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A framework to demonstrate the applicability of New Approach Methodologies (NAMs) in Environmental Risk Assessment (ERA)

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Content

- ✓ New Approach Methodologies (NAMs) application in Environmental Risk Assessment (ERA)
- ✓ Objectives
- ✓ Case-studies applied to validate the approach
- ✓ Key highlights

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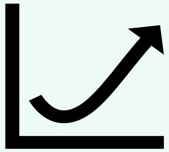
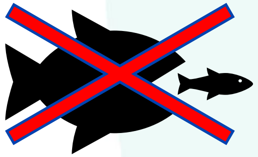
Safety science: what can we do better?

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

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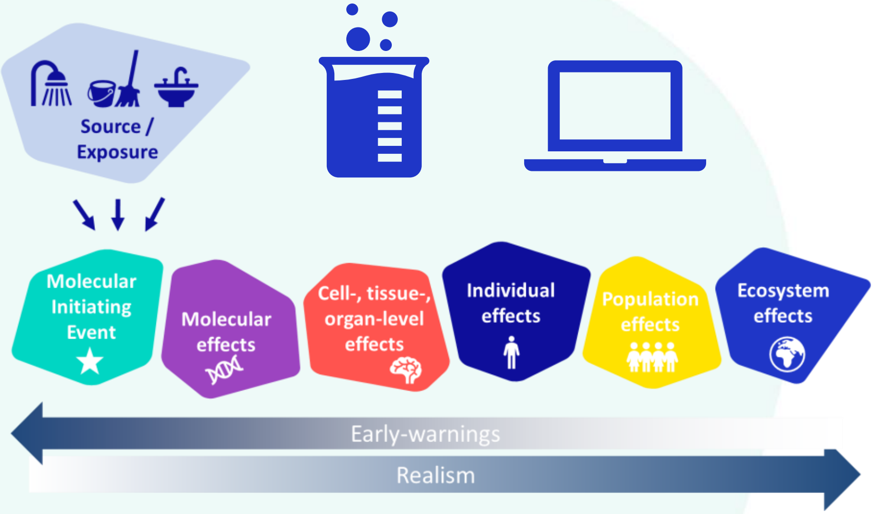
Mechanistic understanding is driving new ways of thinking in RA



Further mechanistic understanding of chemicals

Maximise use of available data

Increasing confidence in Risk Assessment

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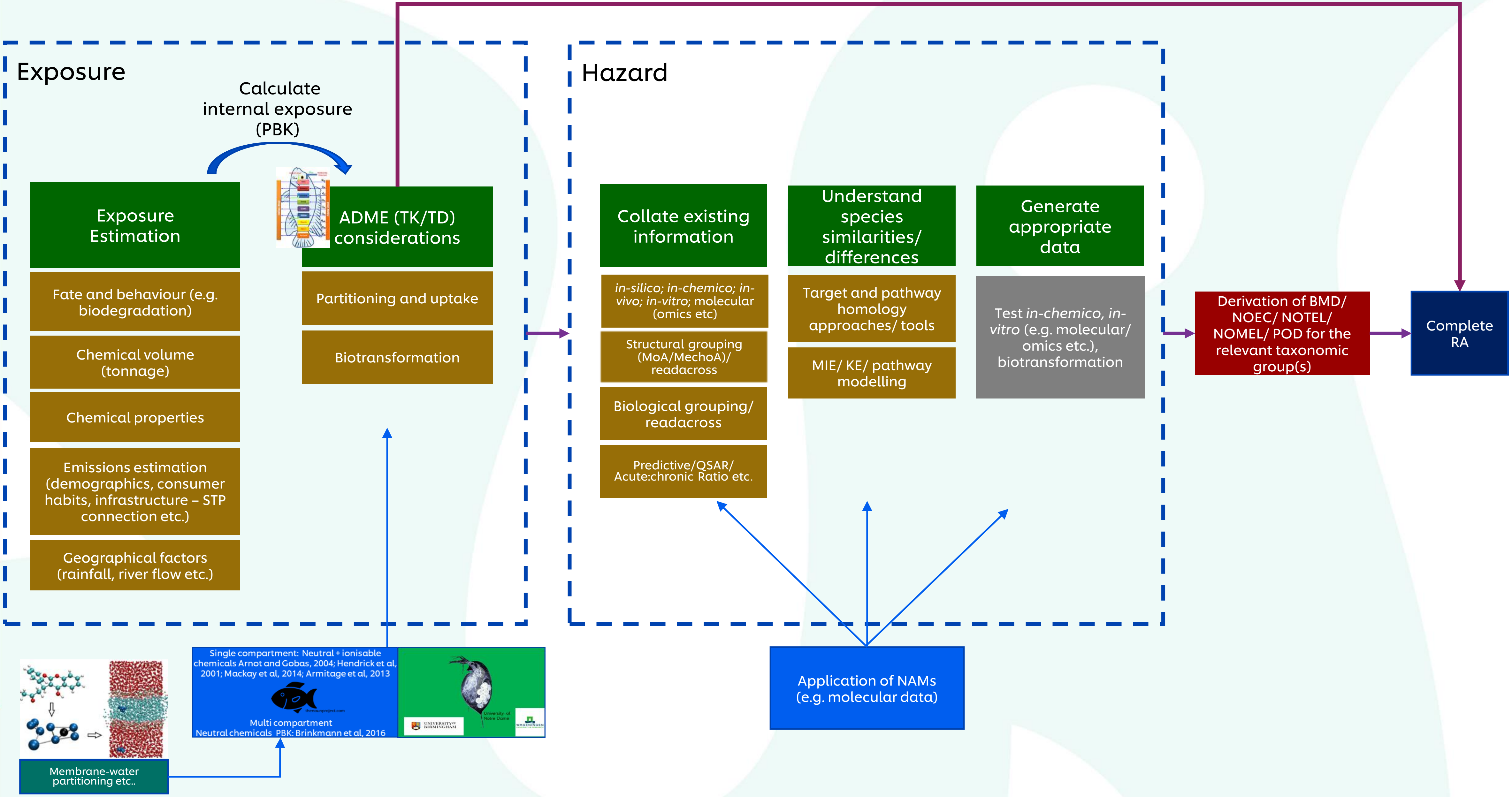
NAMs in environmental safety assessments



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

Development of case studies to exemplify the applicability of the approach

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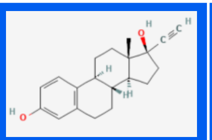
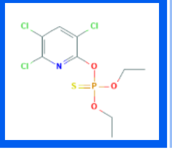
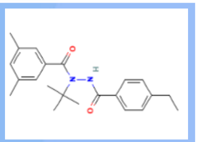
Case studies

Compound	Ethinylestradiol (EE2) 	Chlorpyrifos (CPS) 	Tebufenozide* 
Use	Contraception	Pesticide	Insecticide
Mode of Action	Oestrogen receptor agonist	Acetylcholinesterase receptor agonist	Ecdysone receptor agonist
Expected sensitive species	Vertebrates	*Animalia*	Invertebrates

* Case-study under development

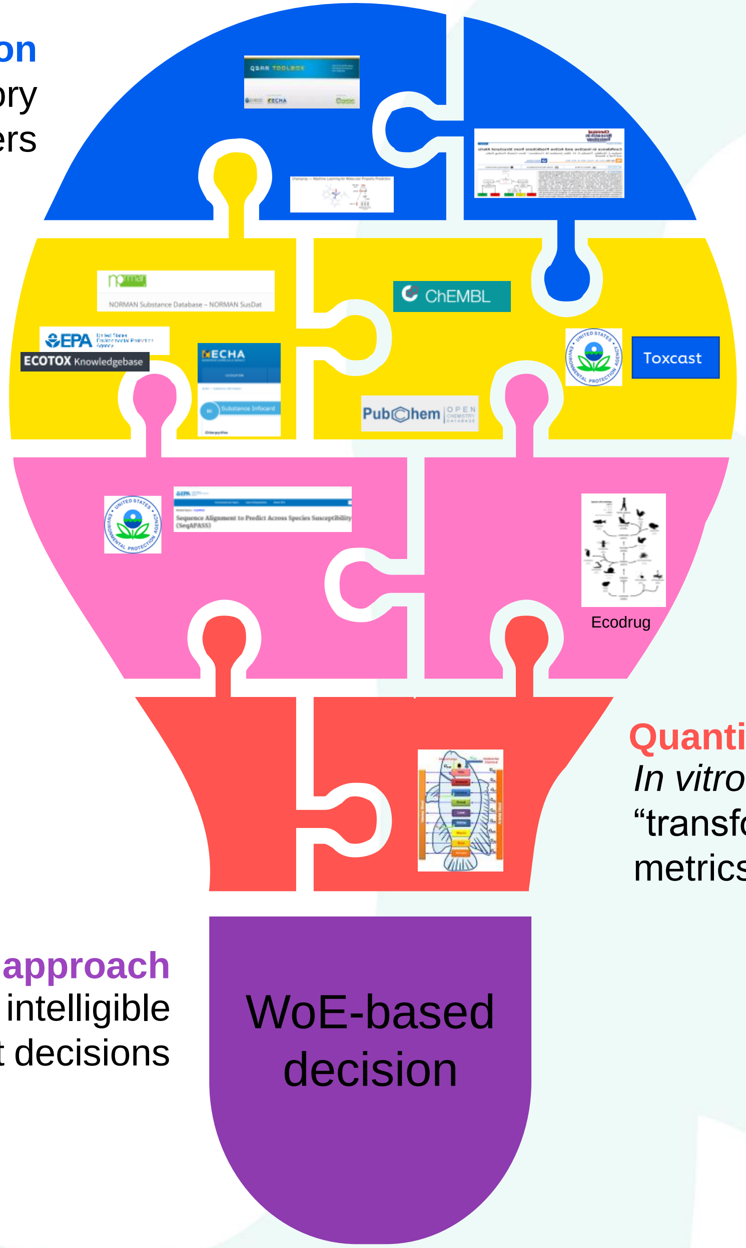
Information gathering process

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

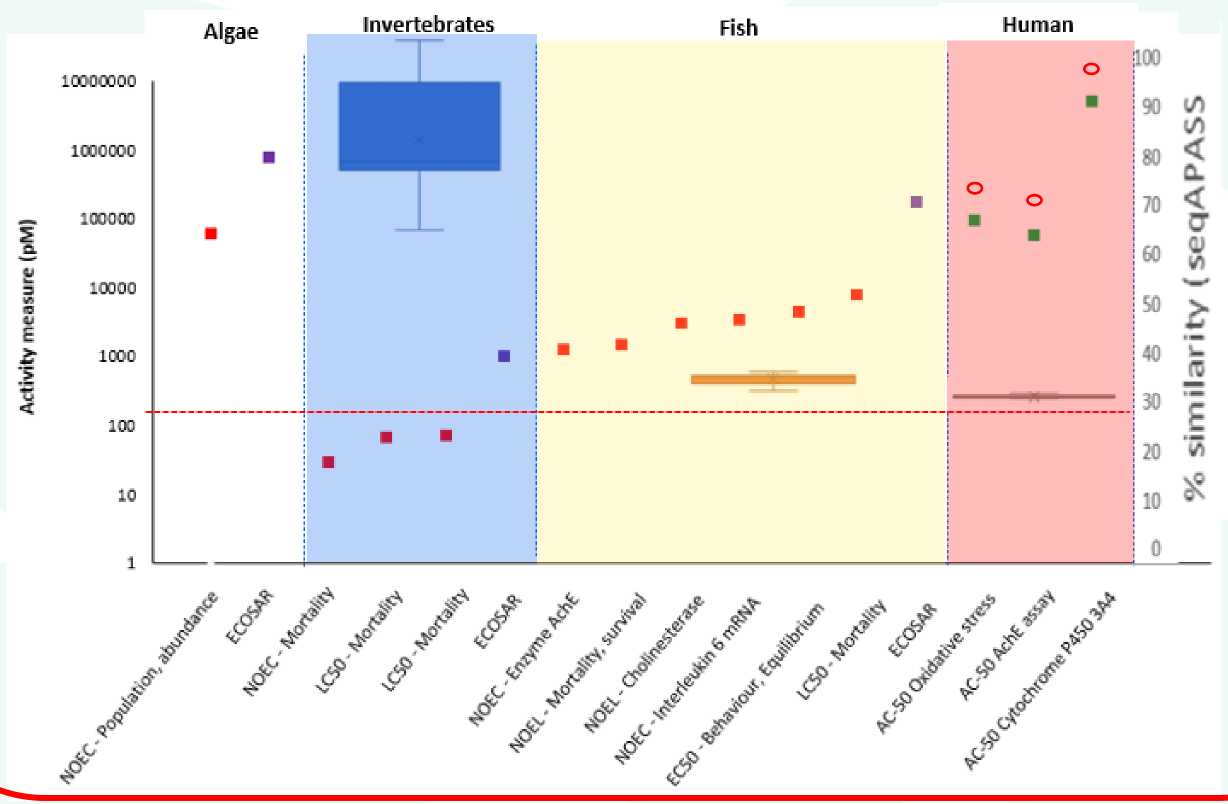
Species at risk identification
Use of publicly available tools and databases to identify susceptible species (based on targets and processes)

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: Chlorpyrifos



Hazard data

Ecotoxicology and Environmental Safety
Volume 73, Issue 3, March 2010, Pages 360-369

Toxicity of selected pesticides to freshwater shrimp, *Paratya australiensis* (Decapoda: Atyidae): Use of time series acute toxicity data to predict chronic lethality

Kumar, A., Correll, R., Grocke, S., Bajet, C.

	96 h
Pesticide	LC_{50}(μg/L)
Chlorpyrifos	0.063

NOEC mortality = 29 pM

SETAC PRESS
Environmental Toxicology and Chemistry, Vol. 32, No. 3, pp. 707–712, 2013
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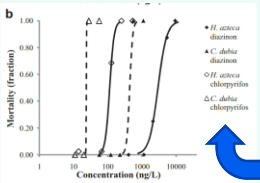
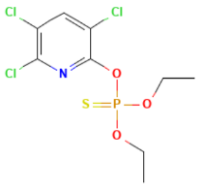
COMPARING THE EFFECTIVENESS OF CHRONIC WATER COLUMN TESTS WITH THE CRUSTACEANS *HYALELLA AZTECA* (ORDER: AMPHIPODA) AND *CERIODAPHNIA DUBIA* (ORDER: CLADOCERA) IN DETECTING TOXICITY OF CURRENT-USE INSECTICIDES

Linda A. Deanovic,† Dan Markiewicz,† Marie Stillway,† Stephanie Fong,‡ and Inge Werner*†



LC50 mortality 66 pM

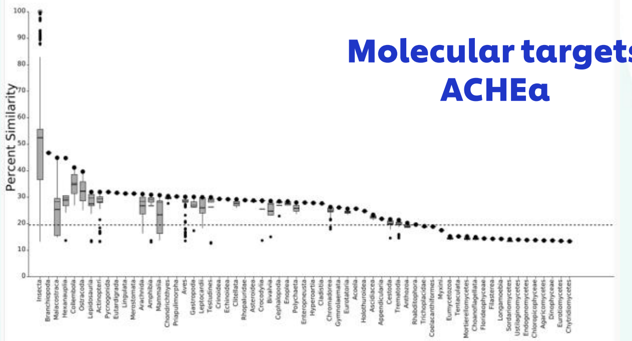
In vitro data



AchE Assay AC50 = 56.6 nM

More	Priority	Source	Type	Subtype	Risk Assessment	Qua lifie	Value	Units	y Typ	osur e Rou	Critical effect	Spe cies	Year
	3	ECOTOX	NOEC	-	acute mortality	-	2.50e-2	mg/L	Mo...	Static	Mortality	pac...	1980
	3	ECOTOX	LOEC	-	acute mortality	-	1.00e-4	mg/L	Mo...	Ren...	Mortality	da...	2006
	3	ECOTOX	LOEL	-	acute mortality	-	1.00	lb/...	Mo...	Mul...	Mortality	jap...	1987
	3	ECOTOX	IC25	-	chronic mortality	-	5.09e-4	mg/L	Mo...	Len...	Mortality/	blu...	1997
	3	ECOTOX	LOEL	-	acute reproduction	-	4.00e-2	%	Re...	Env...	Progeny counts/numbers	rice...	1995
	3	ECOTOX	NOEC	-	chronic growth	-	1.17e-2	mg/L	Gro...	Static	Weight gain	catf...	2012

Cross-Species Extrapolation analysis



Molecular targets ACHEa

Toxicity pathways are conserved throughout the animal kingdom

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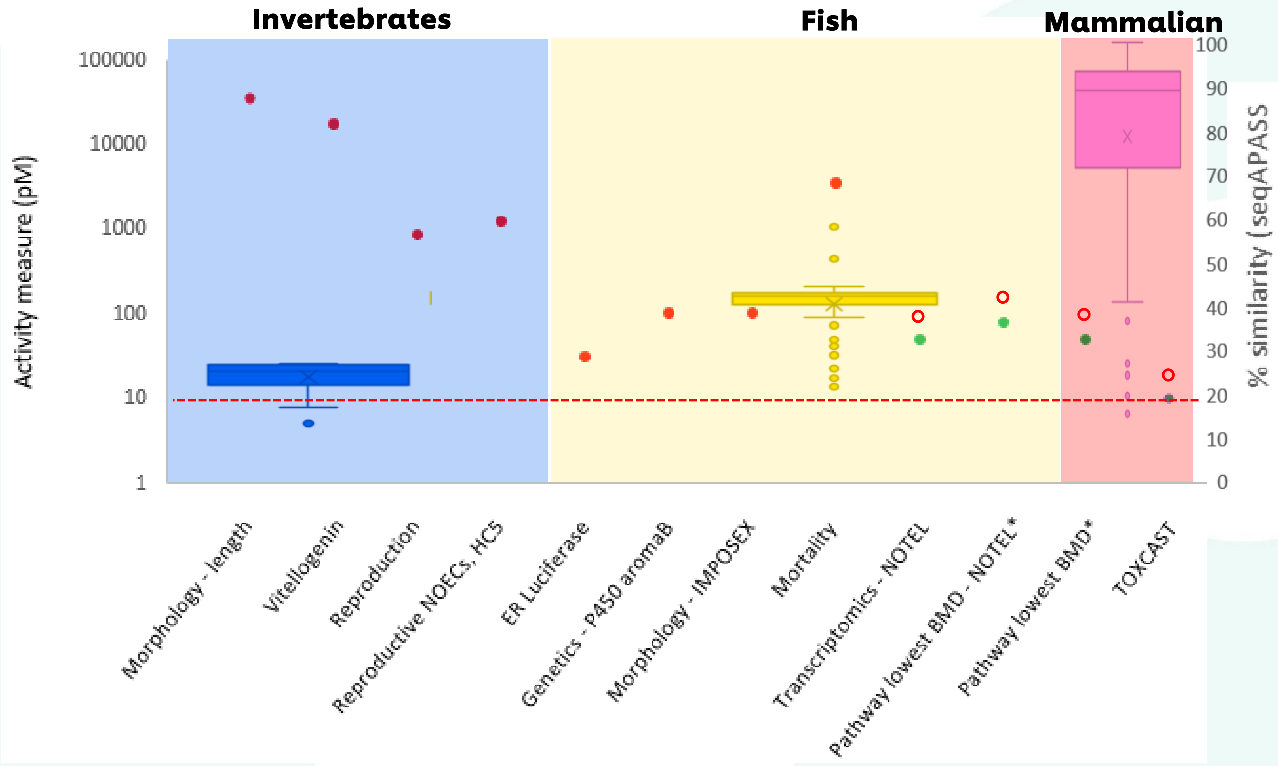
Previous case study: ethinylestradiol



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*

Abstract

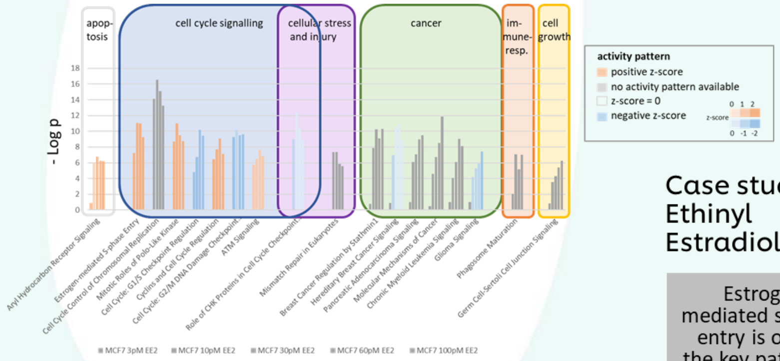
NOTEL 168h* = 50pM

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

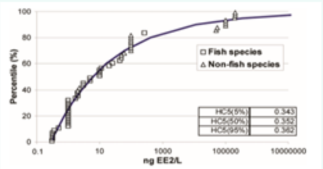


Top 20 pathways predicted by Ingenuity Pathway Analysis (IPA) according to top p-value

Case study: Ethinyl Estradiol (EE2)

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

Literature information



HC5 (50%) = 1200 pM

EC50= 30pM (ER luciferase assay)

Toxcast

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Key highlights

These case studies demonstrate that the integration of traditional *in vivo* data and *in vitro* functional assays from literature coupled with computational tools in a weight of evidence approach can build confidence in safety decision-making.

In summary, the Chlorpyrifos case study :

- ✓Provides confidence that invertebrates are the most sensitive taxa;
- ✓Species sensitivity where the target and pathways are conserved is similar or less sensitive than invertebrates;
- ✓ *in vitro* endpoints are at least as conservative as traditional *in vivo* ones.

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Take-home messages

Challenges that needed to be addressed…

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

If solved can lead to…

Increased use of existing data → Added information from mechanistic vs a "black-box" whole animal study → Opportunities for ethical and efficient data generation → Fully embracing the 'one health' approach to chemical safety

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THANK YOU

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