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Practical Considerations for Estimation of Oral Rat LD50

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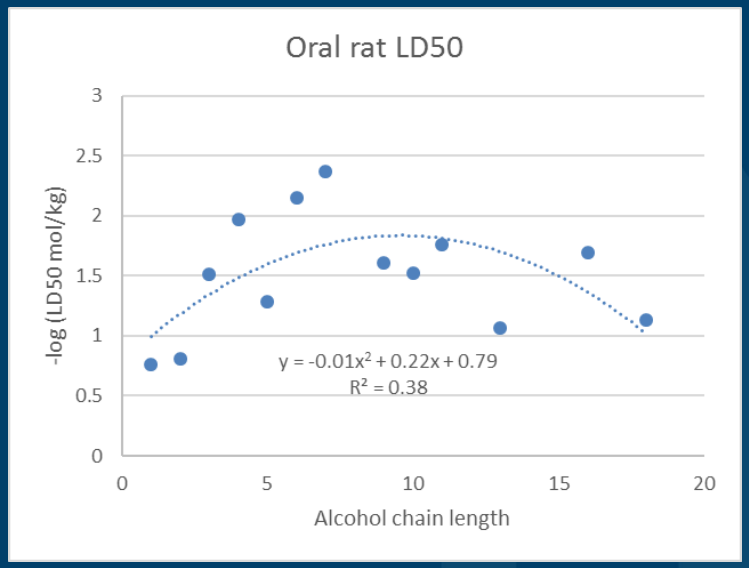
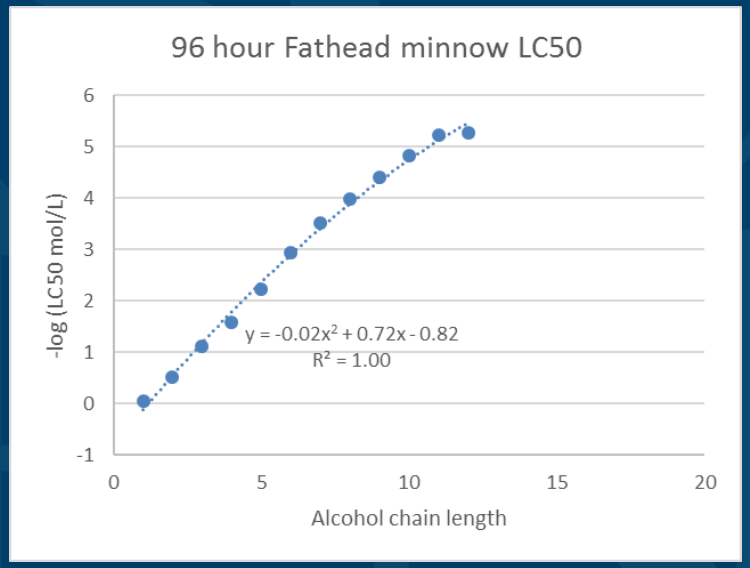
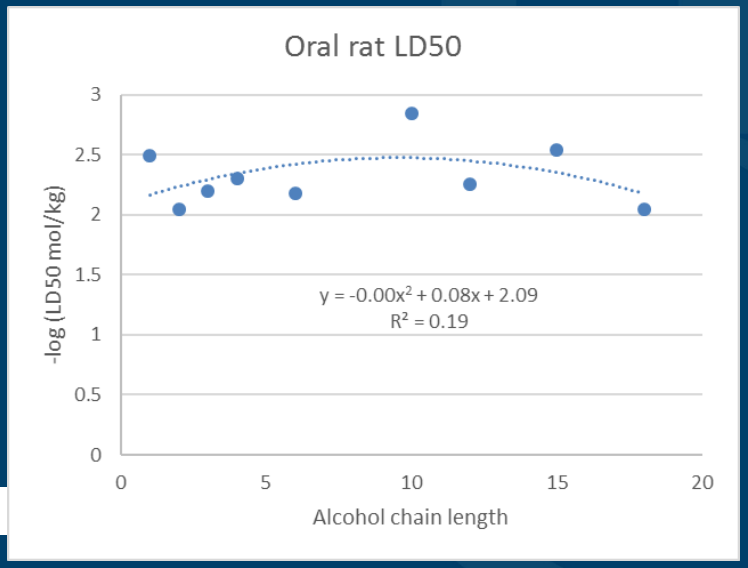
Difficulty with oral rat LD50 endpoint

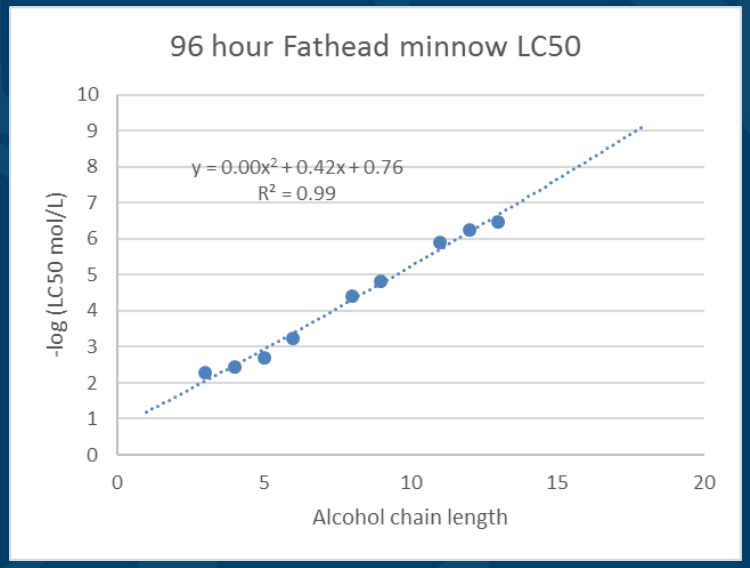
United States Environmental Protection Agency





n-alcohols





n-amines

Additional data to improve results

- ChemIDplus lists effects for some chemicals for oral rat LD50

rat	LD50	oral	930mg/kg (930mg/kg)	BEHAVIORAL: TREMOR BEHAVIORAL: CONVULSIONS OR EFFECT ON SEIZURE THRESHOLD	Toxicology and Applied Pharmacology. Vol. 7, Pg. 767, 1965.

- There is pest target species database:
  - C.L. Russom, *Pesticide Acute MOA Database: Overview of procedures used in compiling the database and summary of results*, US EPA, Duluth, MN, 2013, p. 26.
  - T. M. Martin, C. R. Lilavois & M. G. Barron (2017) Prediction of pesticide acute toxicity using two-dimensional chemical descriptors and target species classification, SAR and QSAR in Environmental Research, 28:6, 525-539, DOI: 10.1080/1062936X.2017.1343204
- Both of these can help bin chemicals but may not improve external prediction accuracy since not available for new chemicals (have to predict them before can bin a chemical)

Practical Considerations

- What were the major practical considerations identified when modelling – are there recommendations you could propose that would have helped resolve some/all of these?
  - Should we fit models to continuous LD50 values or to binary/category endpoints? Or both depending on final goal?
- Were there limits to appropriate methods for the different endpoints?
  - It's very difficult to fit a single regression model to the entire LD50 training set so need clustering or neighbor based method

QSAR Method Selection

- What were the rationale to applying particular methods
  - Needed a method that could be applied to very large dataset with lots of experimental error
- What are advantages/disadvantages of making specific method choices?
  - Hierarchical clustering
    - Slow for model building and prediction
    - Can correlate differences in toxicity for subsets of the data
    - Hard to make “external” predictions for training compounds
  - Nearest neighbor
    - Very fast and easy to understand
    - Can’t quantify differences in toxicity between test compound and the neighbors
    - Can always make “external” predictions for training compounds

Applicability Domain

- How will I know if my chemistry is within the domain of applicability of your model?
  - Hierarchical clustering
    - Model ellipsoid, Rmax, and Fragment constraints

$$h_{00} = X_o^T \left(X^T X \right)^{-1} X_0$$

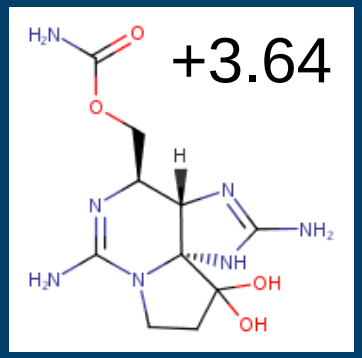
$$distance_i = \sum_{j=1}^{d} \left(x_{ij} - C_j \right)^2$$

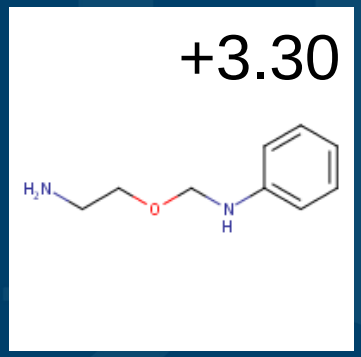
  - Nearest neighbor
    - Three most similar chemicals must exceed a minimum cosine similarity coefficient of 0.5

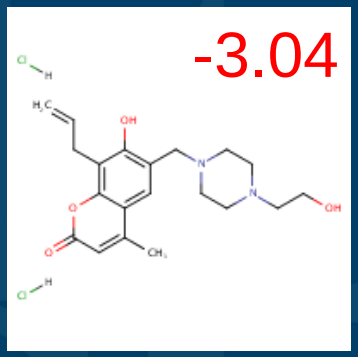
$$SC_{i,k} = \frac{\sum_{j=1}^{\#descriptors} x_{ij} x_{kj}}{\sqrt{\sum_{j=1}^{\#descriptors} x_{ij}^2 \cdot \sum_{j=1}^{\#descriptors} x_{kj}^2}}$$

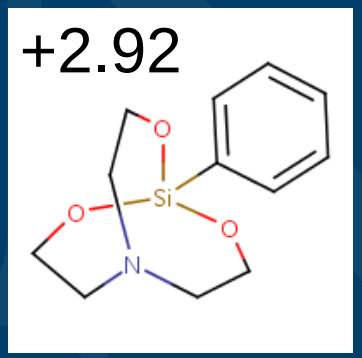
Difficult to predict chemicals

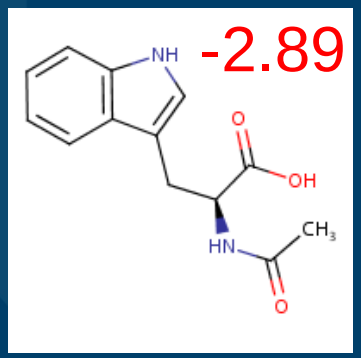
- What elements do “difficult to predict” chemistries have in common?
  - 16 of the top 20 worst predicted compounds contain **Nitrogen**
    - The nitrogens are usually in an aromatic ring or attached to one
  - Usually it’s hard for machine-based methods to detect reactive substructures purely from descriptor values

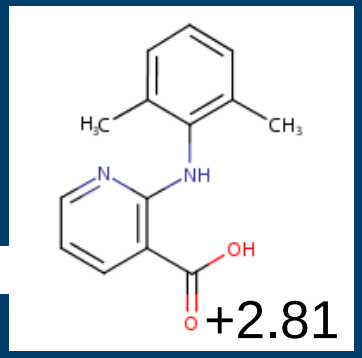


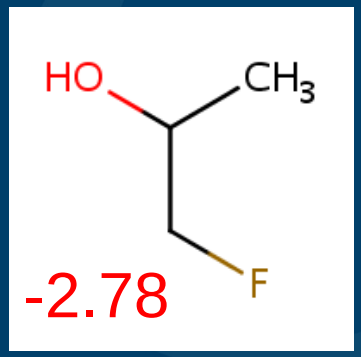


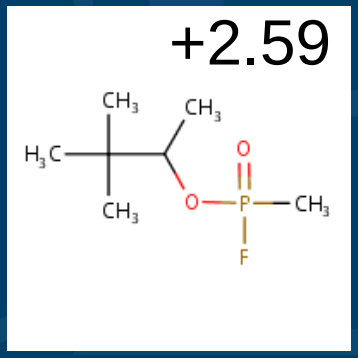


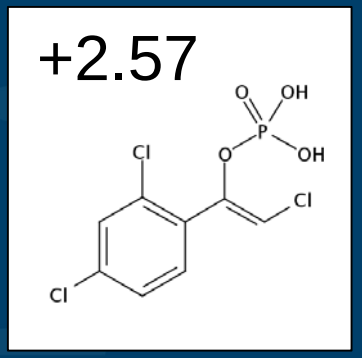


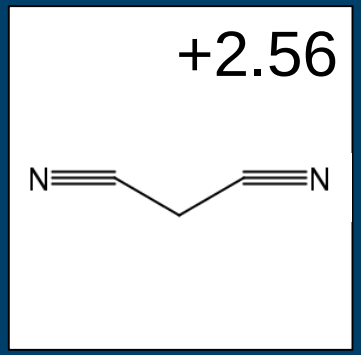






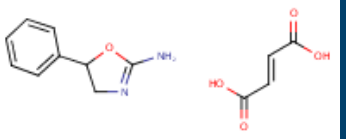






Difficult to predict, cont.

+2.53



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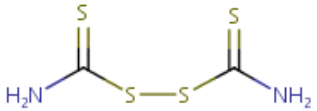

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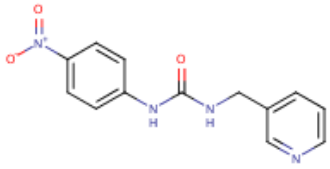

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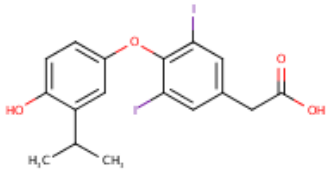

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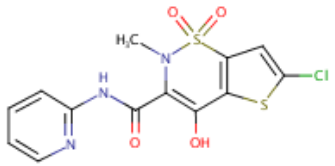

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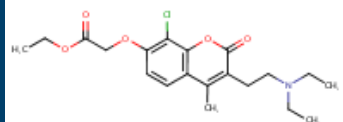

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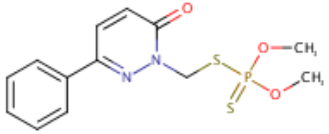

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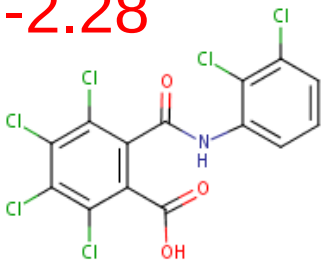

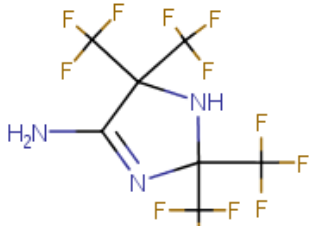

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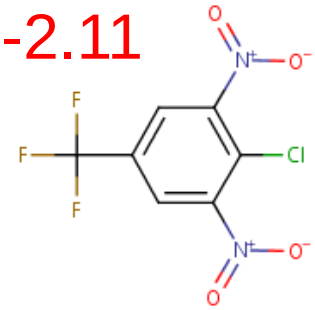


* Numbers represent the prediction error in log10 (LD50 mg/kg)

Metabolism / bioavailability

- Does metabolism (or bioavailability) play a role in the ability to predict acute toxicity?
  - Usually QSAR models take that into account from the different functional groups in the molecule if the training set is big enough
  - May not be able to detect reactive substructures
    - e.g. OH near C=C for an allylic alcohol

Choice of Dependent Variable For Predicting Category Endpoints

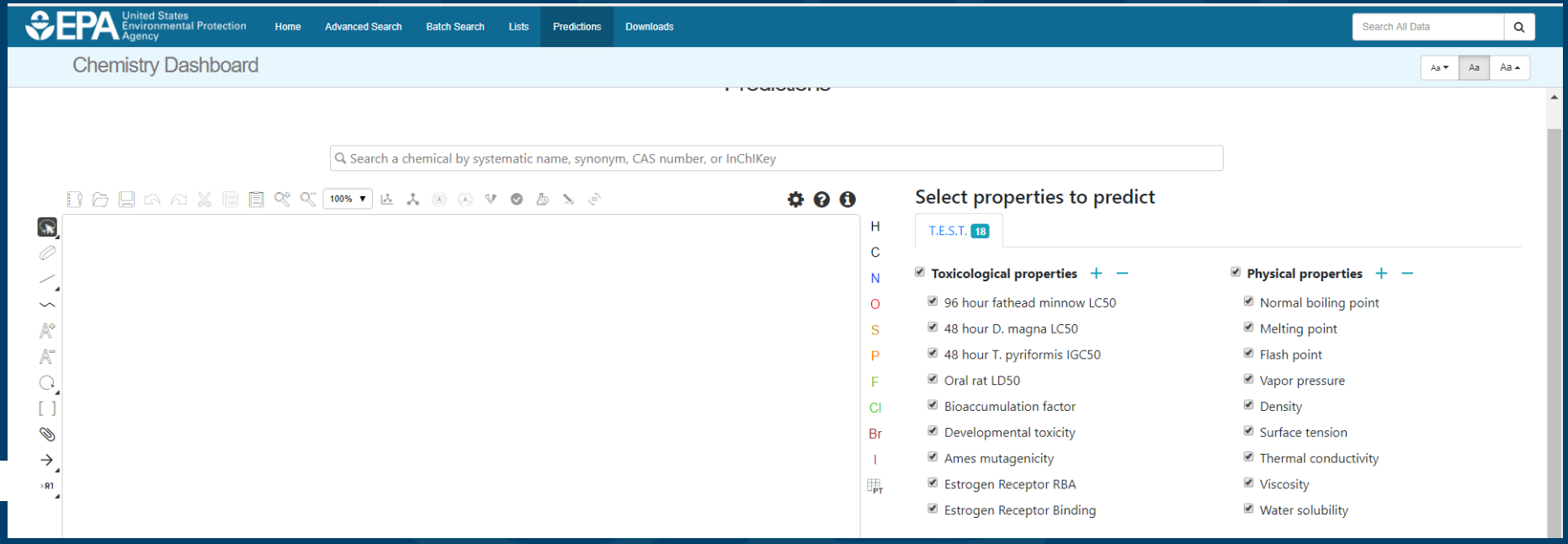
- Additional data points (8953 vs 6706 chemicals for “very toxic” endpoint)
- Continuous endpoint (-log(LD50 mol/kg) has more concentration dependence information

Method	Use method AD: AA*	Use method AD: Cov.	Predictions in common: AA	Predictions in common: Cov.
HC Cat. Input	0.515	0.794	0.527	0.659
HC LD_{50} input	0.467	0.821	0.487	0.659
NN Cat. Input	0.498	0.878	0.498	0.875
NN LD_{50} input	0.426	0.993	0.445	0.875

*AA = average accuracy over five categories,
Cov. = fraction of chemicals predicted

Availability

- How would end-users access your model and run it on new chemicals?
  - T.E.S.T. downloadable Java program
    - https://www.epa.gov/chemical-research/toxicity-estimation-software-tool-test
  - **WebTest:**
    - https://comptox.epa.gov/dashboard/predictions/index
    - Via graphical user interface or API call
  - Training set is probably slightly different



Mechanistic Considerations

- What was there coverage/evaluation of different mechanisms of action?
  - Look at pesticide data or effect data from ChemIDplus?
- What was the approach taken to determine mechanistic interpretations? What were the strengths and weaknesses of that approach? How does that compare/contrast with other approaches?
  - Didn't investigate that since prior work didn't show much promise

Mechanistic Considerations, cont.

- Is "structure-basis" (i.e., SAR or QSAR) sufficient for mechanistic interpretation?
  - In my opinion there is so much experimental scatter that it's hard to validate any sort of mechanistic interpretation
- Should models be linked to adverse outcome pathways? How can we facilitate that?
  - Are there AOPs assigned to enough chemicals?
  - I am not sure that will increase external prediction accuracy aside from increasing confidence by toxicologists in the predicted values

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Questions???

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