Rapid Estimation of Hazard and Risk Using Computational Tools

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Conflict of Interest

- I have no conflicts to declare.
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- Any views presented are those of the presenter.

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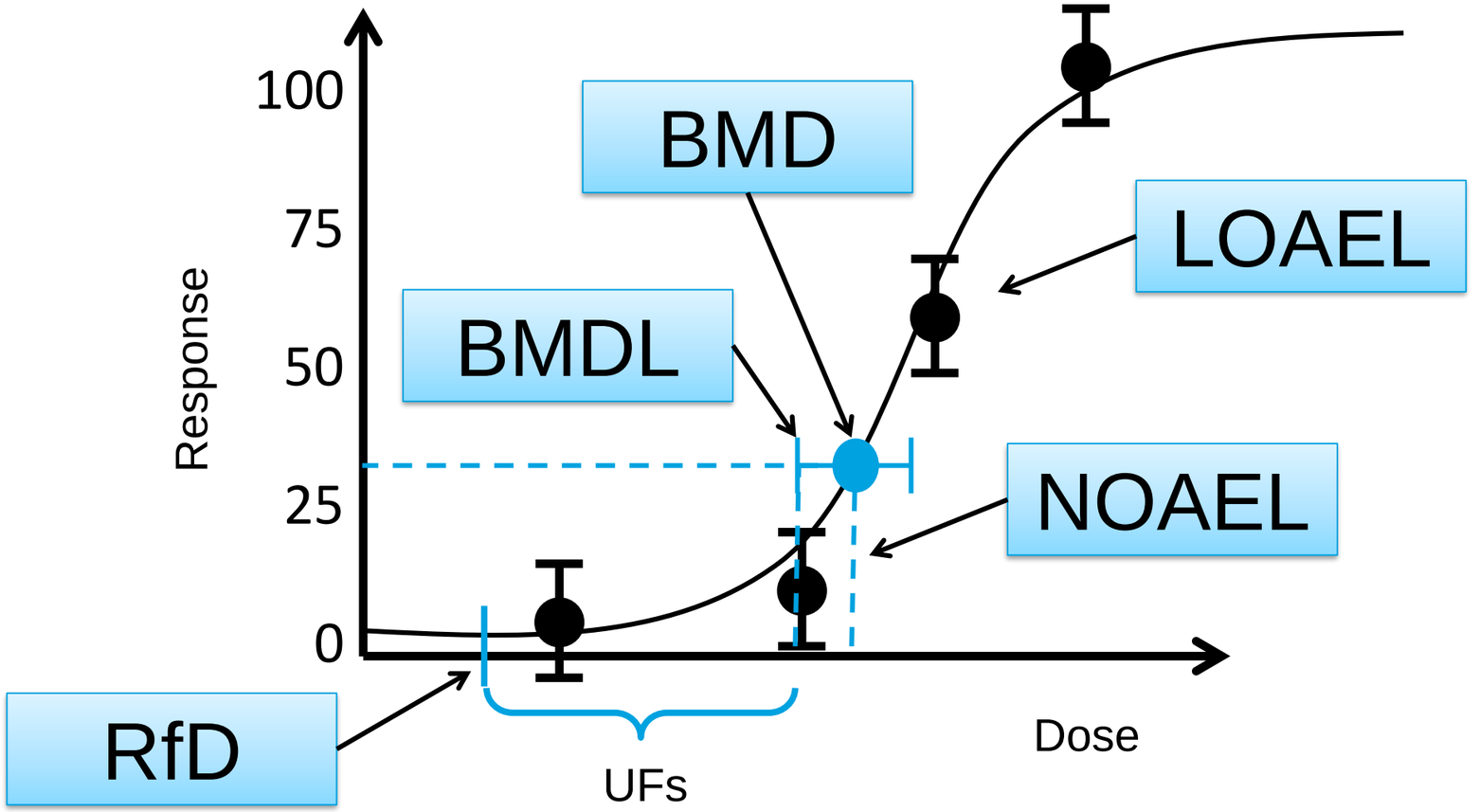
Overview

- Collecting Regulatory Values Used in Decision Making
- Building and Evaluating Quantitative Structure Activity Relationship (QSAR) Models
- Comparing QSAR Results to Other Values Used for Decision Making
- Public Portal and Rapid Response

Toxicity Values Used in Decision Making



NOAEL = No observed adverse effect level
LOAEL = Lowest observed adverse effect level

BMD = Benchmark dose
BMDL = Benchmark dose lower confidence limit

UF = Uncertainty factor
RfD = Reference Dose

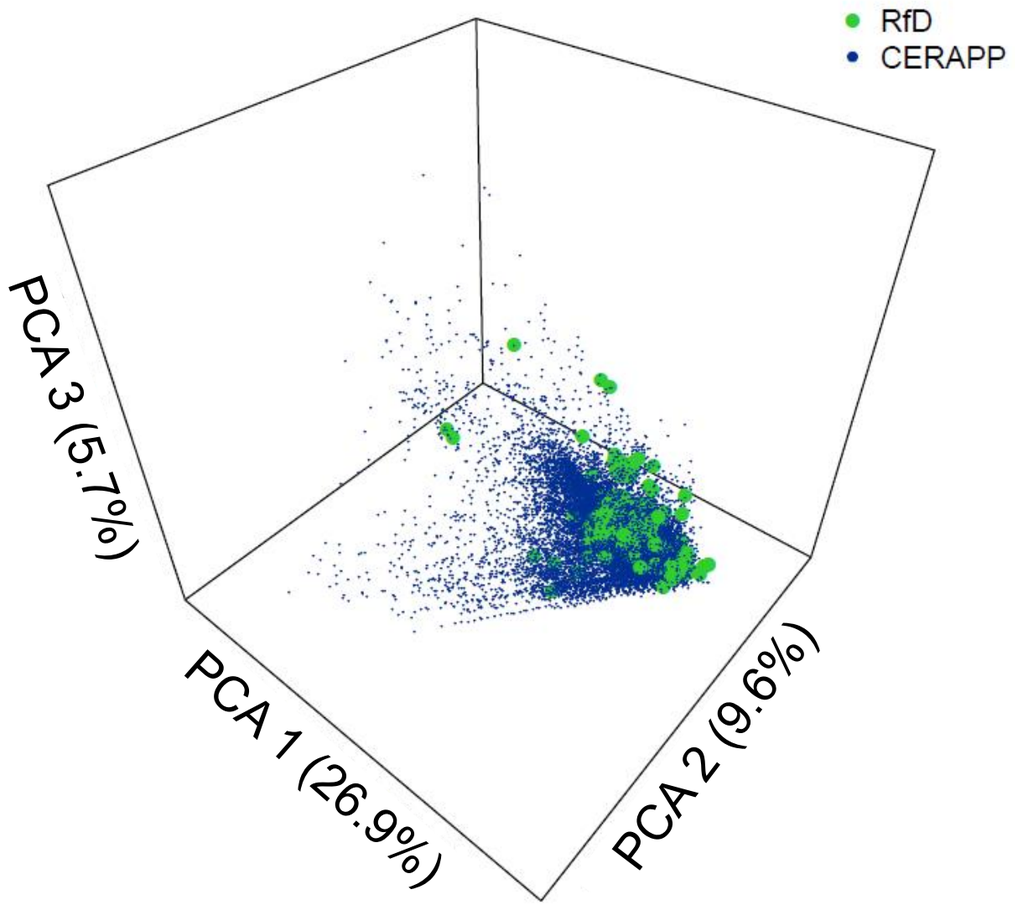
Data Exist for Many Types of Regulatory Toxicity Values

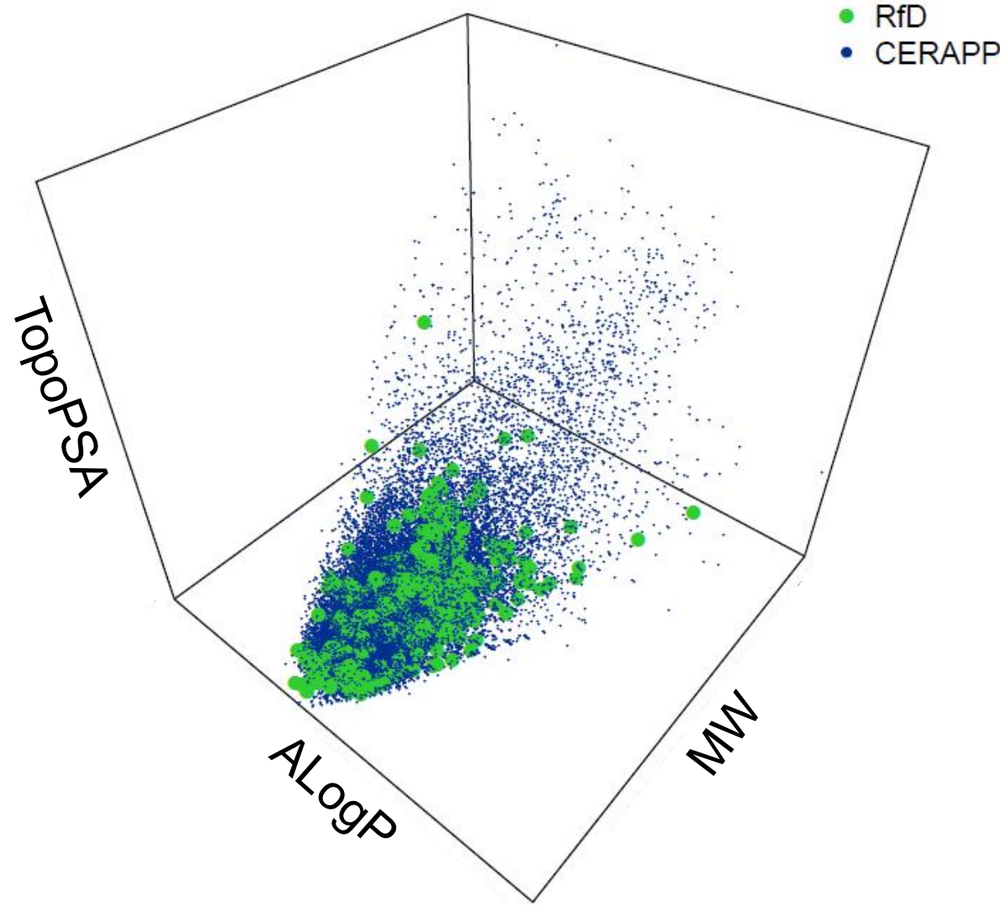
Toxicity value type	Toxicity value name	Number of compounds with a toxicity value
Oral exposure non-cancer	Reference Dose (RfD)	671
	No Observed Adverse Effect Level (NOAEL)	487
	Benchmark Dose (BMD)*	137
	Benchmark Dose Lower Level (BMDL)*	137
Oral exposure cancer	Oral Slope Factor (OSF)	302
	Cancer Potency Value (CPV)	225
Inhalation exposure (non-cancer and cancer)	Reference Concentration (RfC)	152
	Inhalation Unit Risk (IUR)	150

Sources: Integrated Risk Information System; Office of Pesticide Programs; Provisional Peer-Reviewed Toxicity Values; Agency for Toxic Substances and Disease Registry; California EPA; Health Effects Assessment Summary Tables (EPA)

*Modeled as reported in Wignall et al., 2014

Chemicals in Modeling Set are Structurally Diverse





CERAPP = Collaborative Estrogen Receptor Activity Prediction Project

Considerations when Evaluating QSAR Model Performance

- **Should be calculated based on external datasets as much as possible**
  - (Tropsha et al., 2003)
- **Limited by how "good" the experimental data is**
  - "Prediction errors cannot be better than experimental variability"
  - (Lo Piparo et al., 2014)
- **Improved by using both larger datasets and closely related datasets**
  - (McLellan et al., 2011)

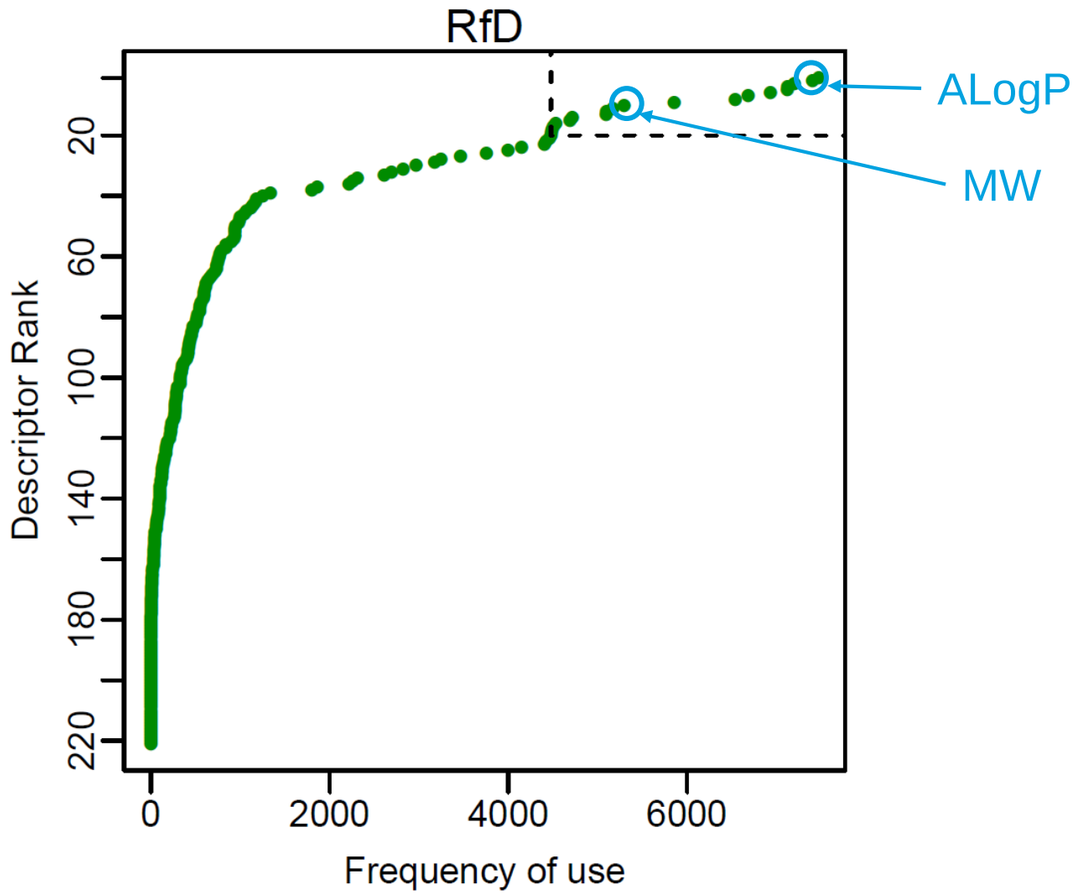
- **These considerations have implications for predicting in vivo outcomes for environmental chemicals, where data is limited and variable.**

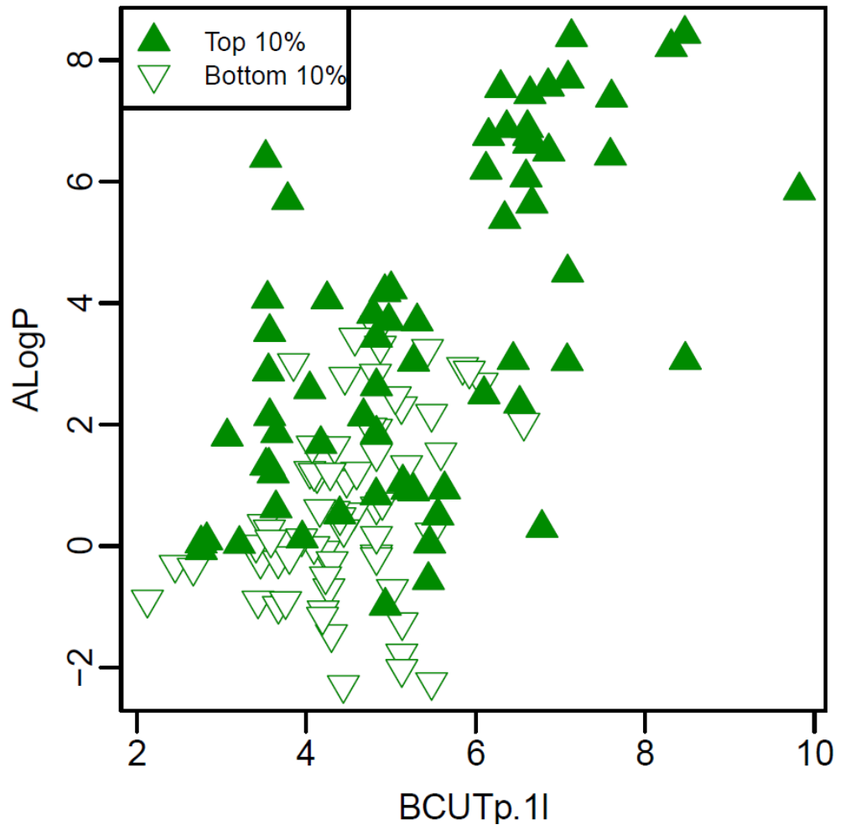
Objectives to Build Predictive Models that are Useful in Rapid Response

1. Predict continuous outcomes that are of use to decision makers, including PODs	▪ Used RfD; NOAEL; BMD; BMDL; OSF; CPV; RfC; and IUR data
2. Facilitate transparency and communication by using publicly available chemical descriptors, easy to understand algorithms, and external validation	▪ Descriptor types: cdk (rcdk package in R) ▪ Algorithm: Random Forest (randomForest package in R) ▪ Validation: 5-fold external cross-validation
3. Provide data through accessible online portals	▪ Models and predictions available through ToxValue.org

Evaluating QSAR Modeling

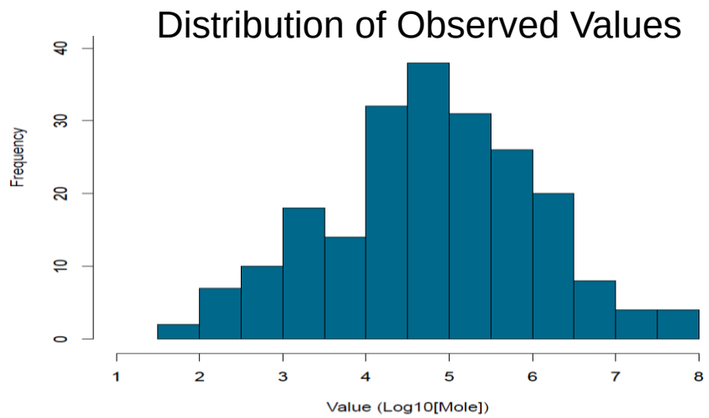
Model Algorithms Use Chemical Features to Predict Chemical Activity

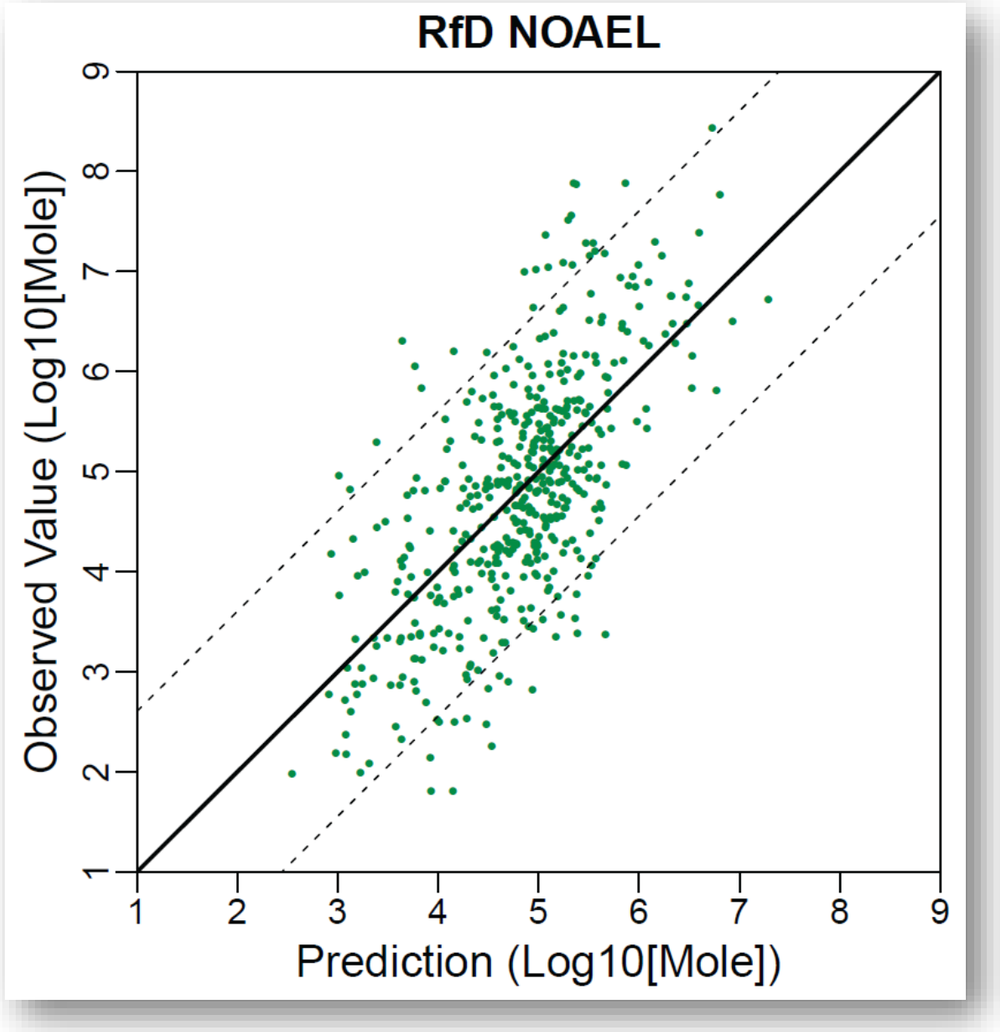




Model Performance Varies Across Toxicity Value Type

Toxicity value (# of compounds)	Consensus model Q^2
RfD (671)	0.41
NOAEL (487)	0.45
BMD Non-Cancer (137)	0.31
BMDL Non-Cancer (137)	0.28
OSF (302)	0.33
CPV (225)	0.25
RfC (152)	0.42
IUR (150)	0.42

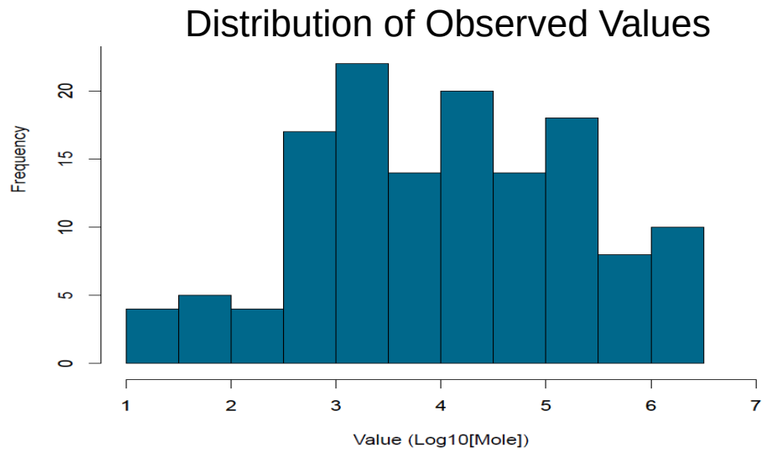


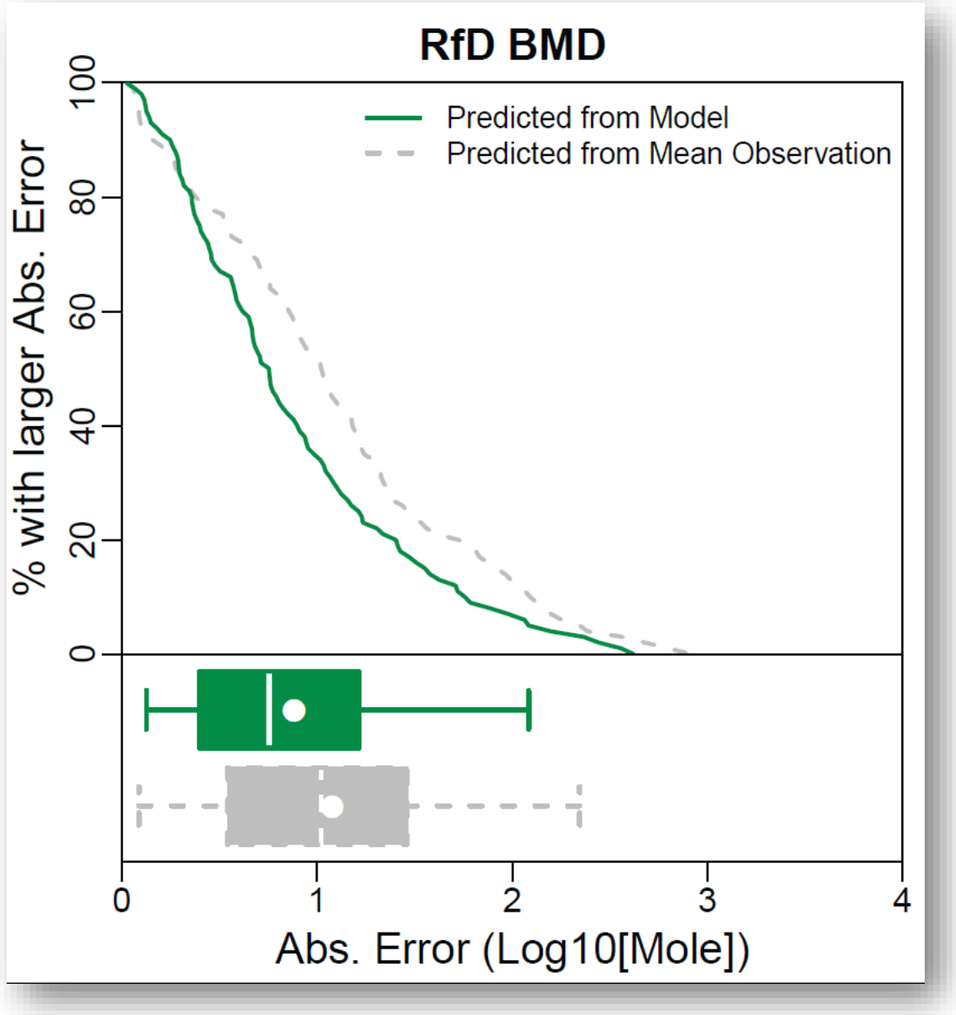


*All models were shown to perform significantly better than chance

Even Models with Low Predictivity Provide Information

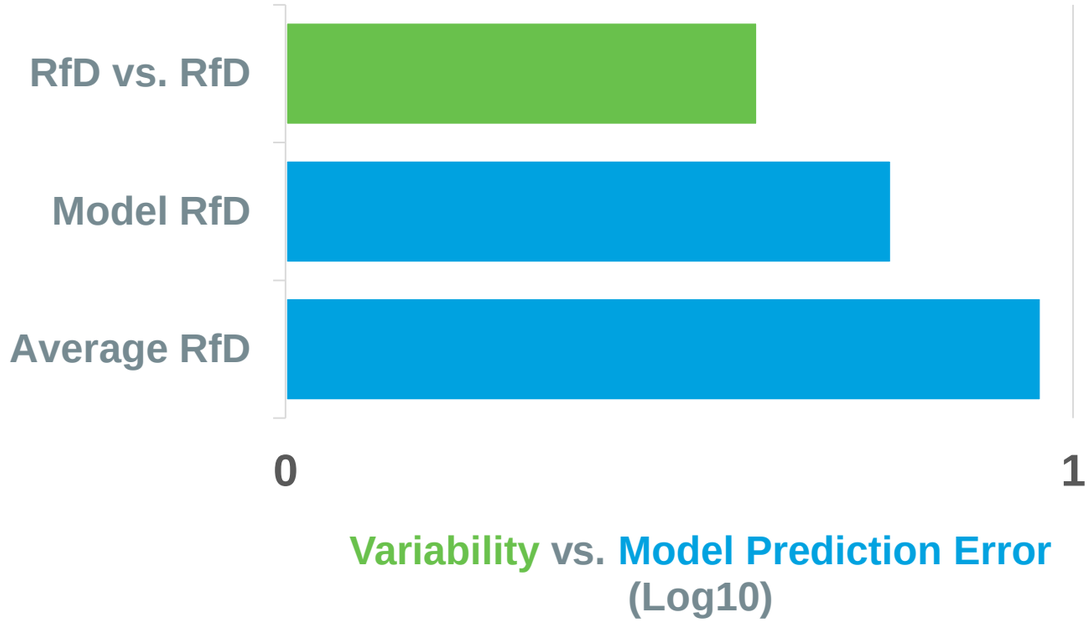
Toxicity value (# of compounds)	Consensus model Q^2	p-value for improvement over average
RfD (668)	0.41	< 0.0001
NOAEL (487)	0.45	< 0.0001
BMD NC (136)	0.31	0.0098
BMDL NC (136)	0.28	0.0098
OSF (300)	0.33	< 0.0001
CPV (223)	0.25	0.0008
RfC (149)	0.42	0.0015
IUR (148)	0.42	< 0.0001





QSAR Models In the Context of Baseline Expectations of Model Uncertainty

- Uncertainty around model predictions can be benchmarked against variation across agencies (RfD vs. RfD)
- QSAR models are close to the accuracy limit imposed by underlying heterogeneity of the data

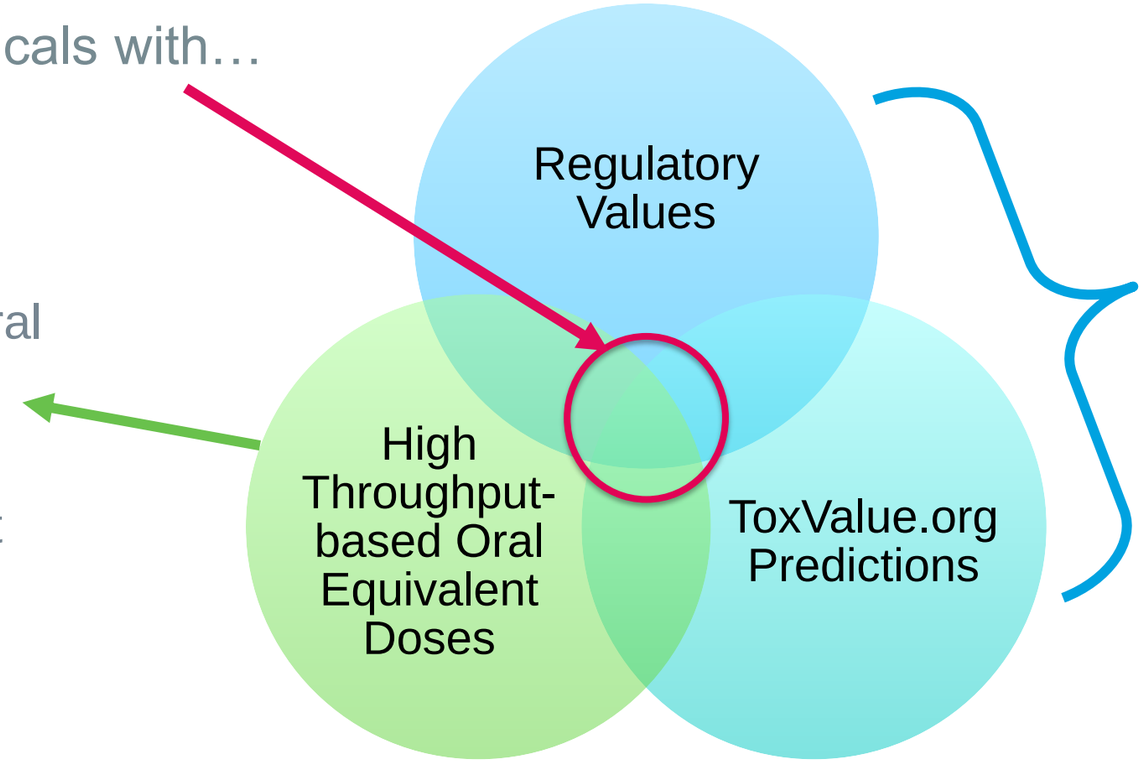


Comparing Use of ToxValue.org Predictions to Use of HTS Data for Decision Making

Chemicals with…

As collected in Wetmore et al., 2015:

- ToxCast HTS data translated to oral equivalent doses (OEDs)
- Used chemical steady-state blood concentrations to convert ToxCast bioactivity to OEDs

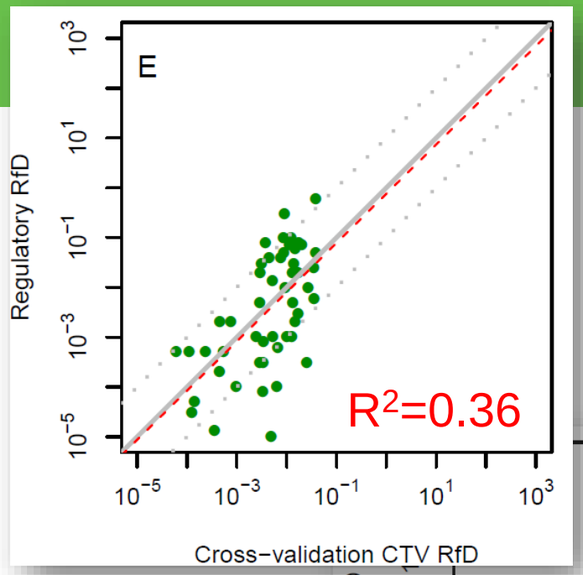


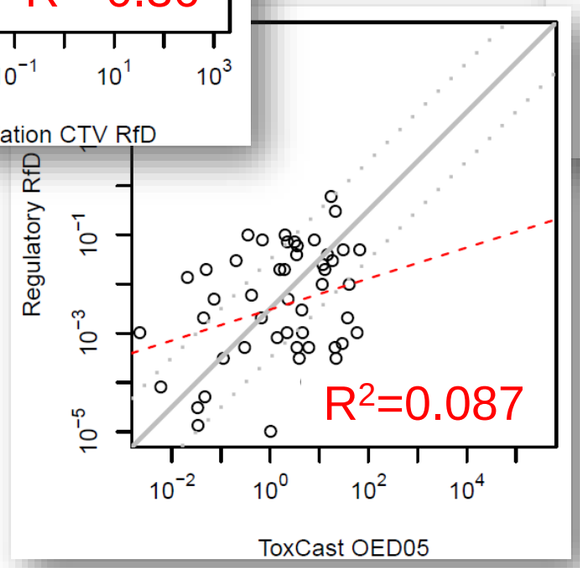
As collected in Wignall et al., 2014, 2018*

*Under revision

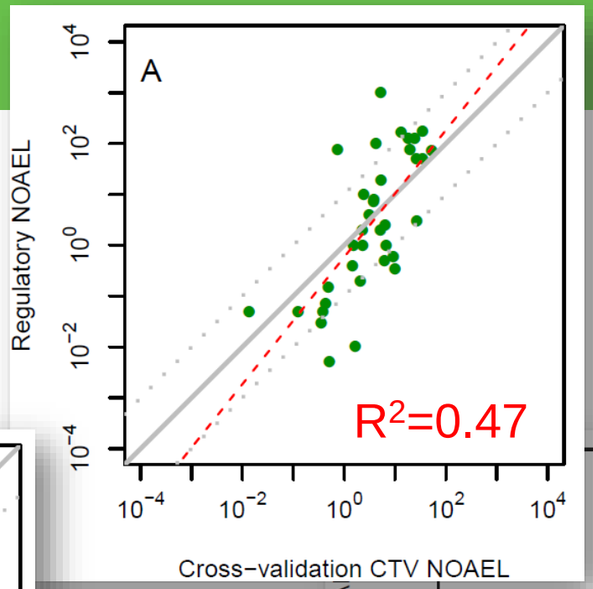
ToxValue.org Predictions Compare Favorably to Other Rapid Response Options

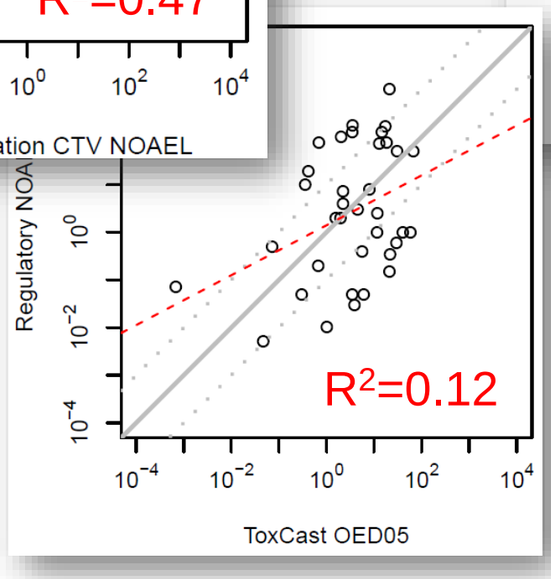
51 chemicals with regulatory RfDs from our database



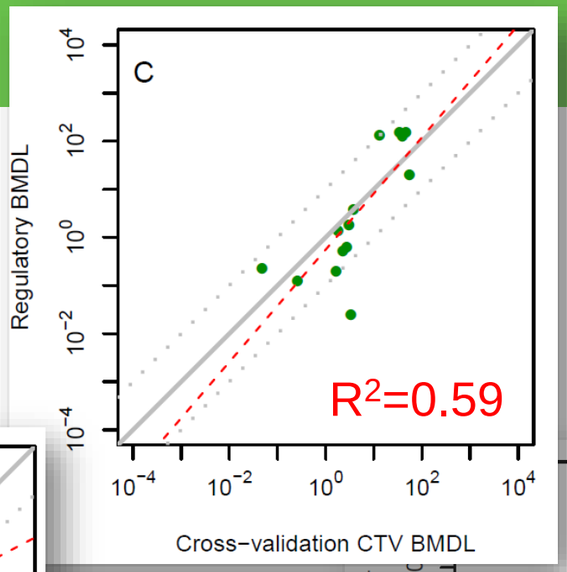


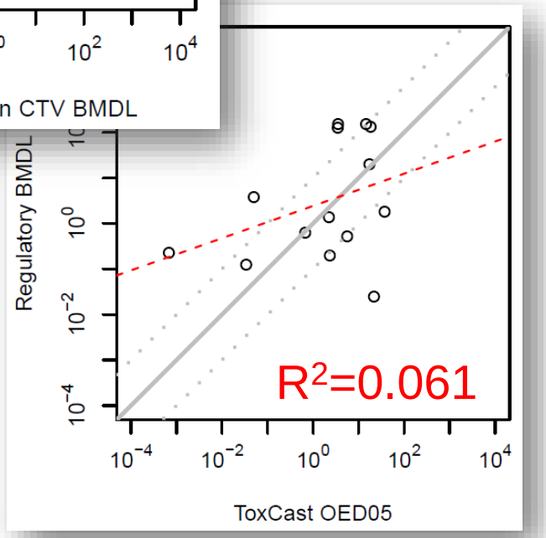
36 chemicals with regulatory NOAELs



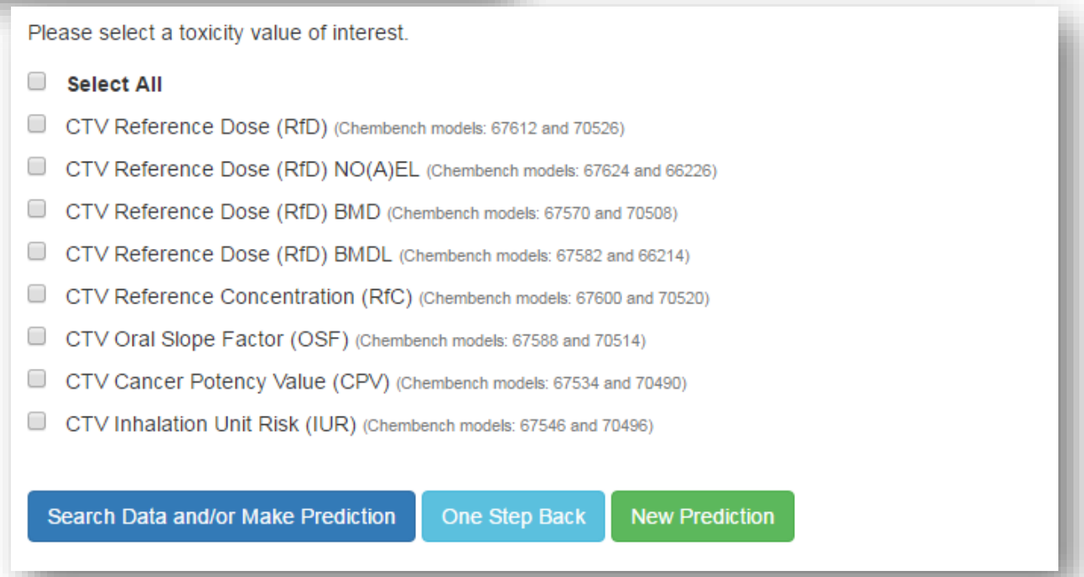


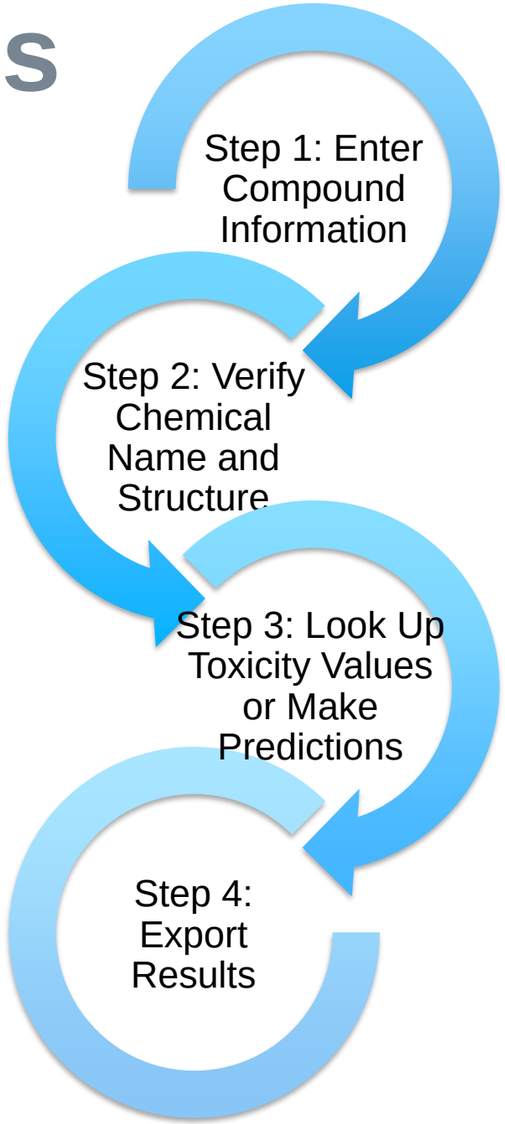
14 chemicals with regulatory BMDLs





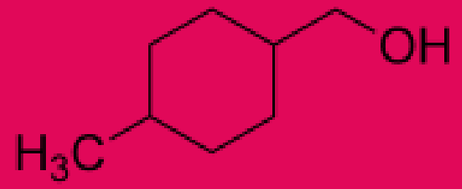
Online Portal for QSAR Predictions



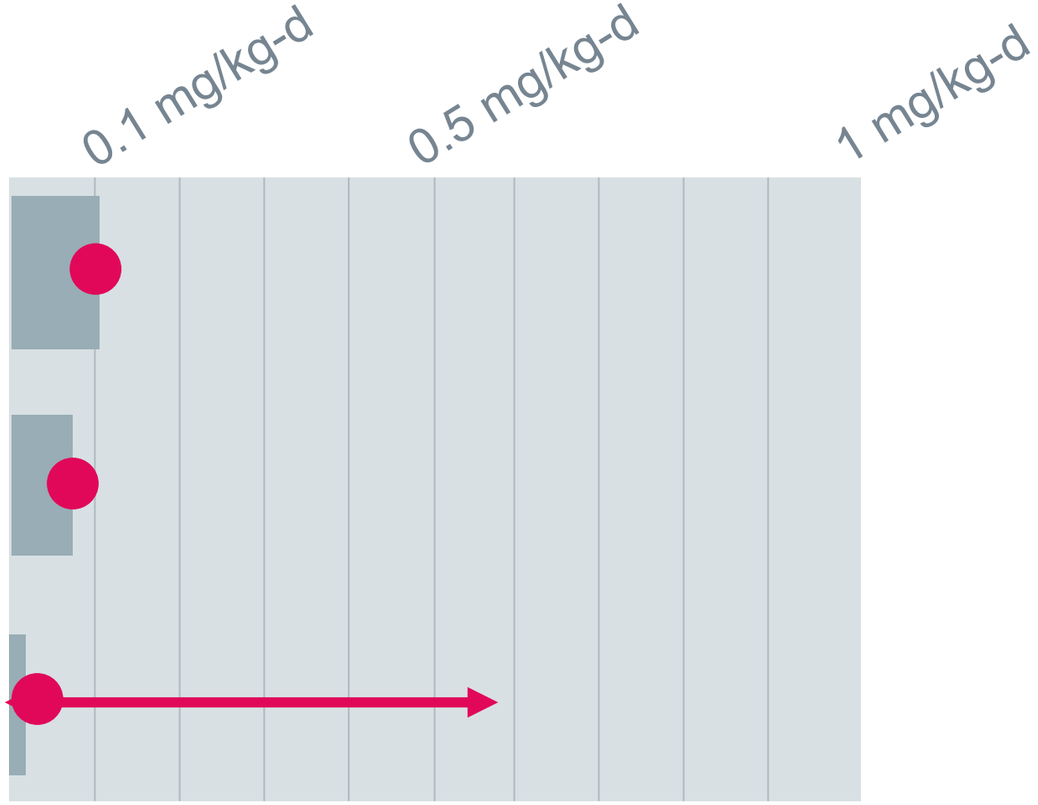


Example With 4-methylcyclohexanemethanol (MCHM)

Rapid Response Decisions



- CDC Screening Level
  - Daily dose of about 0.1 mg/kg-d
- West Virginia-Sponsored Analysis
  - Short-term RfD of 0.07 mg/kg-d
- ToxValue.org Prediction
  - RfD [90% CI] = 0.014 [4.4×10^{-4}, 0.58] mg/kg-d



Conclusions and Next Steps

Emergency response situations often require rapid response to data poor chemicals

QSAR models can be used when no data besides structure is available and when decisions are needed quickly

Contaminations often include many chemicals of various chemistries

ToxValue.org's models cover a wide chemistry space

Communicating to the public requires transparent and accessible methodology

ToxValue.org is built on publicly available data, descriptors, and methodologies

Emergency responders need to have trust in the data informing their decisions

ToxValue.org predicts useful numbers and compares favorably to other approaches that generate rapid results

Models can continue to be updated based on new data

- For example, EPA's ToxRefDB will include thousands of additional BMD values (Watford et al. Abstract #2532)
- Model results can be compared to exposure to estimate risk

Thank you!

Questions?

References

- https://github.com/shapiromatron/bmds/blob/master/notebooks/2014-wignall-ehp-rerun.ipynb
- https://github.com/shapiromatron/bmds
- Models referenced in this presentation can be found at the following sites
  - http://www.toxvalue.org/
- Cdk descriptors: http://wiki.qspr-thesaurus.eu/w/CDK
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