

Case-Study led Evaluation of an Integrated Human Health-Environmental Next-Generation Risk Assessment Framework

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SERS
Safety, Environmental
& Regulatory Science



Talk Outline

- The Case for further Human Health - Environment integration
- Conceptual approach
- Case study Development
- What Next?

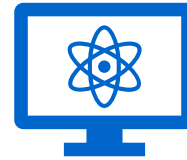
Unilever Policy & Approach

Safe & Sustainable Products without Animal Testing

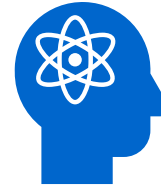
What we believe

- **Every Unilever product must be safe for people and our environment**
- **Animal testing is not needed to assess ingredient & product safety** – there are a wide range of non-animal alternatives grounded in modern science and new technology

How we do it



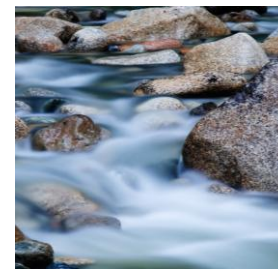
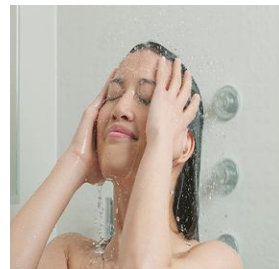
40+ years of non-animal safety science



70+ collaborations

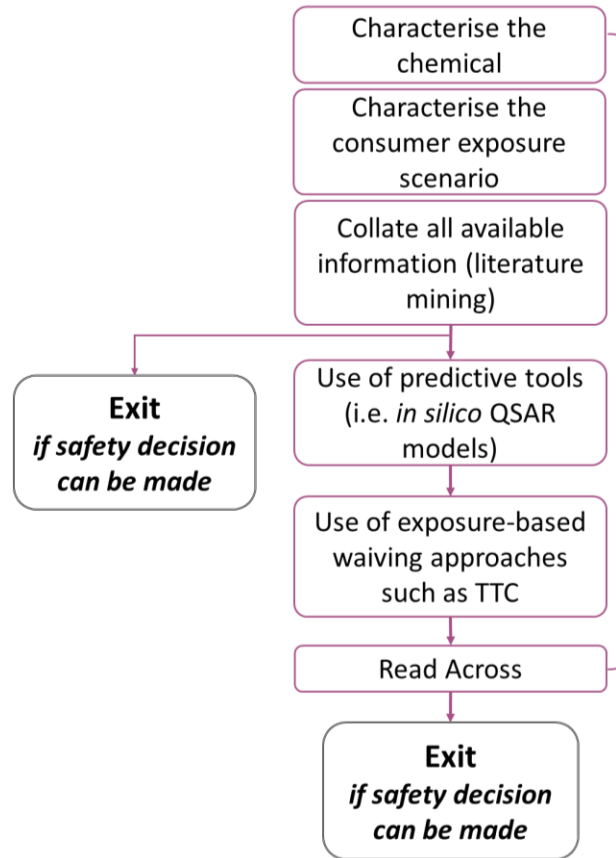


600+ publications

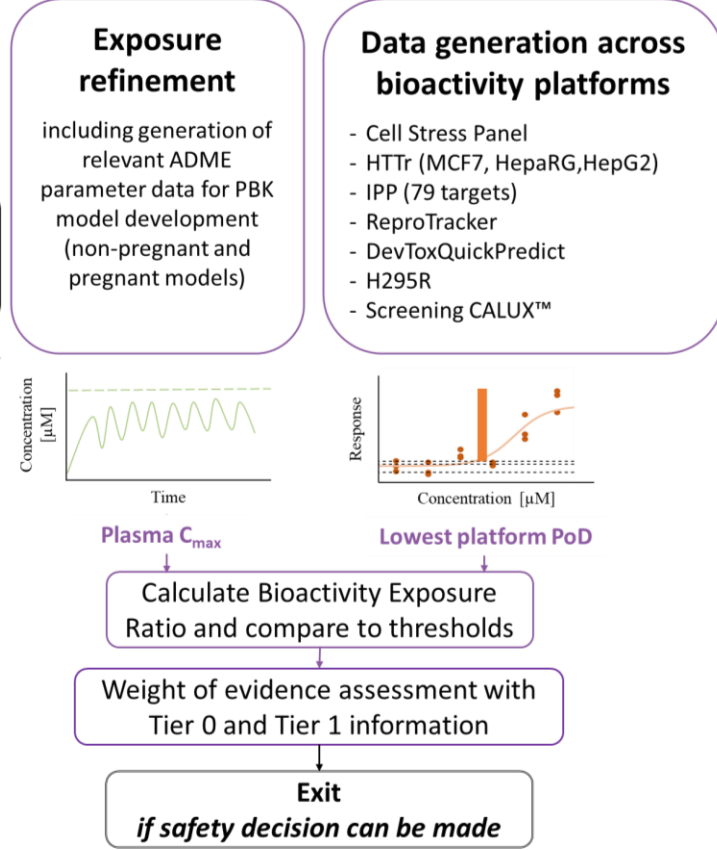


Human Health

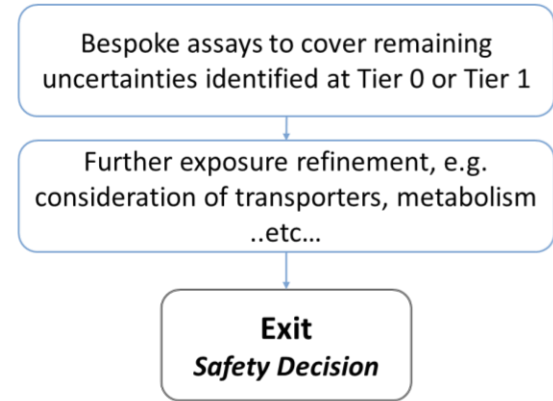
TIER 0: Problem Formulation



TIER 1: Systemic-safety Toolbox

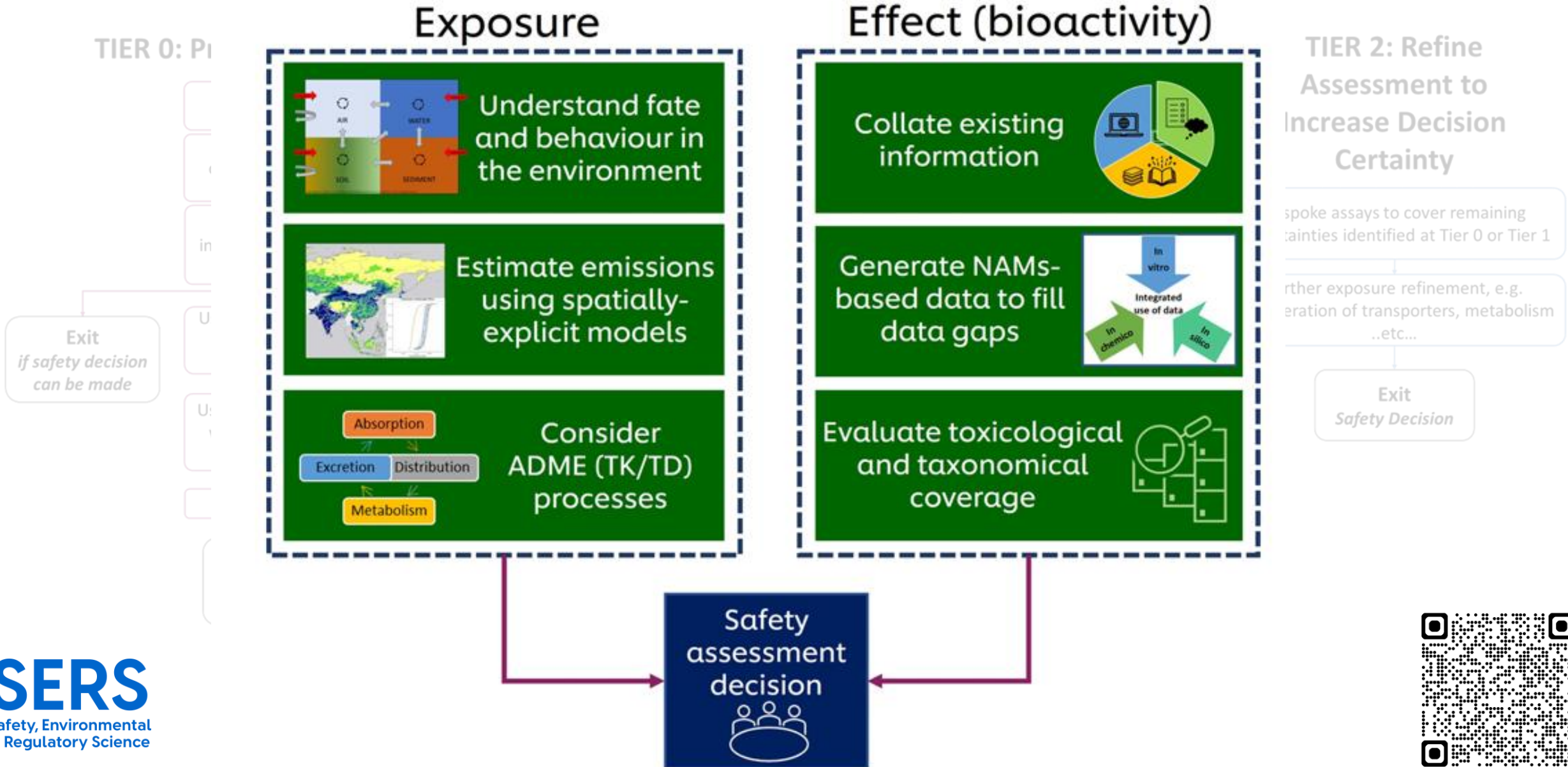


TIER 2: Refine Assessment to Increase Decision Certainty



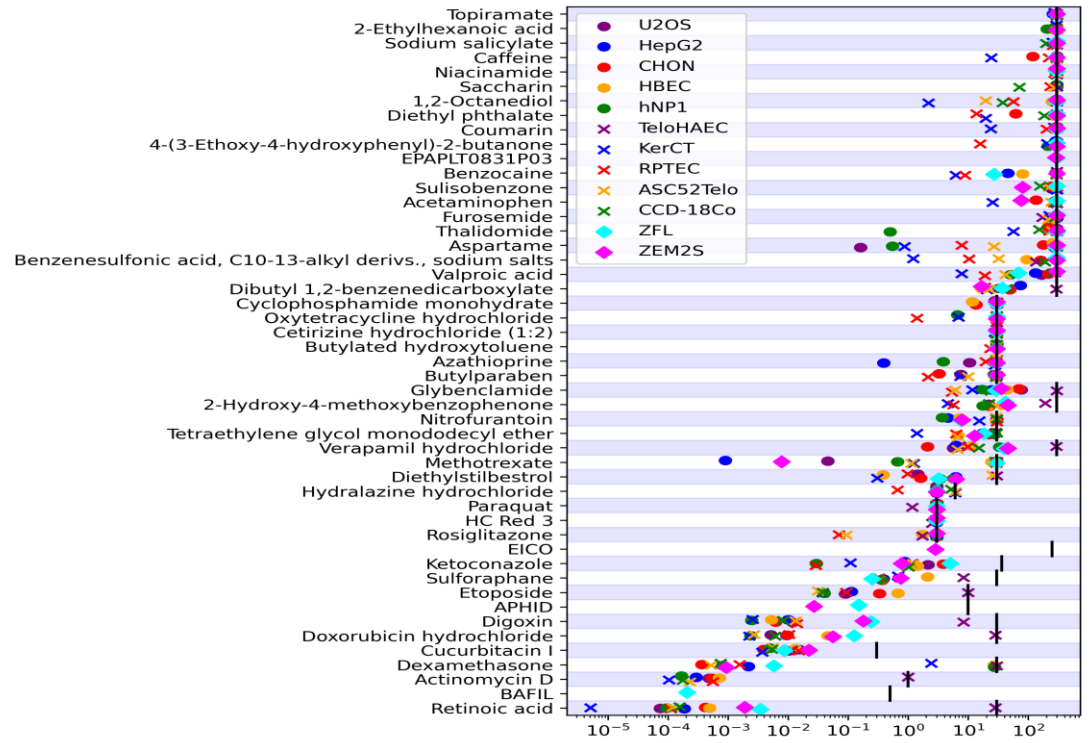
Human Health

Environmental Safety

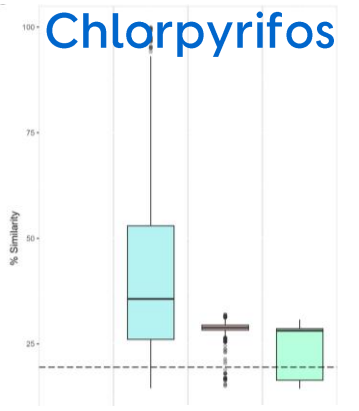
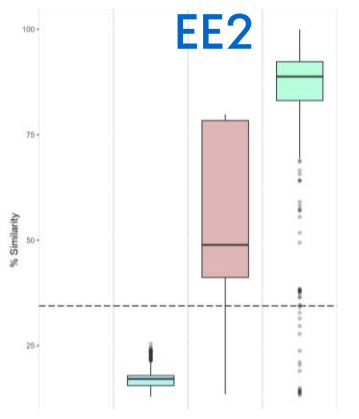
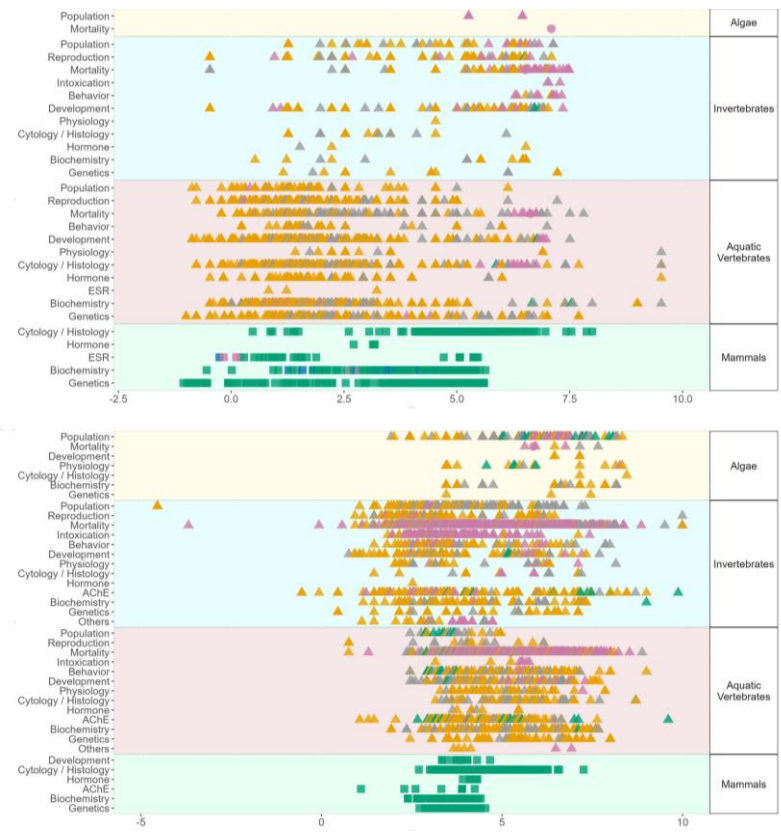


“Previous work indicate strong agreement between species-level toxicological sensitivity and the conservation of underlying molecular targets.”

HTTr (45 chemicals, 10 human+2 fish cell lines)



Data from Harrill, Reynolds et al. unpublished



4 Main overriding principles:

- The overall goal is a human safety risk assessment
- The assessment is exposure led
- The assessment is hypothesis driven
- The assessment is designed to prevent harm

3 Principles describe how a NGRA should be conducted:

- Following an appropriate appraisal of existing information
- Using a tiered and iterative approach
- Using robust and relevant methods and strategies

2 Principles for documenting NGRA:

- Sources of uncertainty should be characterized and documented
- The logic of the approach should be transparent and documented



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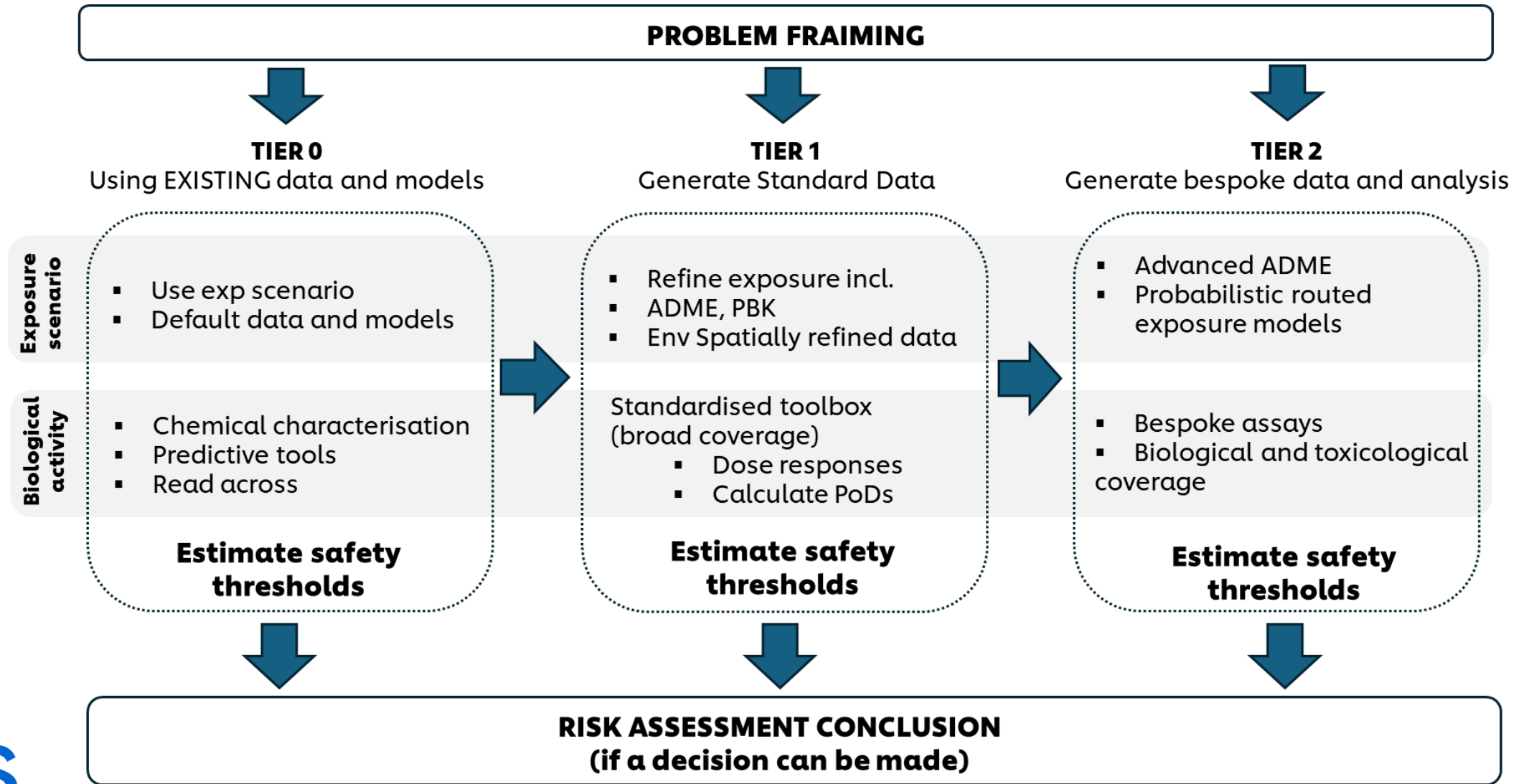
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2 Principles for documenting NGRA:

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1 Integrated framework



Problem formulation:

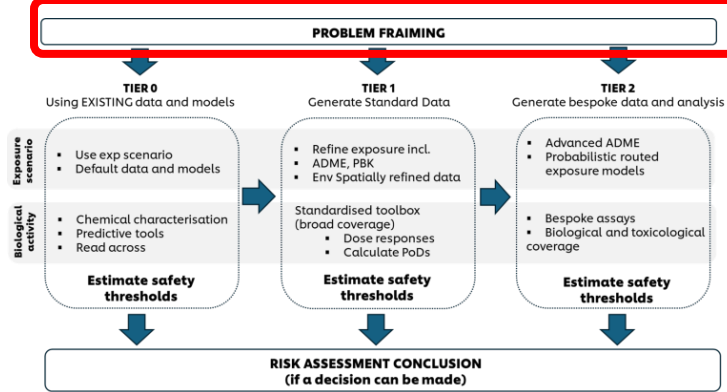
❖ To evaluate how to make a safety decision using non-animal approaches for both human health and the environment.

❖ Case study hypothesis:

Evaluate the introduction of Benzophenone-3, specifically in face cream and body lotion formulations at a 2.2% inclusion level in 2 countries (Spain and China).

❖ Assumptions:

✓ No existing information is available.



Tier 0

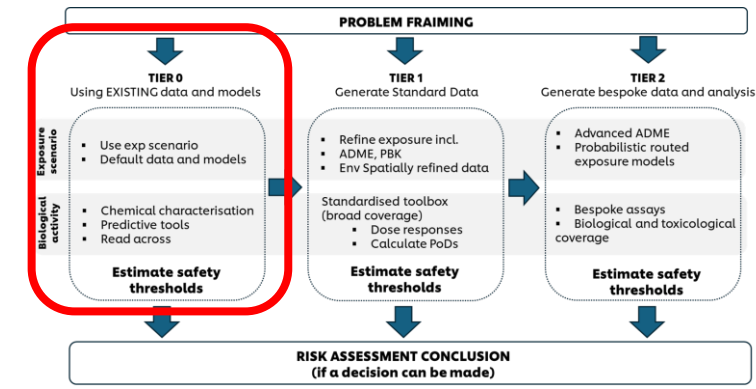
Human exposure :

- Consider Spain and China pop habits and traits (Level 1 PBK)

Product type	Daily exposure (g/d)	Frequency	Surface area (cm2)
Face cream	1.54	2.14/day,	565
Body lotion	7.82	2.28/day	15760

Human hazard :

General Toxicity	MIE Atlas v.2	Hits: MMP9 (1/3), PPARG (1/3) Repeated dose (HESS)
	OECD QSAR Toolbox	2-Acetylaminofluorene (Hepatotoxicity) Alert;2-Amino-4,5-diphenyl thiazole (Renal toxicity) Alert;3-Methylcholantrene (Hepatotoxicity) Alert;Alpha-Naphthyl-isothiocyanate (Hepatotoxicity) Alert;Anthraquinone (Renal toxicity) Alert;Beta-Naphthylisothiocyanate (Hepatotoxicity) Alert;Bromfenac (Hepatotoxicity) Alert;Carbamazepine (Hepatotoxicity) Alert;Carbamazepine (Renal Toxicity) Alert;Diclofenac (Hepatotoxicity) Alert;Indomethacin (Hepatotoxicity) Alert;Mefenamic Acid (Hepatotoxicity) Alert;N-hydroxy-2-acetylaminofluorene (Hepatotoxicity) Alert;Propanolol (Renal toxicity) Alert
Genotoxicity & Carcinogenicity	OECD Toolbox v. 4.7.1	DNA binding by OASIS AN2;AN2 >> [2+2] photoinduced AN2-type cycloaddition;AN2 >> [2+2] photoinduced AN2-type cycloaddition >> Hydroxybenzophenone Derivatives;Non-covalent interaction;Non-covalent interaction >> DNA intercalation;Non-covalent interaction >> DNA intercalation >> Hydroxybenzophenone Derivatives;Radical;Radical >> Radical mechanism by ROS formation;Radical >> Radical mechanism by ROS formation >> Hydroxybenzophenone Derivatives DNA alerts for AMES, CA and MNT by OASIS AN2;AN2 >> [2+2] photoinduced AN2-type cycloaddition;AN2 >> [2+2] photoinduced AN2-type cycloaddition >> Hydroxybenzophenone Derivatives;Non-covalent interaction;Non-covalent interaction >> DNA intercalation;Non-covalent interaction >> DNA intercalation >> Hydroxybenzophenone Derivatives;Radical;Radical >> Radical mechanism by ROS formation;Radical >> Radical mechanism by ROS formation >> Hydroxybenzophenone Derivatives
		1.Estrogen CERAPP - Agonist: 1, Antagonist: 1, Overall binding: 1 Androgen CoMPARA - Agonist: 0, Antagonist: 1, Overall binding: 1
DART	OPERA	3.Estrogen CERAPP - Possible active (LOW reliability)
	VEGA	



Environmental exposure : Regulatory model CHESAR

Country	PEC* continental [ng/L]	PEC* regional [ng/L]	PEC* local [ng/L]
Spain	0.0259	0.197	25600
China	0.6	4.53	4660

*PEC: Predicted Env Concentration

Environmental hazard:

MoA profilers:

TEST	Narcosis
ASTER	Nonpolar narcosis
OASIS	Phenols and Anilines
Verhaar	Class 3 (unspecific reactivity)

Predicted ecotoxicity – ECOSAR

ECOSAR v1.11 Class-specific Estimations

ECOSAR Class	Organism	Duration	End Pt	mg/L (ppm)
Phenols	Fish	96-hr	LC50	2.749
Phenols	Daphnid	48-hr	LC50	1.632
Phenols	Green Algae	96-hr	EC50	6.474 *
Phenols	Fish		ChV	0.347
Phenols	Daphnid		ChV	0.310
Phenols	Green Algae		ChV	2.983
Phenols	Fish (SW)	96-hr	LC50	0.935
Phenols	Earthworm	14-day	LC50	50.457 *
Phenols	Lemna gibba	7-day	EC50	1.345
Neutral Organic SAR (Baseline Toxicity)	Fish	96-hr	LC50	8.009 *
	Daphnid	48-hr	LC50	5.235 *
	Green Algae	96-hr	EC50	6.980 *
	Fish		ChV	0.924
	Daphnid		ChV	0.755
	Green Algae		ChV	2.501

Tier 1 Exposure

Human (internal) exposure :

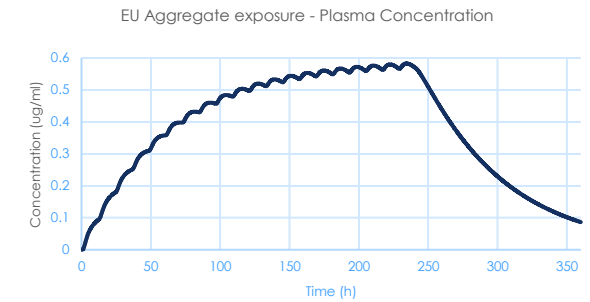
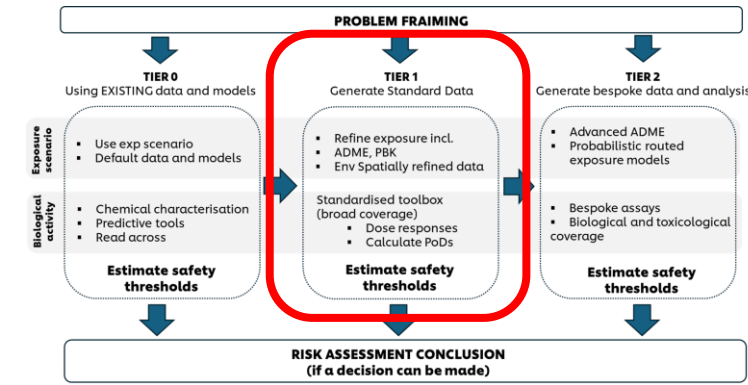
- Models adjusted to reflect body parameters for different countries (Spain vs China)
- PBK simulation – "L2"; 240 hour repeated exposure + 120 hour no exposure)

Environmental Exposure (external):

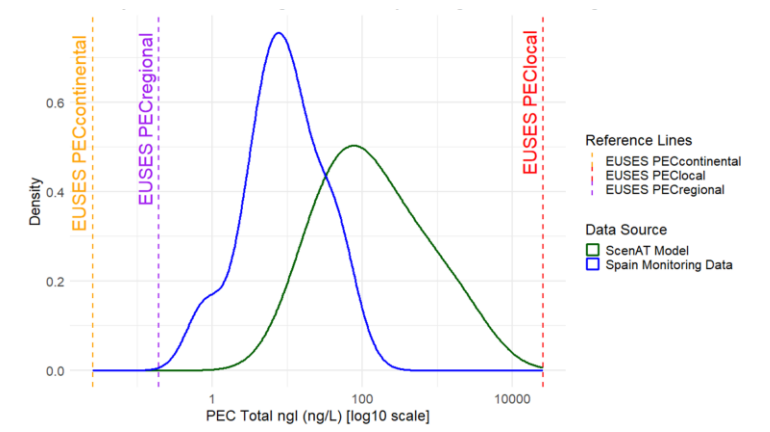
- spatially explicit model ScenAT for Spain, and China using population distribution

Environmental exposure Internal :

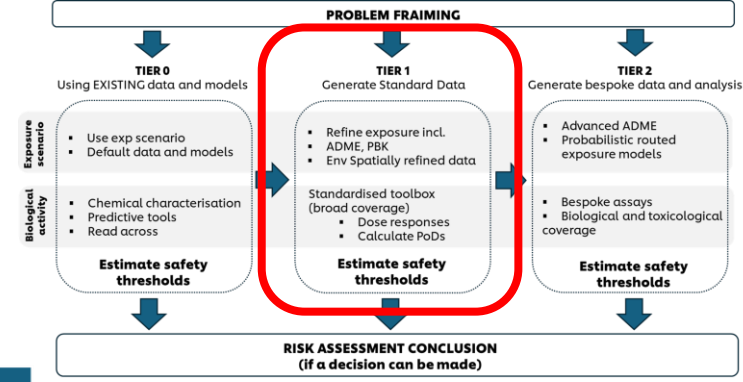
- Reverse dosimetry of in vitro concentrations to water using fish QIVIVE models including biotransformation



C_{max} = 2.09 uM



Tier 1 Hazard



Assay	Design (in vitro)	Lowest POD (uM)
HTTr	10 human cell lines	1.60 (Ker-CT)
	HepaRG, MCF-7, HepG2	1.90 (MCF-7)
	HepaRG, MCF-7, U2OS	18 (U2OS)
HTPP	10 human cell lines	6.97 (RPTEC)
Cell Stress Panel	HepG2	19
IPP		2.8
Reprotracker		16.73 (cytotox, neural)
DevToQP		92.5
Calux		10 (E2)
ToxCAS		2.38



Assay	Design (in vitro)	Lowest POD (uM)
Acute fish toxicity (OECD249)	RT-gill	14.33
HTTr (reduced panel)	ZFL and ZEM2S	32.0 (ZFL)
HTPP	ZFL and ZEM2S	20.8 (ZFL)

Assay	Design (in vivo)	Lowest POD (uM)
Algae acute toxicity test (OECD201)	<i>P. subcapitata</i>	1.79
Daphnia acute toxicity test	<i>D. magna</i>	3.59
Algae chronic toxicity test (OECD201)	<i>P. subcapitata</i>	0.35
Daphnia chronic toxicity test	<i>D. magna</i>	2.19



In vitro

HTTr

HPP

CSP

IPP

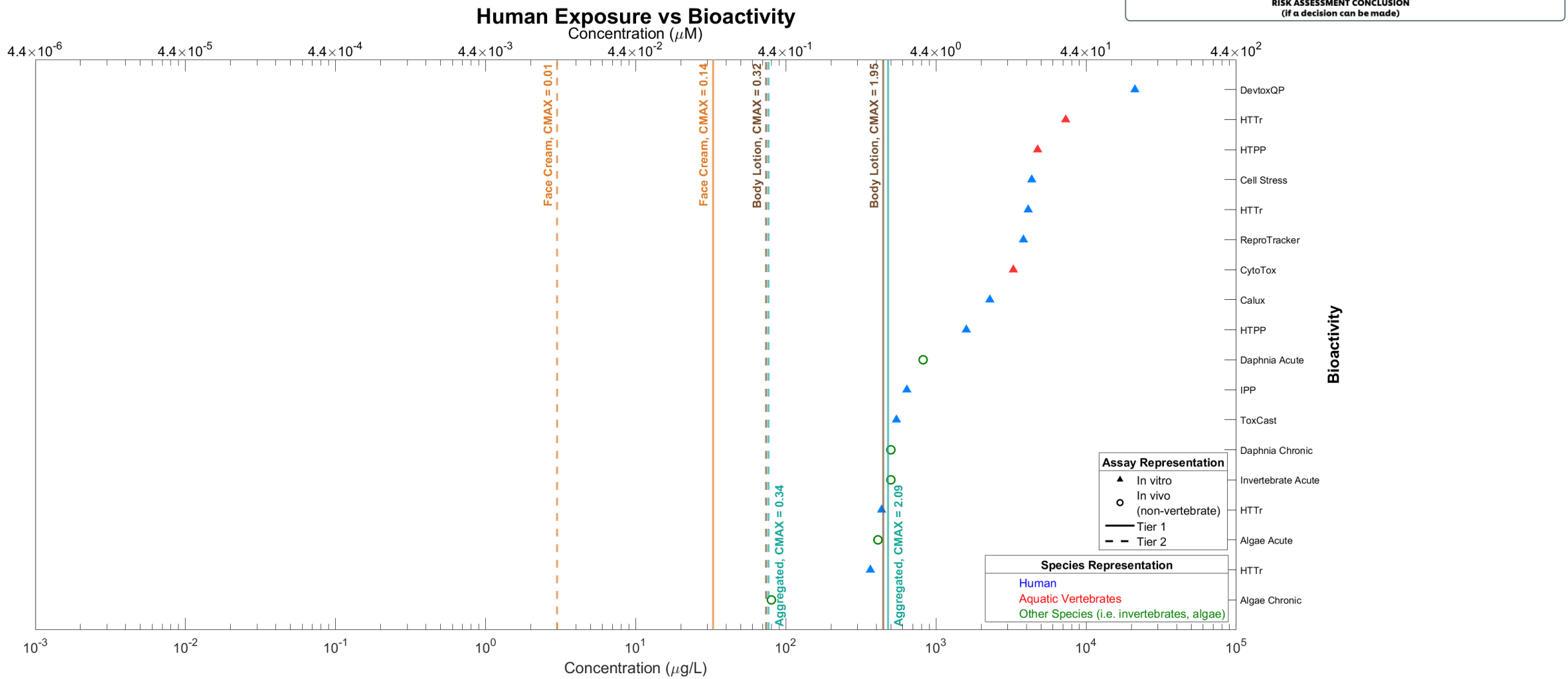
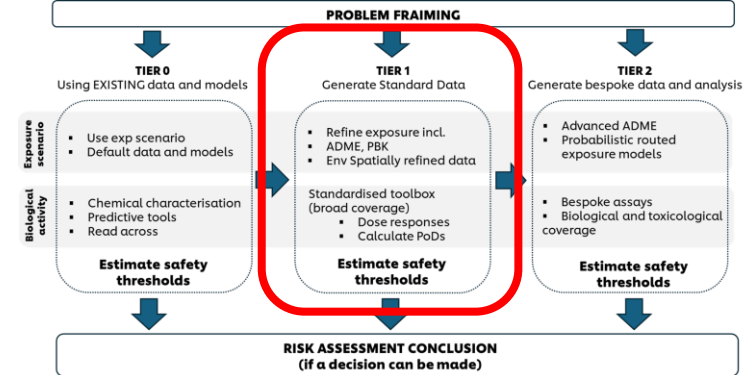
HTS

ReproTracker
DevToxQP
Calux

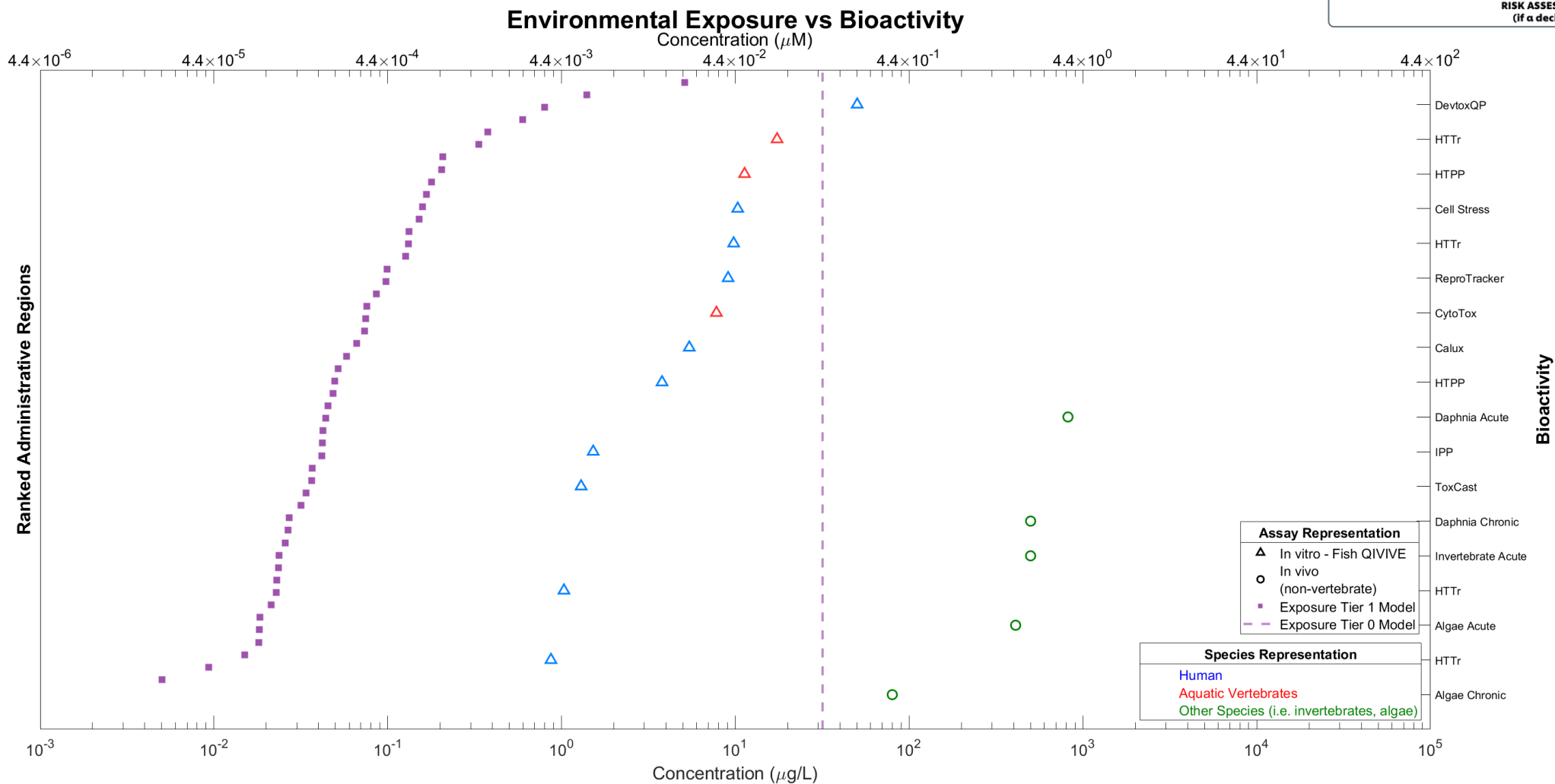
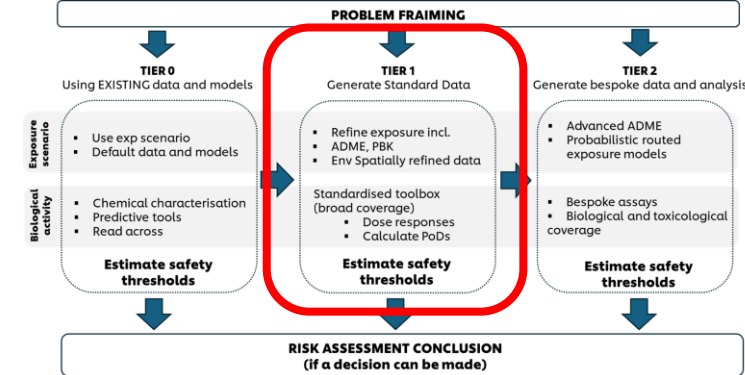
In vivo

Algae
Daphnia

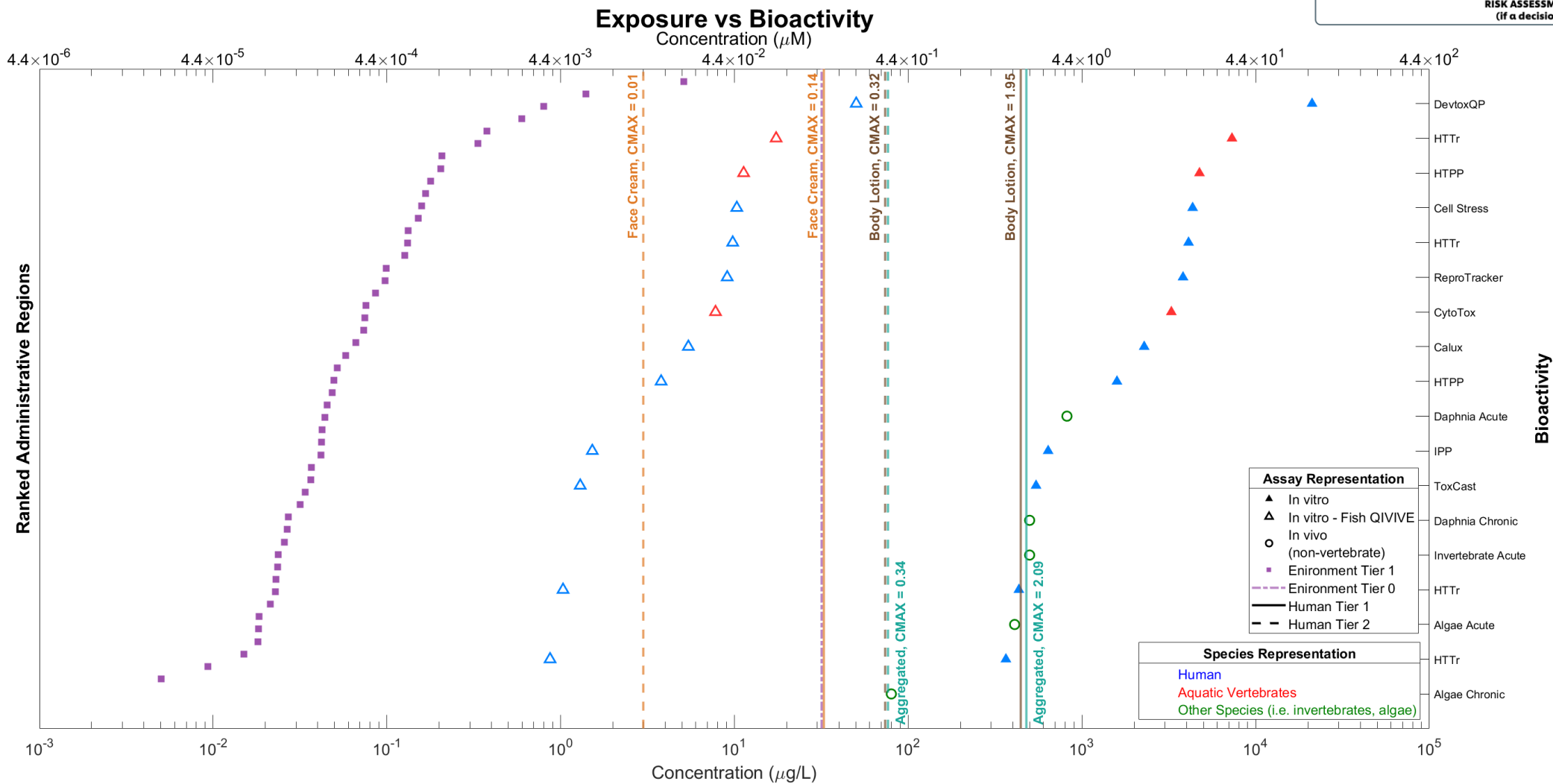
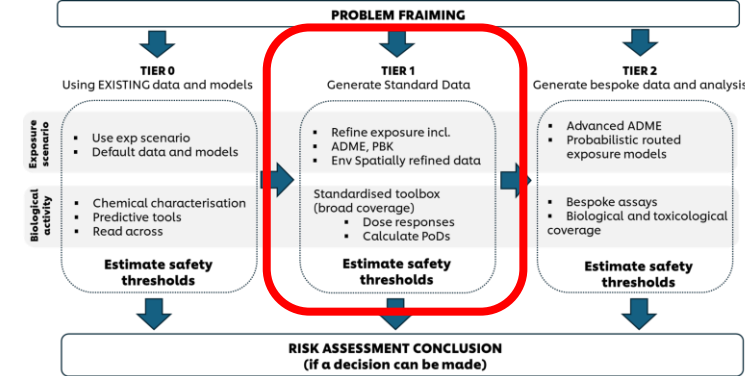
Tier 1 Results- Human



Tier 1 Results- Environment

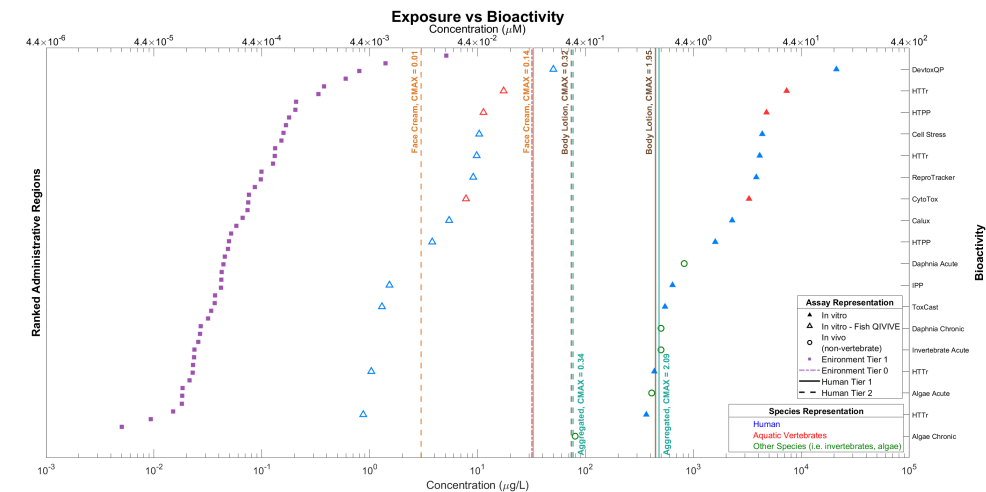


Tier 1 Results- Human Env Integration



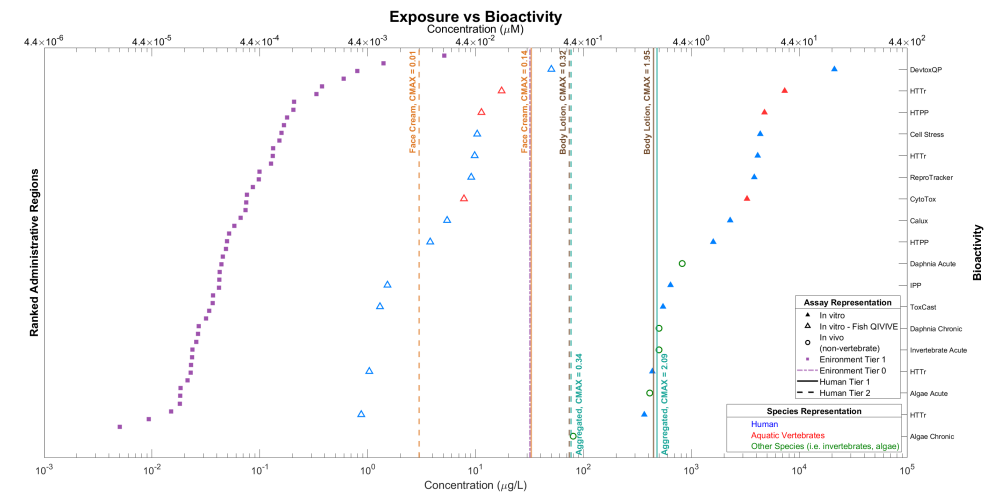
Work in Progress

- ❑ Refinement of bioactivity analyses across tiers
- ❑ Metabolism and biotransformation integration
- ❑ Cross-species mechanistic interpretation
- ❑ Exposure modelling refinement and benchmarking



Key messages

1. Human and environmental evidence converges on consistent conclusions
2. Exposure modelling incl. PBK, qIVIVE and Env Exposure drives risk interpretation
3. Linking bioactivity to realistic exposure is the cornerstone of NGRA
4. The tiered, exposure-led framework works in practice
5. Integrated HH/Env decision-making without animal data is achievable



1

Mechanistic and exposure-led approaches align across domains

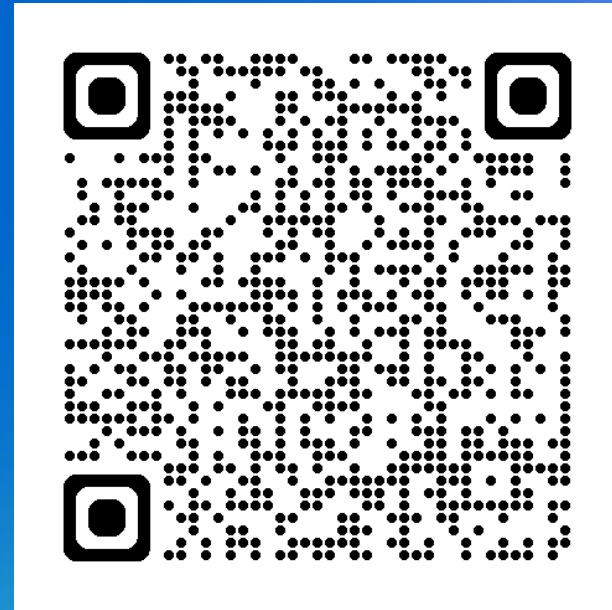
2

Conservation of toxicological targets supports cross-species relevance

3

Outcome: a more robust, efficient and future-fit risk assessment paradigm based on multidisciplinary approaches

Thank you



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