ToxRefDB: Classifying ToxCast™ Phase I Chemicals Utilizing Structured Toxicity Information

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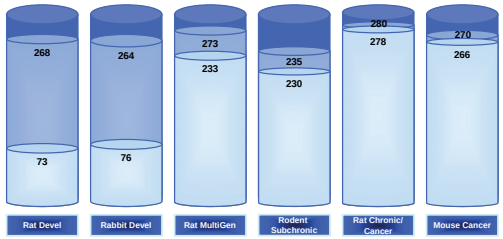
Abstract:
Background: Thirty years and over a billion of today's dollars worth of pesticide registration toxicity studies, historically stored as hardcopy and scanned documents, have been digitized into highly standardized and structured toxicity data, within the U.S. Environmental Protection Agency's (EPA) Toxicity Reference Database (ToxRefDB). The source toxicity data in ToxRefDB covers multiple study types, including subchronic, developmental, reproductive, chronic, and cancer studies, resulting in a diverse set of endpoints and toxicities.
Objectives: Novel approaches to chemical classification are performed as a model application of ToxRefDB and as an essential need for highly detailed chemical classifications within the EPA's ToxCast™ research program. In order to develop predictive models and biological signatures utilizing high-throughput screening (HTS) and *in vitro* genomic data, relevant endpoints and toxicities must first be identified and globally characterized for ToxCast Phase I chemicals.
Methods: Utilizing query and structured data mining approaches, toxicity profiles are uniformly generated for greater than 300 chemicals and analyzed for toxicity endpoint selection.
Results: Based on observation rate, species concordance, and regulatory relevance, individual and aggregated effects have been chosen to classify the ToxCast Phase I chemicals.
Conclusions: Unparalleled amounts of legacy toxicity information on pesticides have been captured in a structured format providing a platform for repeated and updated global chemical characterization.
This work does not necessarily reflect official Agency policy.

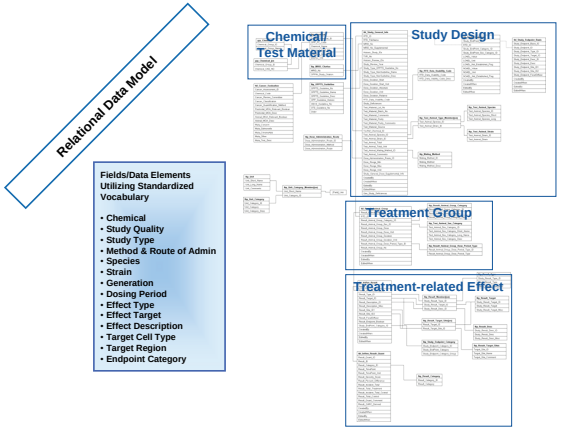
Data Entry Status
ToxCast Phase I Chemicals

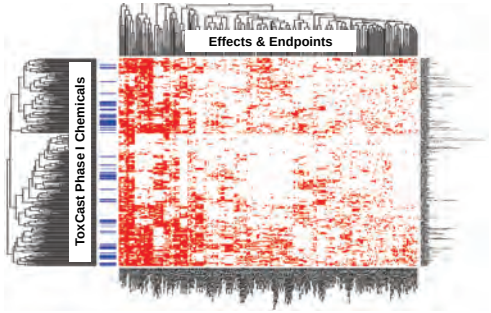


Summary Statistics

	Chemicals	Studies	Treatment Groups	Treatment Groups with Effects	Effects[a]	Critical Effects[b]	Unique Effects[c]	Unique Critical Effects[d]
Total	*334*	*831*	*9,466*	*4,431*	*31,427*	*4,865*	*1,287*	*601*
Subchronic Rat	236	251	2,179	1,370	11,796	1,739	623	314
Chronic/Cancer Rat	281	300	4,228	1,721	12,215	1,822	870	359
Cancer Mouse	266	280	3,059	1,340	7,416	1,304	639	275

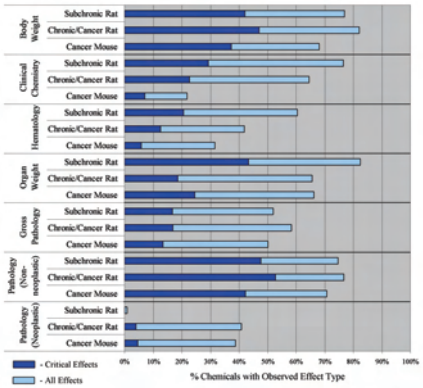
(a) - Total number of effect type, target, and description combinations assigned to any treatment group (e.g., Pathology (Neoplastic) | Liver | Adenoma)
(b) - Effects that are criteria for establishing the systemic LOAEL
(c) - # of distinct effects assigned to any treatment group
(d) - # of distinct critical effects assigned to any treatment group





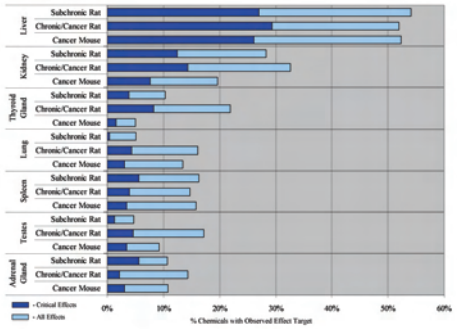
Endpoint Selection Framework

Analysis of Effect Types

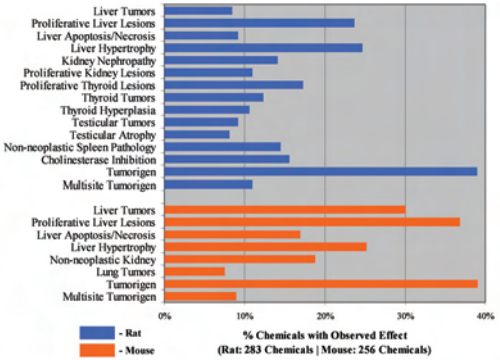


Aggregating Proliferative Pathology Effects

Analysis of Effect Targets



Rat & Mouse Toxicity Endpoints for Prediction In ToxCast



Individual Pathology Effects Observed in >10% of Chemicals

Study Type	Species	Effect Type	Effect Target	Effect Description	% Observed
Cancer	mouse	Pathology (Non-neoplastic)	Liver	Hypertrophy	25%
Chronic/Cancer	rat	Pathology (Non-neoplastic)	Liver	Hypertrophy	25%
Cancer	mouse	Pathology (Neoplastic)	Liver	Adenoma	21%
Cancer	mouse	Pathology (Non-neoplastic)	Liver	Necrosis	16%
Cancer	mouse	Pathology (Neoplastic)	Liver	Adenoma/Carcinoma Combined	14%
Chronic/Cancer	rat	Pathology (Non-neoplastic)	Kidney	Nephropathy	14%
Cancer	mouse	Pathology (Non-neoplastic)	Liver	Pigmentation	14%
Chronic/Cancer	rat	Pathology (Non-neoplastic)	Liver	Vacuolization	12%
Cancer	mouse	Pathology (Neoplastic)	Liver	Carcinoma	11%
Chronic/Cancer	rat	Pathology (Non-neoplastic)	Thyroid	Hyperplasia	11%
Chronic/Cancer	rat	Pathology (Neoplastic)	Thyroid	Adenoma	10%
Chronic/Cancer	rat	Pathology (Non-neoplastic)	Liver	Eosinophilic Focus	10%

Next Steps:

Complete entry and QC of ToxCast Phase I pesticides

Enter and QC ToxCast Phase I non-pesticide toxicity data

Complete endpoint selection for multigeneration & developmental studies

Enter ToxCast Phase II toxicity data (where available)

Public release of ToxRefDB