Framework for Predictive Developmental Toxicity of Chemicals Regulated under TSCA

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Overview

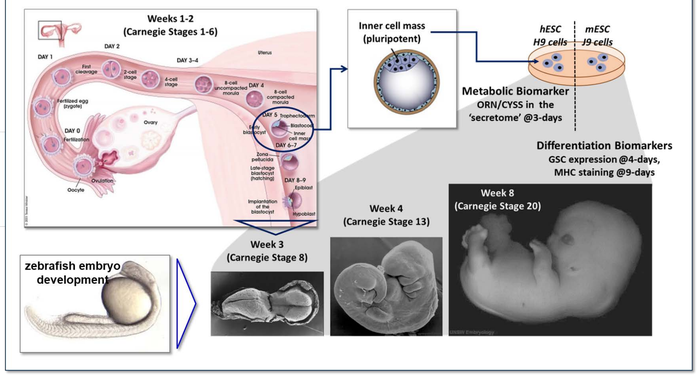
OBJECTIVE: build a framework for pre-prioritizing chemicals for developmental toxicity (DevTox) for potential application to chemicals regulated under TSCA (amended 2016).

INPUTS: ToxCast data including new information on chemical effects in zebrafish embryos and in diverse mammalian embryonic stem cell lines (hESC, mESC).

OUTPUT: generalized workflow to sort compounds by their predicted potential for DevTox and *in silico* modeling of quantitative cellular, tissue and phenotypic responses.

Anatomical development

Timeline of human embryonic development



Specific aims

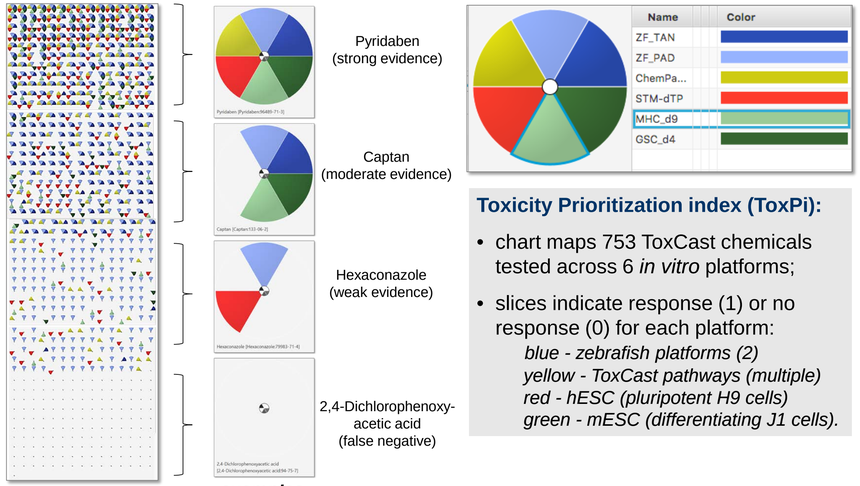
i) assess qualitative performance of the predictive model;

ii) set an exposure-based prediction of teratogenicity;

iii) characterize sensitive response pathways; and

iv) virtually reconstruct quantitative phenotypic response.

Chemicals ranked by enumerated response



Toxicity Prioritization index (ToxPi):

- chart maps 753 ToxCast chemicals tested across 6 *in vitro* platforms;
- slices indicate response (1) or no response (0) for each platform:
  - *blue - zebrafish platforms (2)*
  - *yellow - ToxCast pathways (multiple)*
  - *red - hESC (pluripotent H9 cells)*
  - *green - mESC (differentiating J1 cells).*

Evaluating model performance

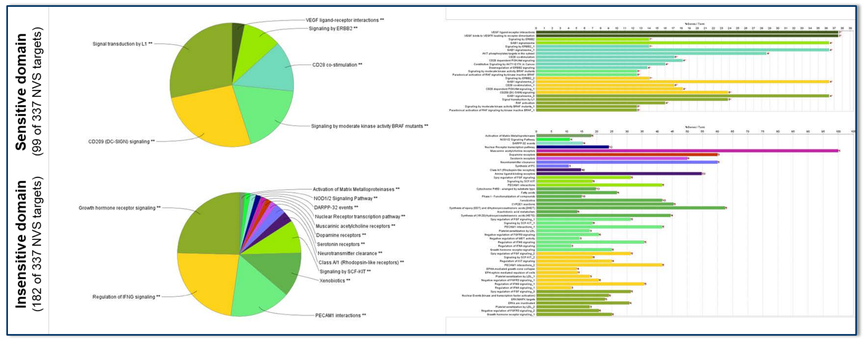
	Low Stringency (any dLEL)					*Moderate Stringency (rat or rabbit)*					*High Stringency (rat and rabbit)*				
	ZFISH-1	*ZFISH-2*	*mESC-1*	*mESC-2*	*hESC*	*ZFISH-1*	*ZFISH-2*	*mESC-1*	*mESC-2*	*hESC*	*ZFISH-1*	*ZFISH-2*	*mESC-1*	*mESC-2*	*hESC*
TP	169	85	62	45	80	55	27	15	10	37	12	10	1	0	20
FP	68	35	23	21	12	67	35	23	21	12	57	26	19	17	9
FN	73	172	159	133	178	15	58	43	35	49	3	20	5	5	11
TN	32	75	71	59	99	31	73	69	57	97	24	65	57	56	83
n	342	367	315	258	369	168	193	150	123	195	96	121	82	78	123
SENS	0.698	0.331	0.281	0.253	0.310	0.786	0.318	0.259	0.222	0.430	0.800	0.333	0.167	0.000	0.645
SPEC	0.320	0.682	0.755	0.738	0.892	0.316	0.676	0.750	0.731	0.890	0.296	0.714	0.750	0.767	0.902
ACC	58.8%	43.6%	42.2%	40.3%	48.5%	51.2%	51.8%	56.0%	54.5%	68.7%	37.5%	62.0%	70.7%	71.8%	83.7%
MCC	0.018	0.012	0.037	-0.010	0.214	0.113	-0.007	0.010	-0.052	0.366	0.078	0.045	-0.051	-0.138	0.560

OBSERVATIONS:

- ZFISH platforms were more sensitive but less specific than mESC or hESC platforms.
- Model performance improves against more stringent *in vivo* criteria for DevTox.
- Overall accuracy approaches 62% (ZFISH), 72% (mESC), and 84% (hESC).
- The hESC model also predicts the critical concentration for human dosimetry.

DEFINITIONS:
(a) LEL, lowest effect level (mg/kg/day) in ToxRefDB prenatal developmental toxicity study: dLEL (fetal endpoint) and mLEL (maternal endpoint) in the same ToxRefDB study for 'n' compounds;
(b) evidence for DevTox: *'CLEAR'* (dLEL≤ 200, dLEL<mLEL); *'SOME'* (dLEL≤ 200, dLEL≥ mLEL); *'EQUIVOCAL'* (dLEL> 200 but <1000); and *'NO'* (dLEL≥1000) in rat and/or rabbit study;
(c) TP (true positive), FP (false positive), FN (false negative), TN (true negative); SENS, sensitivity [TP/(TP+FN)]; SPEC, specificity [TN/(TN+FP)]; ACC, accuracy [(TP+FN)/(TP+FP+FN+TN)].

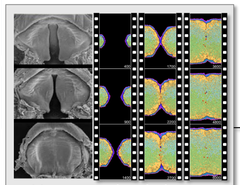
Mining ToxCast to define sensitive pathways



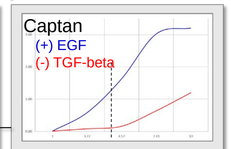
Computational synthesis and integration

- Chemical-Informatics
  - Is the Chemical in the Database
  - Physical-Chemical Properties
  - Nearest Neighbor Chemicals
  - Chemical Structural Alerts
- New Alternative Model (NAM) Assessments
  - Computational NAMs
  - Experimental NAMs
  - Small Model Organisms
- Adverse Outcome Pathway (AOP)-based Assessment
  - Toxicity Reference DataBase - derived AOPs
  - Knock-Out, GWAS, Human Mutation - derived AOPs
  - Chemical Literature - derived AOPs
- Dosimetry and Bioavailability
  - Metabolism
  - Placental Transport
  - High Throughput Toxicokinetics (HTTK)
- Modifiers to Prediction
  - Genetic Susceptibility
  - Preexisting Physiological State
  - Species/Strain

example



Human palatal closure (left) simulated in a virtual embryo (right).



Running the simulation with ToxCast data for 'Captan' predicts a tipping point at 4 µM.

Human HTTK model predicts exposure of a pregnant woman to Captan at 2.39 mg/kg/day would achieve a steady state of 4 µM in fetal plasma.

Summary

- Assigning chemicals under amended TSCA to low and high priority comes with uncertainties in complexity of predicting toxicity during pregnancy.
- A DevTox predictive framework will implement data from *in vitro* assays assessing embryonic cell growth and differentiation.
- The framework will operationalize a defined interpretation protocol for computational synthesis and integration → DevTox decision tree.
- Multiscale modeling and simulation will provide tools and approaches to virtually reconstruct and analyze complexity and quantitative prediction.