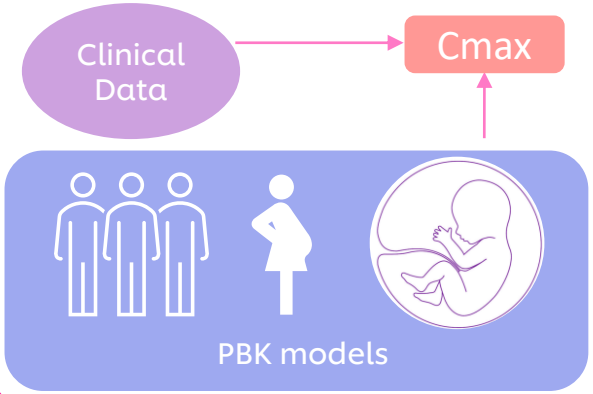
Application of an integrated approach using New Approach Methodologies (NAMs) for Next Generation Risk Assessment (NGRA) protective of developmental and reproductive toxicity (DART).

The NGRA approach

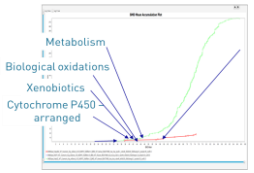
Systemic Exposure Estimates

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

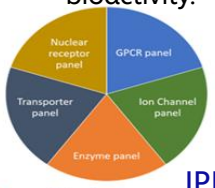


In vitro biological activity characterisation

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.

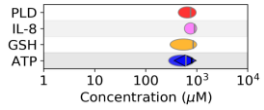


HTTr

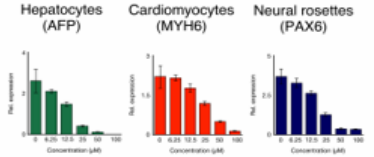


eurofins | Cerep

IPP+



Cell Stress Panel



ReproTracker®

devTox quickPredict™

Calculate Bioactivity Exposure Ratio (BER)

(Middleton et al., 2022)

Framework Evaluation

Evaluation of the protectiveness of the framework

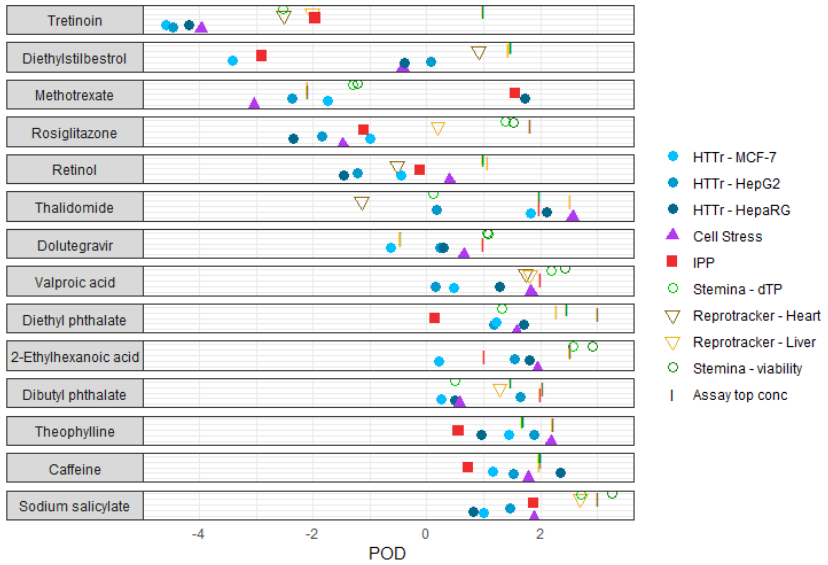
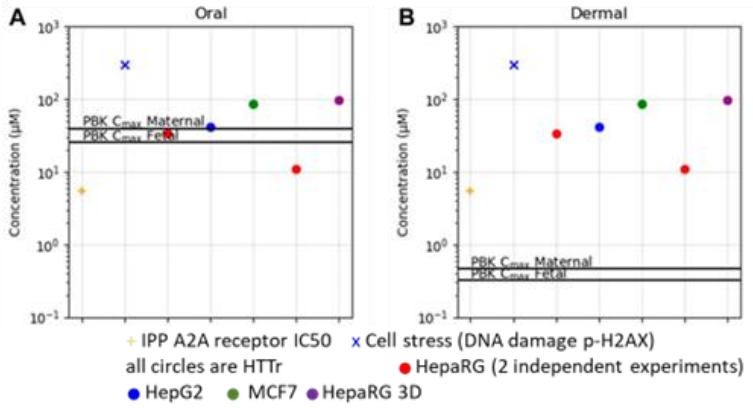


Figure 2- *Point of Departure (PoD) values for the first 14 compounds that have been run through all 5 assays. (Top concentration only shown where PoD not calculated).*

Caffeine Case Study

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

Figure 1- *Comparison of Cmax and PoD values for the exposure scenarios of Caffeine (A- oral 200mg/day, B- dermal 0.1% in body lotion) to illustrate the Bioactivity Exposure Ratio that can be used for safety decisions.*



Conclusions and Outlook

This NGRA framework integrates NAMs with the aim to make safety decisions that are protective for DART. Comparing PoD's to levels of systemic exposure can be used to make a safety decision using Bioactivity Exposure Ratio. The caffeine case study demonstrates the approach to be conservative when compared to published safe levels of caffeine for pregnant women. To build confidence in the approach work is ongoing to expand the datasets to critically evaluate the framework as well as to identify any refinements. A couple of data gaps have already been identified and research has begun on how to fill these. These include placental transfer within PBK modelling and in silico predictions.

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