

Case Study-Led Evaluation of an Integrated Human Health–Environmental



Next Generation Risk Assessment Framework

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HH: Human Health
 ES: Environmental Safety
 NGRA: Next Generation Risk Assessment
 NAMs: New Approach Methodologies
 PoD: Point of Departure
 BER: Bioactivity - Exposure ratio
 PBK: Physiologically-Based Kinetics
 QIVIVE: Quantitative In-Vitro-to-In-Vivo Extrapolation

The Case for Human Health - Environment integration

- ❖ While HH and ES have traditionally been related but separate disciplines, there is growing recognition of the benefits of increased integration to enhance scientific robustness, efficiency, and transparency ^a.
- ❖ The evolution of chemical safety assessment is increasingly shaped by the adoption of NGRA principles, which prioritise non-animal NAMs that are applied alongside robust and refined exposure data and models ^{b, c, d, e}.

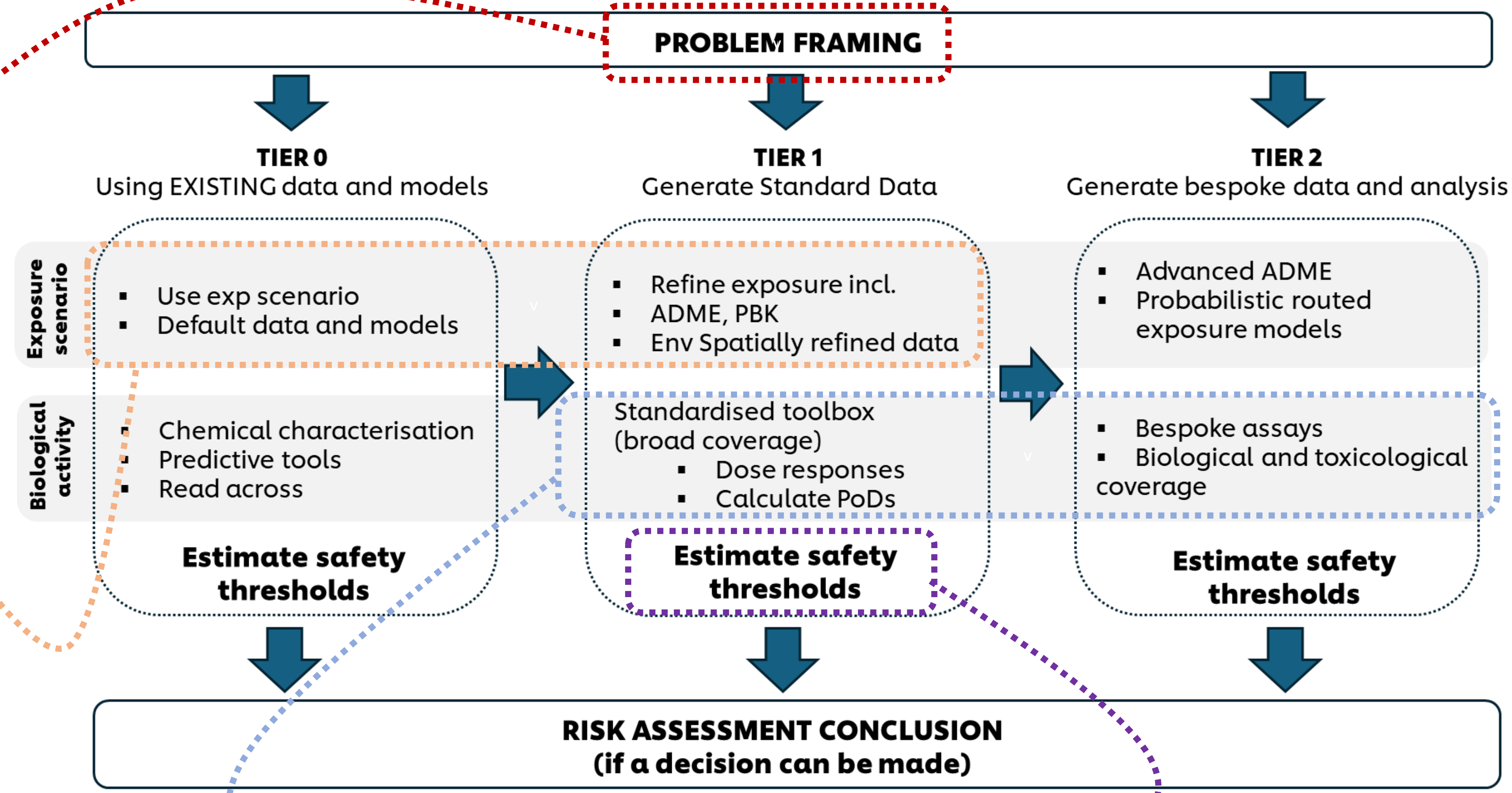
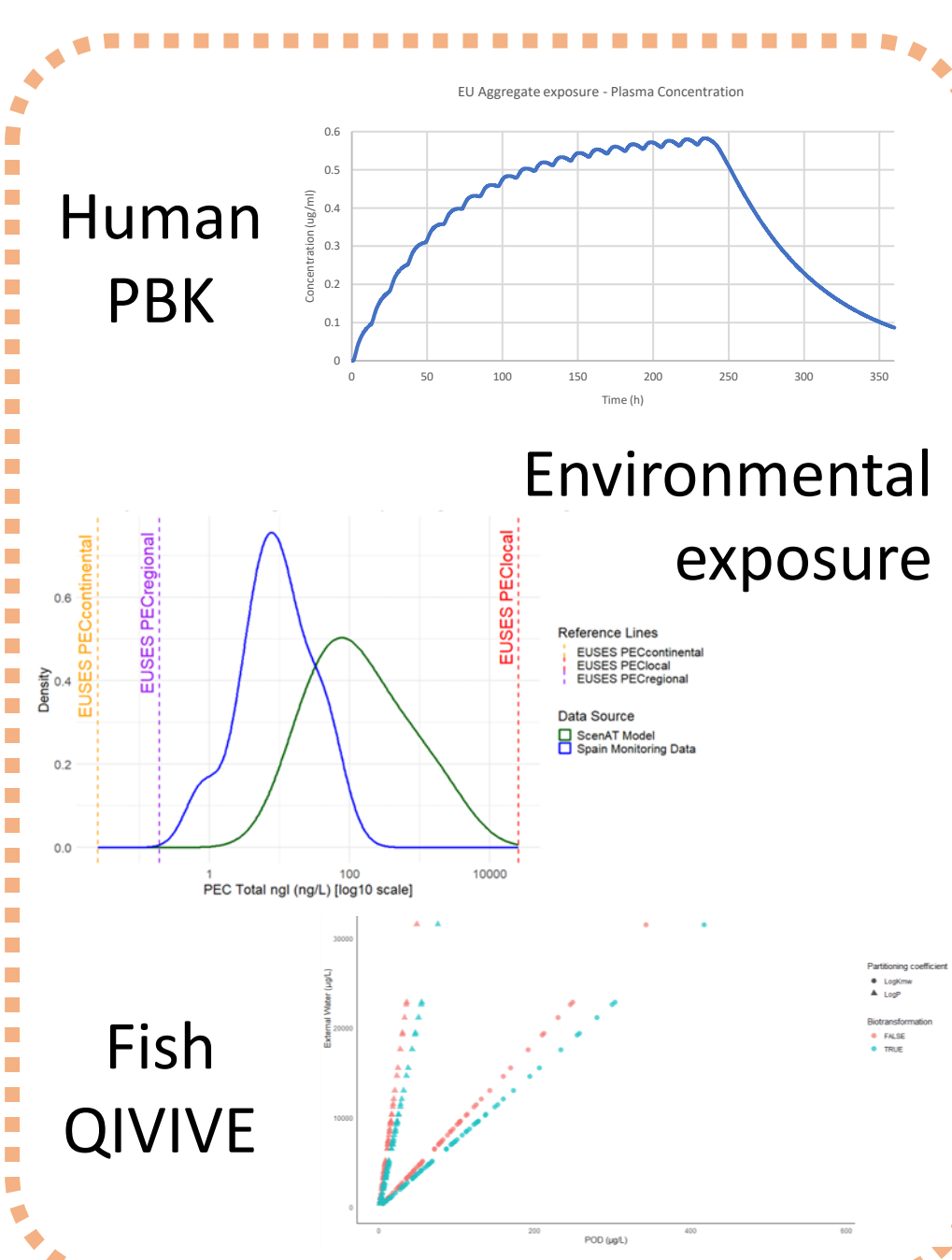
Integrating Safety Assessments: a Conceptual Approach

- ❖ We present a novel, tiered NGRA framework designed to integrate HH and ES, enabling cross-domain alignment over exposure and hazard.
- ❖ It leverages in silico tools and existing data to predict chemical properties and toxicity mechanisms relevant to both HH and ES relevant species, before incorporating a battery of NAMs spanning diverse biological and taxonomic domains to generate protective PoDs for species of interest.

Case-Study

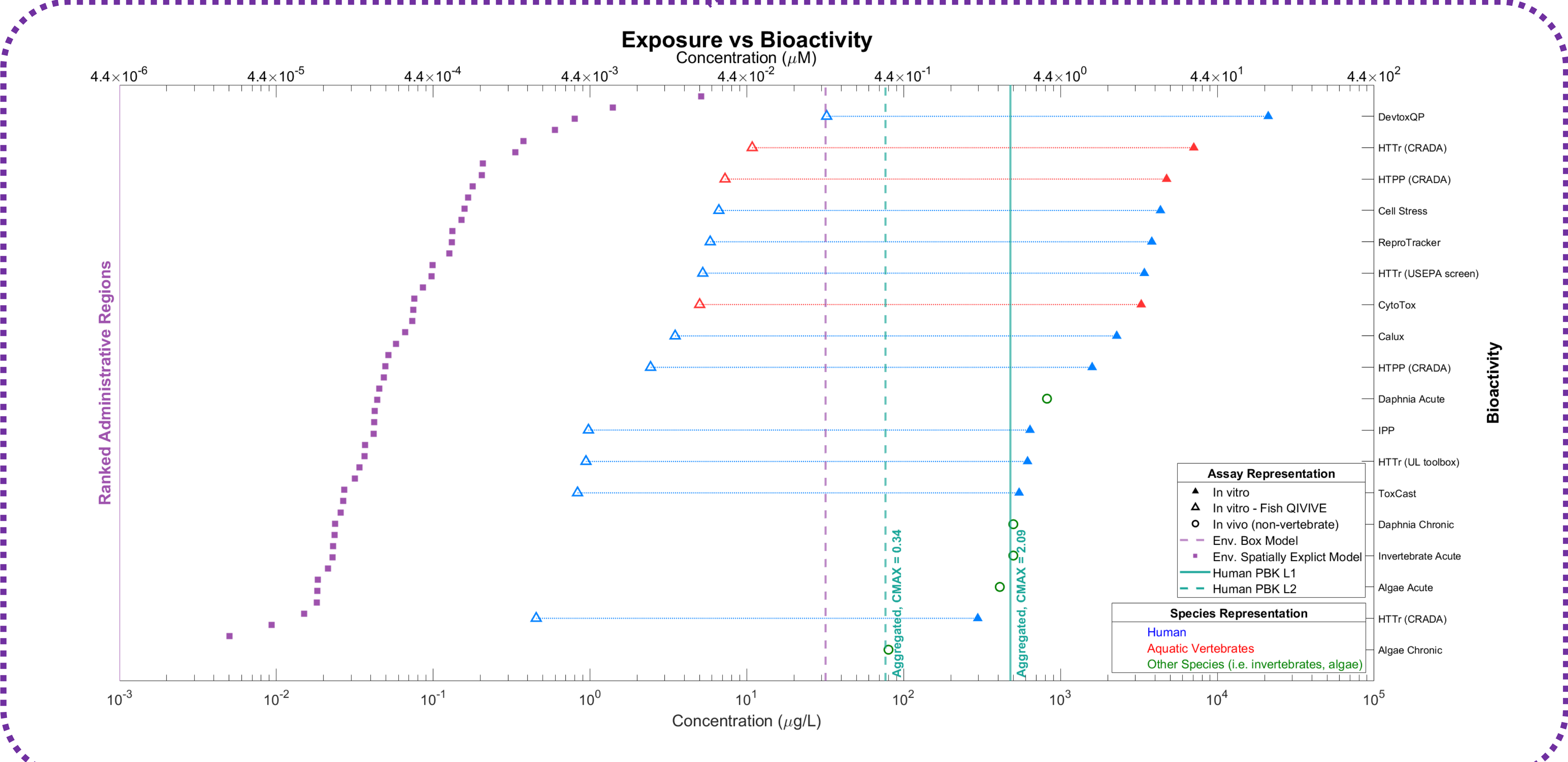
The integrated framework is evaluated using **Benzophenone-3 (BP-3)**, a UV filter used in personal care products, to demonstrate a safety decision using non-animal approaches for both human health and the environment can be made

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



In silico predictions and in vitro bioactivity data from human- and fish-derived models were assessed alongside non-vertebrate in vivo data to define safe exposure levels. Human and environmental exposures were estimated using country-specific scenarios and PBK models. Molecular homology tools are employed to evaluate the evolutionary conservation of biological targets and toxicological processes to support cross-species interpretation of bioactivity data.

	Data Available	Species
In vitro	HTTr	Human (3 cell lines)
	HTPP	Human (3 cell lines)
	CSP	Human 10 cell lines) + fish (2 cell lines)
	IPP	Human 10 cell lines) + fish (2 cell lines)
	HTS	Human
In vivo	ReproTracker	Human
	DevTox	Human
	CALUX	Human
	Algae Daphnia	Invertebrates and plants



Key Messages and Learnings

This case study-driven analysis highlights the practicality and benefits of an integrated NGRA framework, promoting more thorough, ethical, and scientifically sound chemical safety evaluations consistent with modern toxicology principles. Overall, the BP-3 case study shows that human health and environmental safety assessments can be successfully conducted using NAMs when exposure, bioactivity, and kinetics are assessed in a coordinated way. Although the framework seeks to standardize assessment approaches, variations in exposure evaluation, protection objectives, and species biology require tailored domain-specific considerations.

- ✓ Early alignment through shared problem formulation is critical
- ✓ BERs provide a transparent quantitative bridge between HH and ES evidence streams
- ✓ Cross species integration can be achieved but requires context and interpretation
- ✓ The case study highlights where integration is already robust and where expert judgement remains essential, particularly when protection goals or biological relevance diverge
- ✓ Explicit decision gates between tiers are essential to avoid data accumulation without improving decision process



a. Rivetti, et al. *Toxicology In Vitro* 62 (2020): 104692.
 b. Carmichael, et al. 39.3 (2022): 359-366.
 c. Baltazar, et al. *ALTEX* 42.3 (2025): 511-530.
 d. Rivetti and Campos. *IEAM* 19.3 (2023): 571-573.
 e. Rivetti, et al. *NAM Journal* 1 (2025): 100028.

