CTV and Integrating it into Read Across

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Conflict of Interest

- I have no conflicts to declare.
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Overview

- **Building Conditional Toxicity Value Predictor (CTV)**
  - Collecting experimental data
  - Building effective models
- **Evaluating CTV Performance**
  - Understanding model performance and applicability
- **Applying CTV to Read Across**
  - Using QSAR methods for quantitative read across
  - Incorporating dose-response information

CTV Fills a Gap in Computational Tools

- Intended for use with data poor chemicals, such as many read-across applications
- Makes predictions based on chemical structure alone
- Predicts array of quantitative toxicity values of interest to decision making
- Built using comprehensive database and incorporates OECD principles of model building and validation
- All data, models, and results freely and publicly available

ToxValue.org

Building Conditional Toxicity Value Predictor (CTV)

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

Standardized Calculation of BMDs and BMDLs for a Large Number of Chemicals

Proof of Concept

Wignall et al., 2014

- Collected **880** dose-response datasets for **352** unique chemicals with Toxicity Value(s) (e.g., RfD, OSF)
- ~75% of collected datasets can be modeled with BMDS
- Batch-calculated BMD/Ls available for over 300 chemicals

Expansion of Methods

Pham et al., 2019 (In prep.)

- BMDS Python Interface and Web Server
- Large public datasets can be efficiently modeled for predictive toxicology
- Python BMDS users can customize BMDS version and model recommendation logic

Google “python” + “BMDS”
For Python developers, "pip install bmds"

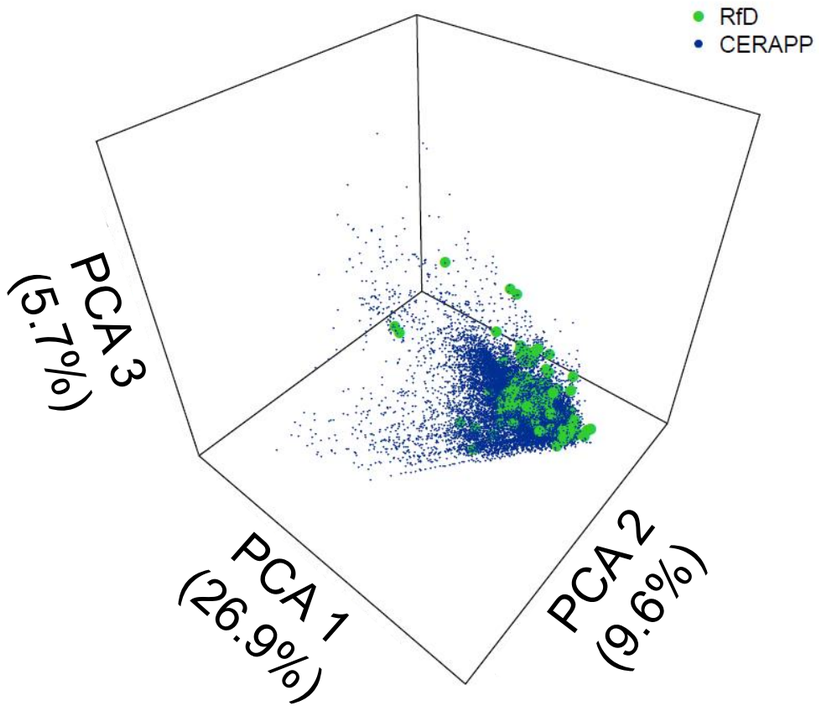
Further Application

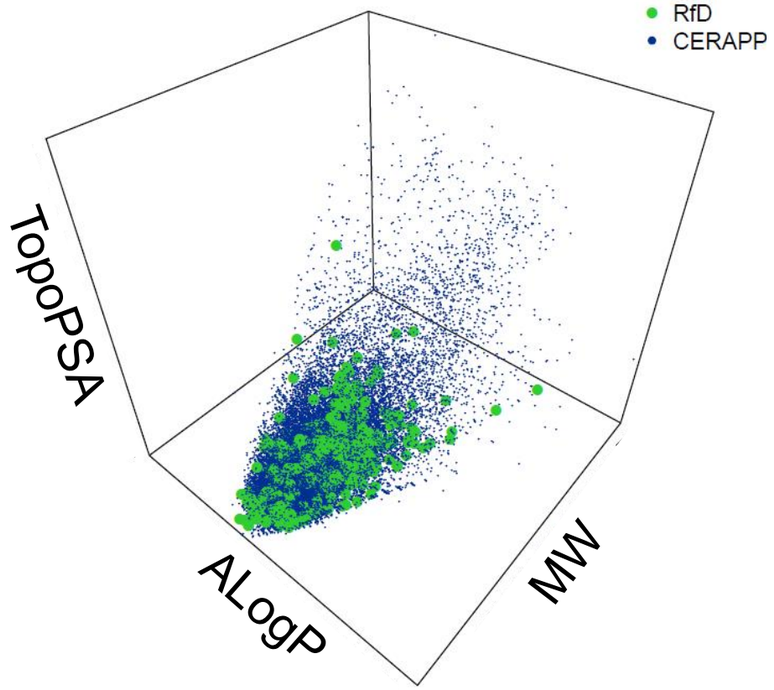
Watford et al., 2019 (In prep.)

- Extracted additional quantitative dose-response data from ToxRefDB animal studies
- Applied Python BMDS
- More than 28,000 datasets for over 600 chemicals successfully modeled

ftp://newftp.epa.gov/comptox/High_Throughput_Screening_Data/Animal_Tox_Data/current/

Chemicals in Modeling Set are Structurally Diverse





Toxicity value	CERAPP AD Coverage
RfD	86.1%
NOAEL	90.4%
BMD	81.8%
BMDL	81.8%

Percent of compounds from CERAPP within toxicity value model's applicability domain (AD) (based on Z-score cutoff < 3) (Wignall et al., 2018).

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 Useful and Predictive Models

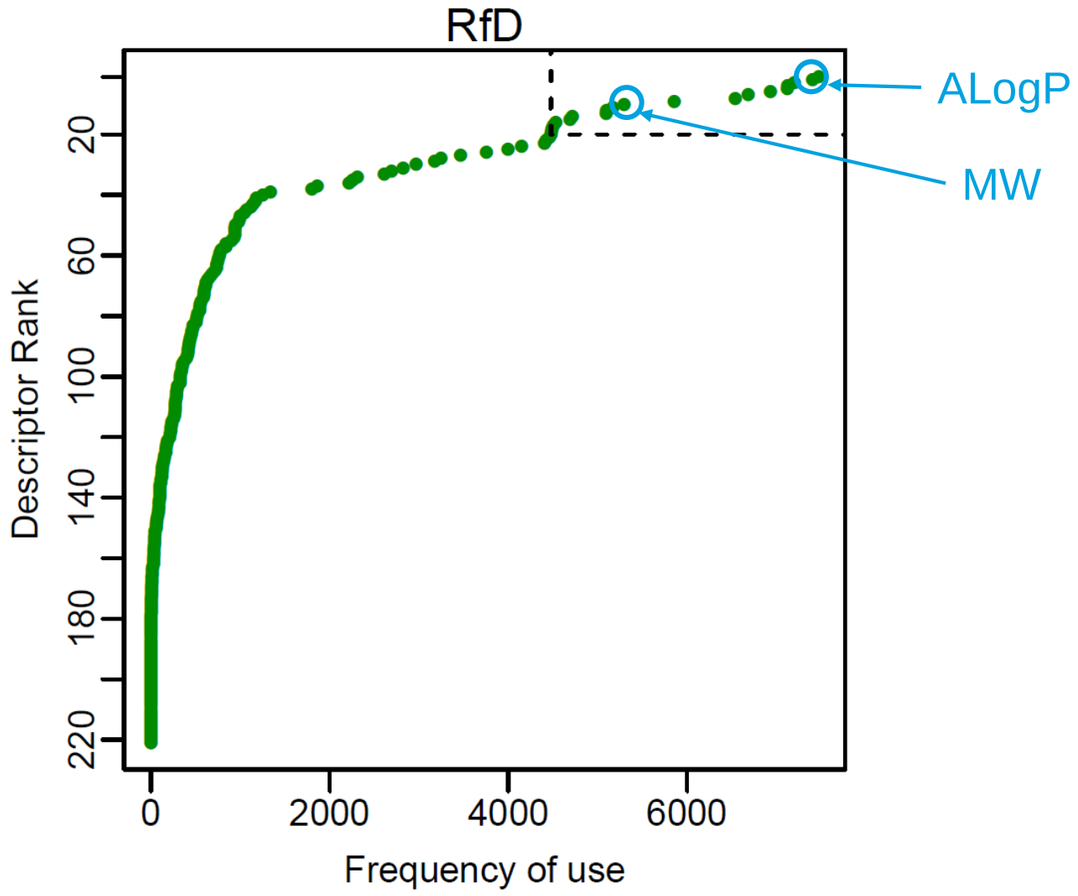
1. **Predict continuous outcomes that are of use to decision makers, including PODs**
   - **Used RfD; NOAEL; BMD; BMDL; OSF; CPV; RfC; and IUR data**

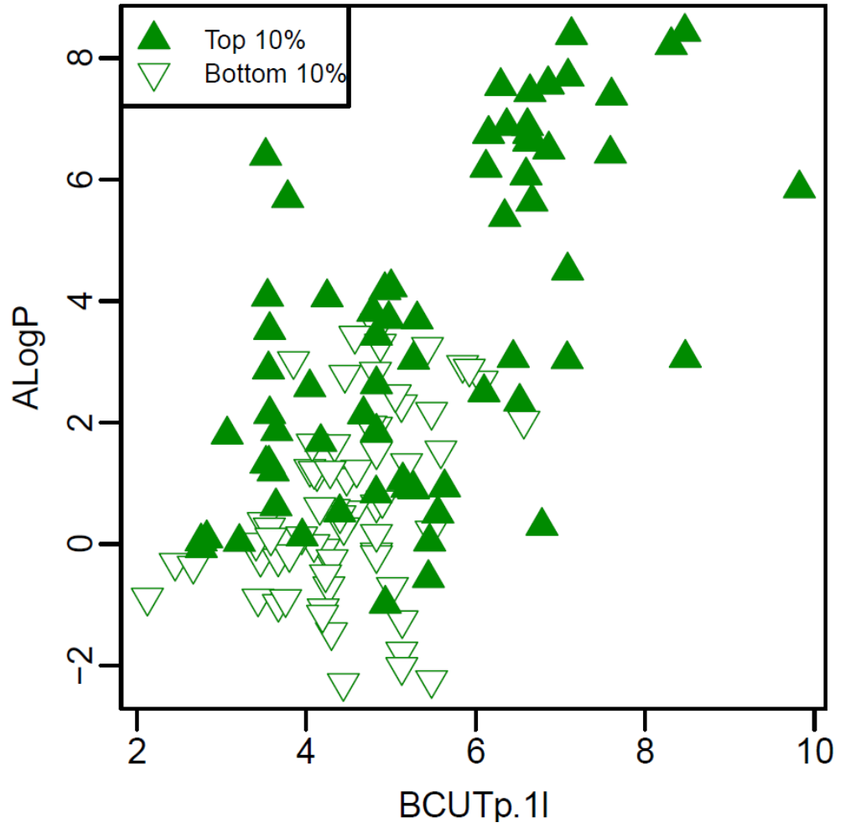
2. **Facilitate transparency and communication by using publicly available chemical descriptors, easy to understand algorithms, and external validation**
   - **Descriptor types: cdk** (rcdk package in R)
   - **Algorithm: Random Forest** (randomForest package in R)
   - **Validation: 5-fold external cross-validation**

3. **Provide data through accessible online portals**
   - **Models and predictions available through ToxValue.org**

Evaluating CTV Performance

Model Algorithms Use Chemical Features to Predict Chemical Activity



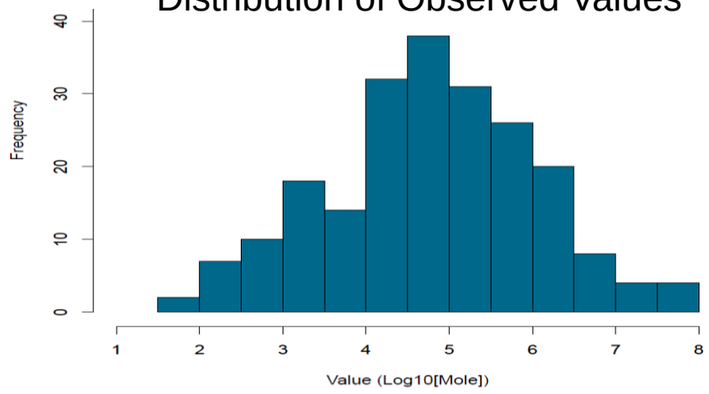


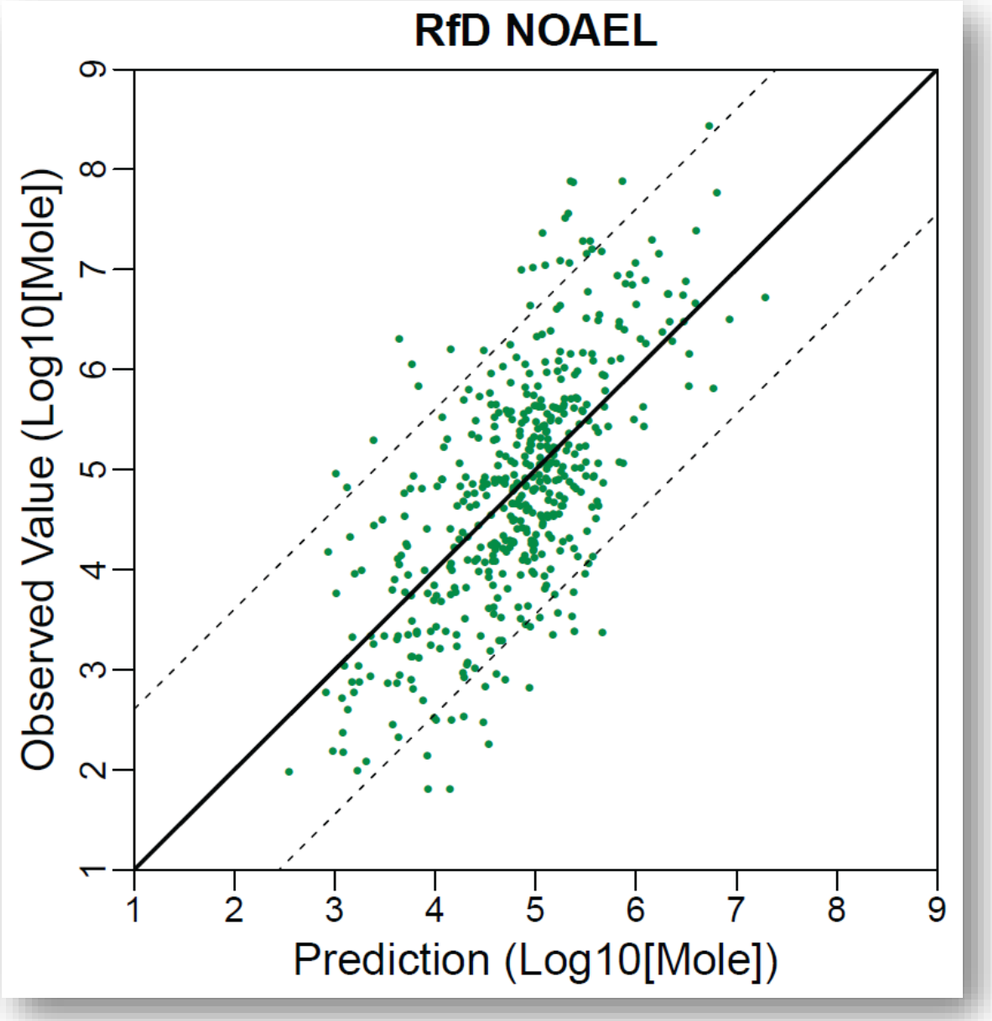
Source: Wignall et al., 2018

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

Distribution of Observed Values





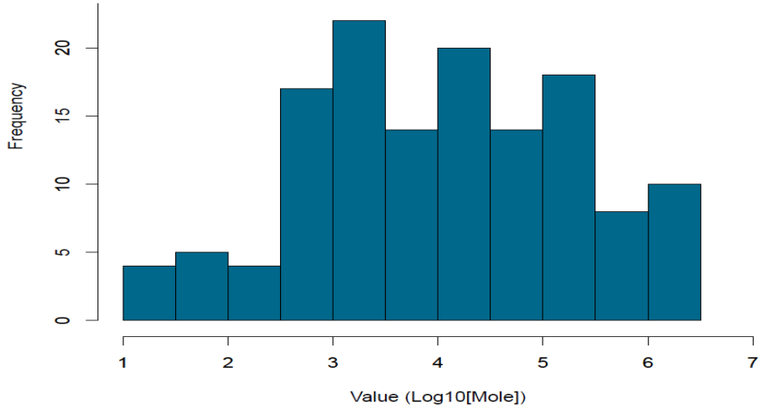
*All models were shown to perform significantly better than chance (Wignall et al., 2018)

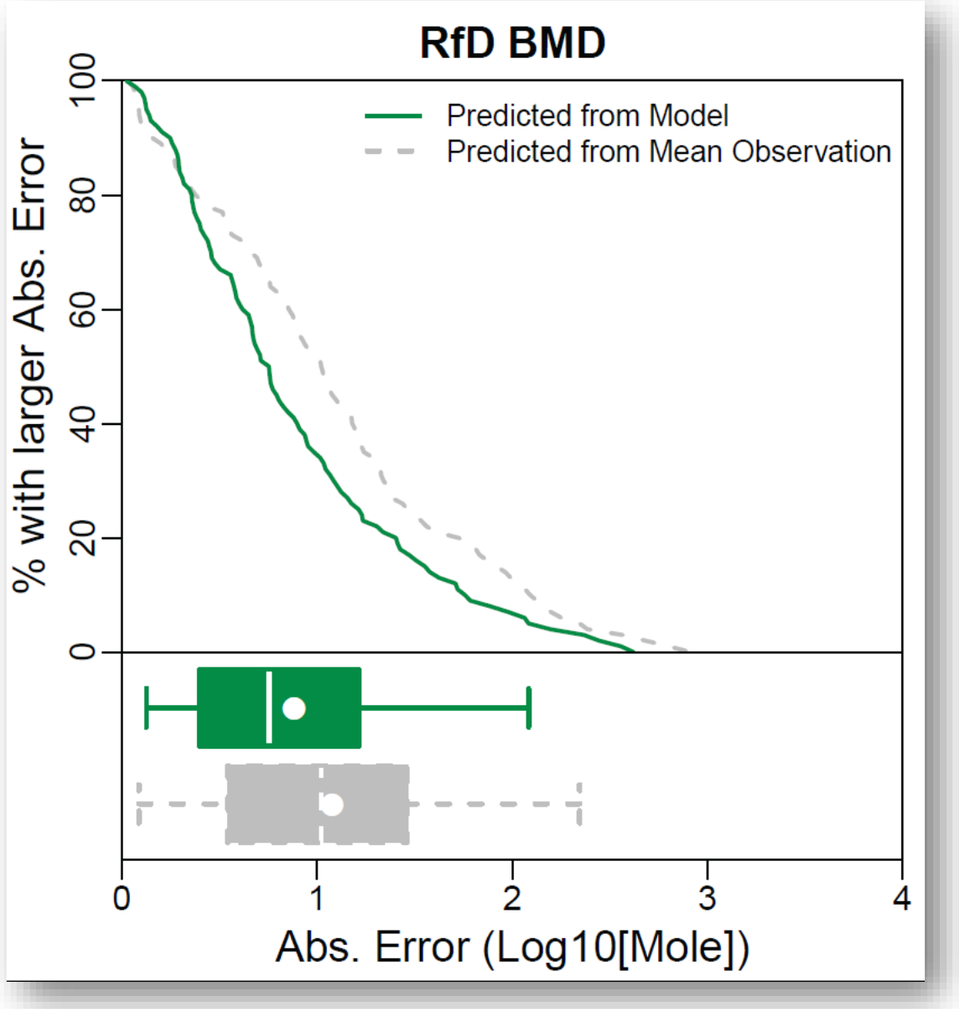
Source: Wignall et al., 2018

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

Distribution of Observed Values

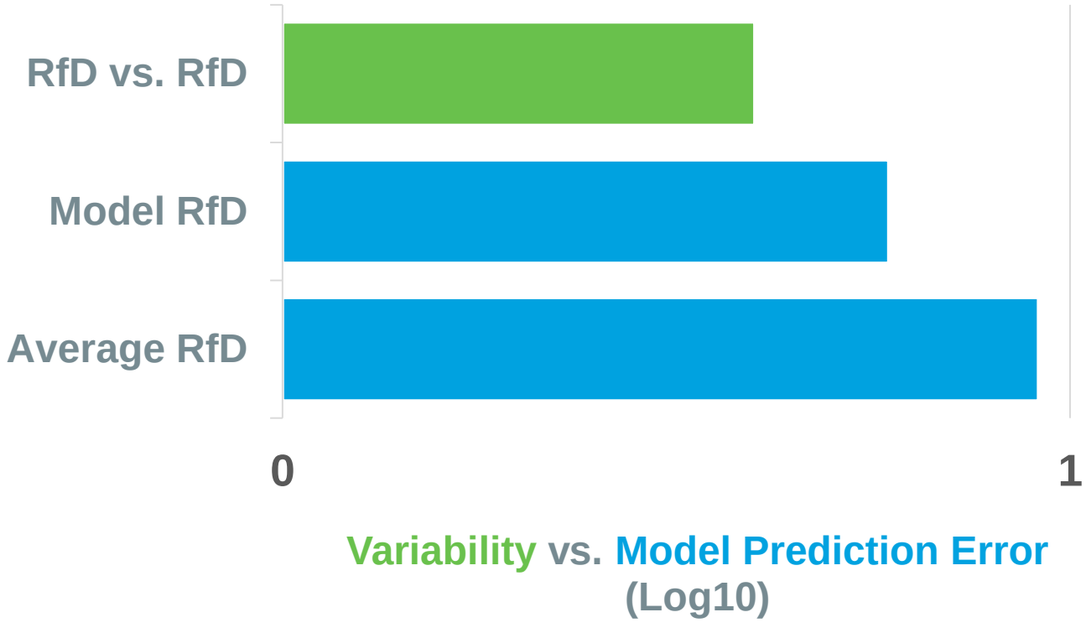




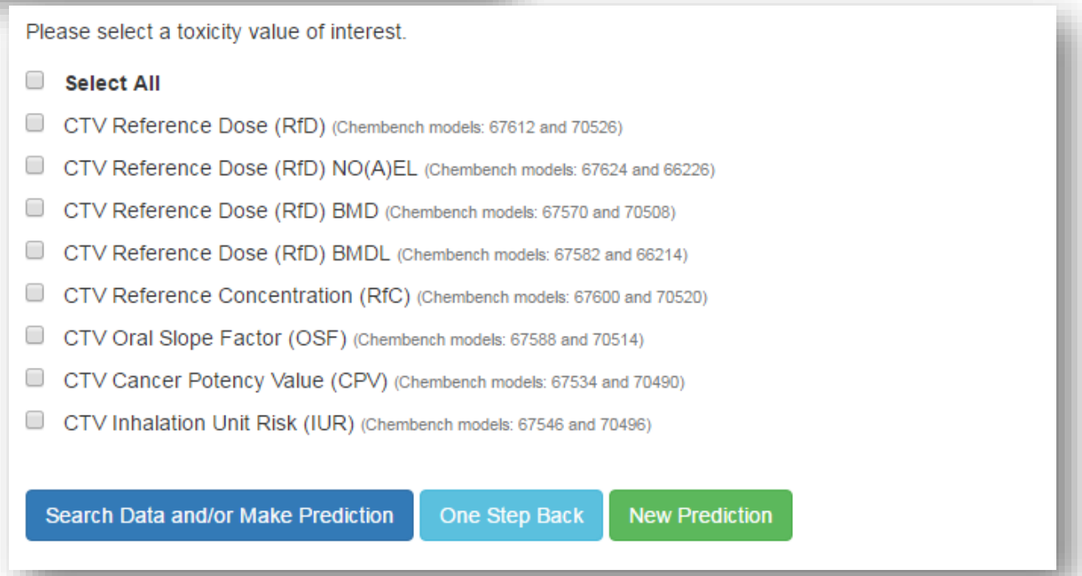
Source: Wignall et al., 2018

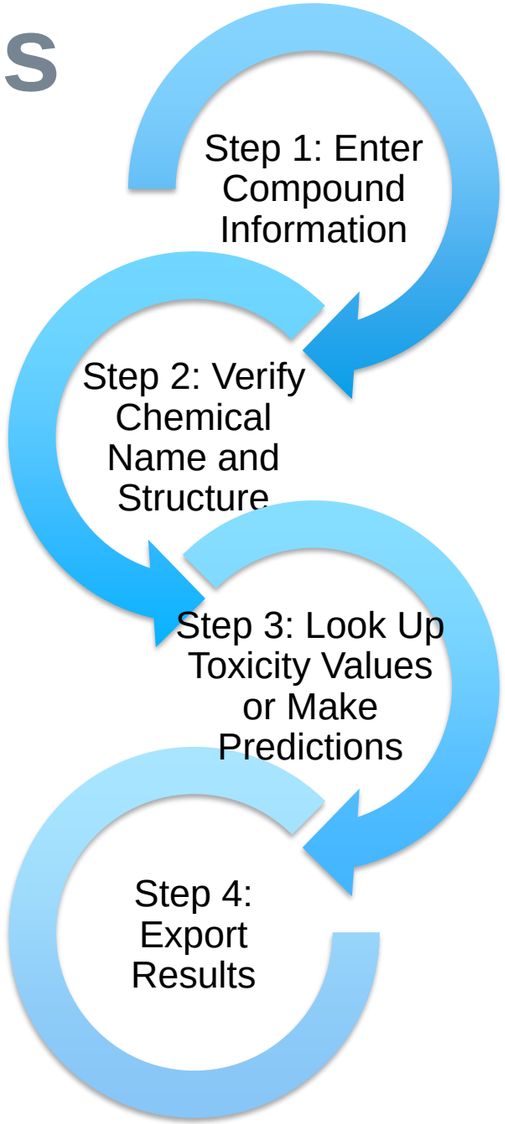
QSAR Models In the Context of Baseline Expectations of Model Uncertainty

- 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



Online Portal for QSAR Predictions





Applying CTV to Read Across

Read-Across Example

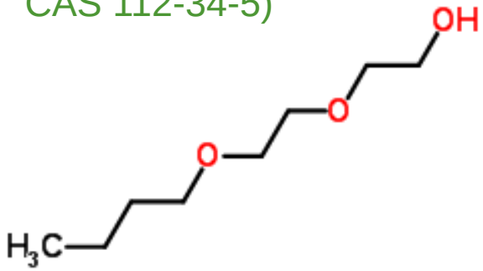
Experimental values

Diethylene glycol ethers (Di EGEs)

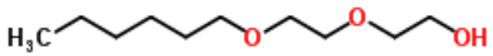
Chemical

Diethylene glycol ethyl ether (DGEE, CAS 111-90-0)

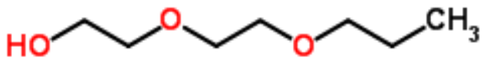
Diethylene glycol monobutyl ether (DEGBE, CAS 112-34-5)



Diethylene glycol hexyl ether (DGHE, CAS No. 112-59-4)



Diethylene glycol propyl ether (DGPE, CAS 6881-94-3)



Critical No Effect Level

NOAEL: 167 mg/kg-day based on kidney and liver effects in pigs

Dose	Incidence
0	0/3
167	0/3
500	1/2
1117	1/1

NOAEL: 50 mg/kg-day for anemia in rats

Dose	#	Mean	SD
0	10	9.27	0.35
50	10	9.13	0.22
250	10	8.94	0.34
1000	10	8.53	0.31

?

50 mg/kg-day

↕

167 mg/kg-day

?

50 mg/kg-day

↕

167 mg/kg-day

Read-Across Example

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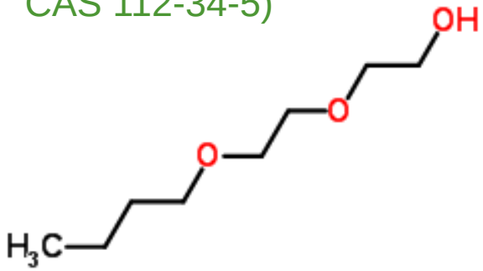

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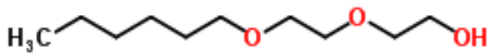

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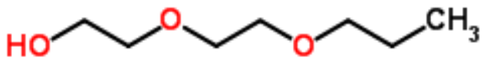


Critical Point of Departure

NOAEL: 167 mg/kg-day based on kidney and liver effects in pigs

NOAEL: 50 mg/kg-day for anemia in rats

?

?

BMD 443 mg/kg-day
BMDL 45.2 mg/kg-day

BMD 222 mg/kg-day
BMDL 81.4 mg/kg-day

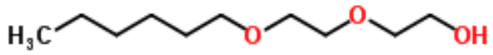
50 mg/kg-day
↕
167 mg/kg-day

50 mg/kg-day
↕
167 mg/kg-day

ICF

ToxValue.org Output

Diethylene glycol hexyl ether
(DGHE, CAS No. 112-59-4)



Chemical name	Model Name	Unit	Prediction	Lower 95%*	Upper 95%*	Appl Domain**
C6E2	CTV Reference Dose (RfD) BMD	$-Log_{10}$Mol/(kg·day)	3.36	1.36	5.30	-0.453
		mg/(kg·day)	83.2	0.960	8.29e+3	
	CTV Reference Dose (RfD) BMDL	$-Log_{10}$Mol/(kg·day)	3.69	1.91	5.41	-0.453
		mg/(kg·day)	38.6	0.739	2.33e+3	

Z-score output: Distance from **your chemical** to the **nearest chemical** in training set **compared** to the average nearest-neighbor-distances in the training set

- 0 = same distance as average distances in the training set
- >0 = your chemical is at a further distance than average distances in the training set
- <0 = your chemical is at a closer distance than average distances in the training set

Use Z > 1 as a conservative cut-off for applicability, Z > 3 as a less-restrictive cut-off (to define anything < cut-off as within AD of model).

Read-Across Example

Diethylene glycol ethers (Di EGEs)

Experimental values
Predicted values

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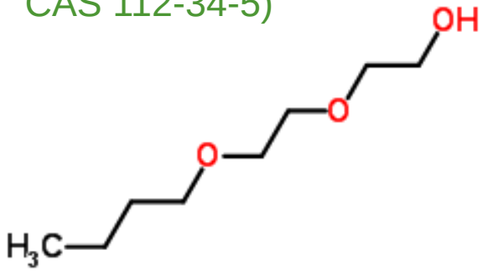

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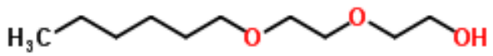

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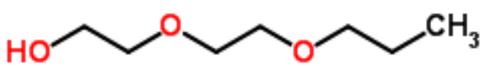

Critical Point of Departure

NOAEL: 167 mg/kg-day based on kidney and liver effects in pigs

NOAEL: 50 mg/kg-day for anemia in rats

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BMD 222 mg/kg-day
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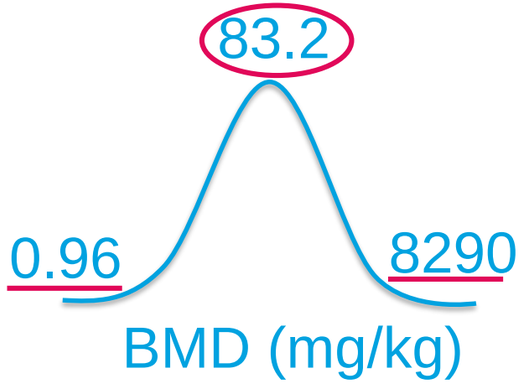
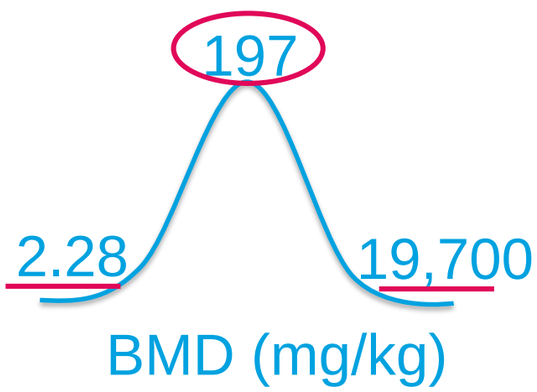
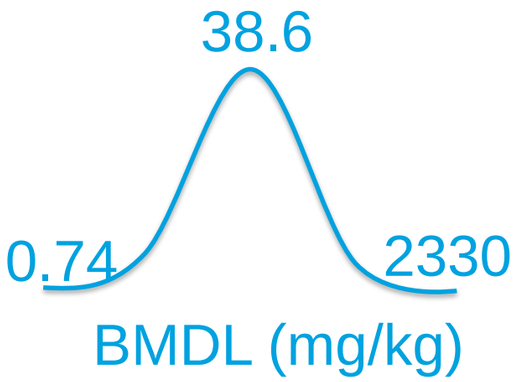
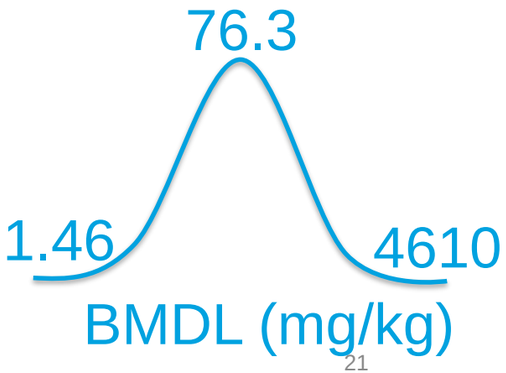








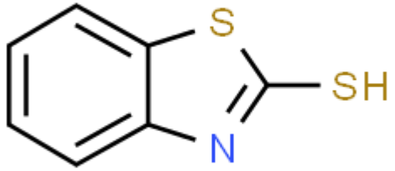
Read-Across Example

Experimental values

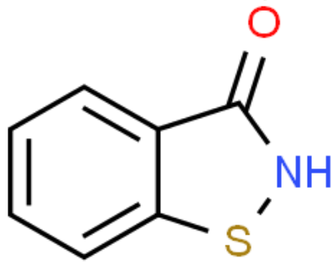
Crumb Rubber: Benzothiazole-like chemicals

Chemical

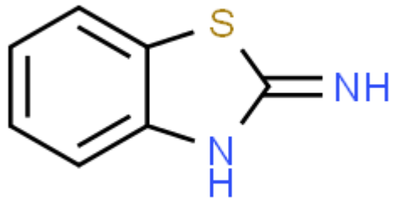
1,3-Benzothiazole-2-thiol
(CAS No. 149-30-4)



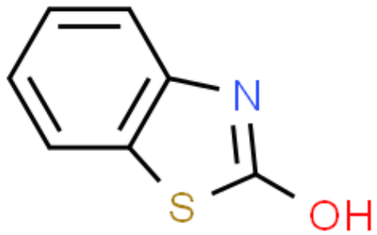
1,2-Benzisothiazol-3(2H)-one
(CAS No. 2634-33-5)



1,3-Benzothiazol-2-amine
(CAS No. 136-95-8)



2-Hydroxybenzothiazole
(CAS No. 934-34-9)



ToxRefDB Data

CHR NOAEL, rats:
<188 mg/kg-day*
based on lethargy and forestomach lesions (inflammation and ulcers)

SUB BMD, rats:
50.81 mg/kg-day*
(liver weight)

SUB NOAEL, rats:
78.3 mg/kg-day*
based on stomach pathology (thickened, hyperplasia)

SUB BMD, rats:
4.13 mg/kg-day*
(stomach inflammation)

?

?

*Data excerpted from ToxRefDB for illustrative purposes only; not intended to reflect critical effect decisions.

Read-Across Example

Crumb Rubber: Benzothiazole-like chemicals

Experimental values
Predicted values

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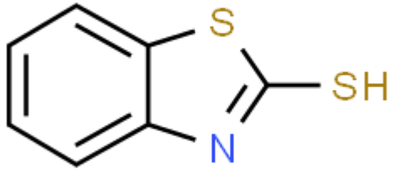

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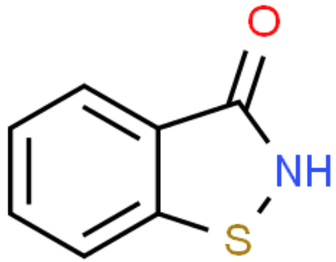

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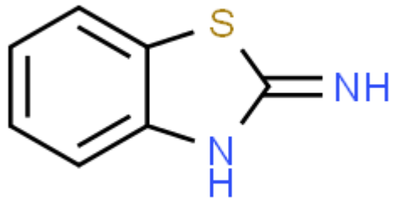

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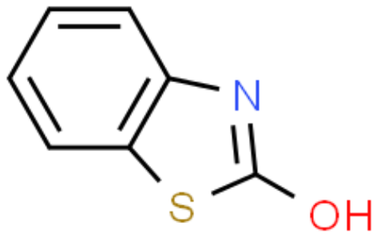

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SUB BMD, rats:
4.13 mg/kg-day*
(stomach inflammation)

CHR BMD (mg/kg):
12.8 mg/kg-day
[0.147,1270]

AD: 1.78

CHR BMD (mg/kg):
11.5 mg/kg-day
[0.133,1150]

AD: 1.16

*Data excerpted from ToxRefDB for illustrative purposes only; not intended to reflect critical effect decisions.

Conclusions and Next Steps

Read across is used for emerging needs and chemical lists

QSAR models can be used when no data besides structure is available

Read across often needs to be applied to many chemicals of various chemistries

ToxValue.org's models cover a wide chemistry space

Communicating read-across results requires transparent and accessible methodology

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

Decision-making contexts sometimes require quantitative data

ToxValue.org predicts useful numbers and quantifies uncertainty

Models can continue to be updated based on new data

- For example, EPA's ToxRefDB now includes thousands of additional BMD values

Acknowledgments

- Texas A&M: Ivan Rusyn, Weihsueh Chiu
- UNC Chapel Hill: Alexander Tropsha, Eugene Muratov, Denis Fourches (now at NC State), Aleck Sedykh (now at Sciome LLC)
- EPA/NCEA: Kate Guyton (now at IARC), Vincent Cogliano
- EPA/NCCT: Matthew Martin (now at Pfizer), Sean Watford (now at Booz Allen), Katie Paul Friedman, Ly Pham (now at ToxStrategies)
- NIEHS: Andy Shapiro (now at Infinia ML)
- California EPA: Lauren Zeise
- UC San Francisco: Tracey Woodruff
- NC State: David Reif

Thank you!

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/
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