Rapid Collection of Experimental Physicochemical Property Data to Inform Various Models and Testing Methods

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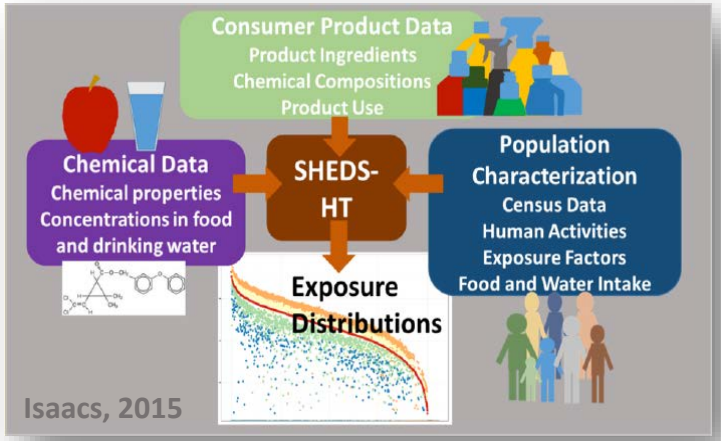
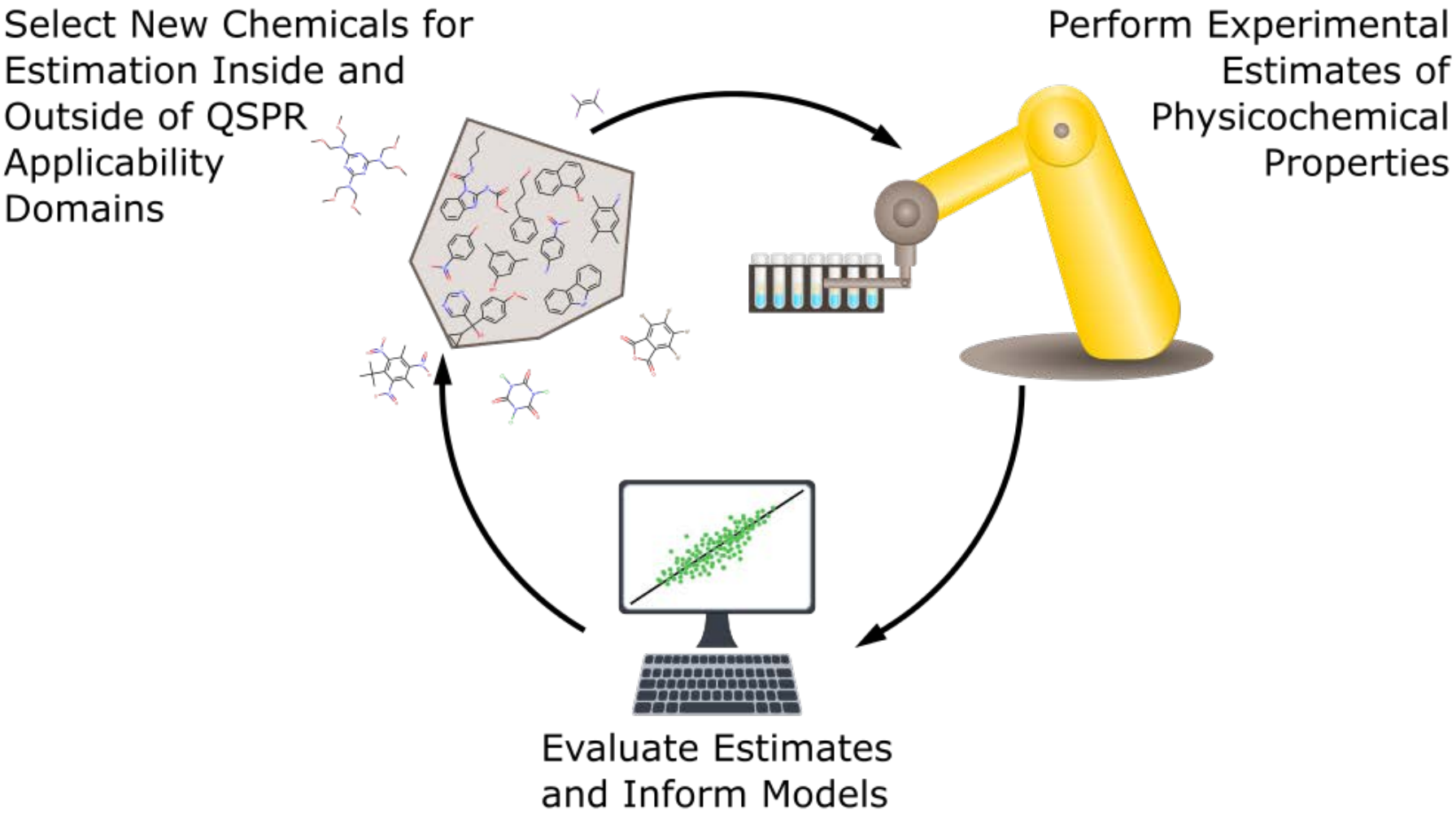
INNOVATIVE CELL BASED SCIENCE

The Need for Reliable Physicochemical Properties

- High-throughput models have been developed to estimate exposure and dose of substances from near-field sources
- Physicochemical properties parameterize many of these models
- Quantitative structure property relationship (QSPR) models to predict these properties have been developed to fill data gaps
- Most measured datasets of "biologically relevant" physicochemical properties are for substances relevant to the pharmaceutical industry



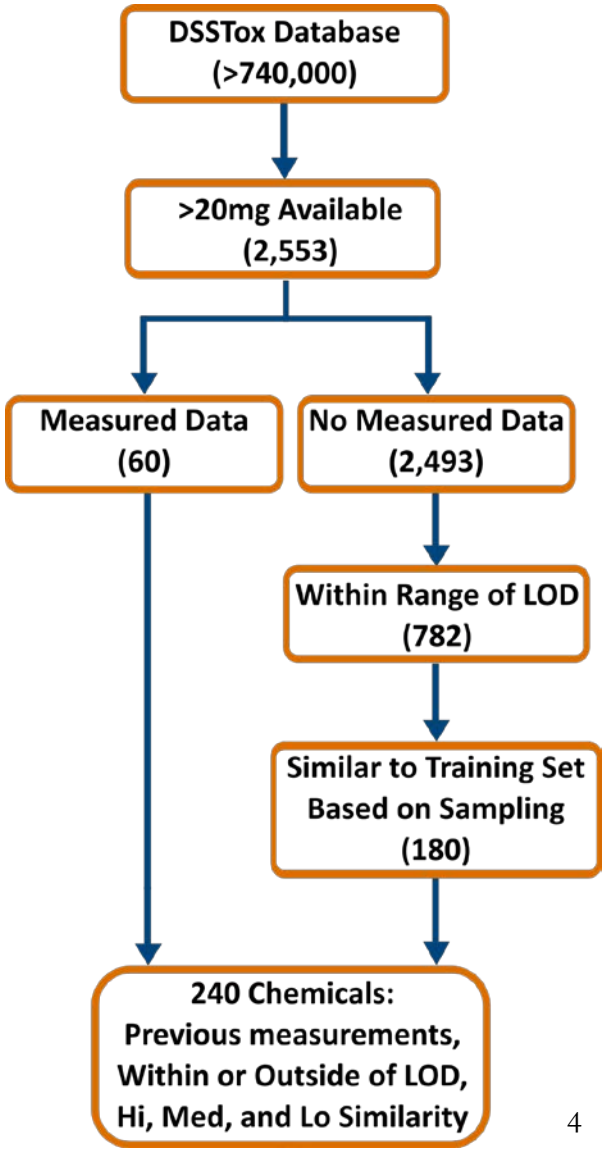
Continuous Updating of QSPR Models



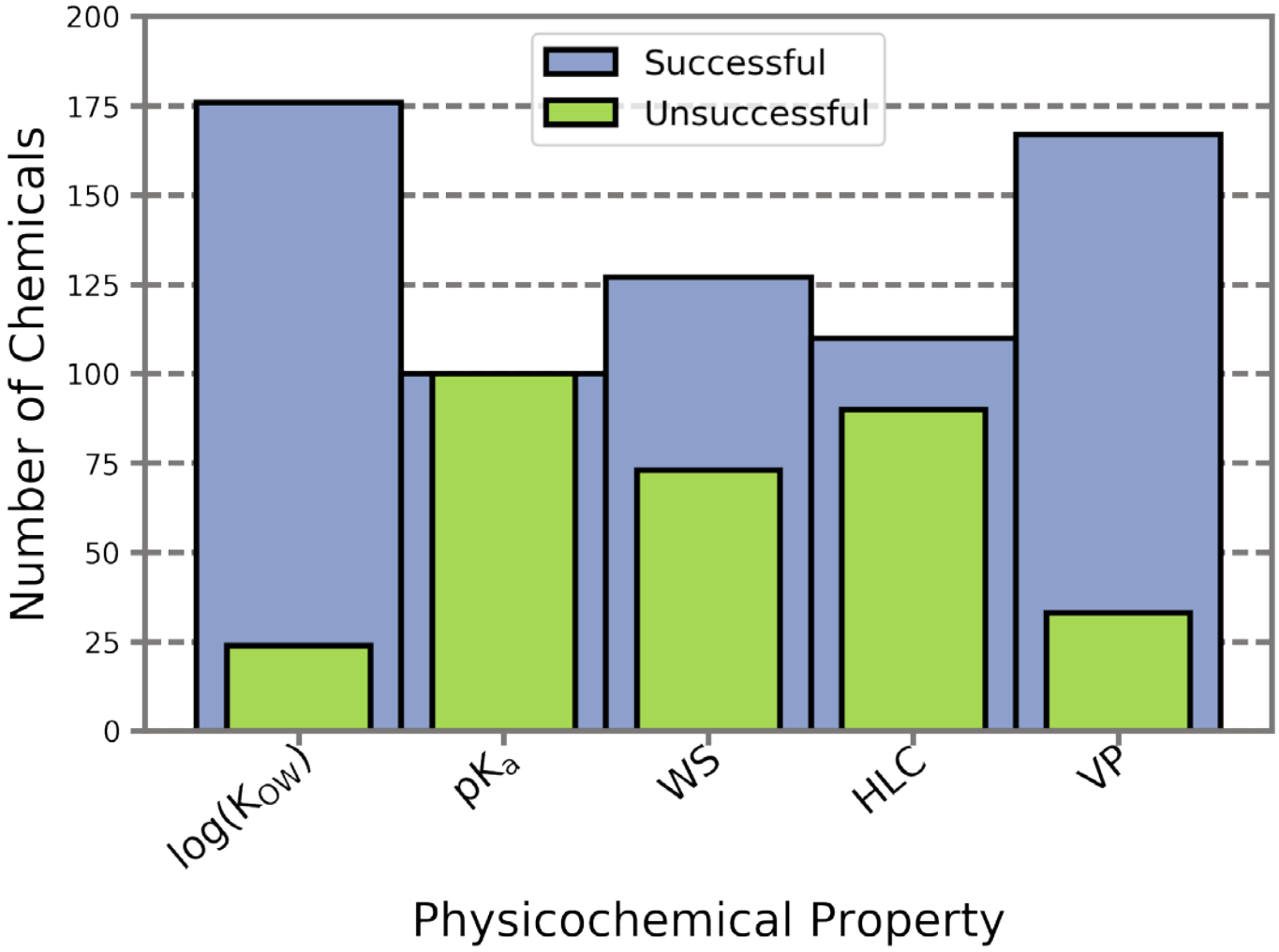
- New measured data are needed for improving QSAR applicability domains

Process for Selecting Pilot Chemicals for Testing

- If we select the same chemicals in current training set (PHYSPROP), then we get a nice comparison, but we get no expansion of chemical space
- If we select all new chemicals, then we get no comparison, but an expansion of chemical space
- For the pilot, 200 chemicals were submitted for measurement of 5 properties:
  - $Log_{10}K_{ow}$
  - Henry's Law constant (HLC)
  - Vapor pressure (VP)
  - Water solubility (WS)
  - Acid dissociation constant (pK_a)

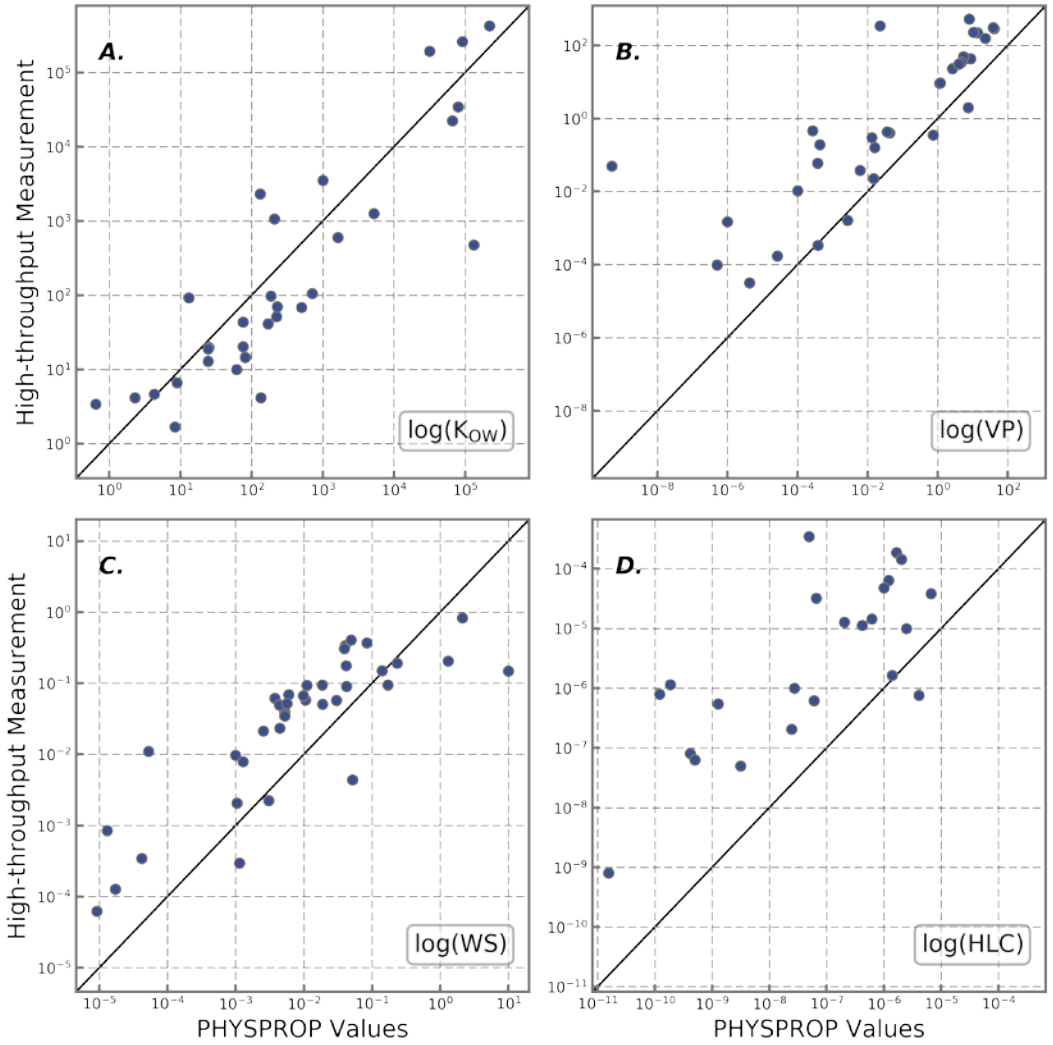


Summary of Successful Measurements



- $Log_{10}K_{ow}$ returned the greatest number of measurements and WS, the least

Success for Compounds in Existing Training Set



- Correspondence between new measurements and those previously reported

QSPR Tools and the Property Predictions Used

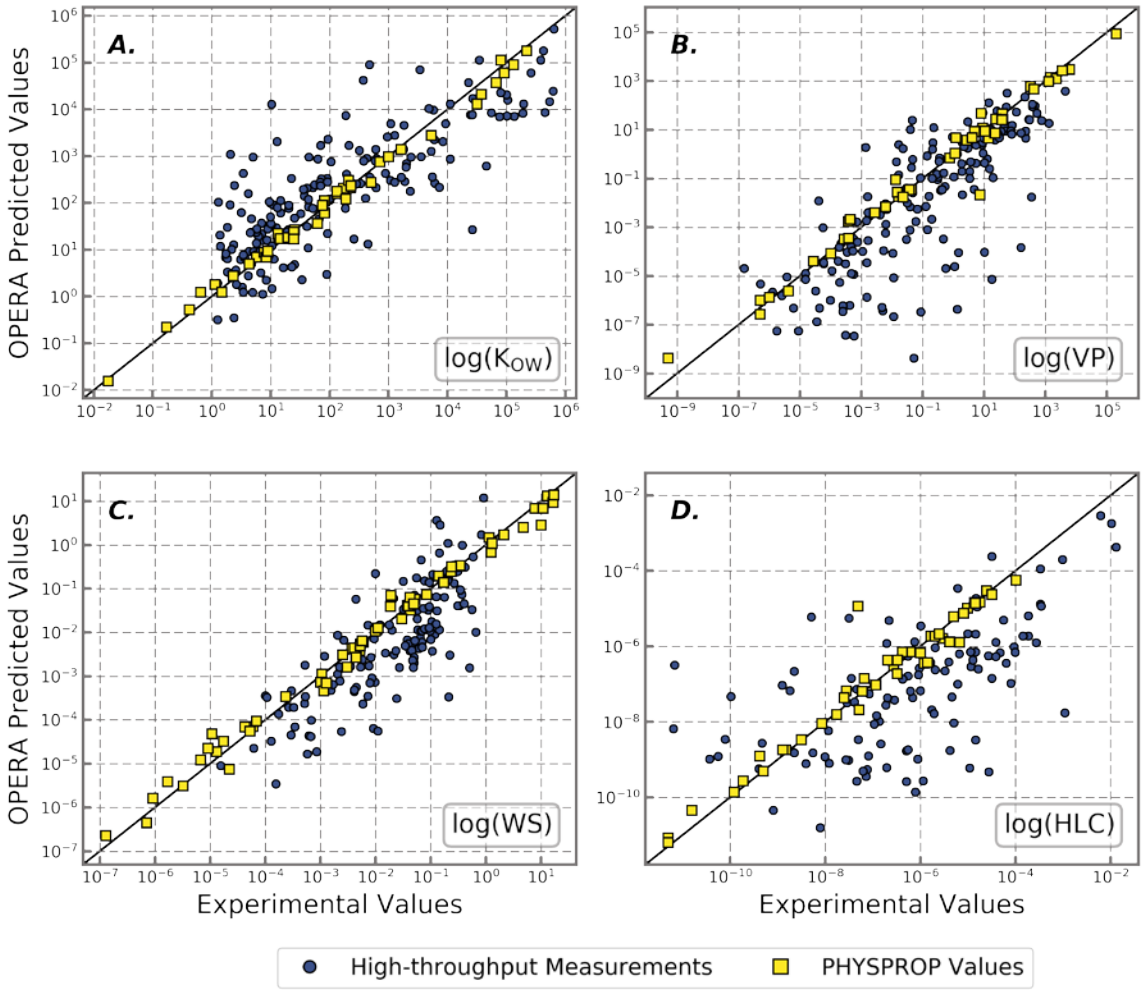
- ACD/Labs
  - Advanced Chemistry Development, Inc.
  - $Log_{10}K_{ow}$, WS, and pK_a
- ChemProp
  - Chemical Properties Estimation Software System (UFZ)
  - $Log_{10}K_{ow}$, VP, and WS
- EPISuite
  - Estimation Program Interface
  - $Log_{10}K_{ow}$, VP, WS, and HLC
- NICEATM
  - NTP Interagency Center for the Evaluation of Alternative Toxicological Methods
  - $Log_{10}K_{ow}$, and WS
- OPERA
  - OPEn (quantitative) Structure-activity Relationship Application
  - $Log_{10}K_{ow}$, VP, WS, and HLC

Trends Across Modeling Tools

		RMSE					
	N	ACD/Labs	ChemProp*	EPI Suite	NICEATM	OPERA	PHYSPROP
$LogK_{ow}$	32	8.30E-01	7.91E-01	8.02E-01	7.75E-01	7.36E-01	7.71E-01
VP	33	-	1.44E+02	1.38E+02	-	1.36E+02	1.38E+02
HLC	23	-	-	5.99E-04	-	8.77E-05	8.96E-05
WS	36	1.20E+00	2.33E-01	3.07E-01	2.28E-01	5.07E-01	1.67E+00
pKa†	76	6.15E+00	-	-	-	-	-

- Root mean squared errors (RMSE) are reported to emphasize average deviations between new values and previous or predicted values.
- The trends are as follows:
  - $Log_{10}K_{ow}$: OPERA < NICEATM < ChemProp < EPI Suite < ACD/Labs
  - VP: OPERA < EPI Suite < ChemProp
  - WS: ACD/Labs < NICEATM < ChemProp < EPI Suite < OPERA
  - HLC: OPERA < EPI Suite

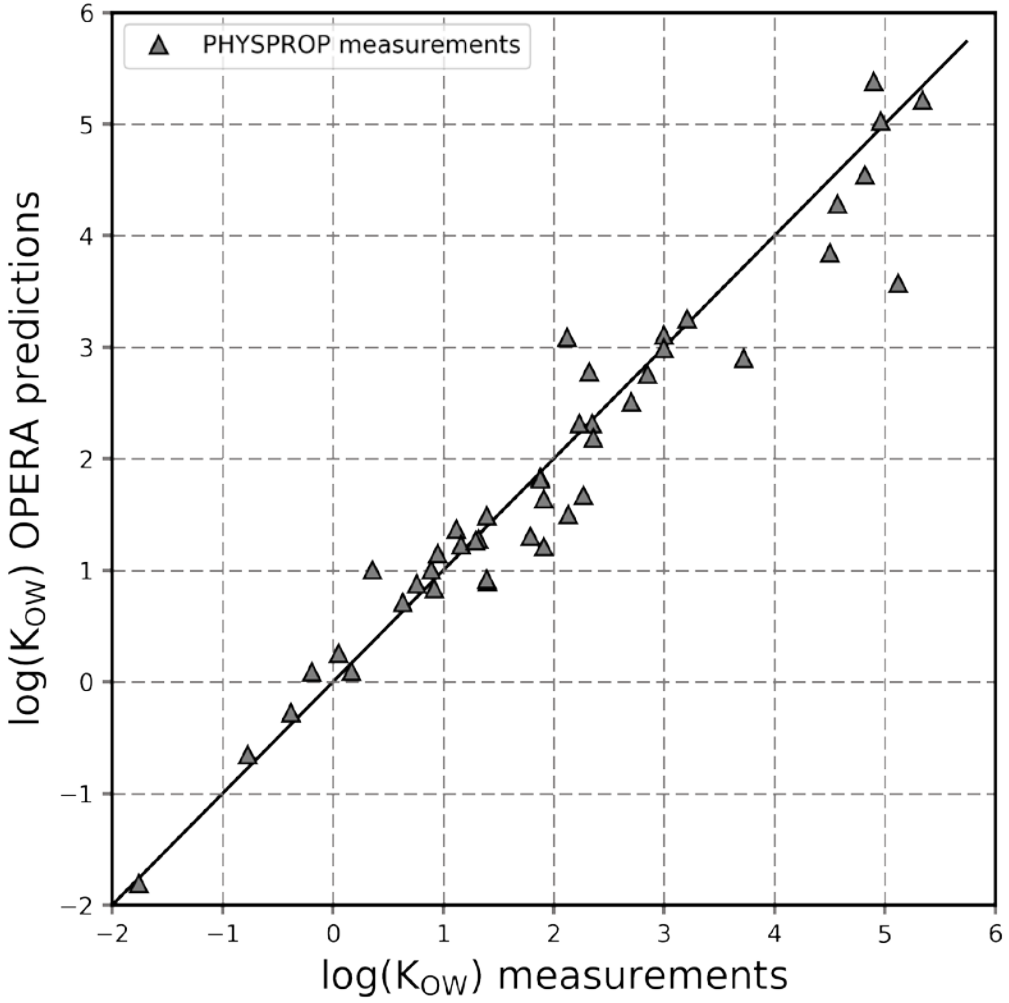
OPERA Trends



- Comparison of OPERA predictions to both new and previous measurements

OPERA $Log_{10}K_{ow}$ Trends and Applicability Domain

- Chemicals not in PHYSPROP were not in OPERA training set
- Chemicals with lower $log_{10}K_{ow}$ values were unamenable to new measurements



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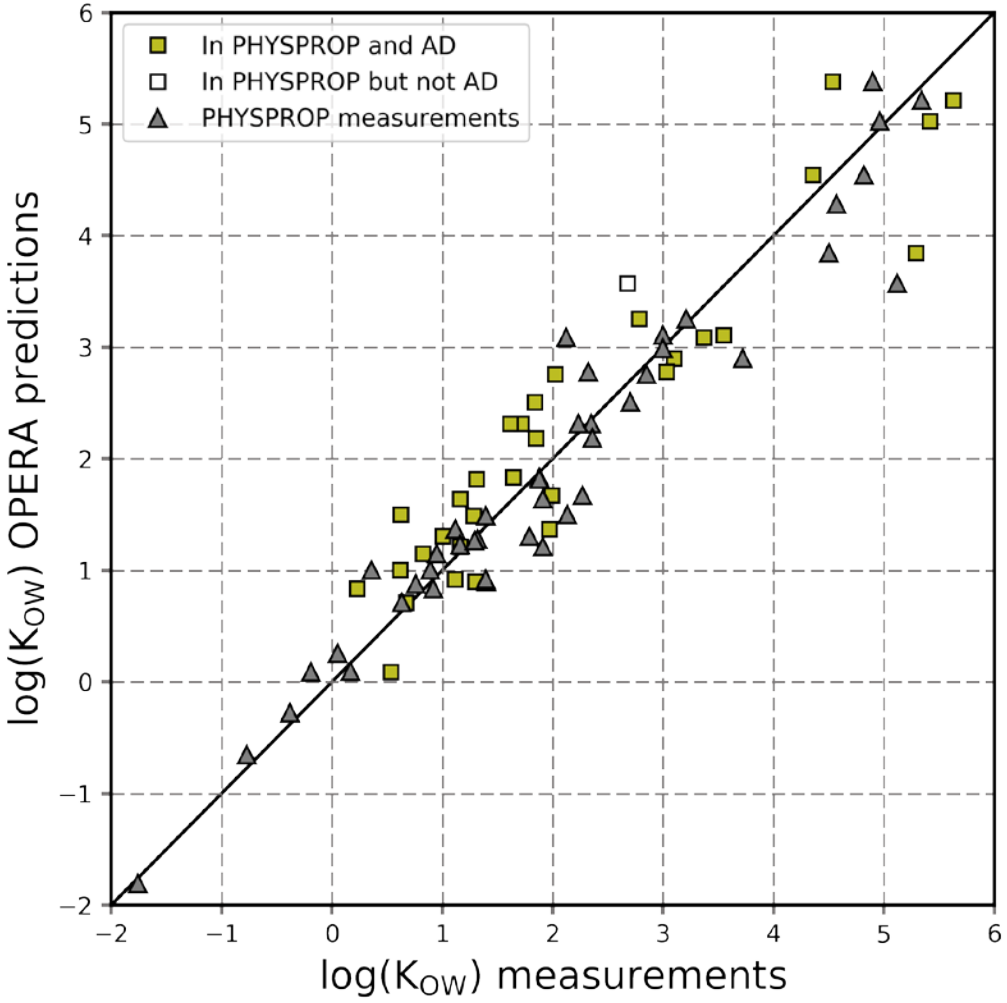

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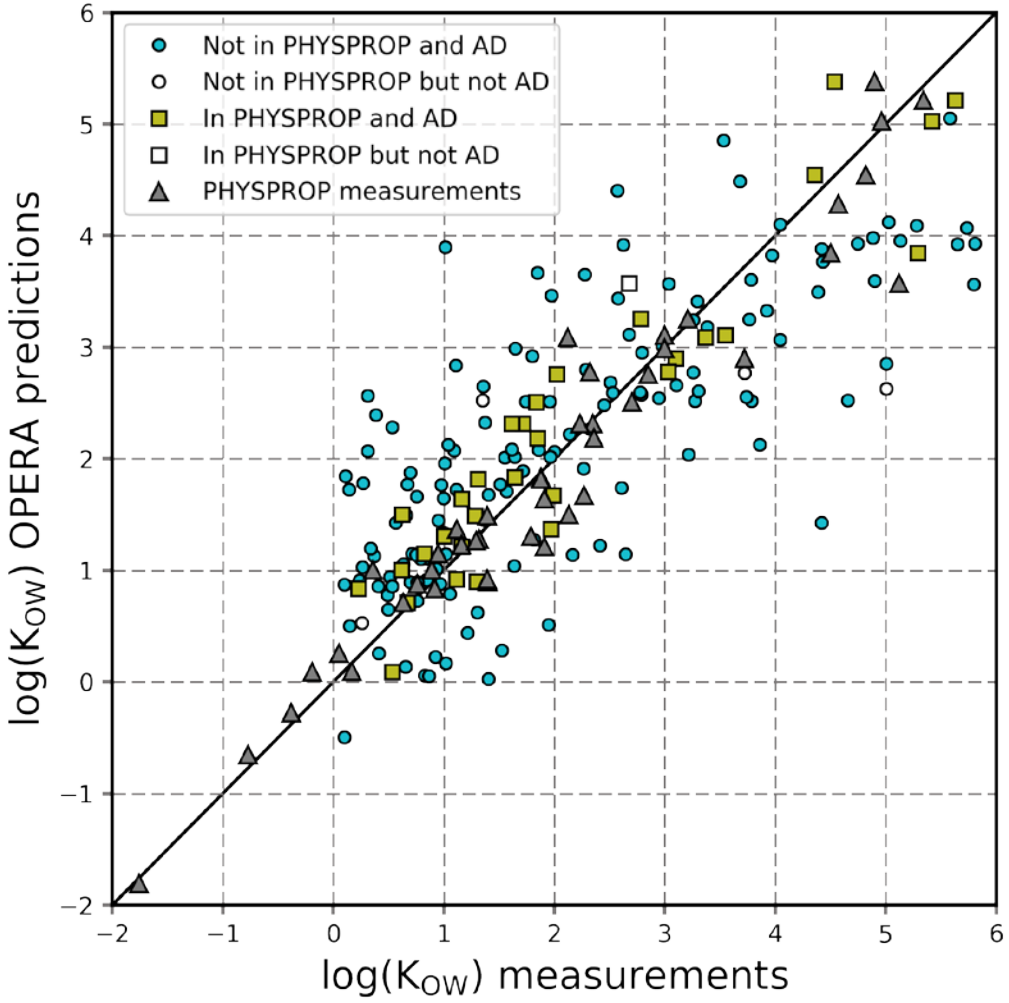
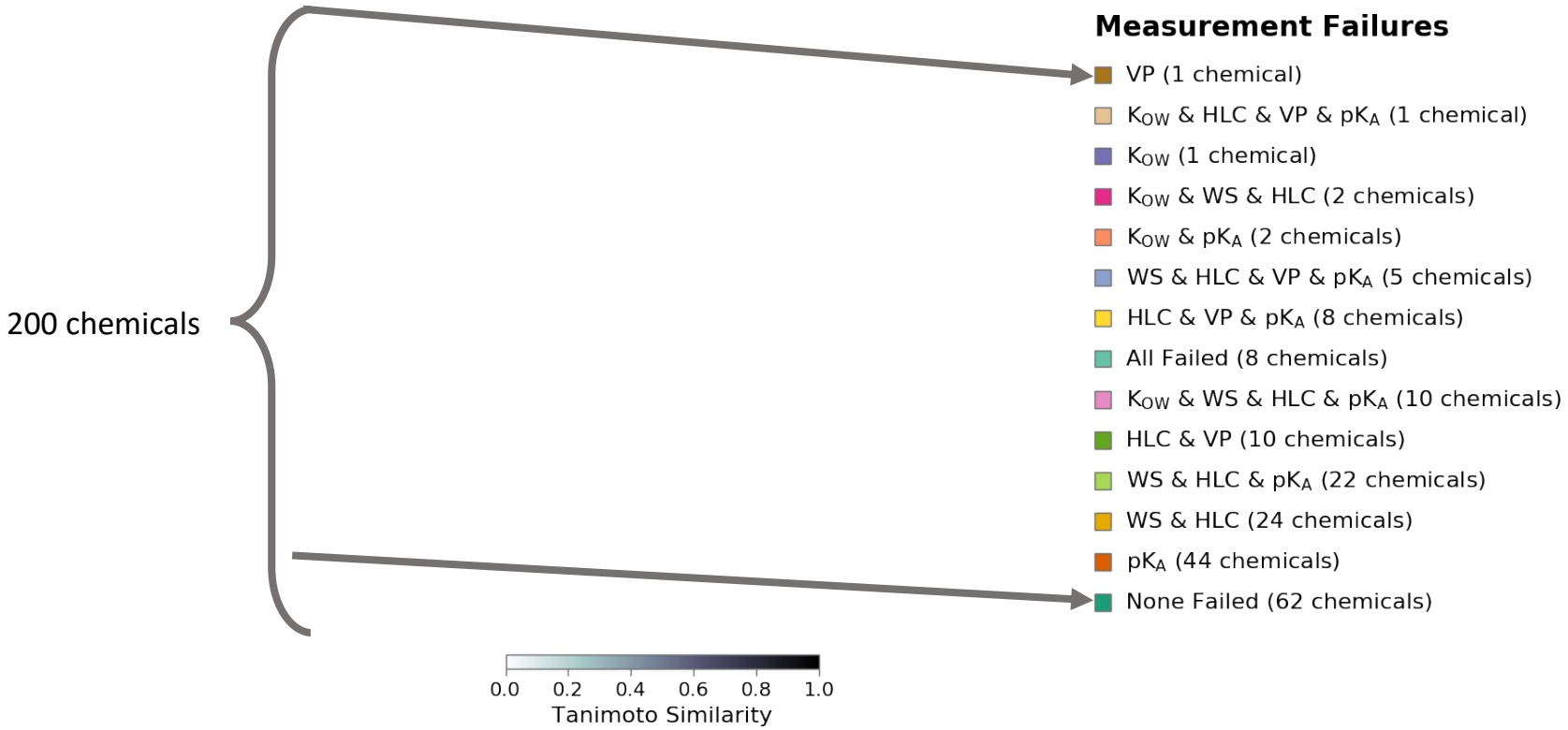
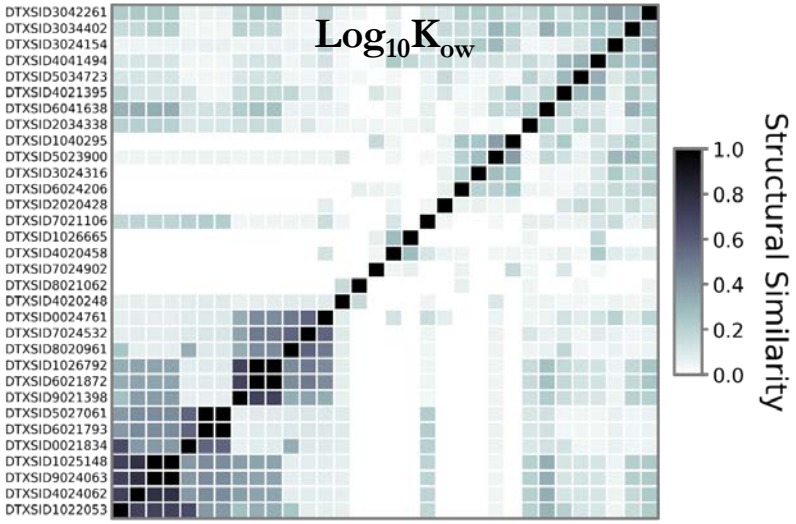


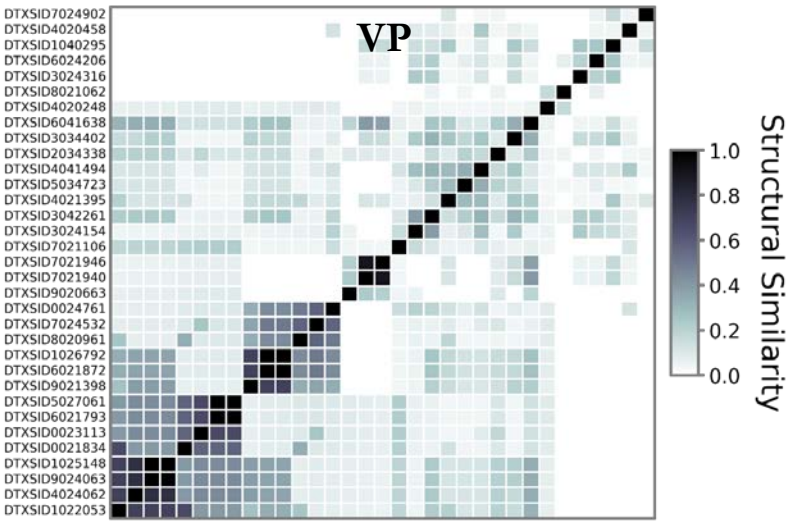
Structure Similarity for Failures based by Property

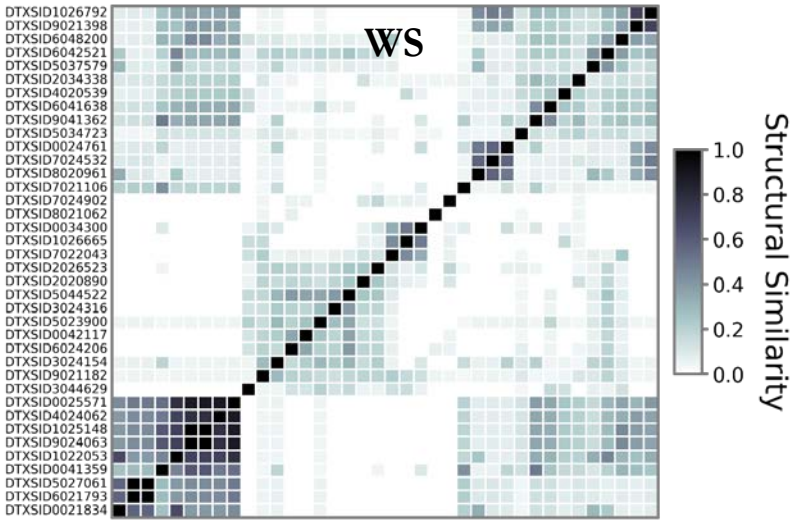


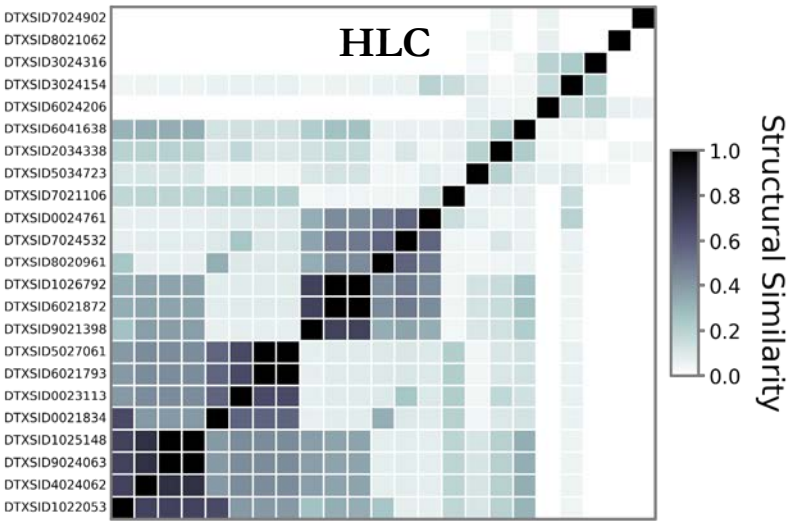
- Chemotypes were used to seek patterns in measurement failures across properties

Structural Similarity For New vs Previous Values



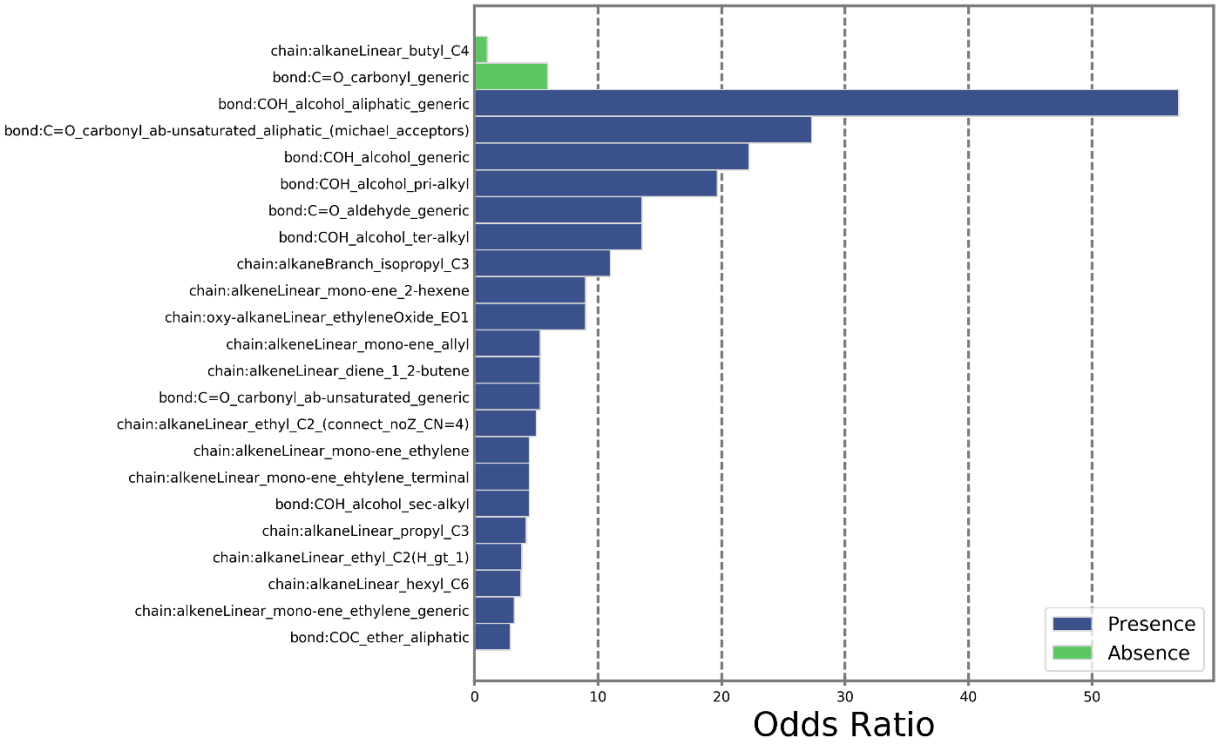






- Structural similarity between chemicals from PHYSPROP and those with new measurements

Odds Ratios for Successful Measurements



- Odds Ratio give the odds that a substructure contributes to failure of all measurements
  - Odds Ratio > 1 → positive association
  - Odds Ratio = 1 → no association
  - Odds Ratio < 1 → negative association
- There were 21 substructures with positive associations
- There were 2 substructures with negative associations

Conclusion

- Five physicochemical properties have been measured in a high-throughput fashion
- A selection process was implemented that allowed for diverse selection of 200 compounds for measurement
- Results from the new measurements were compared against both previously measured values and a collection of QSAR models that predict these values
- These new measurements can help improve chemical space covered by QSAR thus improving parameters for exposure and dose models

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