

A Quantitative Model of Systemic Toxicity Using ToxCast and ToxRefDB

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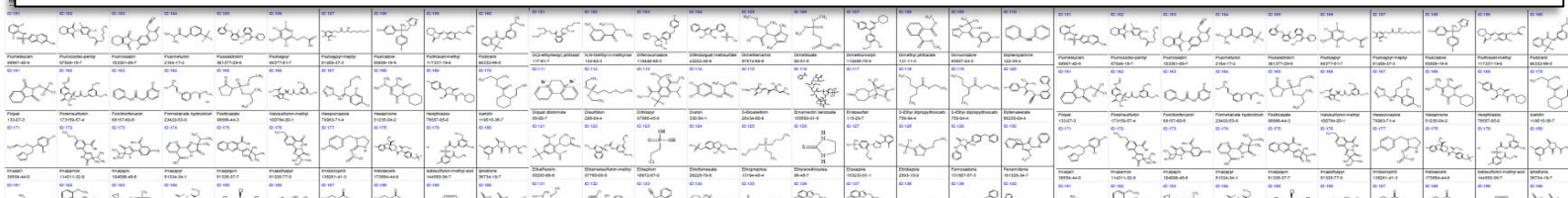


9th World Congress, August 2014

CHALLENGES

Too many chemicals to test with standard animal-based methods

— Cost, time, animal welfare



Mixtures/ Formulations
Rapid Assessment for Prioritization
Mechanistic Insight
3Rs of Animal Testing
Shifting Regulatory Environment
REACH 2018, Cosmetics Directive

GOALS

Recycle & Reuse Legacy Animal Data

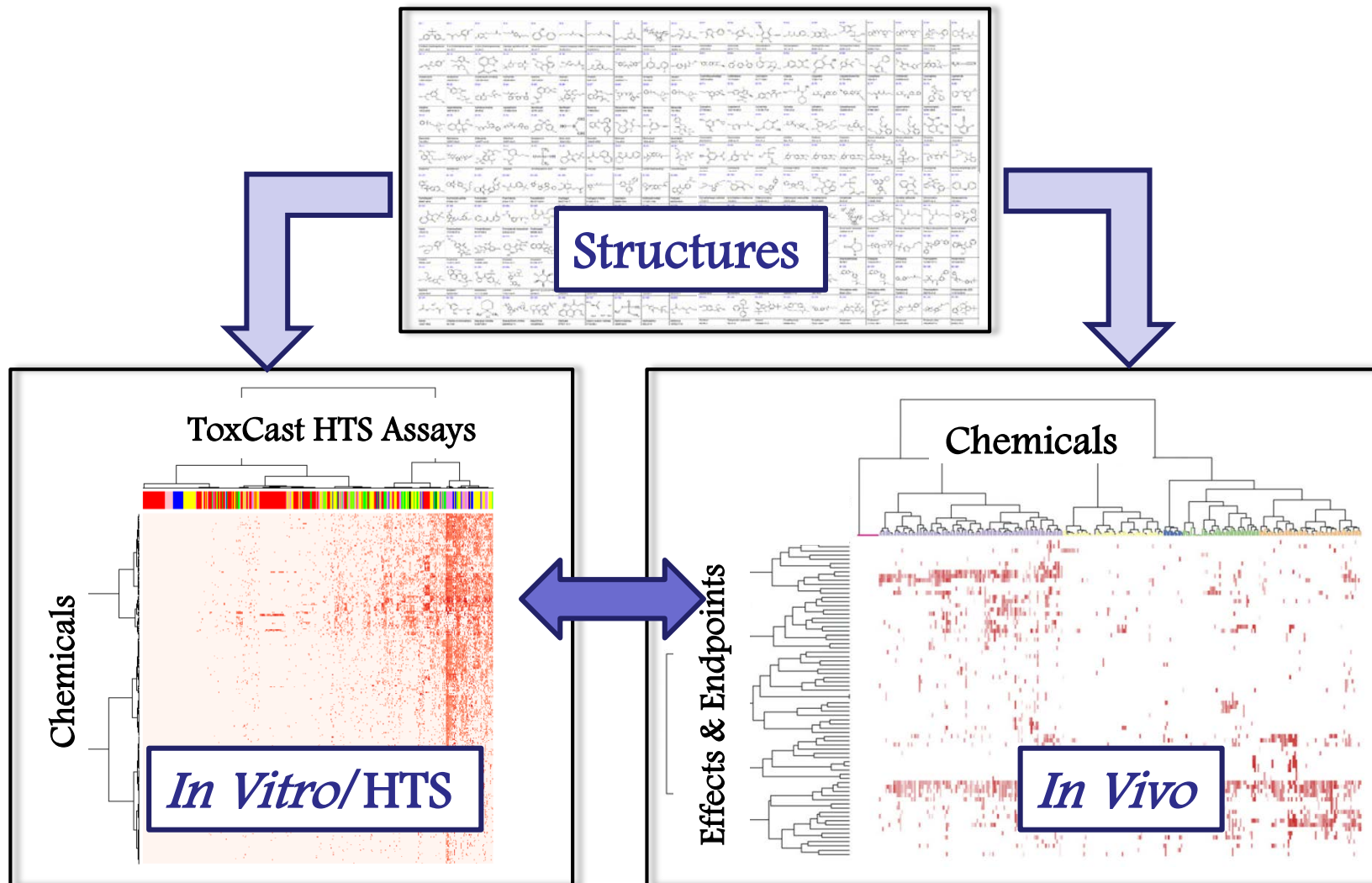
Generate High Throughput & Other Data On Many Chemicals

Develop Models to Predict Human Toxicity and Disease Potential

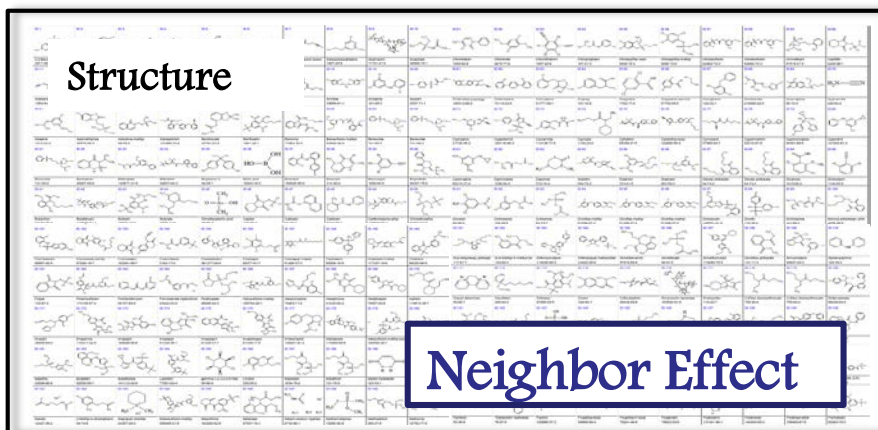
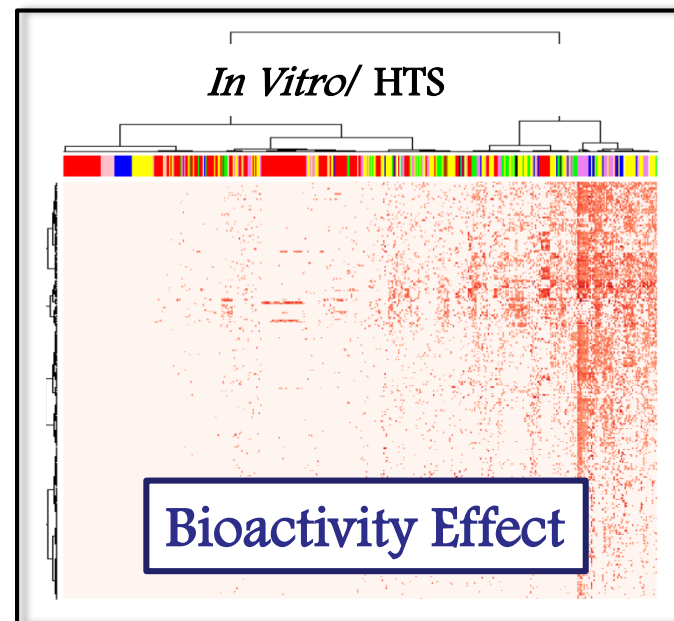
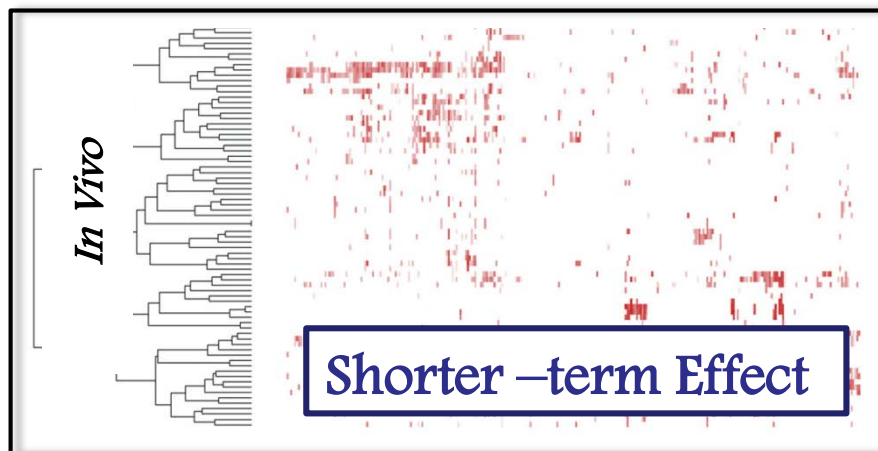


Computational Toxicology

ADDRESSING THE CHALLENGE



FORMULA:: REPEAT~DOSE EFFECT

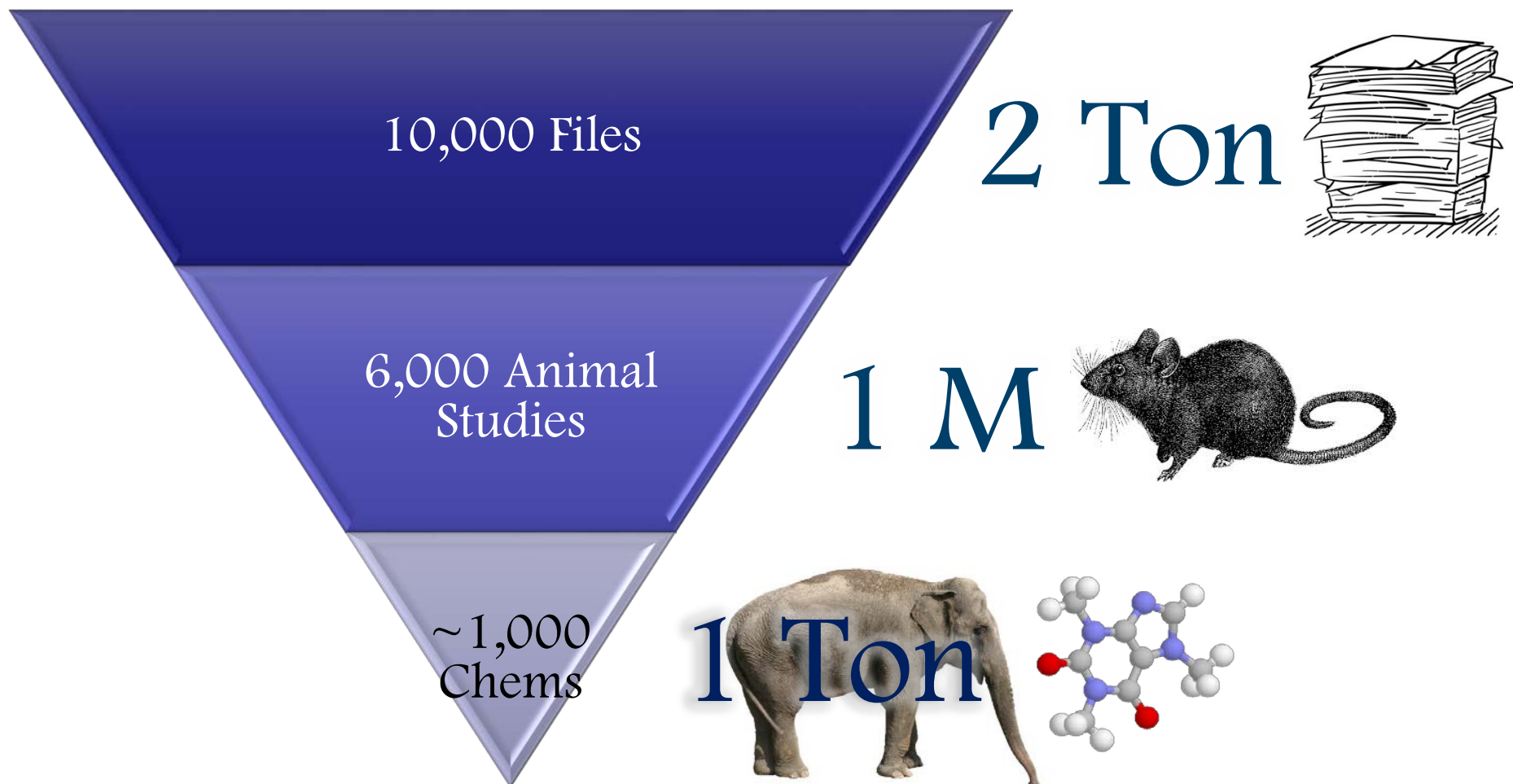


Lots of Variability



Lots of Uncertainty

TOXREFDB: *IN VIVO* DATA



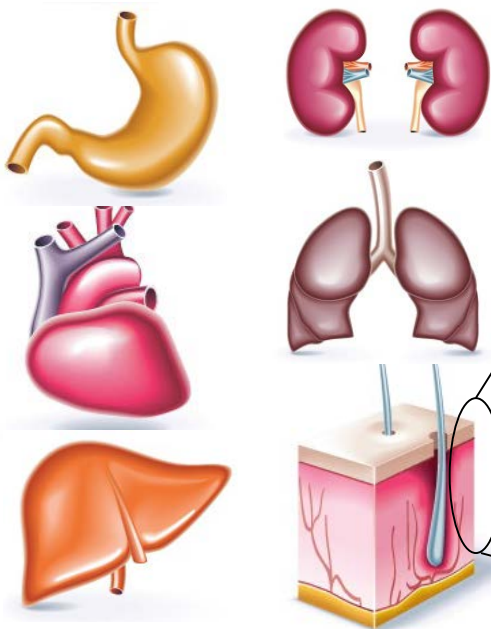
ToxRefDB: *IN VIVO* DATA

150,000 Effects



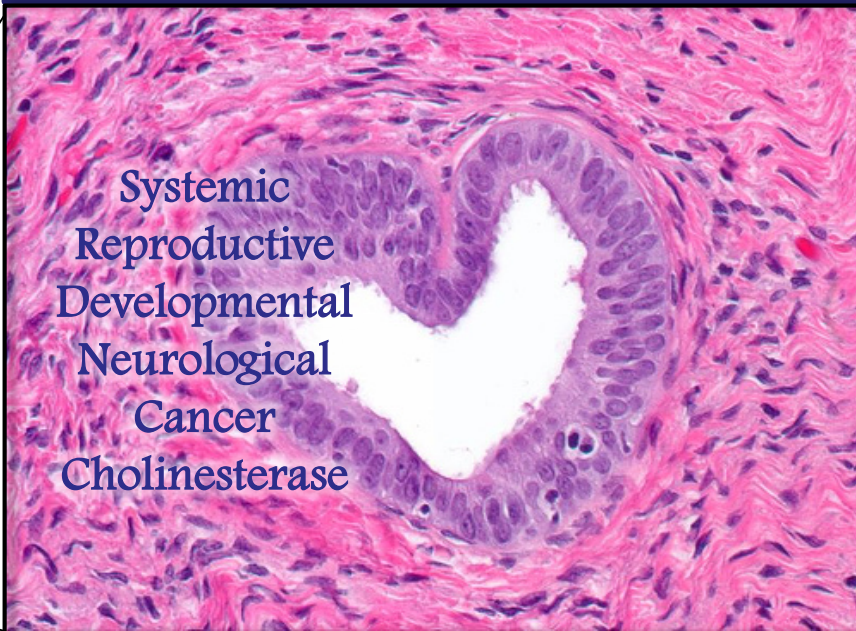
5,000 Unique Effects

Organs

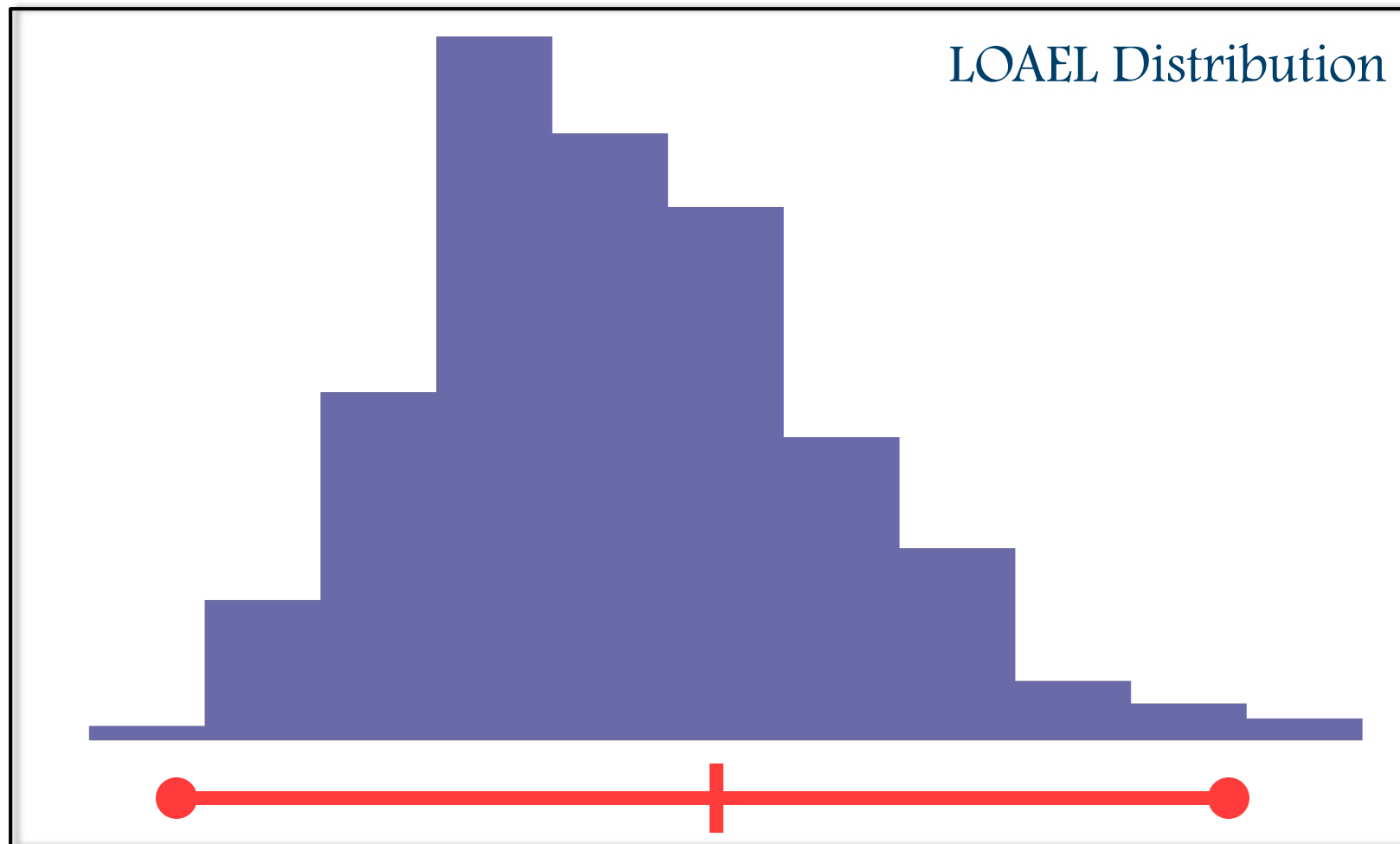


Microscopic/Pathology

Systemic
Reproductive
Developmental
Neurological
Cancer
Cholinesterase



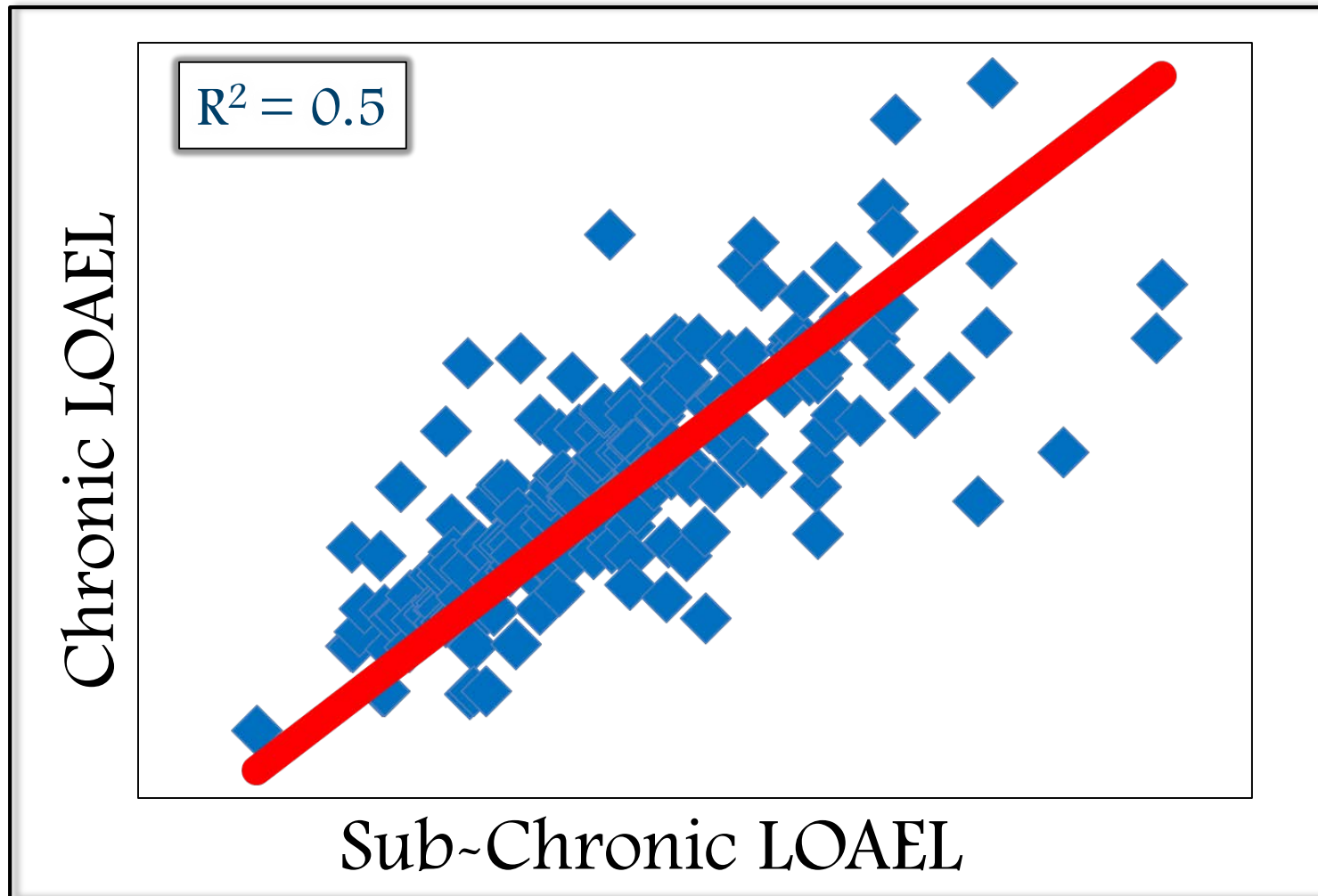
EXPECTATIONS



~ 4 OMU

OMU = Orders of Magnitude
LOAEL = Lowest Adverse Effect Level

EXPECTATIONS

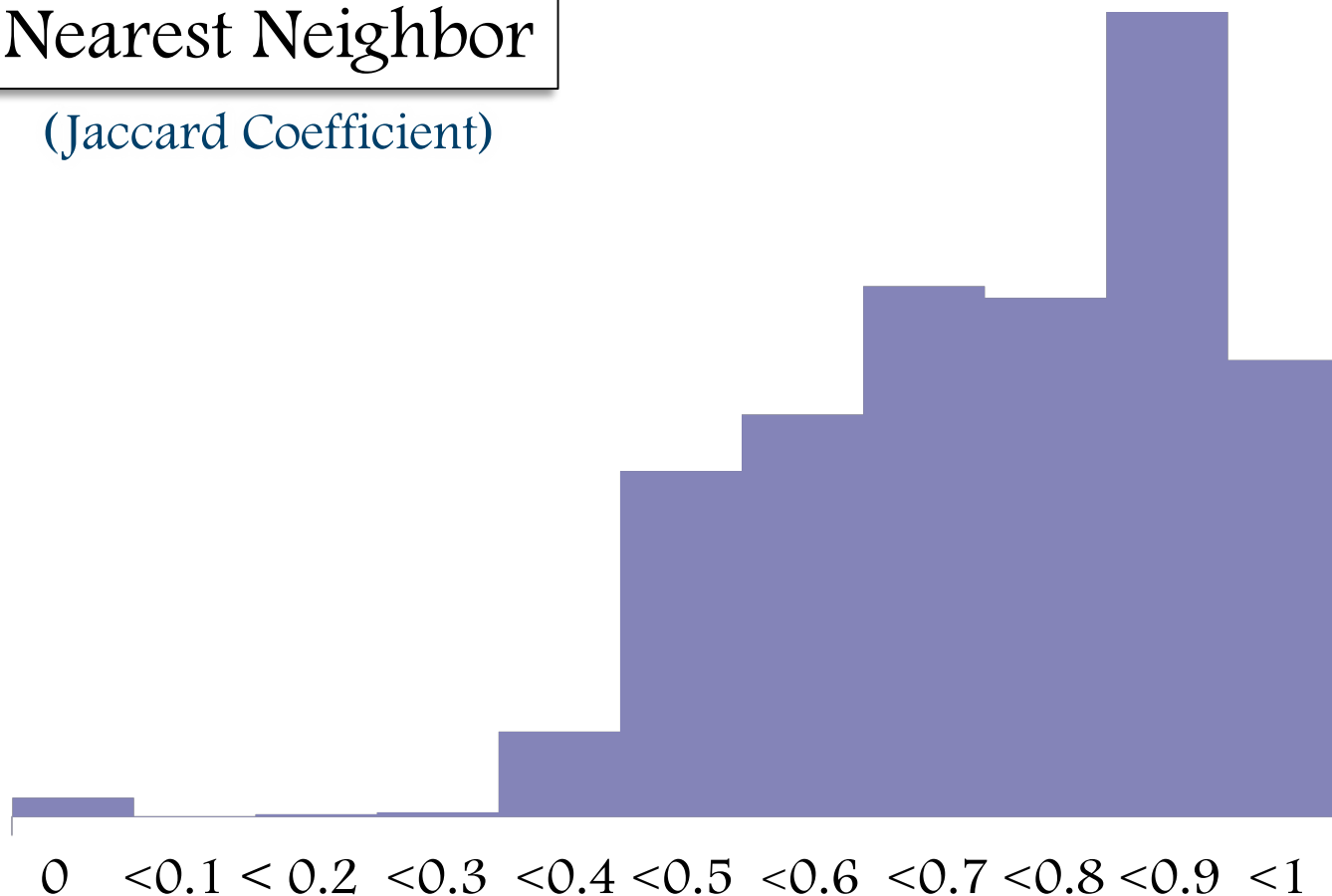


~ 2 OMU

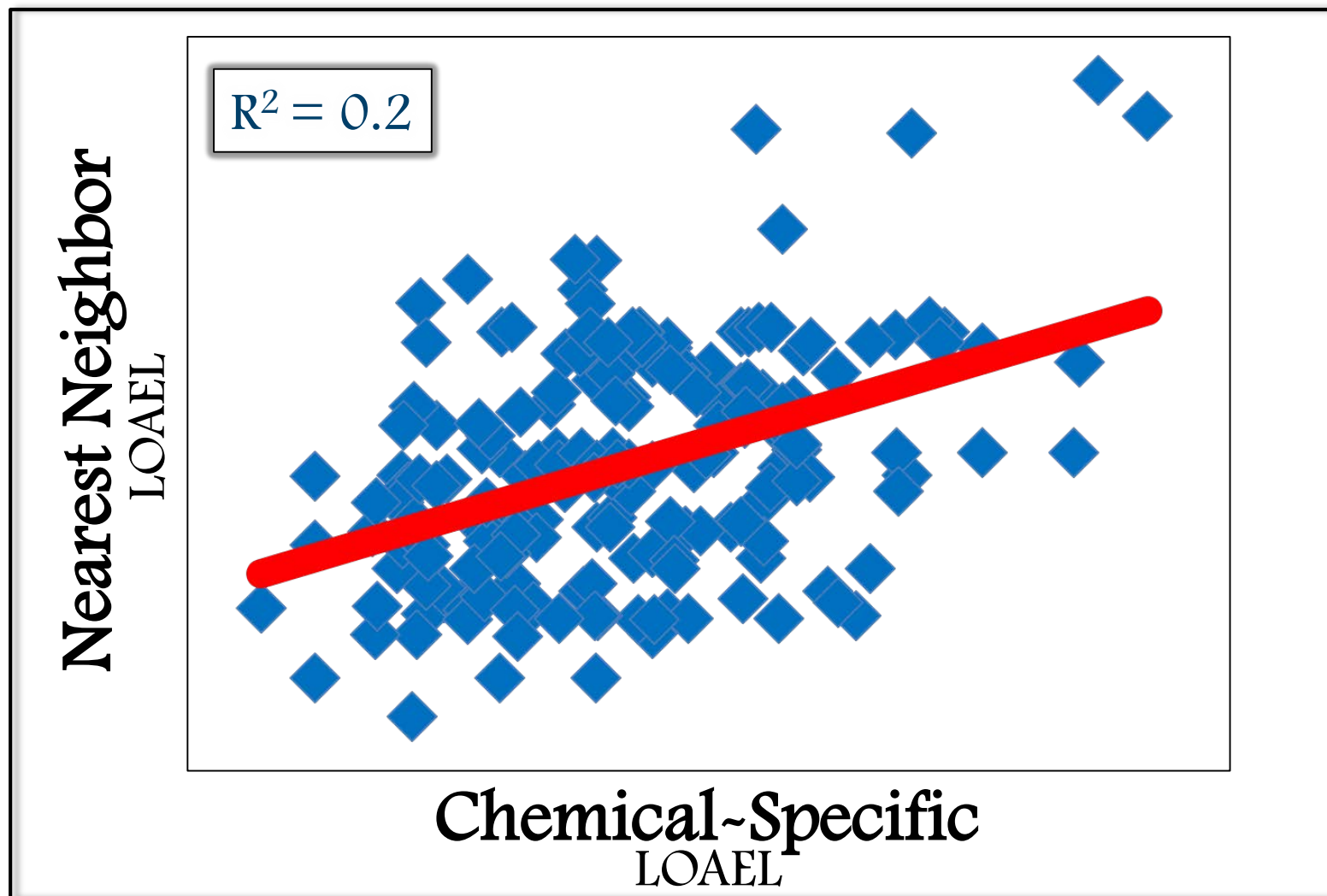
READ ACROSS

Nearest Neighbor

(Jaccard Coefficient)



READ ACROSS



~ 3.25 OMU

TOXCAST GOALS

Identify targets/pathways linked to toxicity

Chemicals perturbing these can lead to adverse effects

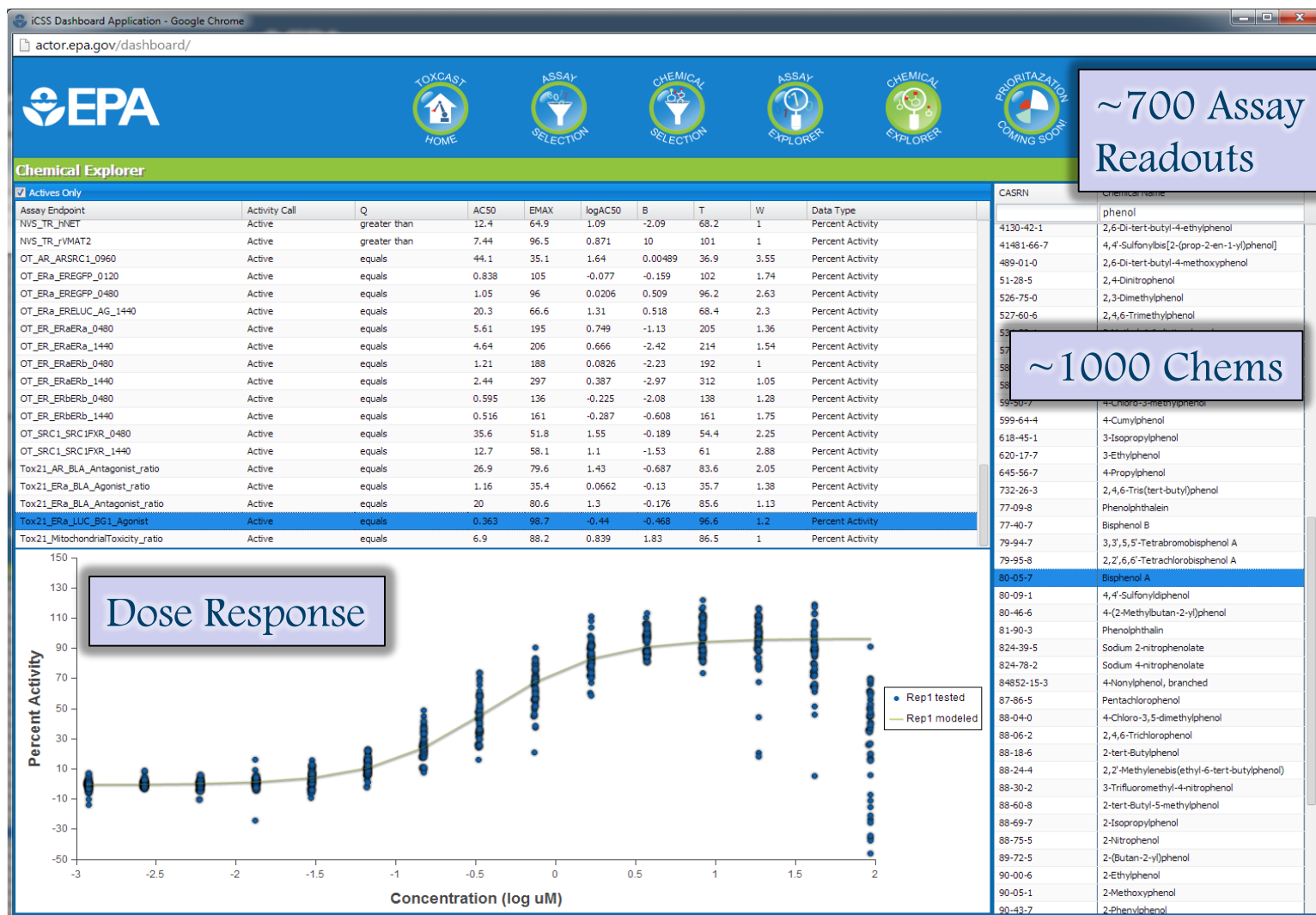
Develop assays for these targets/pathways

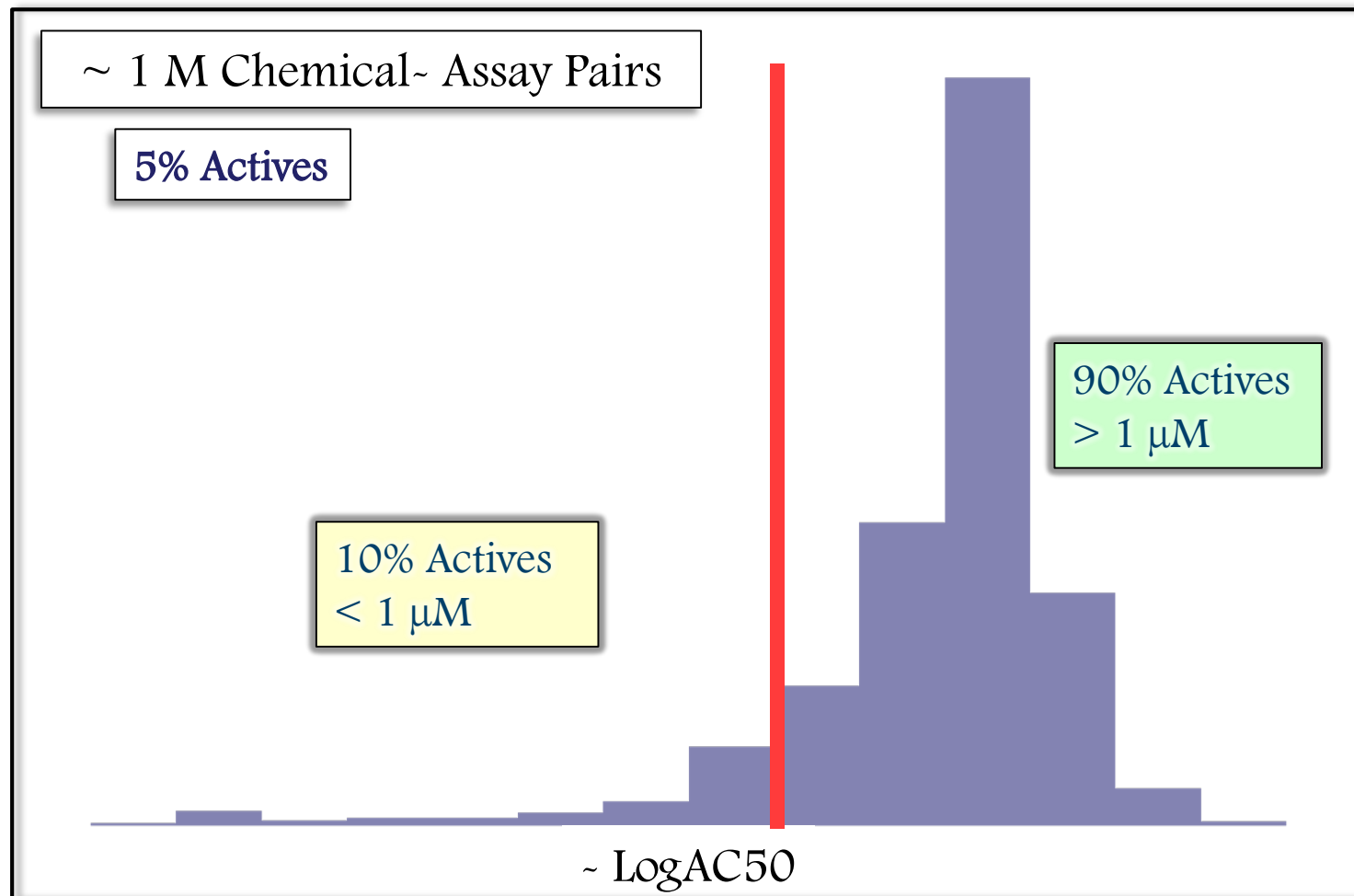
Develop predictive models: *in vitro* ~> *in vivo*

“Toxicity Signatures”

Use signatures to prioritize chemicals for targeted testing
e.g., “Too many chemicals” problem

ToxCAST: DASHBOARDS

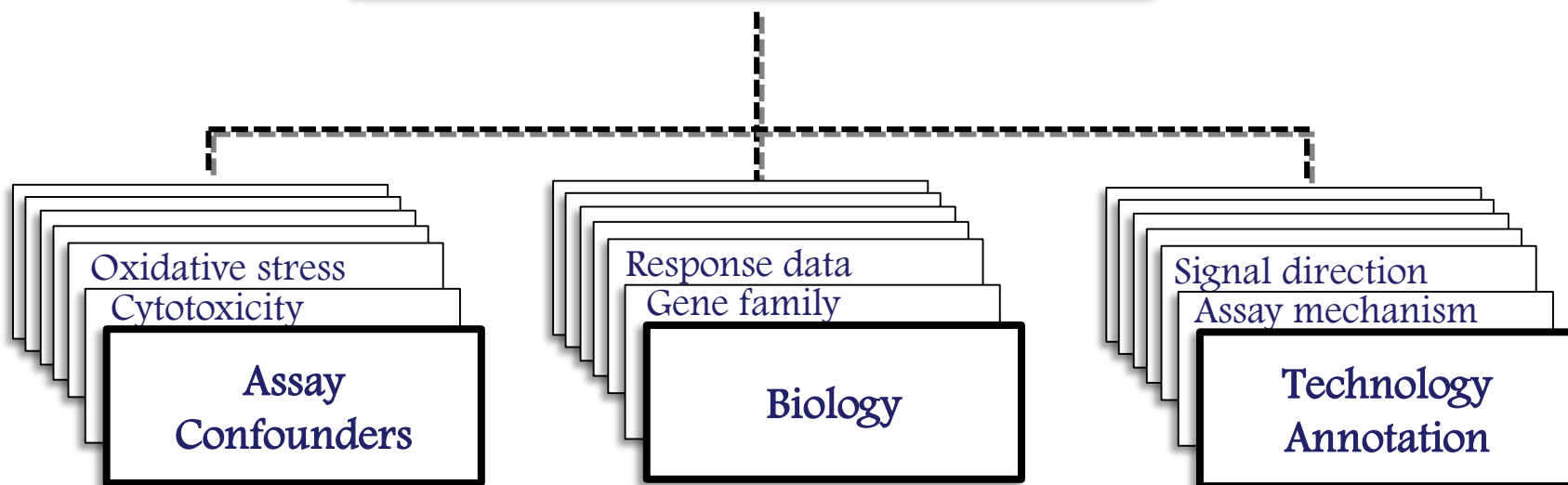




ToxCast

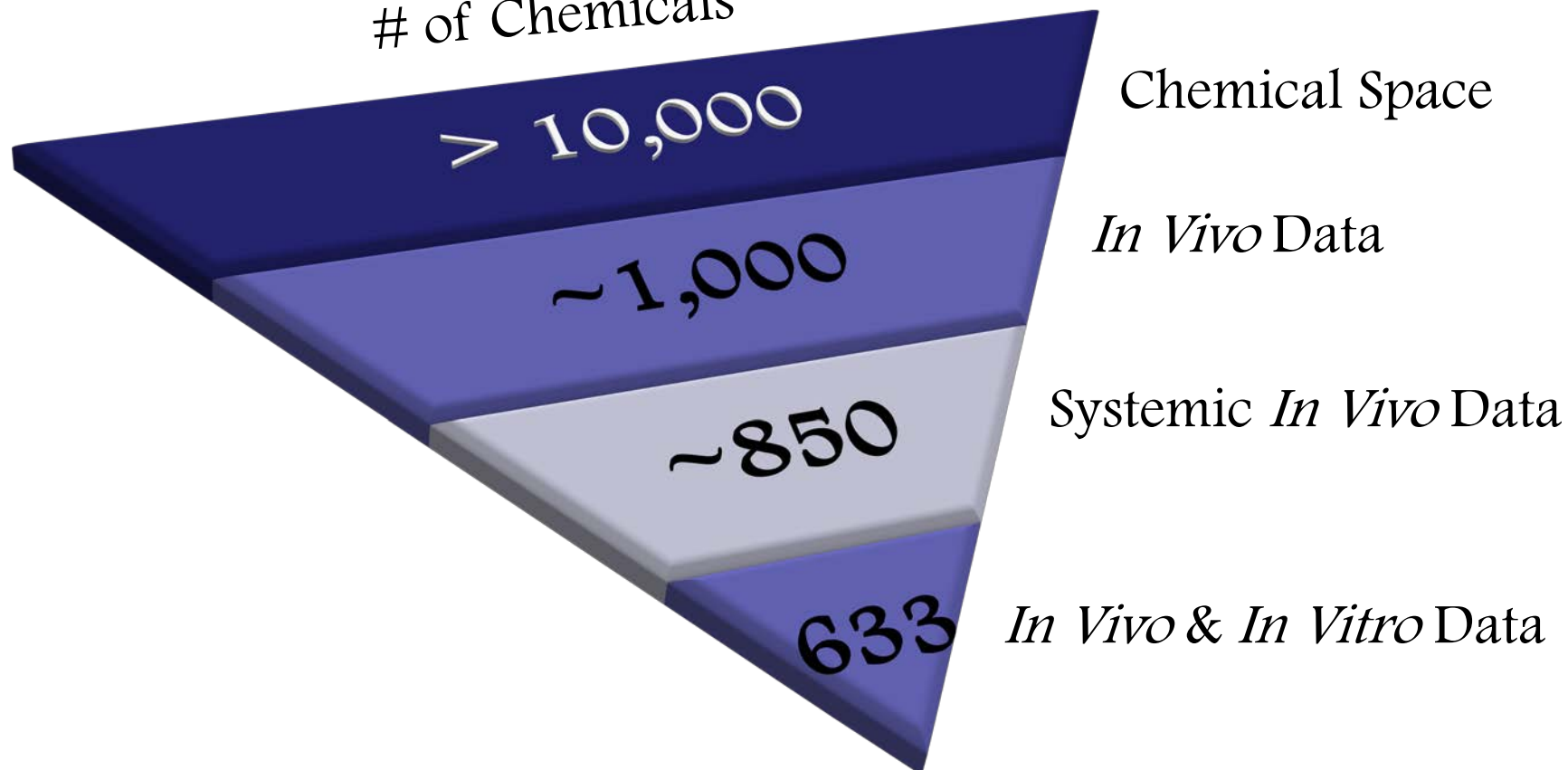
BIOLOGICAL GROUPINGS (BP)

Group ToxCast Assays (74) based on:



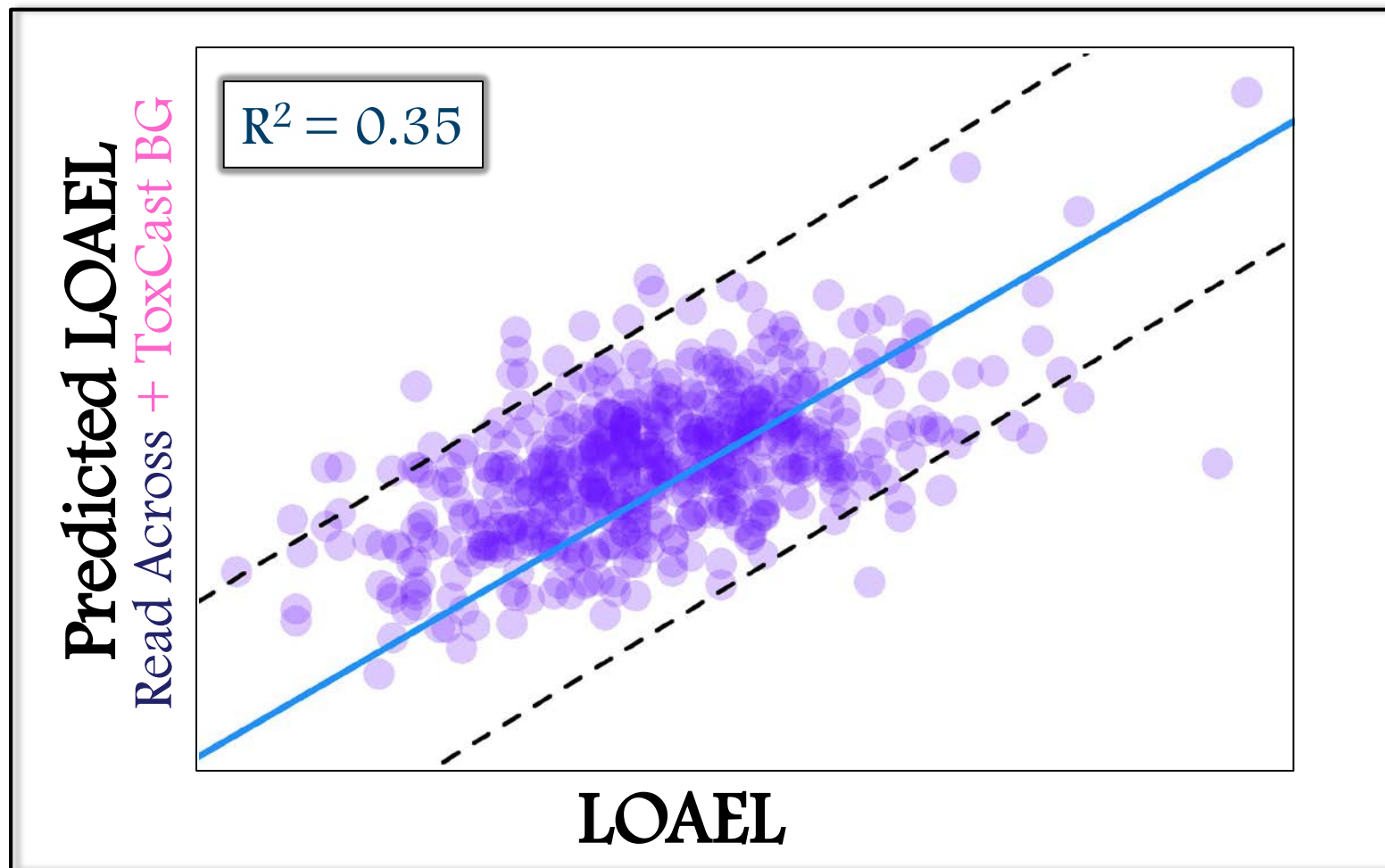
CHEMICAL DATA

of Chemicals



MODEL FRAMEWORK

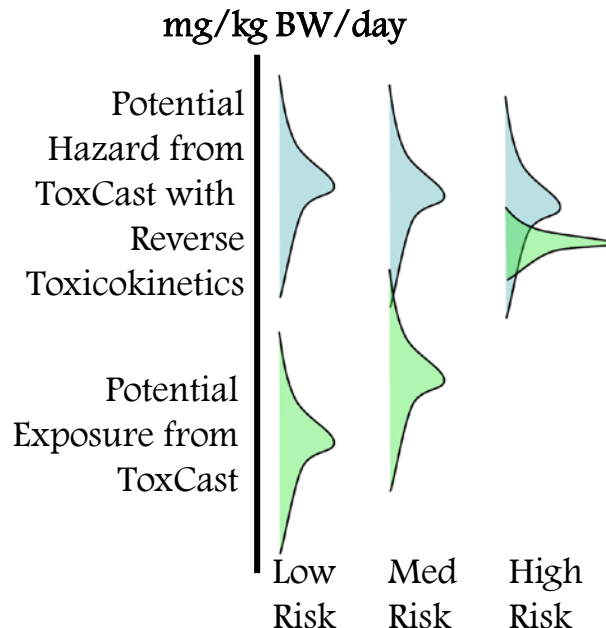
Chemicals	Sources	Outputs	Model Building
	ToxRefDB	LOAELs	Ground Truth
	Structures (ToxPrint*)	Nearest Neighbors LOAELs (Read Across)	Parameters
	ToxCast	Biological Grouping Activity Score	



HIGH THROUGHPUT PHARMACOKINETICS

High throughput pharmacokinetic (HTPK) *in vitro* methods have been developed by pharmaceutical industry for predicting efficacious doses in clinical trials

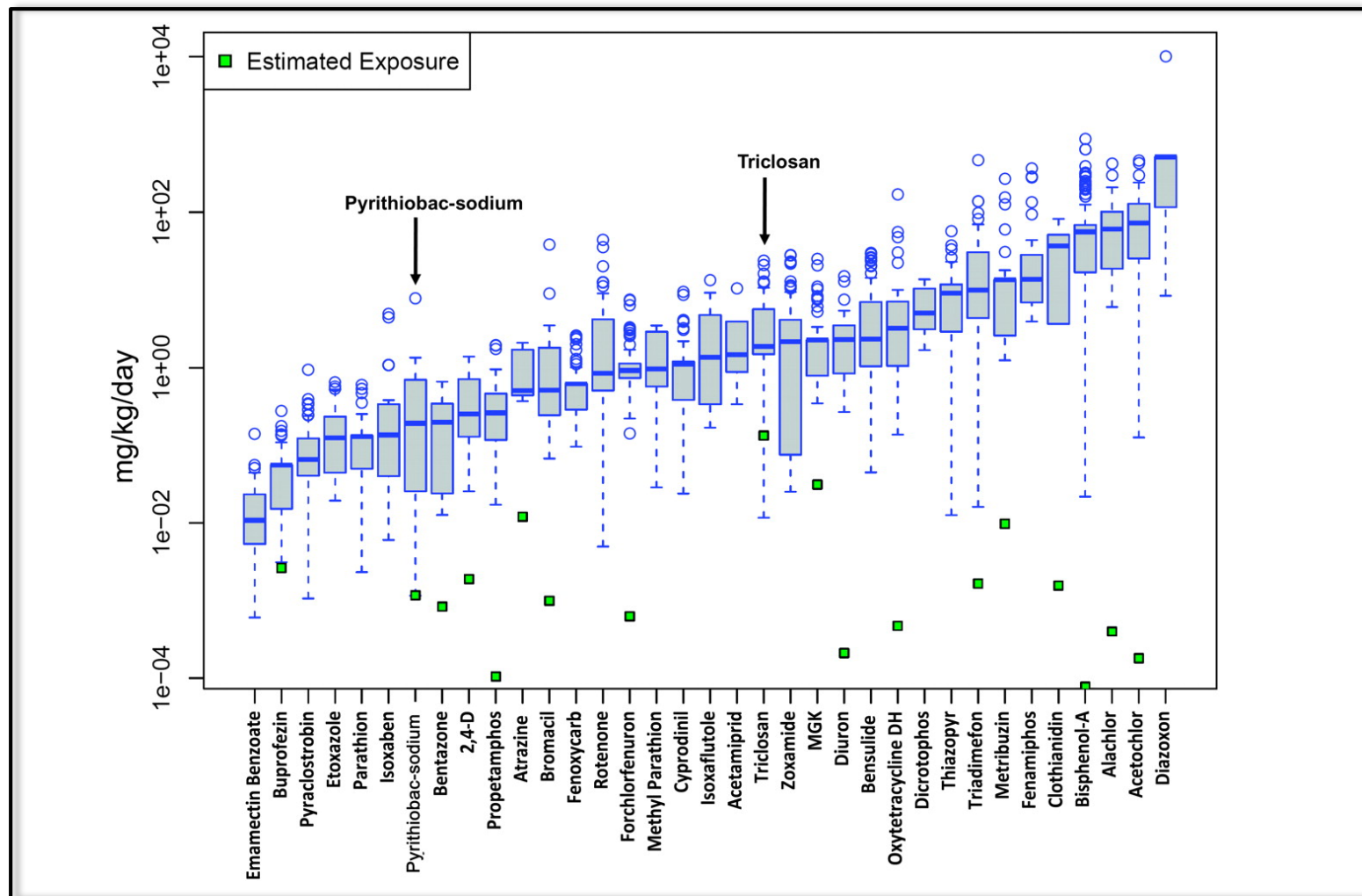
Apply same methods* to convert ToxCast *in vitro* bioactive concentration (μM) into daily doses needed to produce similar levels in humans (mg/kg BW/day)



$$\text{Oral Equivalent (mg/kg/day)} = \text{ToxCast AC50 } (\mu\text{M}) \times \frac{1 \text{ mg/kg/day}}{C_{ss}(\mu\text{M})}$$

$$\text{Concentration of Steady State (C}_{ss}\text{)} = \frac{\text{Hepatic Clearance}}{\text{Plasma Protein Binding}}$$

REVERSE TOXICOKINETICS (RTK)



ToxCast + Rtk

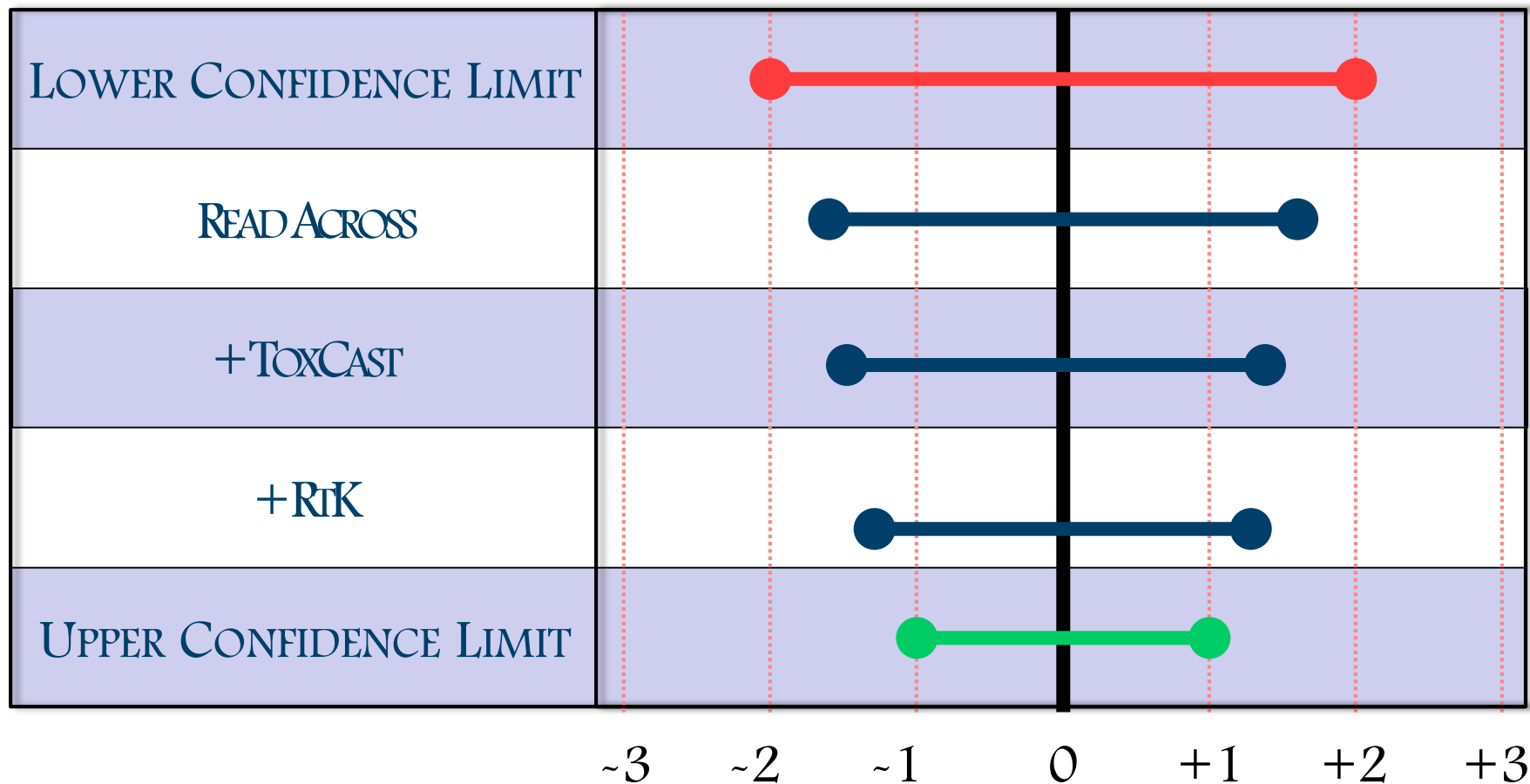
Predicted LOAEL
Read Across + ToxCast BG + Rtk

$$R^2 = 0.4$$

LOAEL

~ 2.5 OMU

SUMMARY (OMU)



FUTURE DIRECTIONS

Target organ and pathological specificity

Developing developmental and reproductive quantitative models

ToxRefDB v2.0 – Quantitative data
Capture tested/non-tested/unknown &

CONCLUSIONS

Leverage existing data

Characterize inherent variability and uncertainty

Understand structure of data

Combine for knowledgeable decision making and prioritization

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