Application of an integrated approach using NAMs for NGRA protective of DART

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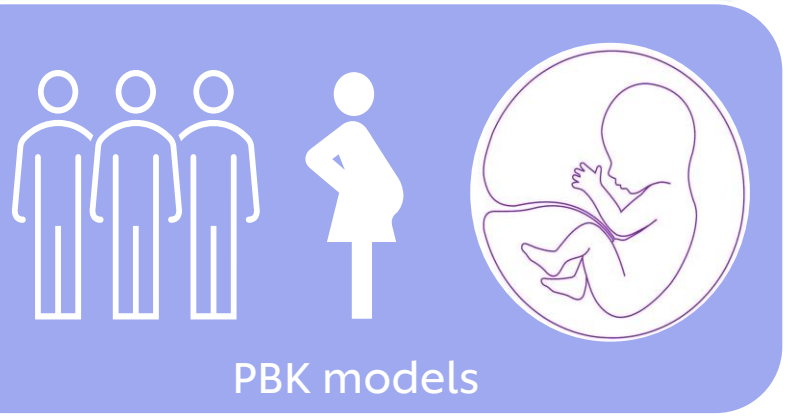
The Next Generation Risk Assessment (NGRA) Approach

Systemic Exposure Estimates

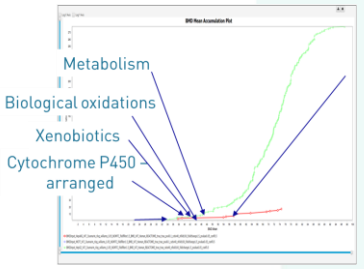
Estimation of systemic exposure to a compound through physiologically-based kinetic modelling or clinical data

Clinical Data → Cmax

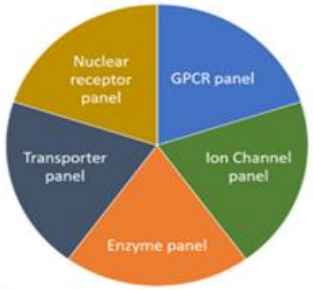


In vitro biological activity characterisation

Dose response analysis of NAMs used to create a NGRA approach which is protective for DART, (Rajagopal et al., 2022). Point of Departure (PoD) calculated for each assay which is the lowest concentration that elicits bioactivity.



HTTr



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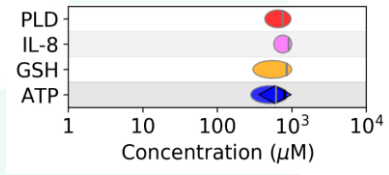
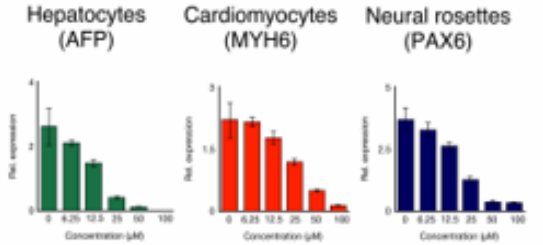
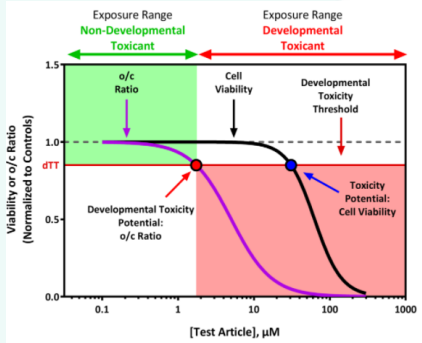


Cell Stress Panel



ReproTracker

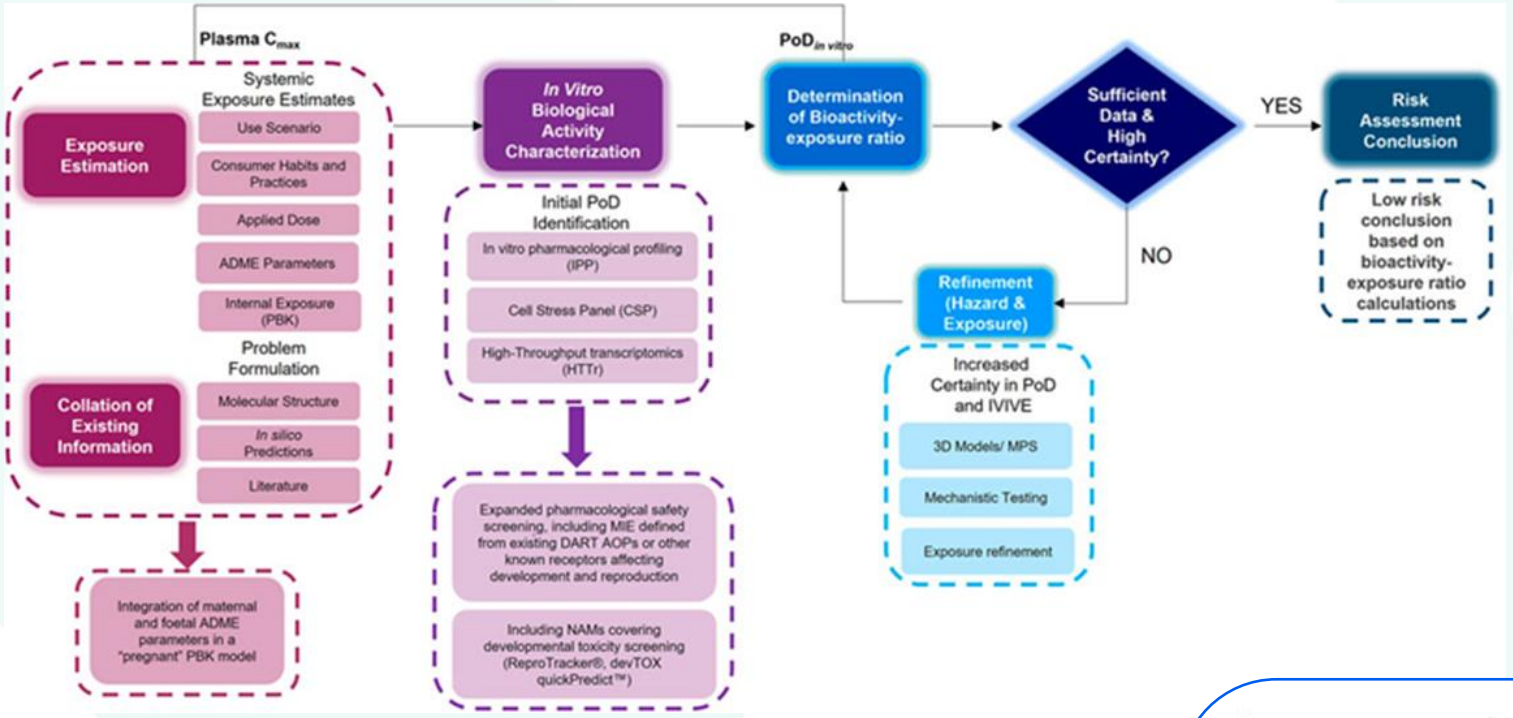


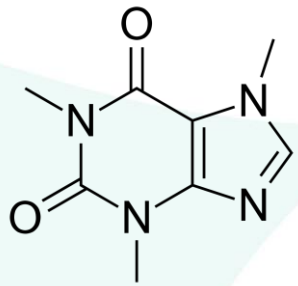
devTox quickPredict™

Calculate Bioactivity Exposure Ratio (BER)

(Middleton et al., 2022)

Caffeine Case Study

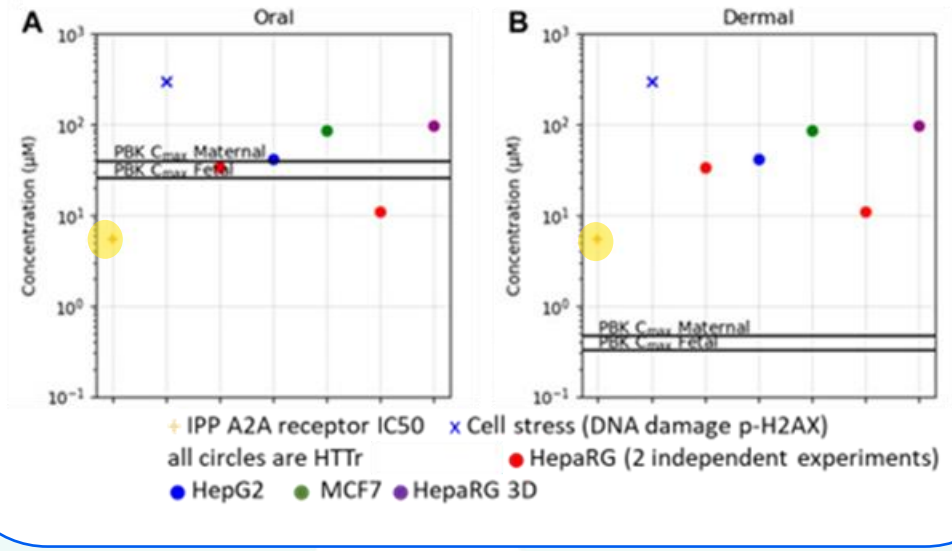




Rajagopal et al., Front. Toxicol., 07 March 2022
https://doi.org/10.3389/ftox.2022.838466

Adenosine 2A receptor – most sensitive target

Compound	Exposure Scenario	Cmax (µM)		Bioactivity-Exposure Ratio (BER)	Safety Decision
		Maternal Plasma	Foetal Plasma		
Caffeine	Oral- 200mg/day	39.72	25.27	0.1-12	High Risk
	Dermal- 0.1% in body lotion	0.46	0.32	12-950	Low Risk



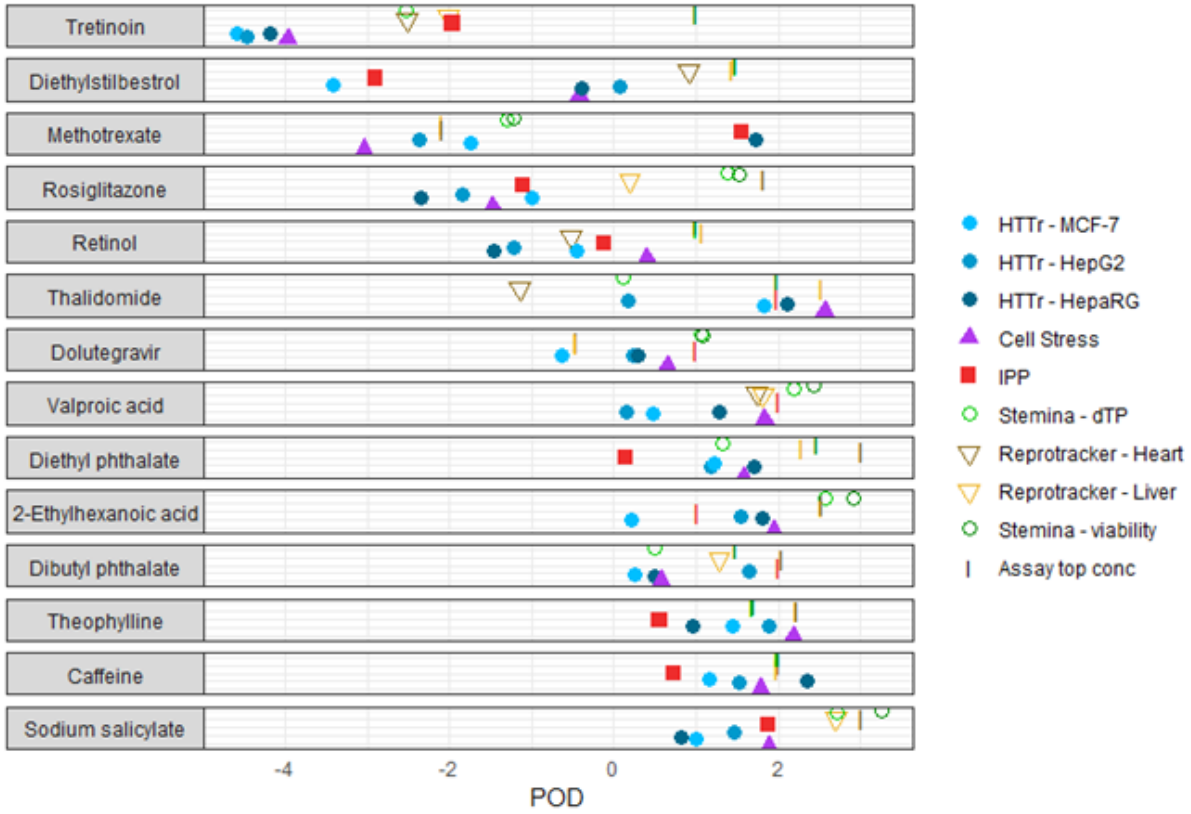
Framework Evaluation

Aims & Objectives

- Build confidence in our approach
- Run 40 compounds through framework
- Identify refinements

Refinements

- Placental transfer parameters
- In silico predictions



Point of Departure (PoD) values for the first 14 compounds that have been run through all 5 assays. (Top concentration only shown where PoD not calculated).

Acknowledgements

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