United States Environmental Protection Agency

Revisiting and updating chemical groupings with new approach methodologies

US EPA in collaboration with Health Canada, Environment Climate Change Canada

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Office of Research and Development
Center for Computational Toxicology and Exposure

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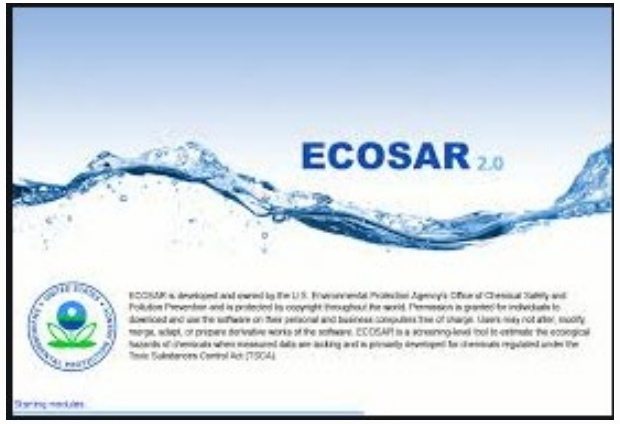
Overview

A chemical category is a group of chemicals whose physicochemical and human health and/or ecotoxicological properties and/or environmental fate properties are likely to be similar or follow a regular pattern, usually as a result of structural similarity. - OECD

Applications of chemical categorization include first tier assessment efforts and read across from structurally similar analogs:

- Toxic Substances Control Act (TSCA) New Chemical Program Chemical Categories (NCC; US EPA)
- ECOSAR (focus of presented work)

US EPA ECOSAR chemical classifications



- Class-based SAR to predict aquatic toxicity
- Classification scheme identifies excess toxicity
- Estimates **acute** and **chronic toxicity** based on accumulated data and past decisional precedents

Acute Effects:	Chronic Effects:
Fish 96-hr LC_{50}	Fish ChV
Daphnid 48-hr EC_{50}	Daphnid ChV
Algae 72/96-hr EC_{50}	Algae ChV

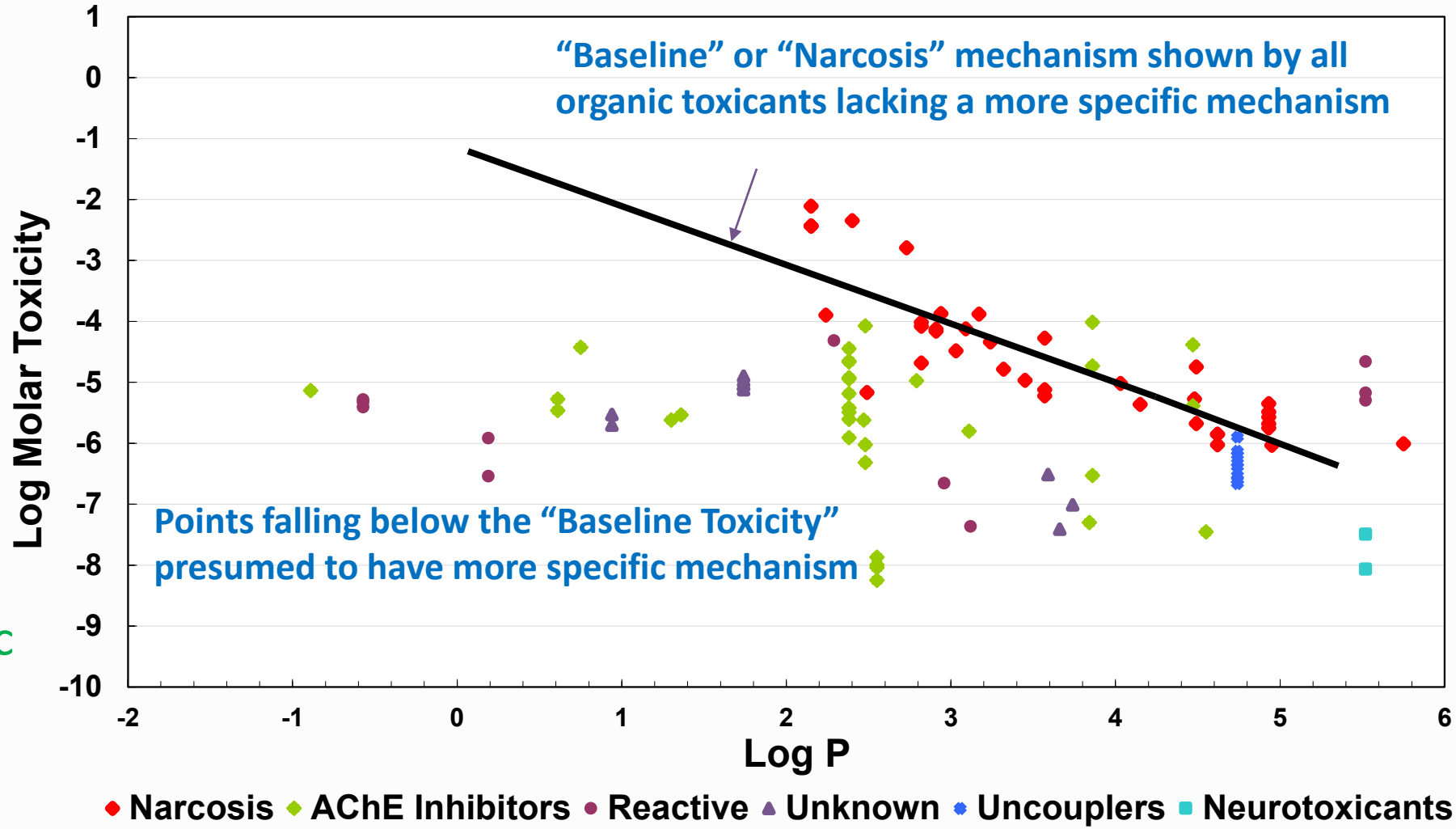
- Profiler in OECD QSAR Toolbox

Narcosis vs. specific-acting toxicity MOA

Less Toxic

Regulators (ECCC) consider MOA information to determine the size of assessment factors

More Toxic



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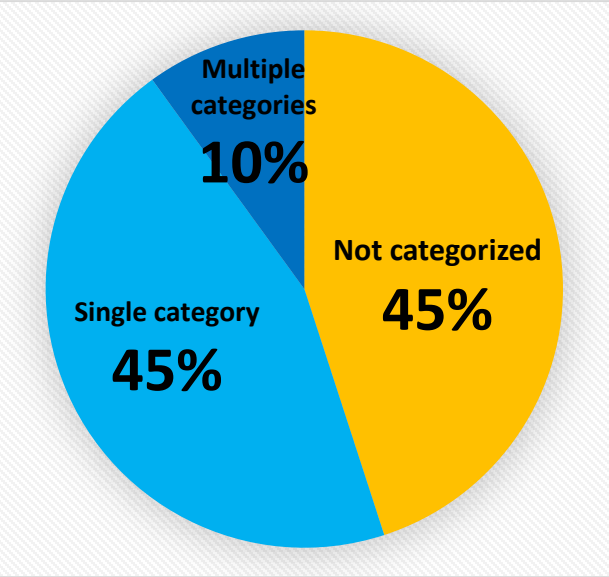
Potential approach for updating chemical categories

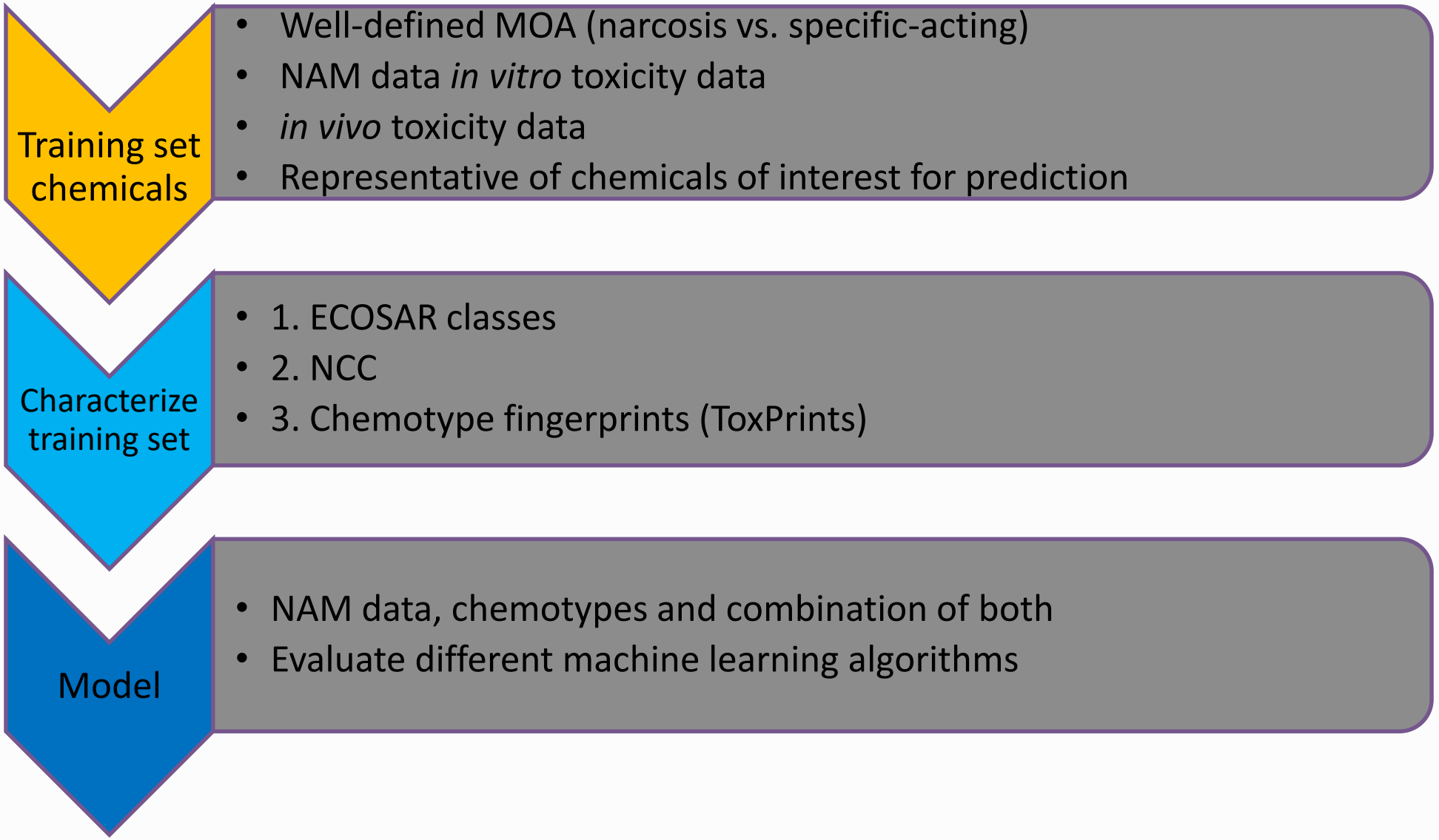


- Almost half of all New Chemical inventories across regulatory jurisdictions cannot be categorized using NCC or ECOSAR
- Some fall into multiple categories

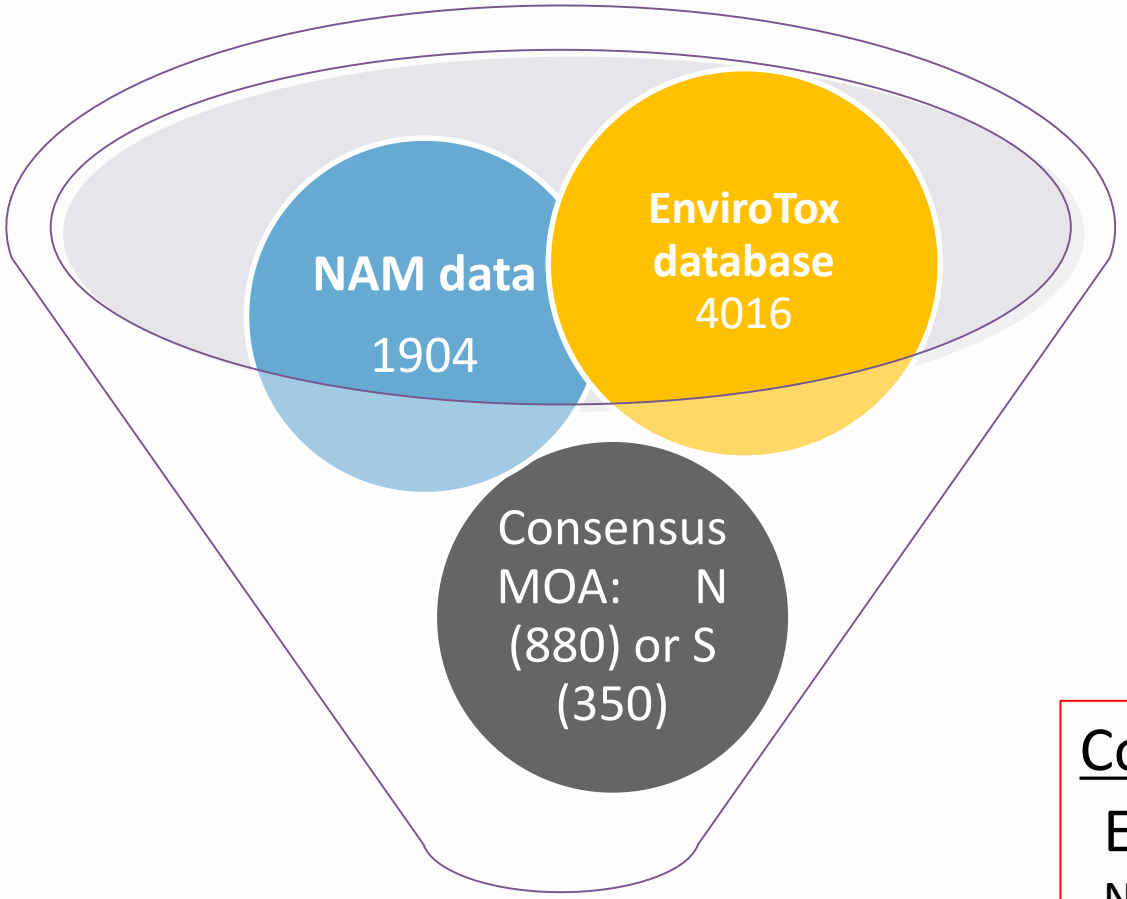
How do we update?

- Incorporate New Approach Methodologies (NAMs) – *i.e.*, ToxCast and Tox21 biological activity information
- Apply cheminformatic approaches

General approach



EnviroTox training set chemicals



Training set chemicals

1. Chemicals with *in vivo* eco-data – from the EnviroTox[1] database – 4016
2. Sub-selection for chemicals with NAM data (ToxCast and Tox21) - 1904
3. MOA predictions based on 4 publicly-available classification models
   - VERHAAR, ASTER, OASIS, TEST
   - Each predicts Narcotic, Specific-Acting or Unclassified

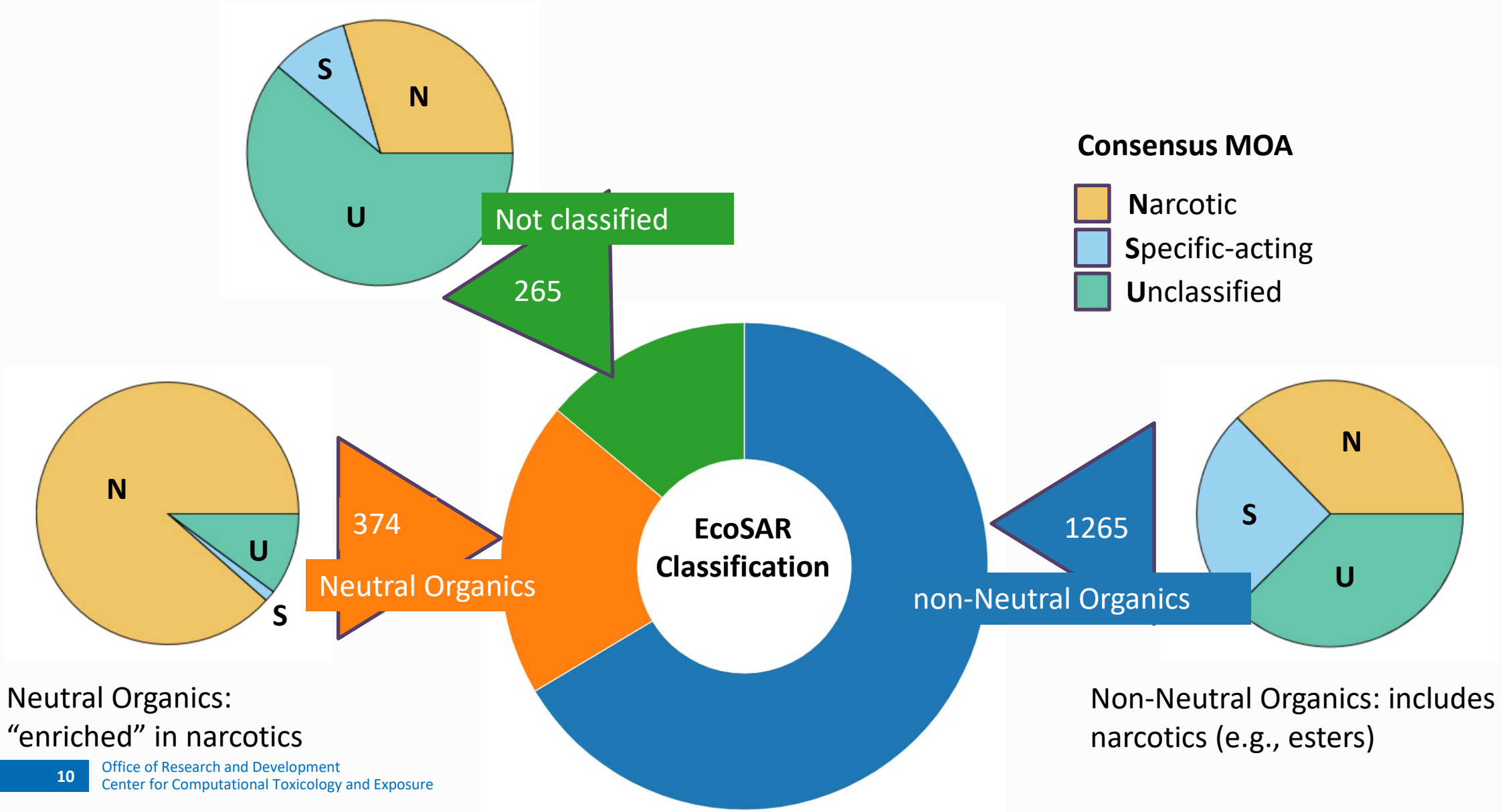
Consensus MOA with confidence scores[2]

Examples:	Results:
NNNN = N, score =3	880 Narcotic
NNSN = N, score= 2	350 Specific-acting
SUSS = S, score= 2	674 Unclassified
NUNS = U, score = 0	

[1]Health and Environmental Sciences Institute (HESI). 2019. EnviroTox Database & Tools. Version 1.1.0 Available: http://www.envirotoxdatabase.org/

[2] Kienzler et al.. Environ Toxicol and Chem. 2019, 38(10) 2294-2304

Characterize EnviroTox training set chemicals: ECOSAR classes

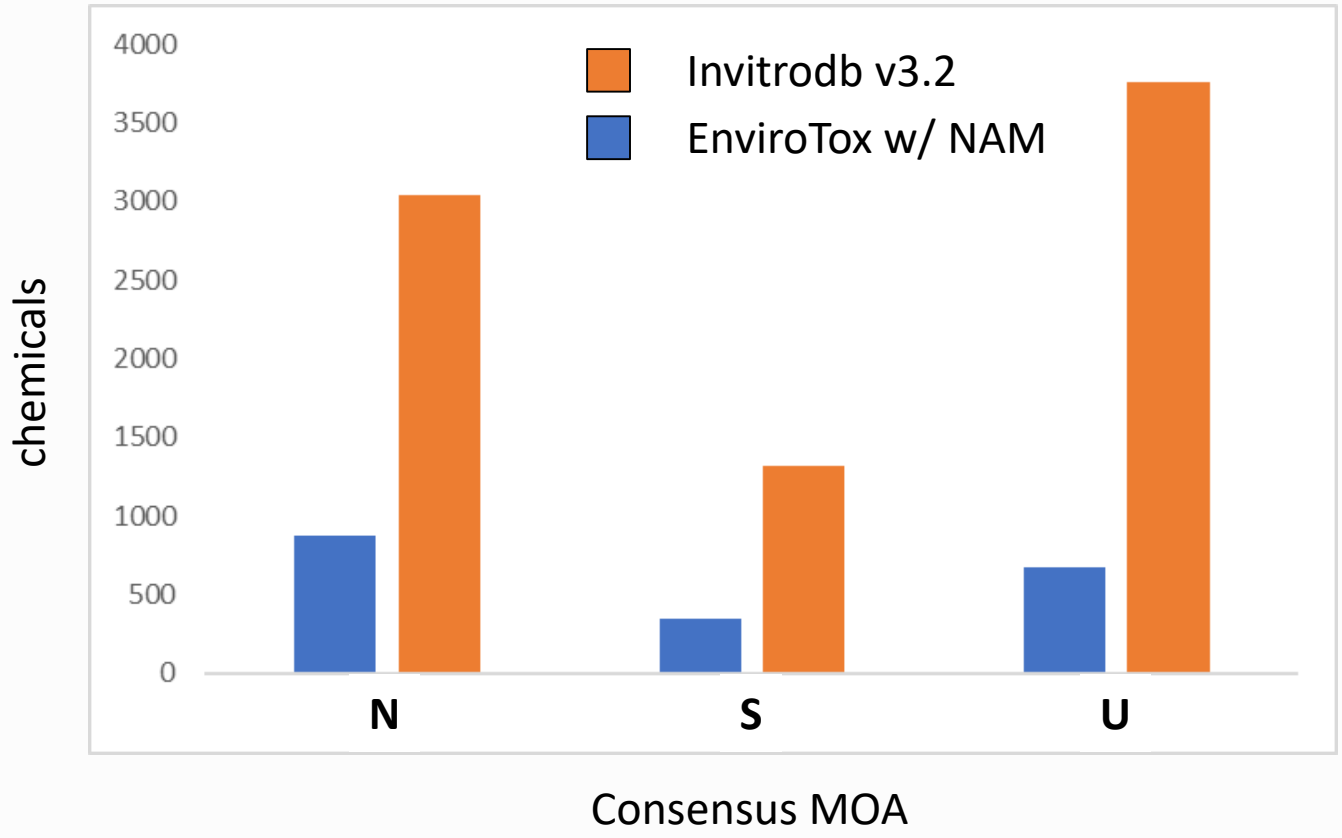


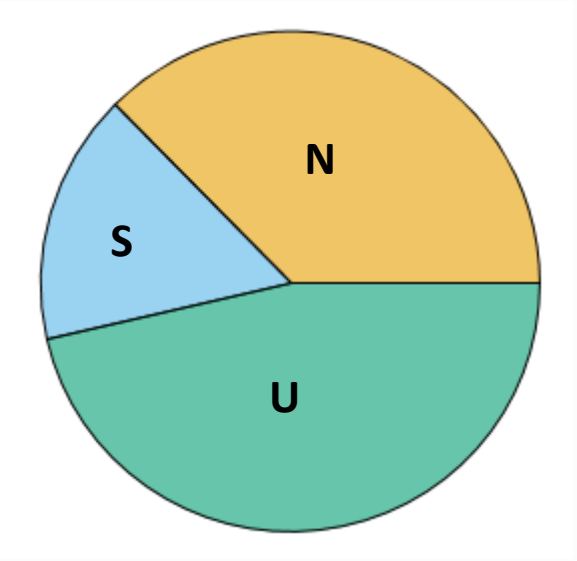
Neutral Organics:
"enriched" in narcotics

Non-Neutral Organics: includes narcotics (e.g., esters)

Expanding the chemical space of the EnviroTox dataset

- Added 6215 chemicals with NAM data (invitrodb v3.2)
- Applied the same consensus MOA methodology





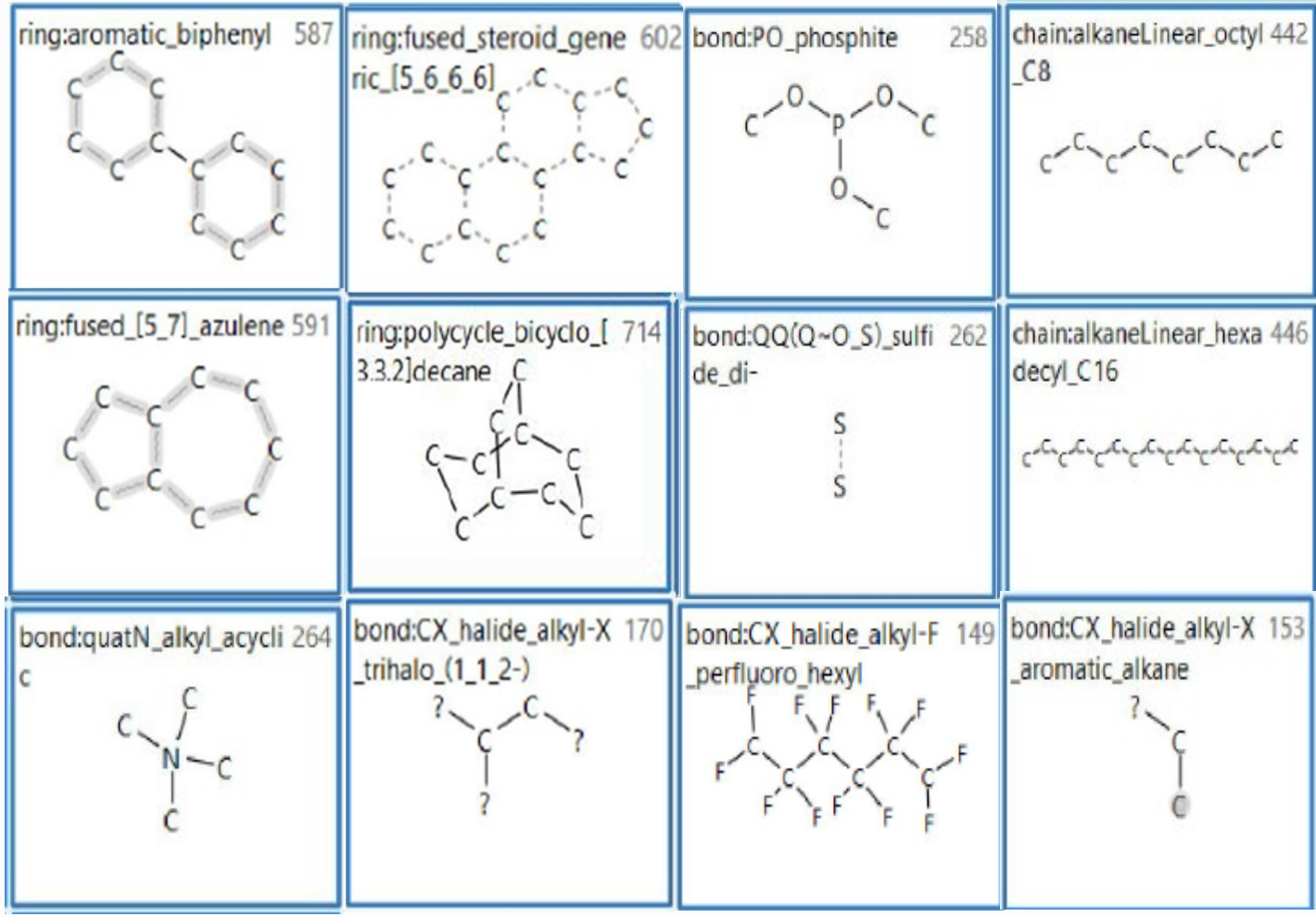
- Additional chemical coverage across all classes, with a slight increase in Unclassified MOAs relative to N/S classes
- Possible implications for N/S predictions

Characterize training set chemicals: ToxPrints

- Pull in chemotype information for our chemicals via ToxPrints (TxPs)
  - Publicly available tool
  - EPA Comptox Chemicals Dashboard

ToxPrints:

- ✓ *729 chemical features*
- ✓ *Chemically interpretable*
- ✓ *Coverage of diverse chemistry*
- ✓ *Hierarchical: Includes scaffolds, functional groups, chains, rings, bonding patterns, atom-types*



Yang et al. J. Chem. Inf. Model. 2015. Richard et al., Chem. Res. Toxicol. 2016, 29(8) 1225 – 1251; Strickland et al., Arch Toxicol. 2018 92(1) 487 – 500; Wang et al., Environment International 2019, 126 377 – 386

Classification model development

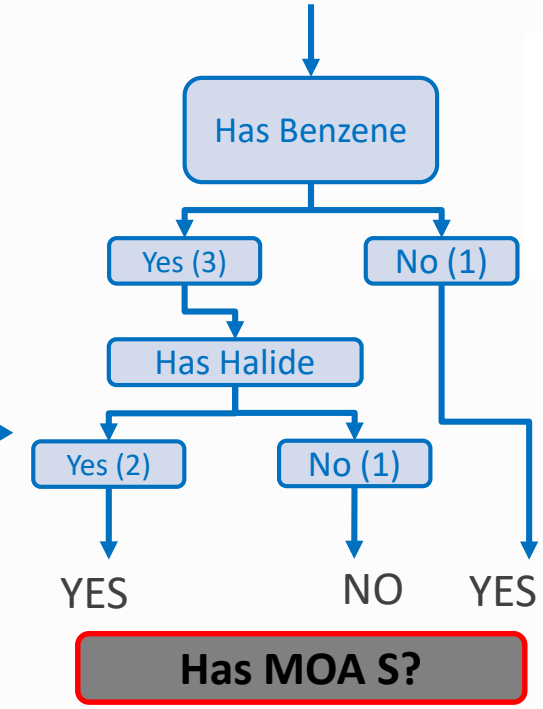
Figure adapted from Katherine Phillips

Train the Model

ToxPrints, NAM data or both

	cMOA	Has Metal	Has Halide	Has Benzene	Has Alkyne
Chemical 1	N	0	1	0	0
Chemical 2	N	0	0	1	1
Chemical 3	S	0	1	1	0
Chemical 4	S	1	1	1	1

cMOA Features



Repeated many times with different samples to build "forest" of classifier trees.

Valid models **must**:

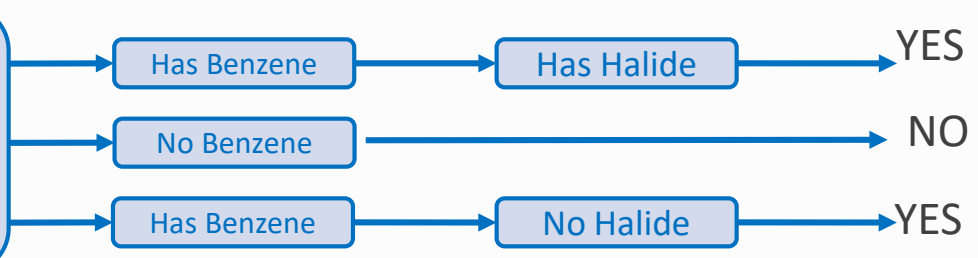
- accurately predict the training set
- predict beyond the training set
- be more predictive than a model built on randomized data

Predict with the Model

Chemical 5	0	1	1	0
Chemical 6	0	1	0	0
Chemical 7	0	0	1	1

Features

In Applicability Domain of Model?



Predict target with ***valid*** models using features

Repeated with each "tree"

p

Probability for N or S

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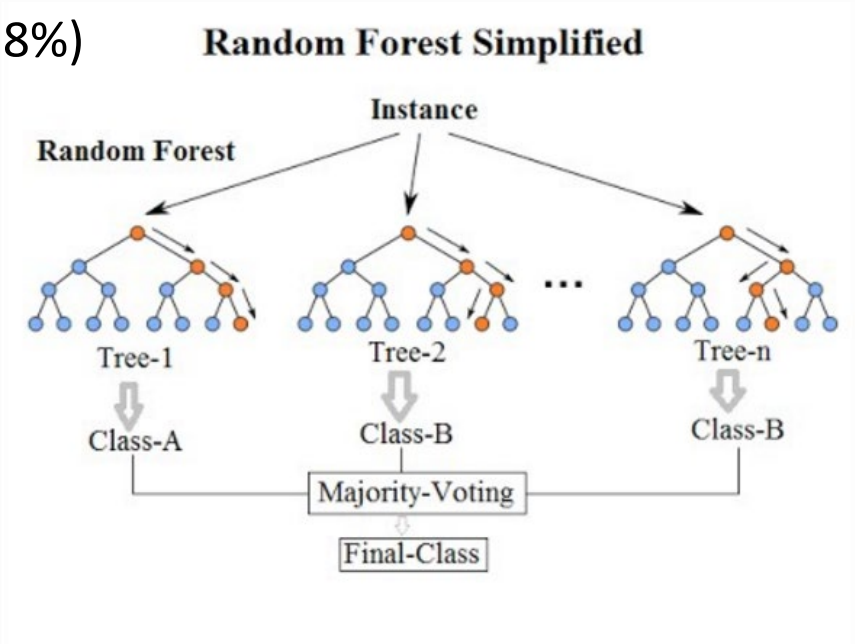
Classification model details

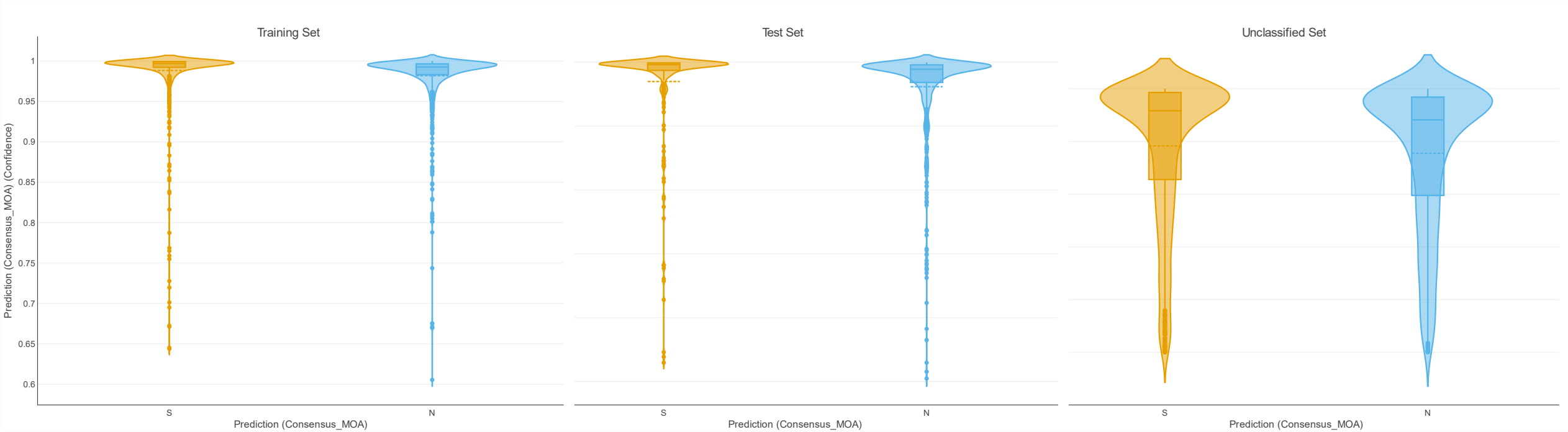
- Random Forest (Boosted Gradient Method) provided the best model results:
  - Split data into 80% training and 20% hold out (test) sets
  - Hyperparameter tuning with 5-fold cross validation, square-root sampling, etc.

  - Training set: “balanced” down-sampled subset (2104 chemicals w/ a cMOA = N or S)
  - High accuracy in both training and test sets (training = 99.7%; test = 95.8%)
  - Total Accuracy on all N + S data set = 97.6% (4356 cMOA = N or S)
    - Across all N + S chemicals -> 105 chemicals misclassified:
      - 24 F_{pos}{predicted S}
      - 81 F_{neg}{predicted N}



https://medium.com/@williamkoehrsen/random-forest-simple-explanation-377895a60d2d

Distribution of prediction confidence [0,1] by (N,S) class



Training Set
Median: 0.999, 0.993
Mean: 0.988, 0.982

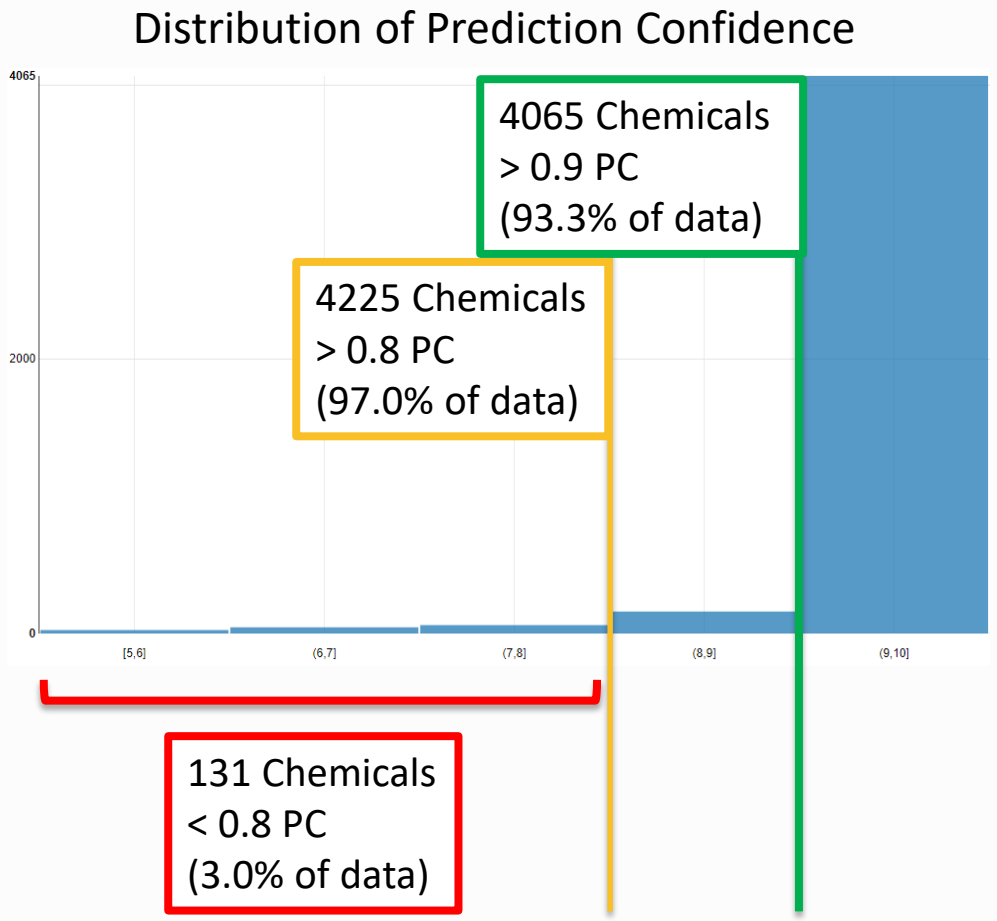
Test Set
Median: 0.996, 0.989
Mean: 0.970, 0.962

Unclassified Set
Median: 0.958, 0.941
Mean: 0.892, 0.877

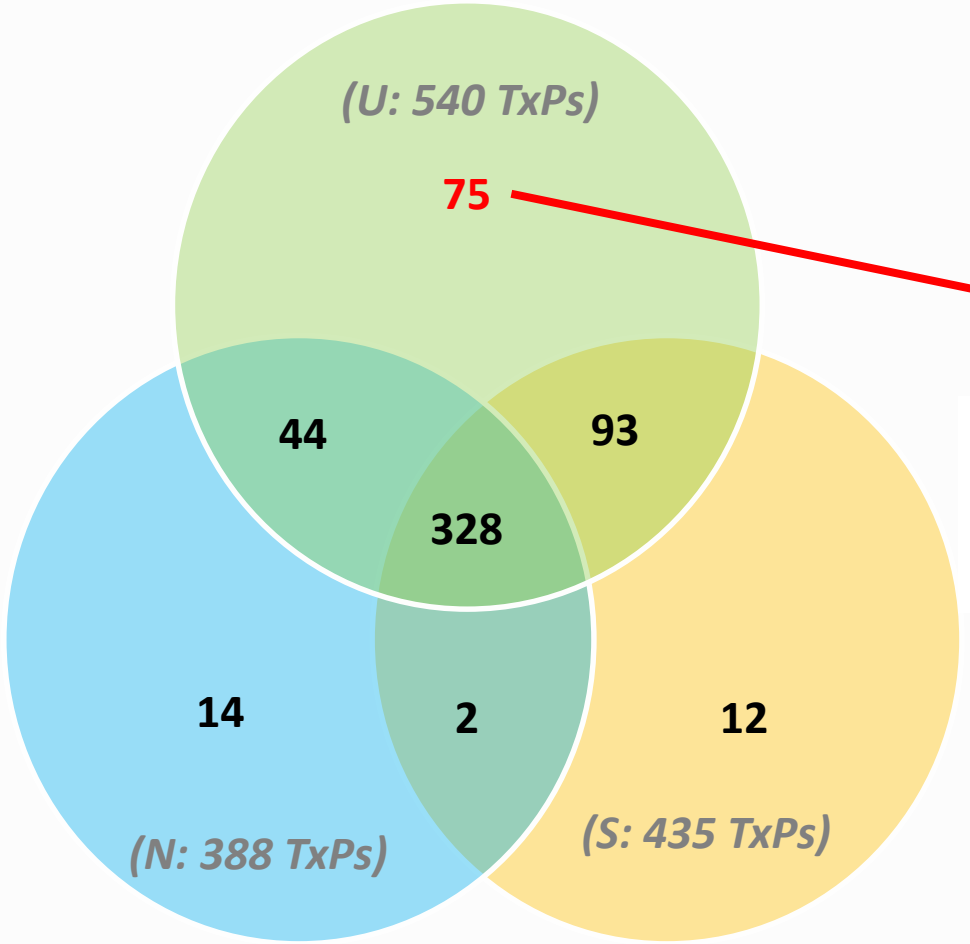
Specific-acting Narcotic

Prediction confidence across the cMOA = N or S

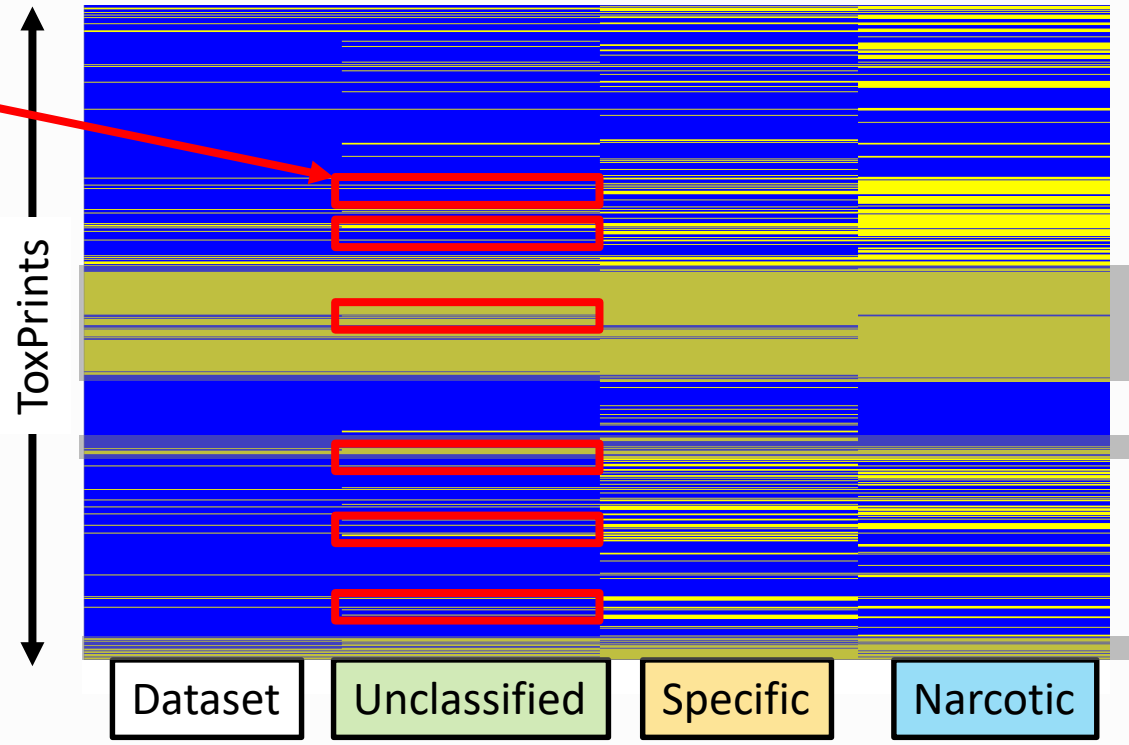
- Distribution of prediction confidence (PC) tends to be > 0.8 for the classified data (cMOA = N or S)
- Model has fewer # misclassifications in S
  - Misclassifications for 93 cMOA confidence = 2, and 12 with 1,3 scores (recall 3>2>1 for confidence)
  - ~46% of the misclassifications can be attributed to the chemicals with PC < 0.8
  - ~67% of the misclassification can be attributed to chemicals with PC < 0.88



Characterization of ToxPrint coverage across different classes



Heatmap representation of ToxPrints



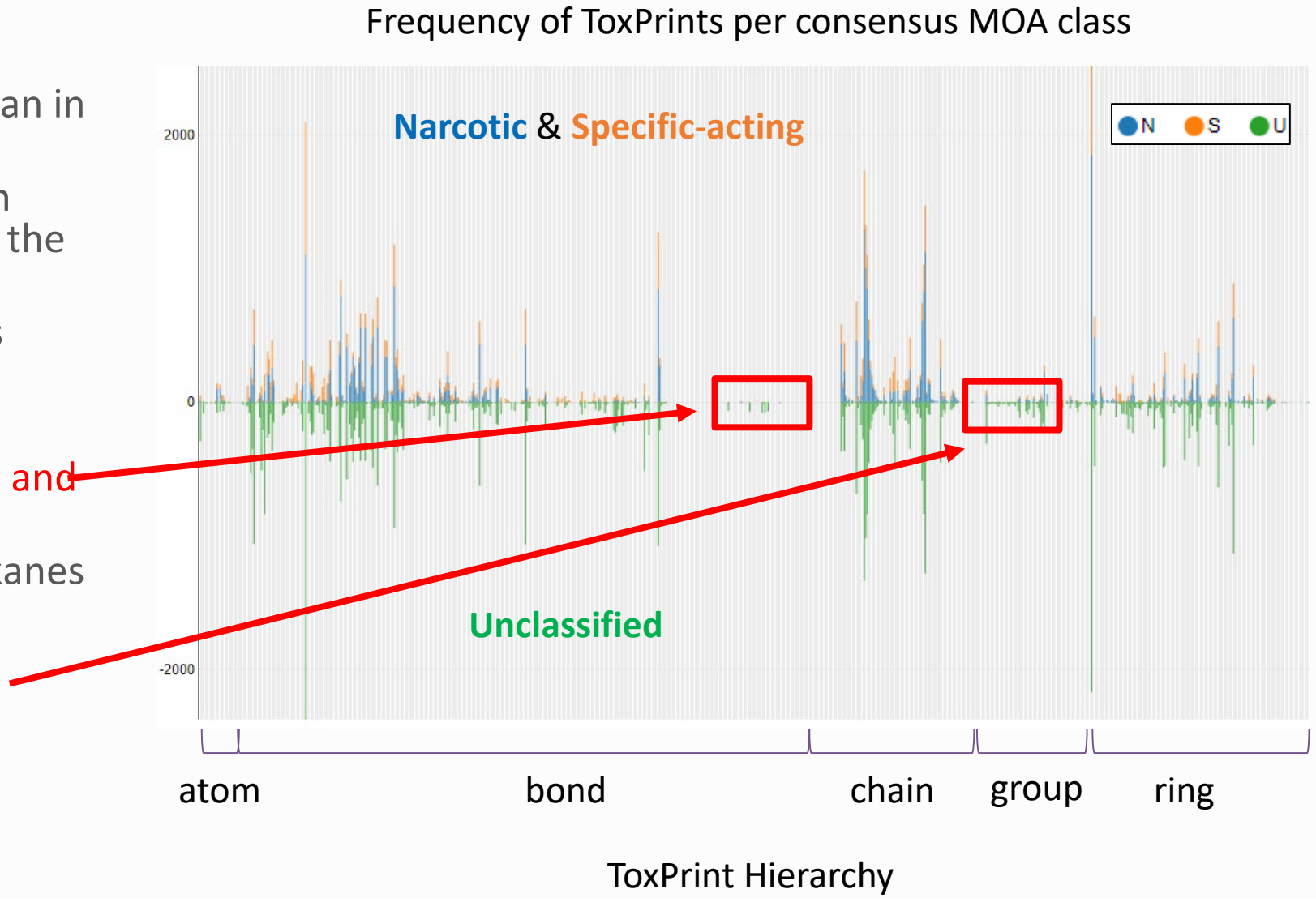
Missing structural Domains across full dataset:

- Metal & metalloid bonds
- Propyleneoxide chains
- Bicyclo ring structures

ToxPrints: Dataset > Unclassified > Specific-acting > Narcotic

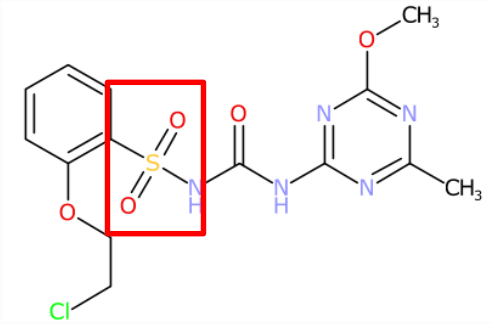
What are these 75 unique ToxPrints in the Unclassified set?

- ~7x more unique features in U (than in N or S)
- Could explain the lower prediction confidence in N/S classification of the U set
- Potential for additional categories based on structures:
  - 2 atom TxPs (metal group III)
  - 38 bond TxPs (metalloid: silane and siloxanes…)
  - 8 chain TxPs (ethyleneoxide alkanes C10 – C20)
  - 19 group TxPs (amino acids, polydentate ligands)
  - 8 ring TxPs



Example: Differences in model prediction vs. cMOA: Triasulfuron

- N-sulfonylurea herbicide
- Model prediction: Specific-acting
- EnviroTox consensus MOA: Narcotic
- ECOSAR classification: Sulfonyl Urea
- S(=O)_sulfonyl ToxPrint is enriched in the specific-acting MOA space and 47 assays



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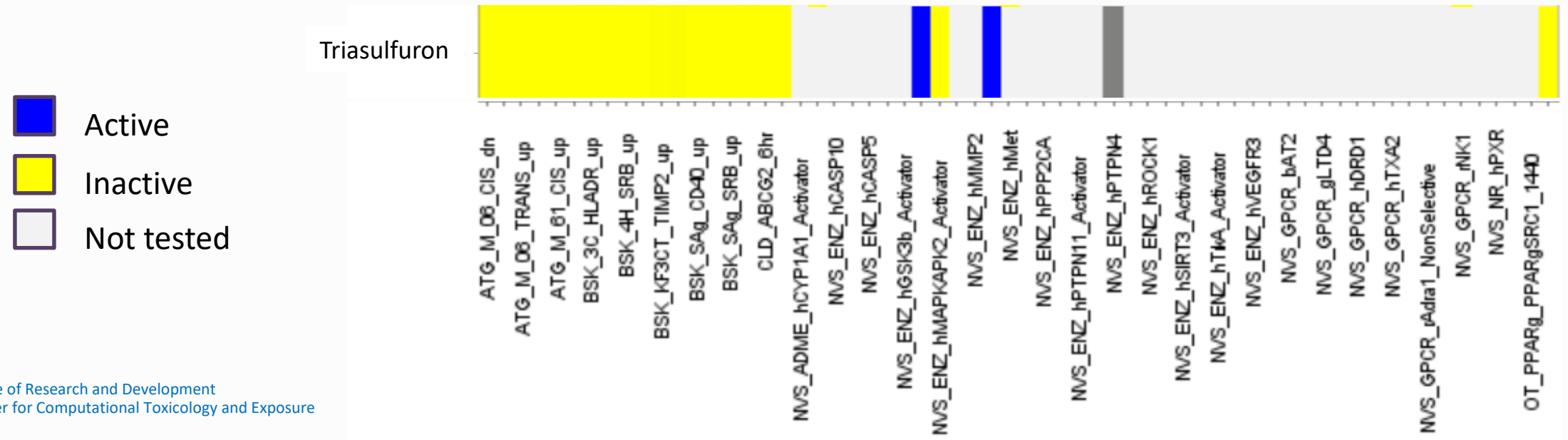
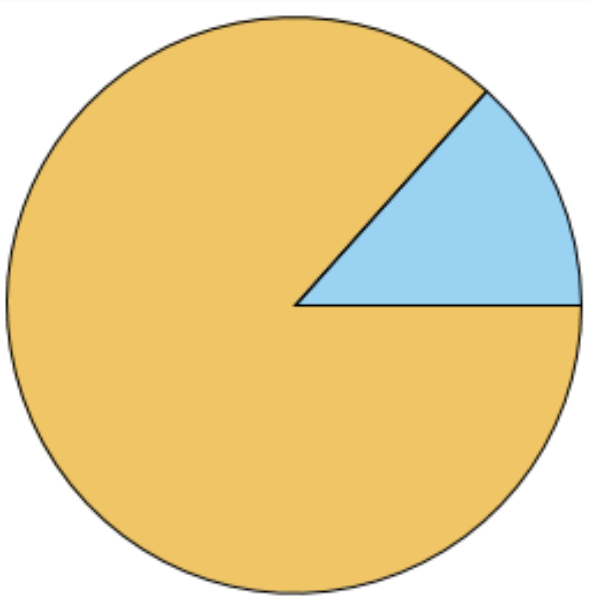
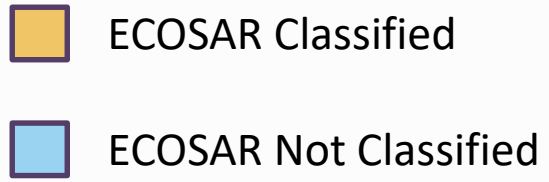


Preliminary predicted MOAs of the EnviroTox Unclassified set

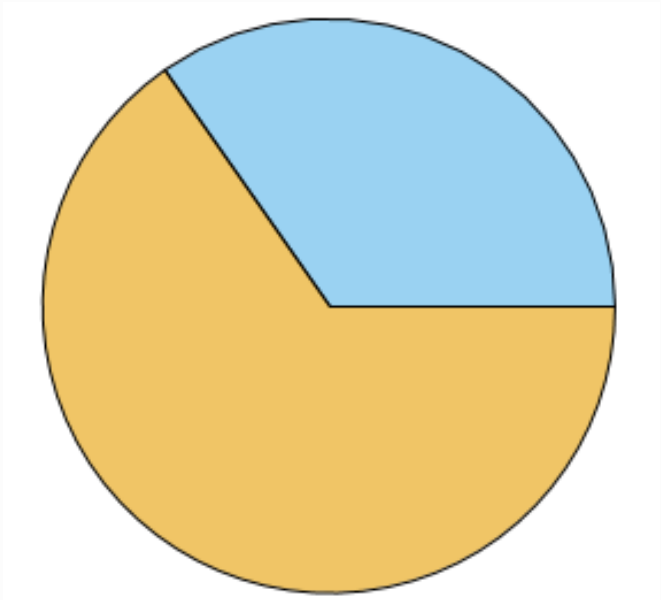
- 674 chemicals in the EnviroTox dataset that had low confidence or ambiguous consensus
- Applied model to the Unclassified set and compared predictions to ECOSAR classification
- ***Currently extending this analysis to the additional 3089 unclassified chemicals***

361 predicted as Narcotic





313 predicted as Specific-acting



Unclassified chemicals, predicted Specific-Acting: Enriched ToxPrints

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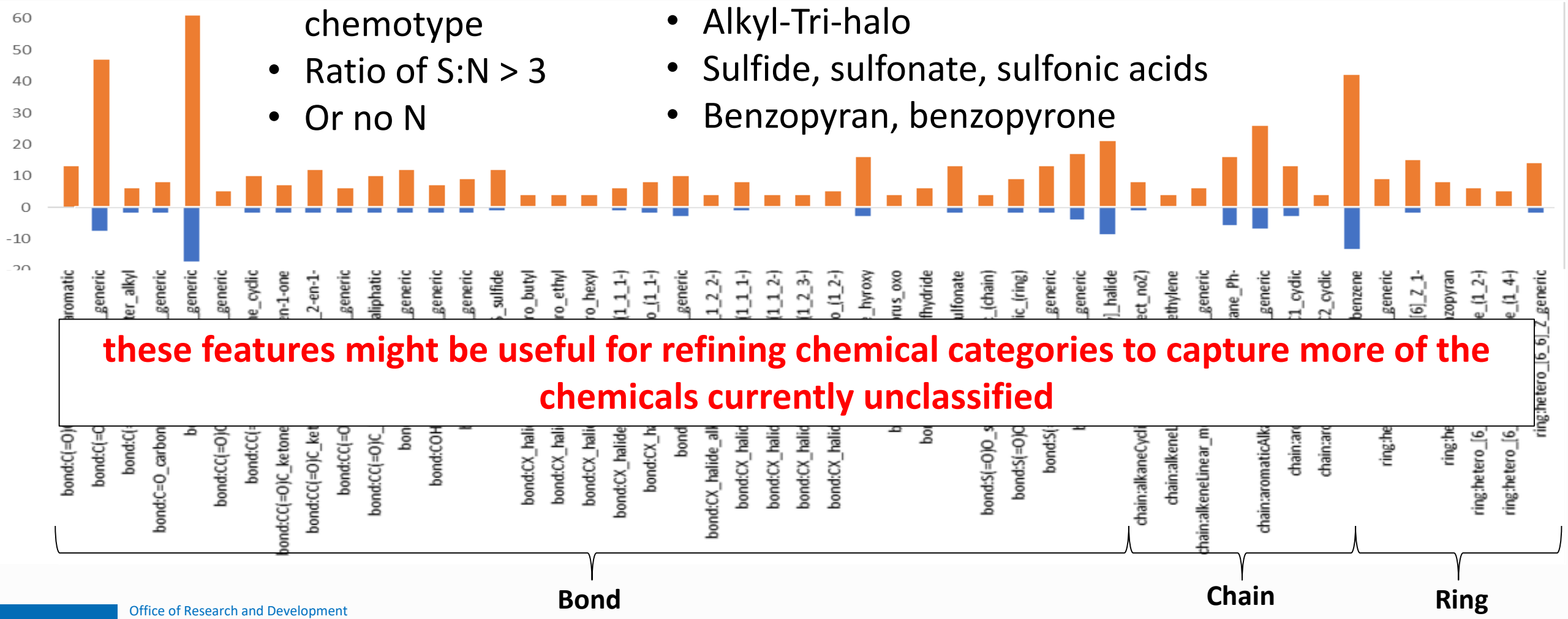
Criteria:

- ≥ 3 chemicals per chemotype
- Ratio of S:N > 3
- Or no N

Results:

- Ketones
- Alkyl-Tri-halo
- Sulfide, sulfonate, sulfonic acids
- Benzopyran, benzopyrone



Summary

- Identified relevant NAM information to develop a classification model for specific-acting MOAs
  - Increased the available chemical space of EnviroTox
- Explored differences in predicted and consensus MOA via chemotype enrichments
- Used model to inform ECOSAR preliminary set of unclassified chemicals
  - Majority of unclassified chemicals were predicted to have a specific acting MOA
  - Identified primary chemotypes for specific acting MOAs

- Use methods to inform classification models for TSCA (New Chemical Categories)
- Use chemotype enrichments to identify potential bioassays with bioactivity to provide support of NAM data in category development

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Thank you!