2763/ P229. Quantifying the DARTable Genome for Prediction of Teratogenic Doses - a case study using retinoic acid pathway-induced developmental toxicity

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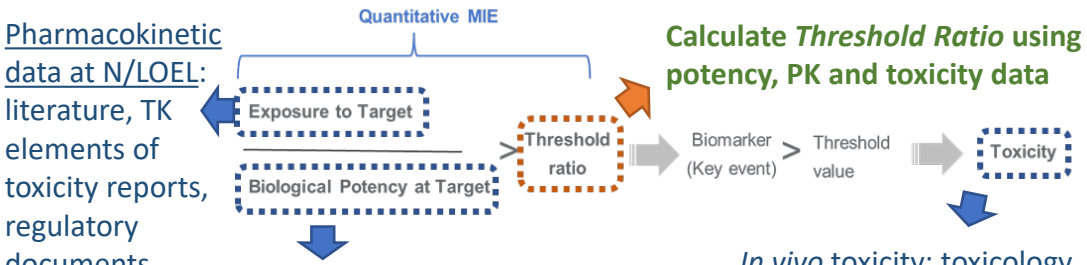
1. Introduction

- The goal of the HESI DARTable Genome Working Group is to build a compendium of quantitative molecular initiating events (MIEs) and key event biomarkers for teratogenicity prediction.
- Our initial case study focused on an AOP framework linking adverse developmental outcome(s) to perturbation of each of the three retinoic acid receptor isotypes: alpha (RARa) , beta (RARb) and gamma (RARg).
- This investigation focused on the relationship(s) between chemical potency on RAR targets and the quantitative threshold of maternal systemic exposure necessary to produce a teratogenic outcome.

2. Building a quantitative model for the DARTable genome: all-trans retinoic acid (ATRA) signaling.

This model can be used to calculate a Threshold Ratio of exposure below (or above) which the likelihood of a chemical causing a toxicity by that AOP is low (or high).



Pharmacokinetic data at N/LOEL: literature, TK elements of toxicity reports, regulatory documents

In vitro assay potency: databases, patents, regulatory documents

Calculate *Threshold Ratio* using potency, PK and toxicity data

In vivo toxicity: toxicology study reports, literature, regulatory documents

3. Reference Compounds.

- For 20 compounds with known retinoid agonist or antagonist activity we compiled RAR potency for each RAR-isotype, including pharmacokinetic and toxicology information for rat and rabbits.
- Here, we present results for 3 retinoids that had complete data in the rat, and 2 of which also had suitable rabbit data.

4. Results of Threshold Ratio visualization on 3 retinoid case examples.

- We calculated Threshold Ratios for each RAR isotype utilizing the estimated dam or doe steady-state blood concentration at the NOEL and LOEL.
- Model returns a Threshold Ratio for exposure-biological potency driving developmental toxicity at each RAR isotype.
- An exposure-potency threshold > 2 for RARa or RARg best characterized LOELs for retinoid developmental toxicity; RARb did not fit the pattern.

compound	*receptor*	Rat ratio		Rabbit ratio	
		NOEL	LOEL	NOEL	LOEL
alitretinoin	RARa	1.3	2.9	nd	1.91
	RARb	0.10	0.22	nd	0.14
	RARg	0.29	0.65	nd	0.43
trifarotene	RARa	0.01	0.03	0.002	0.02
	RARb	0.04	0.12	0.008	0.06
	RARg	0.69	2.1	0.126	1.04
tazarotene	RARa	0.65	13	nd	nd
	RARb	2.8	57	nd	nd
	RARg	0.65	13	nd	nd

5. Conclusions, lessons learned and next steps

- The model derived DART-predictive exposure-potency Threshold Ratios to predict developmental toxicity; PK data was the largest missing data type.
- Toxic responses considered as thresholds were driven by RARa or RARg from public data sources; however, RARb did not fit the pattern.
- Relevant data overall can be unstructured or incomplete and difficult to find, access, or compile into a computable model.
- 'FAIR' data principles are vital to enable sharing of the toxicity, potency and pharmacokinetic data for predictive toxicology.
- It will be informative to determine if patterns for retinoid-based RAR target ratios generalize to chemicals that alter ATRA metabolism.
- The next case study selected for the DARTable genome will focus on Thalidomide-like compounds.