Predicting Five Rat Acute Toxicity Endpoints with ANNE Models using ADMET Predictor™

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Introduction

- Alternative methods are being explored to predict the toxicity of chemicals to reduce use of animals.
  - ✓ Laboratory/Animal tests are costly in time and money
- Cheminformatics (QSTR) presents a good alternative to animal testing
  - ✓ Once the model is ready, predictions can be made quickly

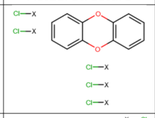
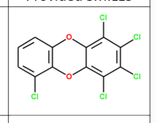
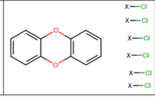
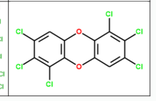
Why Artificial Neural Network Ensemble (ANNE)?

- Toxicity prediction is a tough problem
  - ✓ Multiple underlying mechanisms of action
  - ✓ Datasets studied (e.g., rat LD50) are large and chemically diverse
  - ✓ Multiple and wide variety of data sources
  - ✓ Simple regression methods like MLR may prove insufficient
- Ensemble methods, such as ANNE and Random Forest, have proven to be robust enough to tackle this intensive task
- Five endpoints were provided to model
  - ✓ Rat LD_{50} and "Very Toxic", "Non Toxic", "EPA Cat" & "GHS Cat"
  - ✓ The labels in the four end-points are dependent upon rat LD_{50}

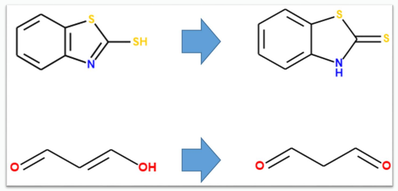
Why is Dataset Curation Necessary?

- The "**QSAR-ready structures**" provided as training set needed careful curation

Uncertainty in structures is not useful

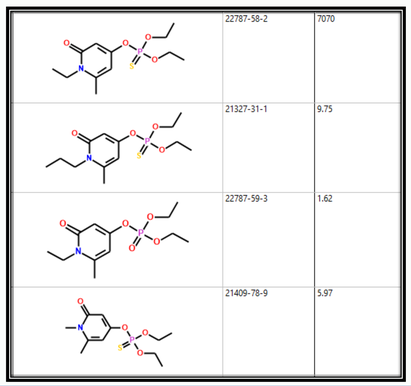
CASRN	Actual Structure	Provided SMILES
36088-22-9		
34465-46-8		

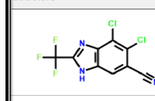
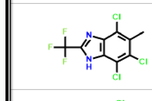
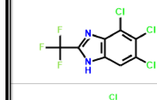
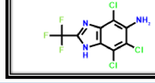
Incorrect tautomer updated to Correct tautomer



Correct tautomer assignment is necessary in model building exercise as well as for correct prediction

- Matched Molecular Pair Analysis shows a few large activity cliffs
- The data is questionable and hence excluded



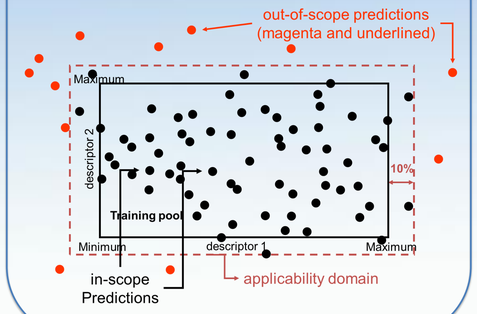
Structure	Identifier	LD50_mgkg
	89427-25-8	3955
	4228-99-3	18.286
	2338-27-4	1.519
	89427-41-8	23

Molecular Descriptors

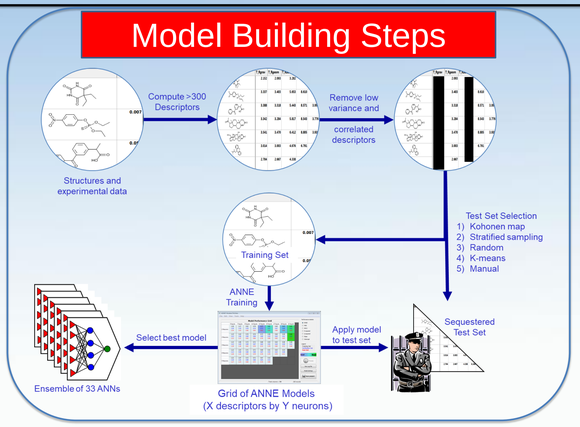
ADMET Predictor™ generated 341 molecular descriptors

- ✓ Constitutional Descriptors
- ✓ Topological Indices
- ✓ Electrotopological State Indices
- ✓ Charge-based Descriptors
- ✓ Hydrogen Bonding Descriptors
- ✓ Moriguchi Descriptors
- ✓ Functional Groups

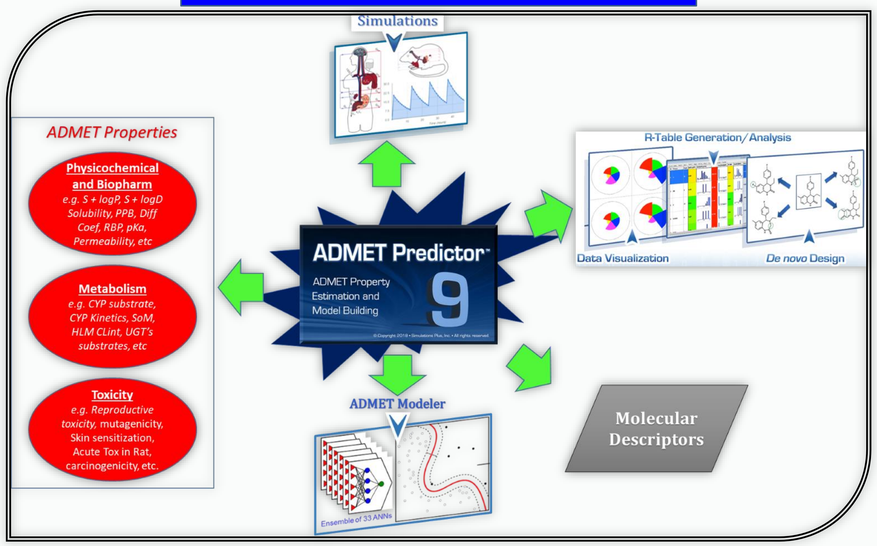
Applicability Domain

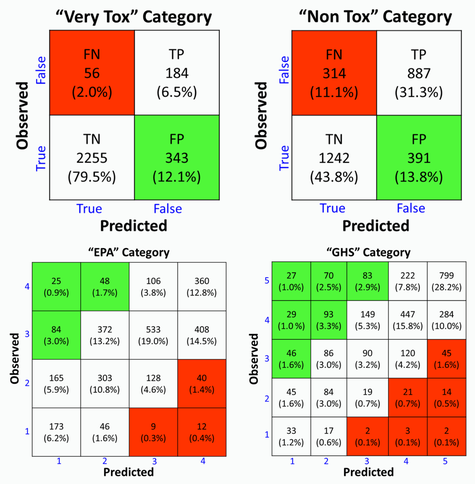


Model Building Steps



ADMET Predictor™





Models predicted fewer false negatives compared to false positives. Thus, they erred on the side of caution, e.g., fewer toxic compounds were incorrectly predicted. This can be seen in the EPA and GHS category predictions which show fewer incorrect compounds in the lower right-hand corner than the upper left-hand corner.

Model	Endpoint	Validation Data Size	Training Set	Test Set	Outside AD (%)	Performance On Training[1]	Performance On Ext Test[1]
EPACat_1	EPA class (1-4)	2812	6531	1633	50 (1.8%)	0.689	0.696
EPACat_2	EPA class (1-4)	2812	6531	1633	51 (1.8%)	0.693	0.691
GHSCat_1	GHS class (1-5)	2882	6951	1648	51 (1.8%)	0.708	0.666
GHSCat_2	GHS class (1-5)	2882	6951	1648	51 (1.8%)	0.689	0.671
LD50_1	LD_{50}	2172	Existing Model[2]		41 (1.8%)	0.595	0.638
LD50_2	LD_{50}	2172	5037	1209	41 (1.8%)	0.614	0.605
NonTox_1	LD50 > 2,000 mg/kg	2887	7059	1246	54 (1.9%)	0.765	0.750
NonTox_2	LD50 > 2,000 mg/kg	2887	7059	1246	55 (1.9%)	0.771	0.748
VeryTox_1	LD50 ≤ 50 mg/kg	2891	6699	1675	52 (1.8%)	0.675	0.620
VeryTox_2	LD50 ≤ 50 mg/kg	2891	6699	1675	53 (1.8%)	0.809	0.825

[1] BA for EPA, GHS, NT, and VT. TST_RMSE for LD_{50}; [2] Existing model from ADMET Predictor was used to predict LD_{50}

Model Performance & Analysis

- All the models show comparable performance on both training & test set
- Overall statistics suggests that models are **NOT OVERTRAINED**
- Almost all compounds were predicted within applicability domain of models.
- Only ~50 compounds (1.5%) were predicted out of the AD, 48 contained a Si, Se, or heavy metal atom and 2 compounds exceeded the 256 heavy atom limit of ADMET Predictor.

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