Brill, B.B. Price, G.J. Carr, D.J. Versteeg

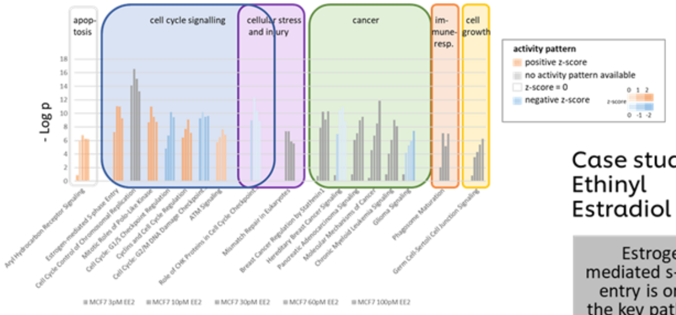
NOTEL 168h* = 50pM

Pathway with lowest BMD at 168h: 78pM

*Threshold FC >2, p < 0.05, a cut of at FDR < 0.1 would change the numbers of DEGs but not the NOTEL

Hoffmann et al., (2006)

Canonical Pathway analysis

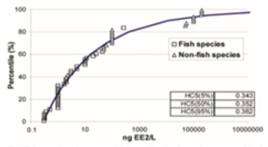


Case study: Ethinyl Estradiol (EE2)

Estrogen mediated s-phase entry is one of the key pathways but other pathways are also identified

Top 20 pathways predicted by Ingenuity Pathway Analysis (IPA) according to top p-value

Literature information



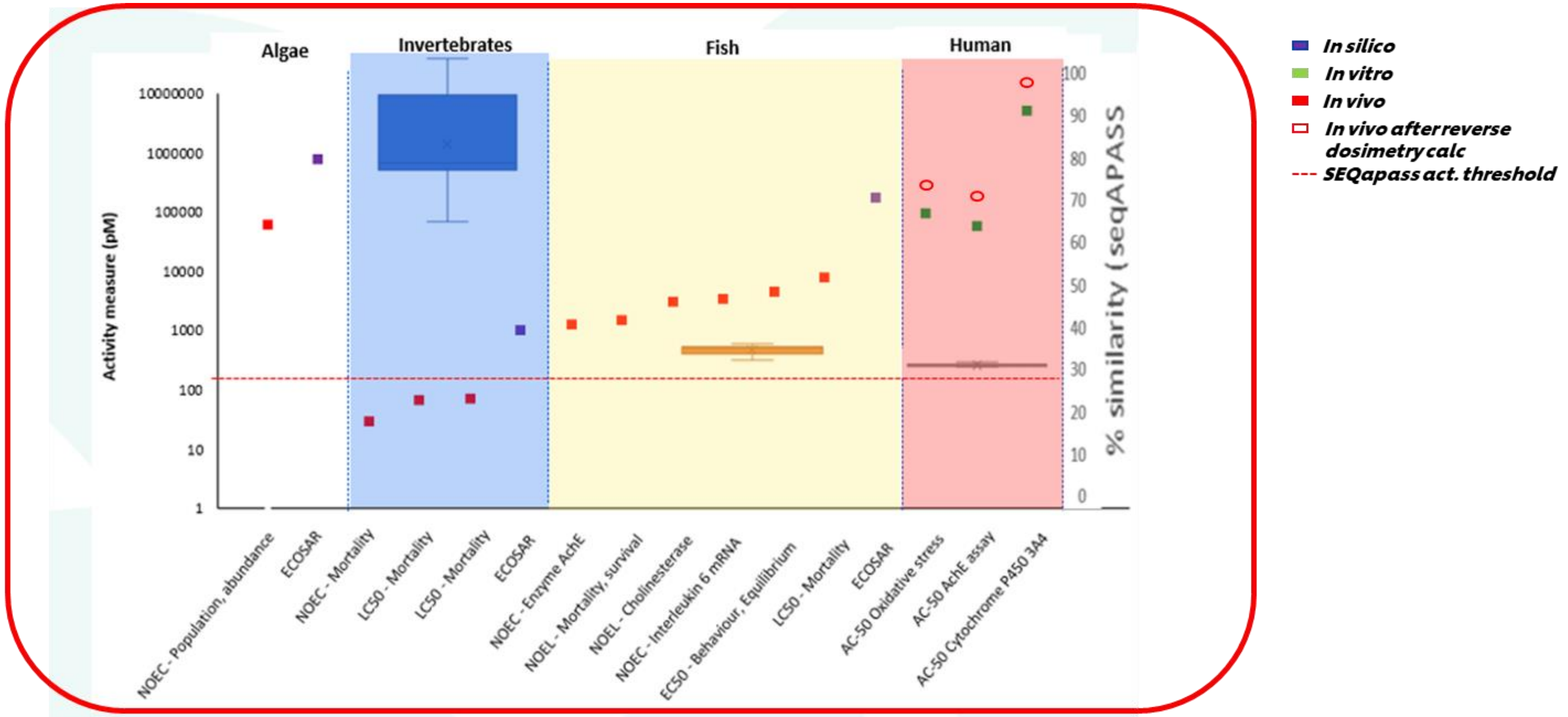
HC5 (50%) = 1200 pM

EC50= 30pM
(ER luciferase assay)

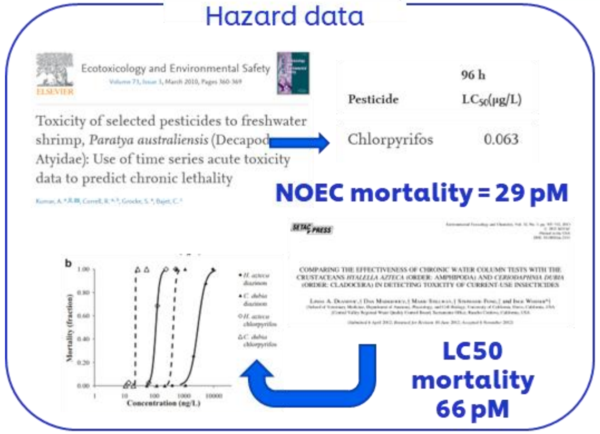
Toxcast

Unilever

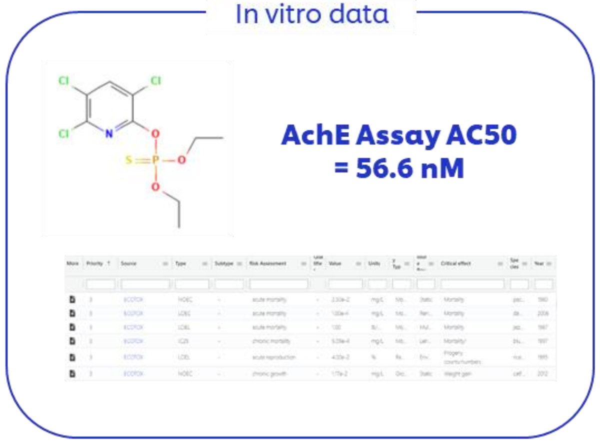
Case-study 2: Chlorpyrifos



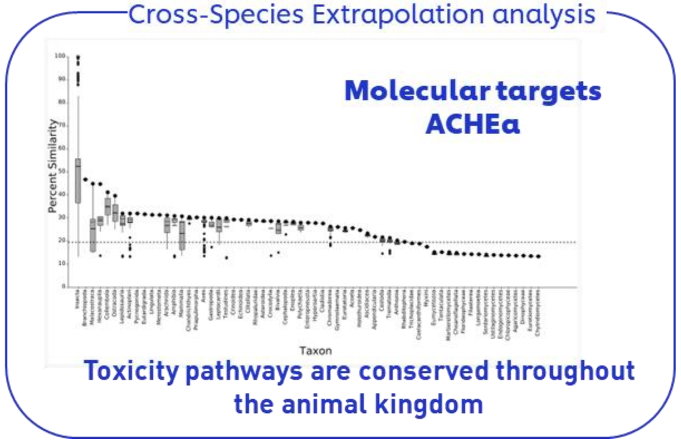
Hazard data



In vitro data



Cross-Species Extrapolation analysis



Key highlights

Integration of *in vivo, in vitro and in silico data* in a weight of evidence approach can build confidence in safety decision-making.

- ✓ provides confidence that most sensitive species can be identified (in line with historical knowledge of chemicals);
- ✓ Species sensitivity is in line with MoA and target conservation
- ✓ *in vitro* endpoints seem to be at least as protective as traditional *in vivo*.

Challenges to be addressed

- ➢ Lack of standardised study designs may hinder data usage
- ➢ Challenges for data-poor chemicals
- ➢ No one-size-fit-all approach

Take home messages

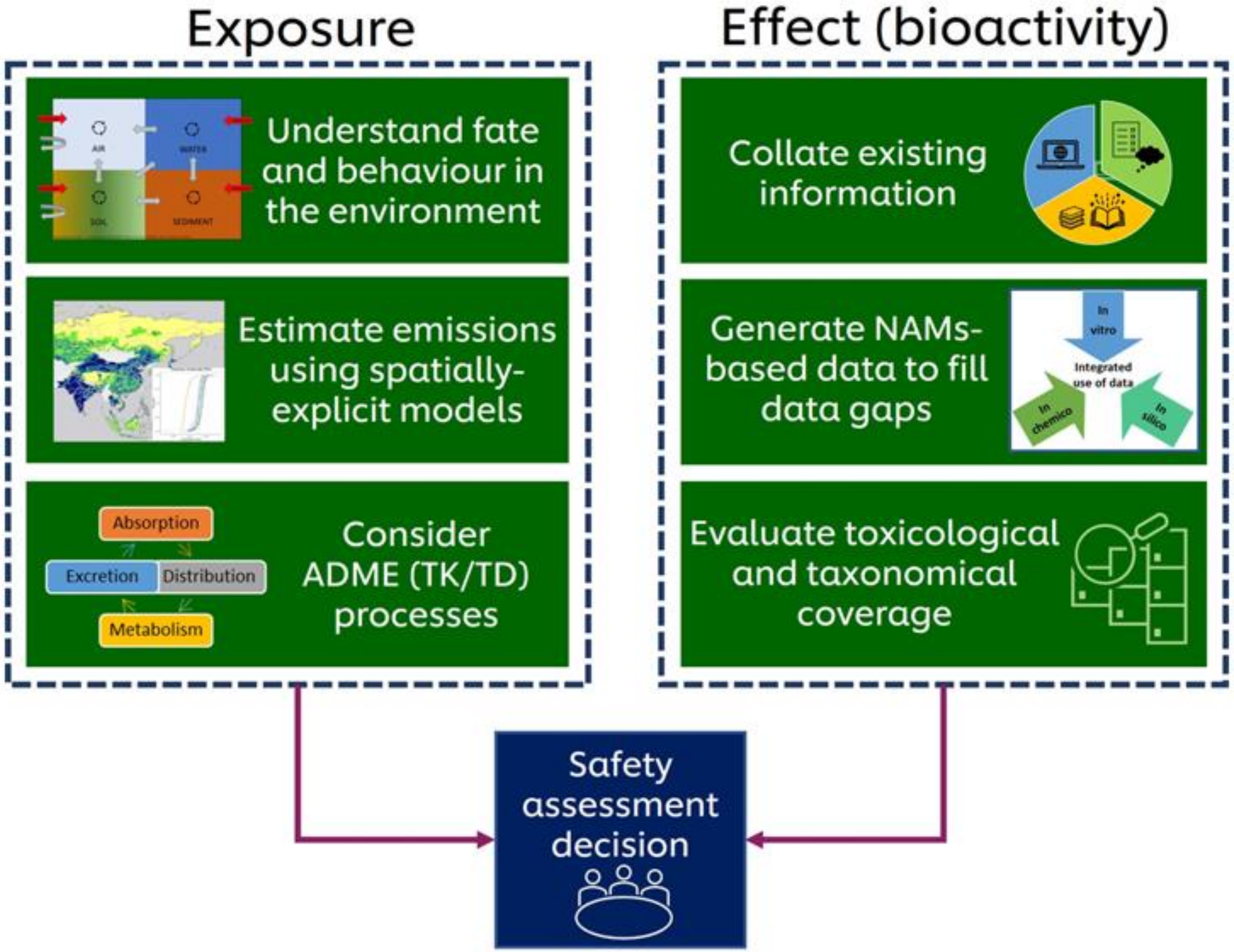
- Understanding exposure is critical to applying/ interpreting NAMs for safety assessment.

- Tangible opportunities already available to improve environmental protection by applying NAMs approaches and all available information

- Mechanistic understanding allows to move away from black box in vivo studies, to better understand how chemicals impact species and to identify potential impacts which in vivo studies would not identify.

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

Establishing better environmental protection through Nexgen, mechanistic based environmental risk assessment paradigm shift



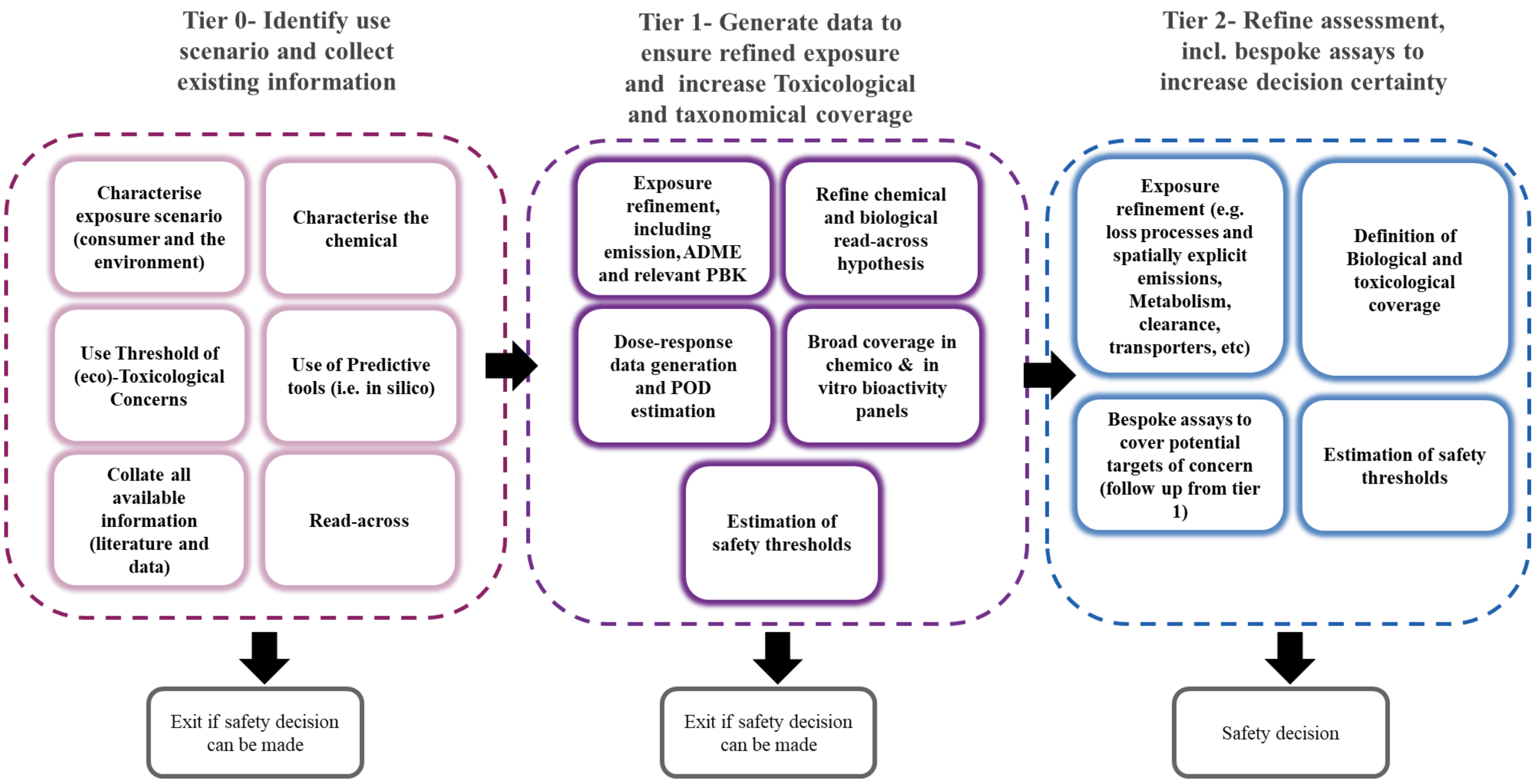

Editorial

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

Rivetti & Campos, IEAM 2023

Ultimate goal: Increased integration of human & environmental safety decisions

First step– developing a common framework & language



Thank You

"the team"

- Emilia Gattas
- Nicola Furmanski
- Jayne Roberts
- John Kilgallon
- Claudia Rivetti
- Geoff Hodges
- Alexandre Teixeira
- Chris Finnegan
- Ian Malcomber
- Juliet Hodges
- David Gore
- Yaping Cai
- Katie Endersby
- Paul Carmichael
- Mathura Theiventhran
- Danilo Basili
- Predrag Kukic
- Iris Muller
- Simran Sandhu
- Baile Xu
- and many more...

seac.unilever.com

Unilever