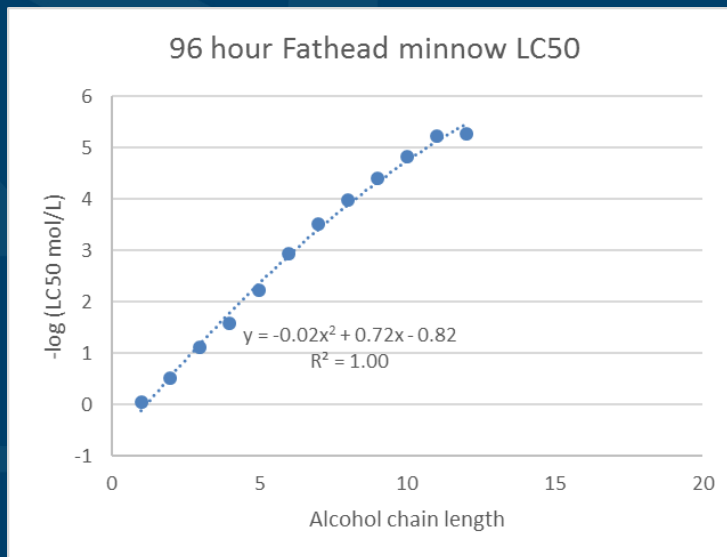
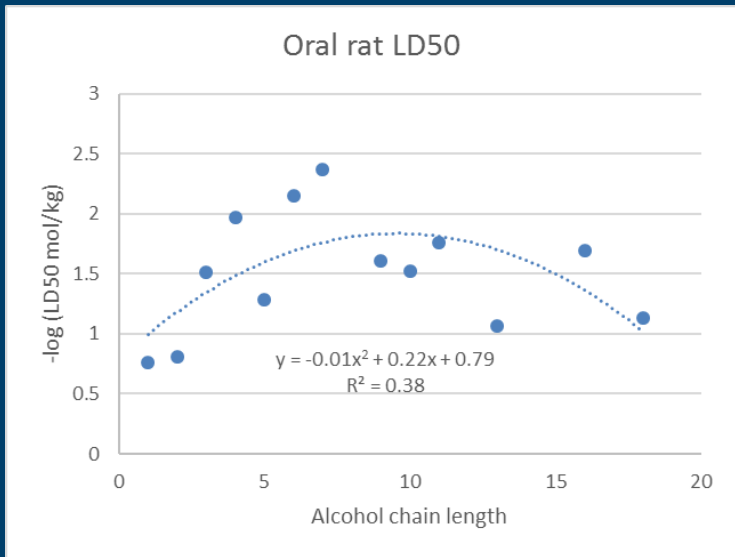




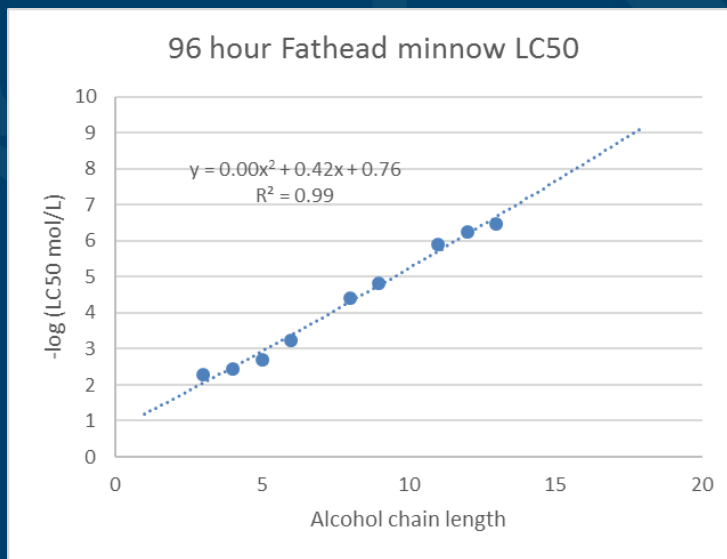
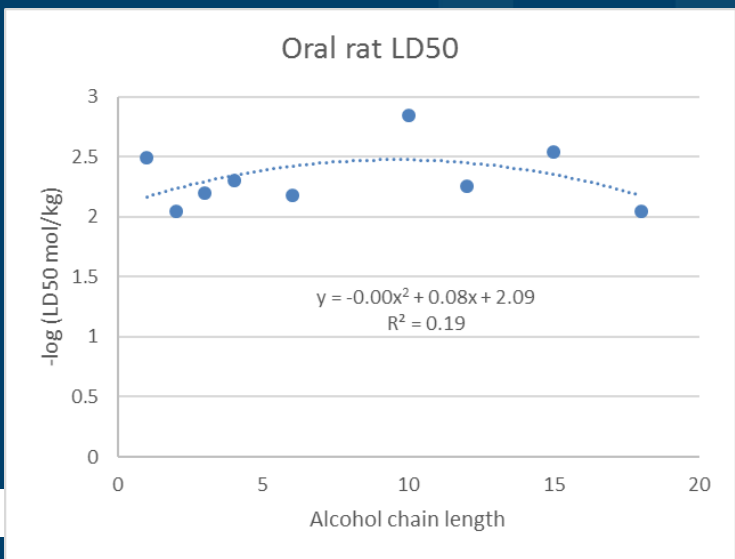
Practical Considerations for Estimation of Oral Rat LD50

Todd Martin, US EPA

Difficulty with oral rat LD50 endpoint



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.
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➤ 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

$$h_{00} = X_o^T (X^T X)^{-1} X_o$$

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

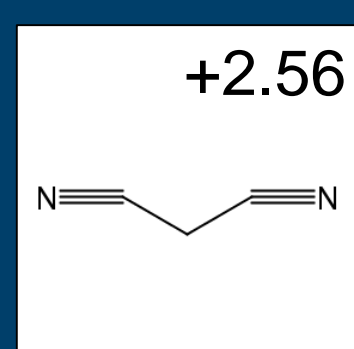
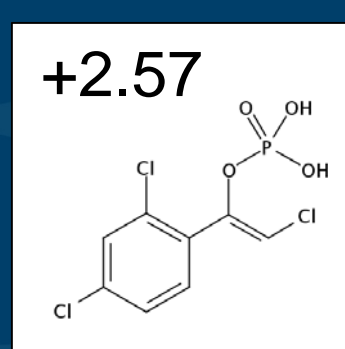
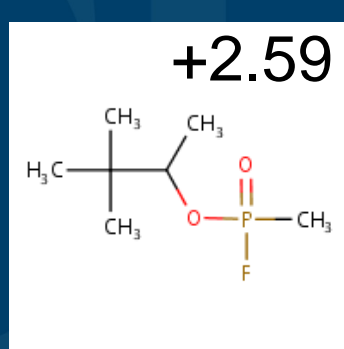
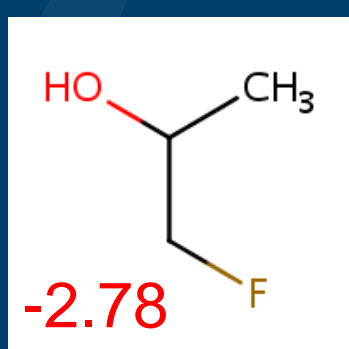
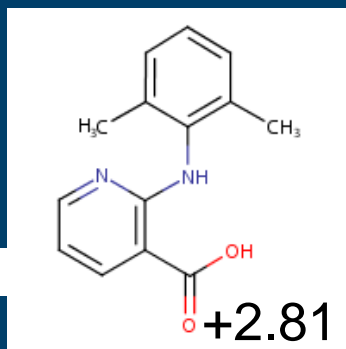
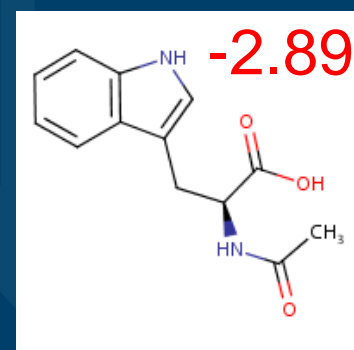
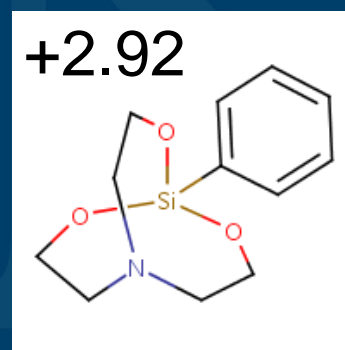
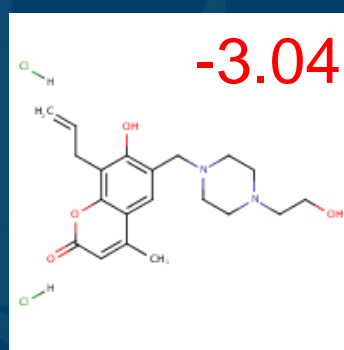
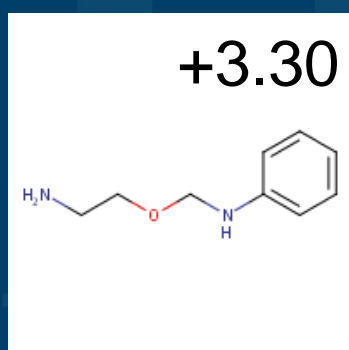
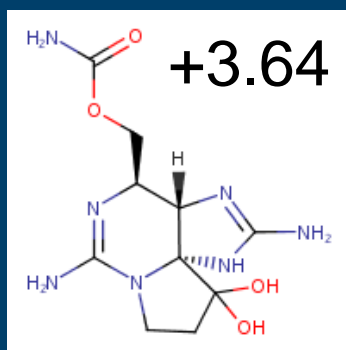
- Nearest neighbor

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

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

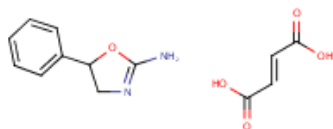
Difficult to predict chemicals

- 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

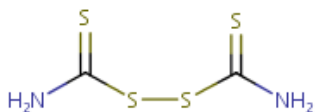


Difficult to predict, cont.

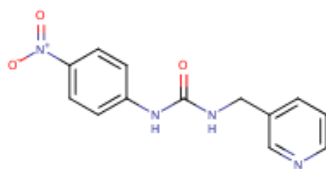
+2.53



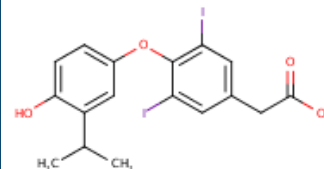
-2.50



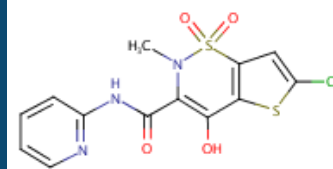
2.40



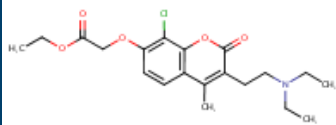
+2.38



+2.33

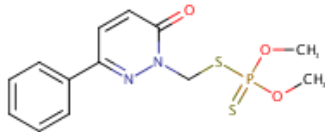


-2.30

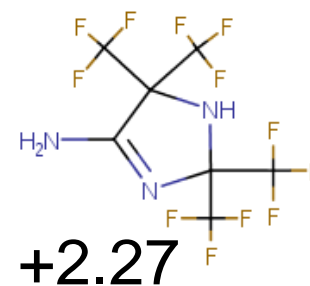
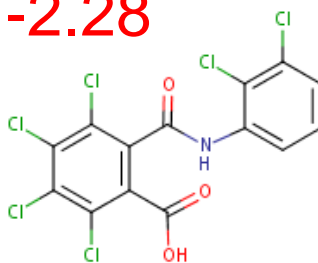


7

-2.29

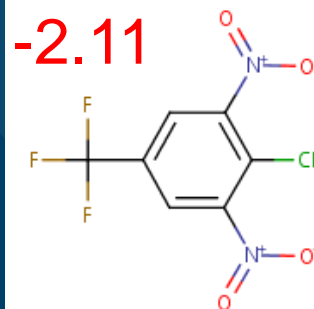


-2.28



+2.27

-2.11



* 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 ($-\log(\text{LD}_{50} \text{ mol/kg})$) 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

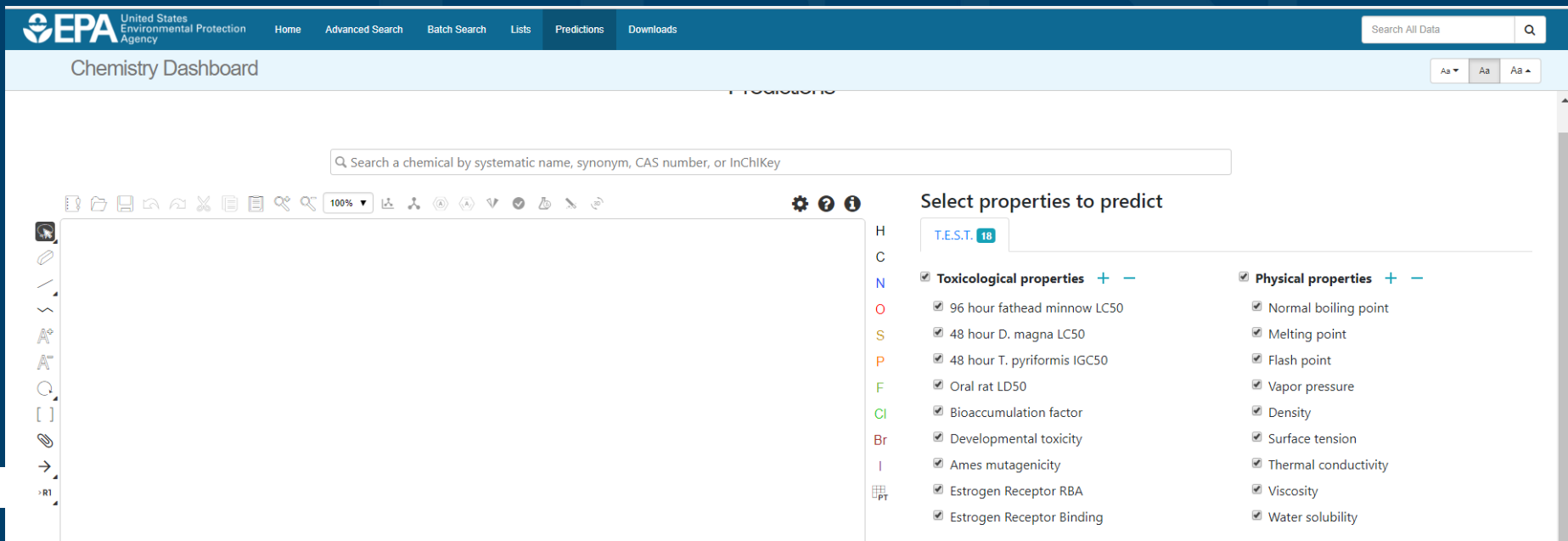
- <https://www.epa.gov/chemical-research/toxicity-estimation-software-tool-test>

- **WebTest:**

- <https://comptox.epa.gov/dashboard/predictions/index>

- Via graphical user interface or API call

- Training set is probably slightly different



The screenshot displays the EPA Chemistry Dashboard interface. At the top, the EPA logo and navigation menu (Home, Advanced Search, Batch Search, Lists, Predictions, Downloads) are visible. A search bar is present with the text "Search All Data". Below the navigation, the page title "Chemistry Dashboard" is shown. A central search bar prompts the user to "Search a chemical by systematic name, synonym, CAS number, or InChIKey". On the right side, a section titled "Select properties to predict" is active, showing a list of properties with checkboxes. The "T.E.S.T." tool is selected. The properties are categorized into "Toxicological properties" and "Physical properties".

Select properties to predict

T.E.S.T. 18

Category	Property	Selected
Toxicological properties	96 hour fathead minnow LC50	<input checked="" type="checkbox"/>
	48 hour D. magna LC50	<input checked="" type="checkbox"/>
	48 hour T. pyriformis IGC50	<input checked="" type="checkbox"/>
	Oral rat LD50	<input checked="" type="checkbox"/>
	Bioaccumulation factor	<input checked="" type="checkbox"/>
	Developmental toxicity	<input checked="" type="checkbox"/>
	Ames mutagenicity	<input checked="" type="checkbox"/>
	Estrogen Receptor RBA	<input checked="" type="checkbox"/>
	Estrogen Receptor Binding	<input checked="" type="checkbox"/>
	Physical properties	Normal boiling point
Melting point		<input checked="" type="checkbox"/>
Flash point		<input checked="" type="checkbox"/>
Vapor pressure		<input checked="" type="checkbox"/>
Density		<input checked="" type="checkbox"/>
Surface tension		<input checked="" type="checkbox"/>
Thermal conductivity		<input checked="" type="checkbox"/>

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

Questions???

The views expressed in this presentation are those of the author and do not necessarily represent the views or policies of the U.S. Environmental Protection Agency