BIG DATA IN ENVIRONMENTAL SCIENCE AND TOXICOLOGY

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TEXAS A&M UNIVERSITY
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Welcome !

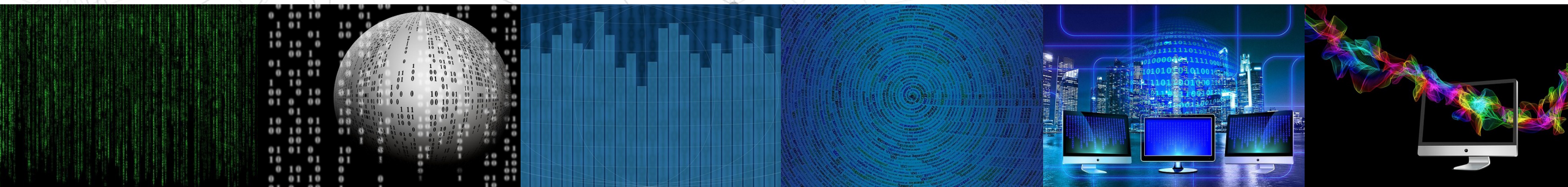
This Session will Begin at 2:00 pm Eastern US Time

"Experiments are too hard: How to use online resources for predictive toxicology"

Sciome LLC

Ruchir Shah Eric McAfee Alex Sedykh

Vijay Gombar Austin Ross



Ruchir Shah, Ph.D.
Chief Scientific Officer

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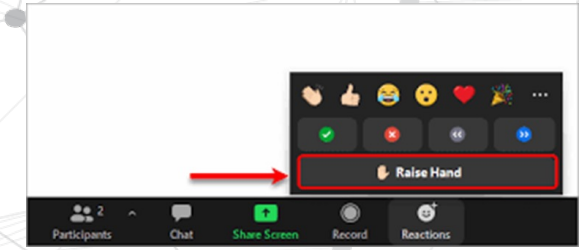
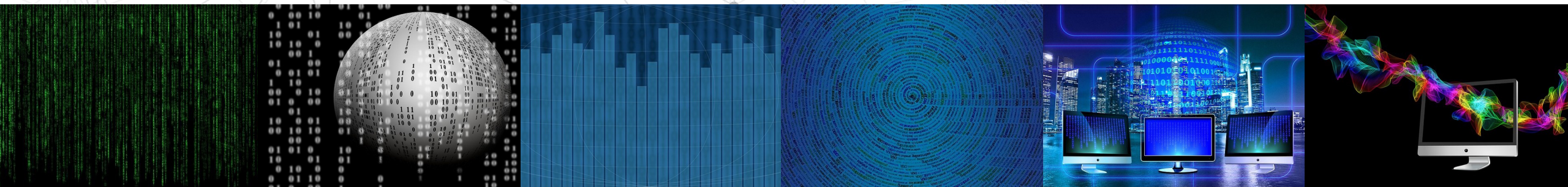
- All participants are muted to enable the speaker to present without interruption.
- Please rename yourself and designate Full Name and Affiliation.
- Use the Chat or Reaction icon at the bottom of your screen.



- This meeting will be recorded, and posted on the @tamusuperfund website https://superfund.tamu.edu/big-data-series-2021/ in the coming weeks.



https://www.sciome.com

Sciome

WHAT WE DO | WHO WE ARE | WHO WE SERVE | SOFTWARE | PUBLICATIONS | NEWS | CAREERS | CONTACT

Bioinformatics

- Next-Generation Sequence data analysis
- Microarray data analysis
- Structural & Functional genomics
- SNP/Genotype analysis & GWAS
- Biostatistics and Mathematical Modeling

Cheminformatics

- Quantitative Structure-Activity Relationship (QSAR) modeling
- Computational Toxicity Predictions
- Active site and Protein-Protein Docking
- Pharmacophore Modeling

Text-Mining and Literature Review

- Document Tagging and Visualization
- Full-Text Conversion and Search
- Document Clustering, Ranking & Classification
- Literature Prioritization and Screening
- Data extraction
- rapid Evidence Mapping (rEM) and systematic reviews
- Web mining and information retrieval

Data Science and Analytics

- Integration and visualization of large volumes of heterogeneous data
- Development and implementation of Deep Learning methodologies for predictive science
- Automated Image analysis using artificial intelligence
- Natural Language Processing (NLP) methods using Deep Learning

Software Development

- Requirements gathering
- Software architecture design
- User interface design
- Implementation, deployment and maintenance
- User support

25 Full time Informaticians

>Half with PhD, Most with a Masters

All of us program, develop methods, analyzed data, and publish

~190 total publications, 2 patents

Sciome

Sciome, Fall 2021

Open Positions at Sciome

- Bioinformatics Scientist
- Cheminformatics Scientist
- Data Scientist / ML Engineer / NLP expert
- Software Developer
- Statistician

Publicly available predictive models and resources

OCHEM: https://ochem.eu/home/show.do

Contains 3917726 records for 923 properties (with at least 50 records) collected from 16996 sources

Available models: LogP, LogS, Solubility in DMSO, Melting point, Boiling point, CYP 450 Inhibition, AhR Activation, AMES Test, BioConcentration factor, T. Pyriformis tosicity, Bioavailability, Gastrointestinal absorption, BBB permeability, CACO-2

OECD QSAR Toolbox: https://qsartoolbox.org/

The Toolbox is a software application intended to be used by governments, chemical industry and other stakeholders in filling gaps in (eco)toxicity data needed for assessing the hazards of chemicals. The Toolbox incorporates information and tools from various sources into a logical workflow.

59 databases containing ~100 000 chemicals with above 3 million measured data points (https://qsartoolbox.org/resources/databases/)

ECOSAR: https://www.epa.gov/tsca-screening-tools/ecological-structure-activity-relationships-ecosar-predictive-model

A computerized predictive system that estimates aquatic toxicity. The program estimates a chemical's acute (short-term) toxicity and chronic (long-term or delayed) toxicity to aquatic organisms, such as fish, aquatic invertebrates, and aquatic plants, by using computerized Structure Activity Relationships (SARs).

EPI Suite: https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface

A suite of physical/chemical property and environmental fate estimation programs developed by EPA's and Syracuse Research Corp. (SRC).

Includes ECOSAR.

ICE: https://ice.ntp.niehs.nih.gov/

Provides curated data from NICEATM (National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), its partners, and other resources, as well as tools to facilitate the safety assessment of chemicals.

OPERA: https://ntp.niehs.nih.gov/whatwestudy/niceatm/comptox/ct-opera/opera.html

To provide robust QSAR/QSPR models for chemical properties of environmental interest that can be used for regulatory purposes

Overview

Mr. Eric McAfee: .. Will present NTP's ICE tool, which hosts curated data from NICEATM and its partners.

Dr. Vijay Gombar: .. Will present the OPERA tool followed by latest research in predictive toxicology using SAAGAR features and OrbiTox

Mr. Austin Ross: .. Will demonstrate OrbiTox

Eric McAfee

Sr. Software Developer

Eric.McAfee@sciome.com

ICE
(Integrated Chemical Environment)

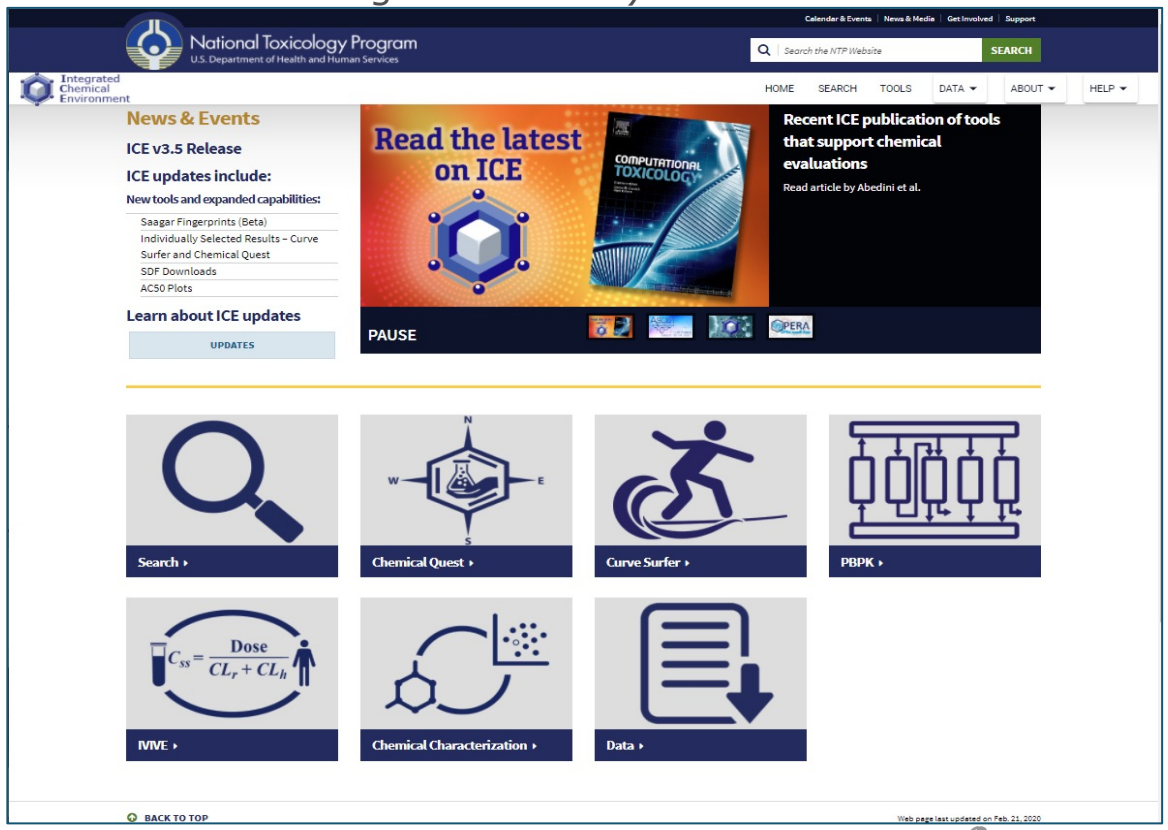
Sciome: Ruchir Shah, Eric McAfee, Alex Sedykh, Vijay Gombar, Austin Ross

12/01/2021

What is ICE?

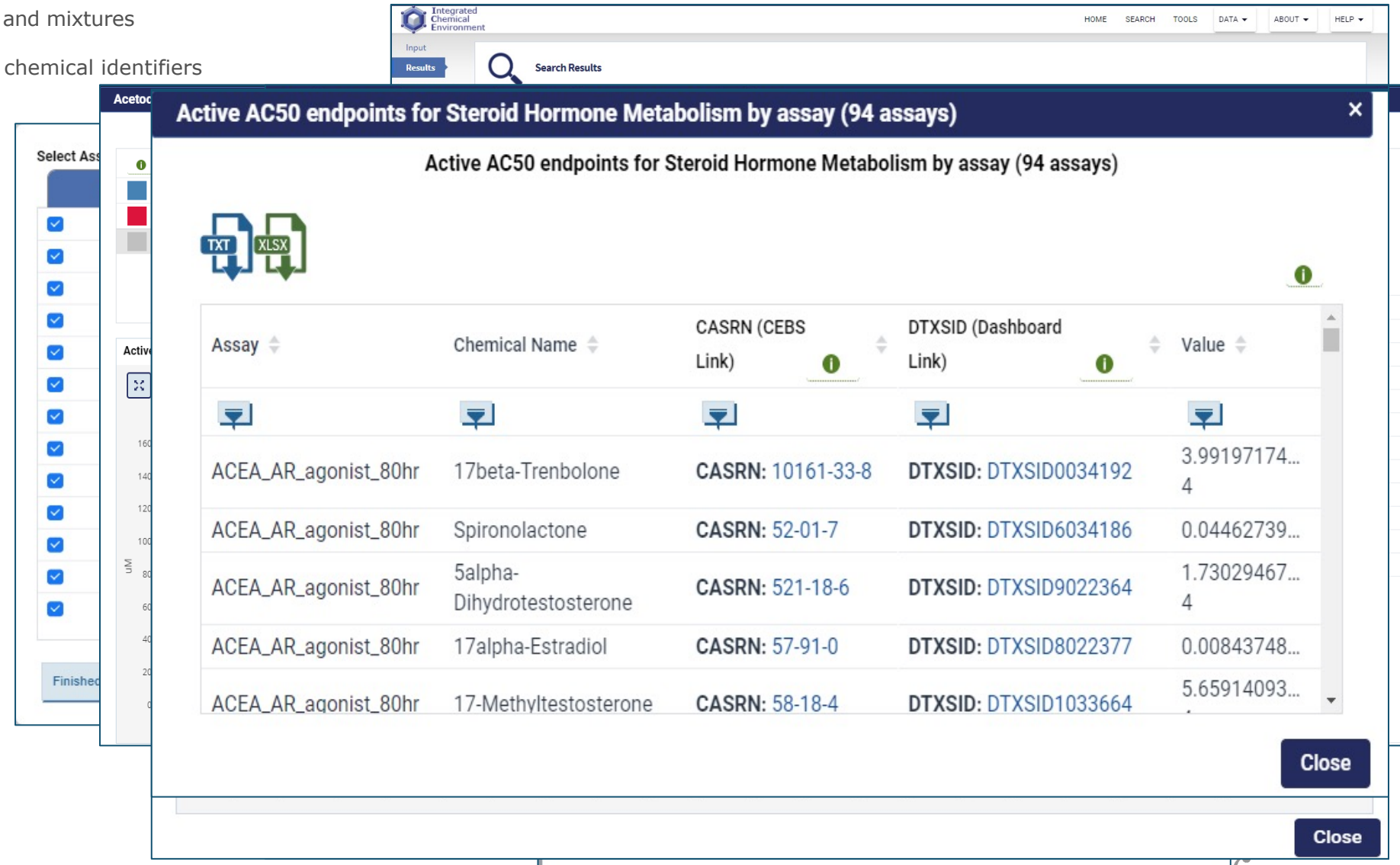
https://ice.ntp.niehs.nih.gov/

- Portal with high-quality data for computational workflows
- Data curated and aggregated from various NTP sources:
  - NICEATM (NTP Interagency Center for the Evaluation of Alternative Toxicological Methods)
  - EPA (Environmental Protection Agency)
  - CEBS (Chemical Effects in Biological Systems)
- Support for inputs of multiple chemical identifiers:
  - CASRNs
  - DTXSIDs
  - SMILES
  - InChIKeys (International Chemical Key)
- Chemical Lists – Curated lists, known activities
- Assay Groups – In Vitro, In Vivo, In Silico
- Dose response data, find adverse reactions (AC50, LD50)



Chemical Search

- Support for individual chemicals and mixtures
  - Support for inputs of multiple chemical identifiers
  - Integrated view
  - Data Downloads
    - Text
    - Excel
    - PDF
    - SDF
  - Detail Visualizations
    - Chemical
    - Mixture
  - Summary Visualizations
    - Activity Call Data
    - AC50 values
      - By Chemical
      - By Assay
      - Downloads

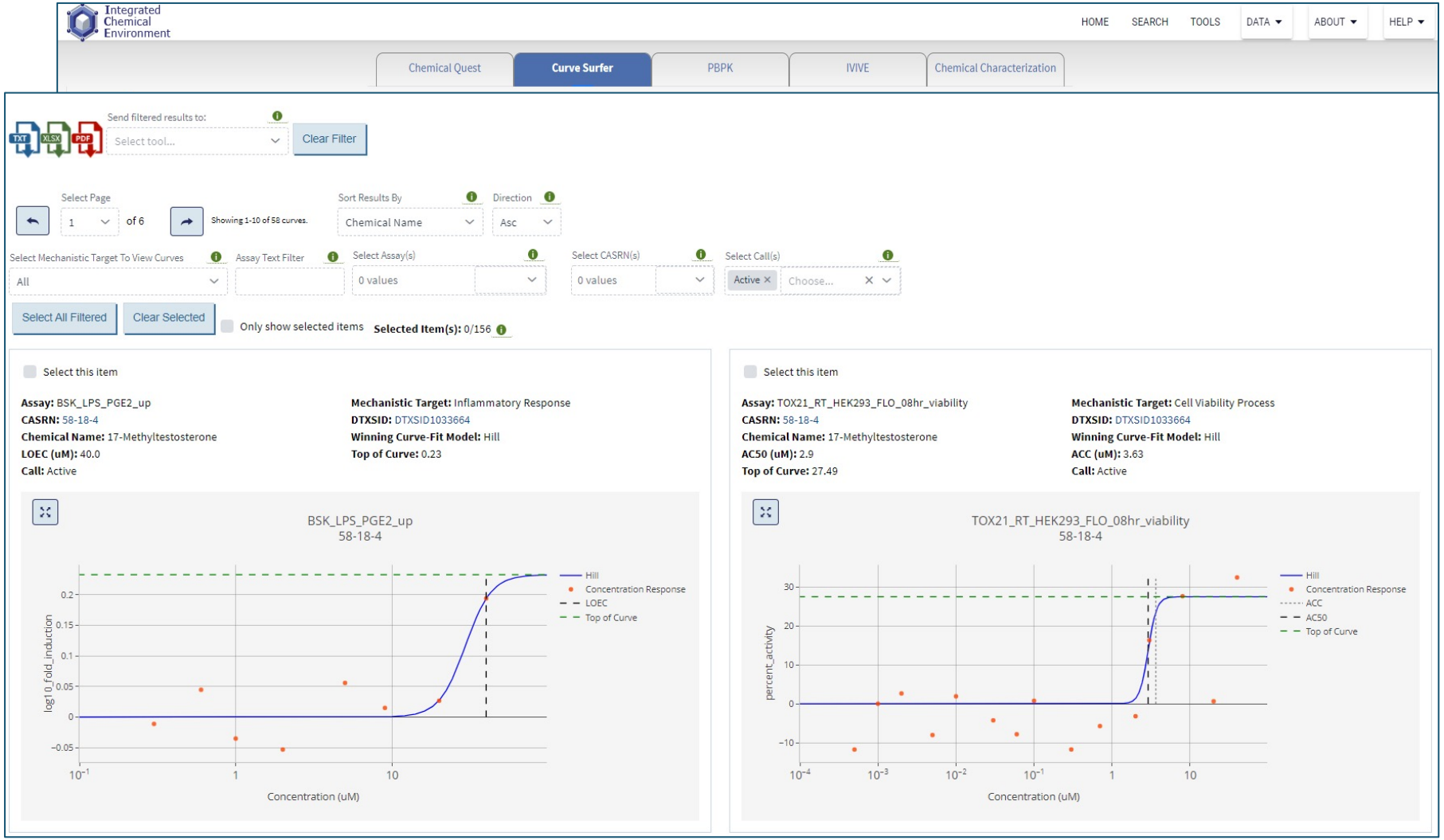


Tools and Workflows

- Curve Surfer
  - The Curve Surfer tool allows the user to view and interact with concentration response curves from cHTS
- PBPK (Physiological based pharmacokinetic modeling and simulation)
  - PBPK tool allows the user to generate predictions of tissue-specific chemical concentration profiles following a dosing event
- IVIVE (In Vitro to In Vivo Extrapolation)
  - The IVIVE tool uses pharmacokinetic models to predict the equivalent administered dose (EAD) from the activity concentration of selected assays
- Chemical Characterization
  - The Chemical Characterization tool allows the user to view and compare one or two chemical lists based on their physicochemical properties
- Chemical Quest
  - The Chemical Quest tool uses fingerprints to predict structure similarity

Curve Surfer

- Curve Surfer - view and interact with concentration response curves from cHTS
- Input a chemical list and select assays
- Output Results
  - Downloaders
    - Text
    - Excel
    - PDF
  - Filter chain
  - Dose response curves (overlay coming)



PBPK

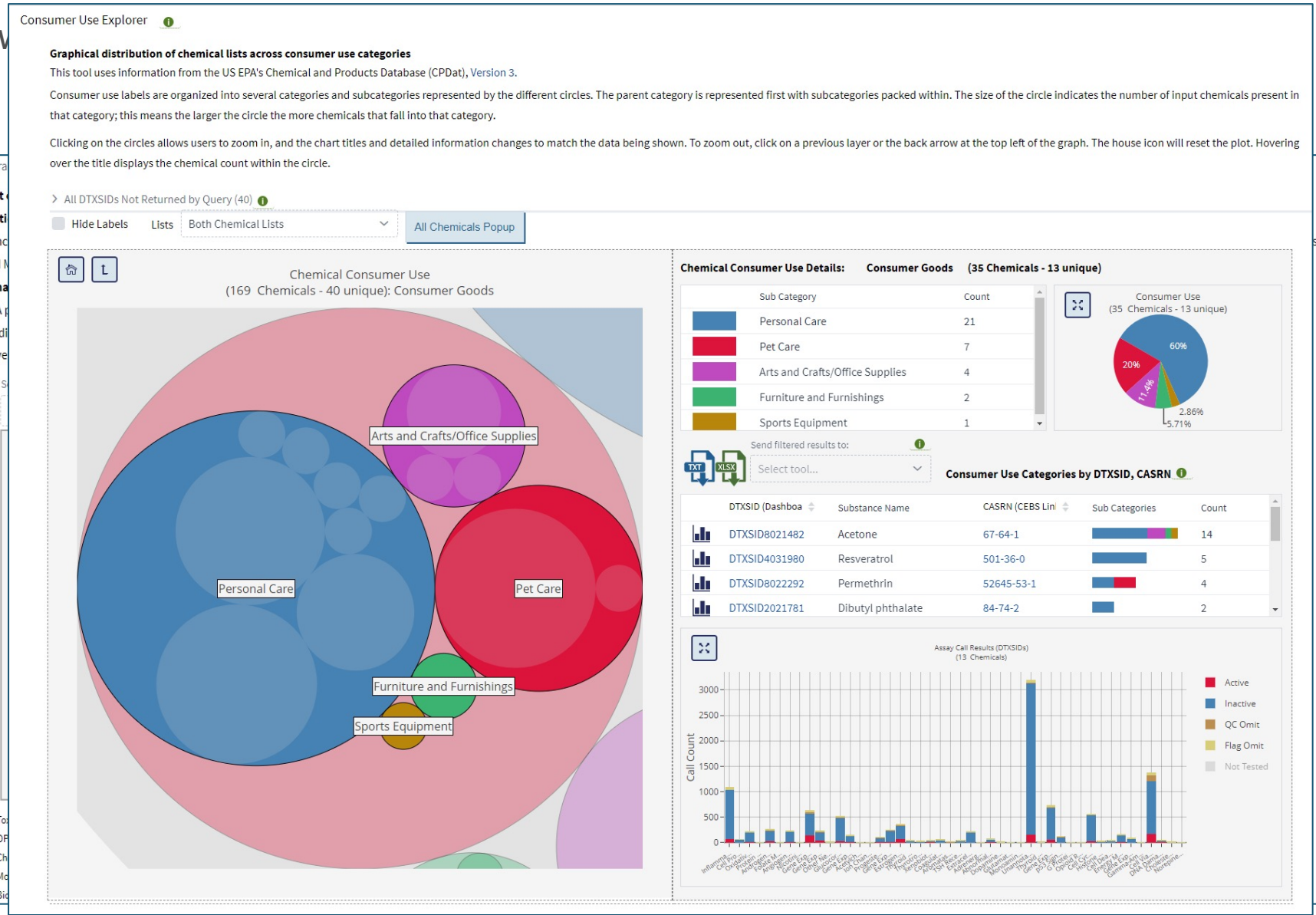
- PBPK (Physiological based pharmacokinetic modeling and simulation)
  - PBPK tool allows the user to generate predictions of tissue-specific chemical concentration profiles following a dosing event
- Input a chemical list and PBPK parameters
- Output
  - Download files
  - PBPK Results
    - Chemical
    - Compartment
    - CSS
    - Cmax
  - PBPK Results Visualizations
    - Does response curves with compartment overlay
    - Box Plots (Cmax across compartments)

IVIVE

- IVIVE (In Vitro to In Vivo Extrapolation) - uses pharmacokinetic models to predict the equivalent administered dose (EAD) from the activity concentration of selected assays
- Input a chemical list, select assays, params
- Output
  - Download files
  - IVIVE Results
    - Chemical
    - Assay
    - Mode of Action
    - Mechanistic Targets
    - AC50
    - EAD 50%
    - EAD 95%
  - IVIVE Results Visualizations
    - EAD 95th Box and Whisker
    - Distribution of in vitro bioactivity (AC50)

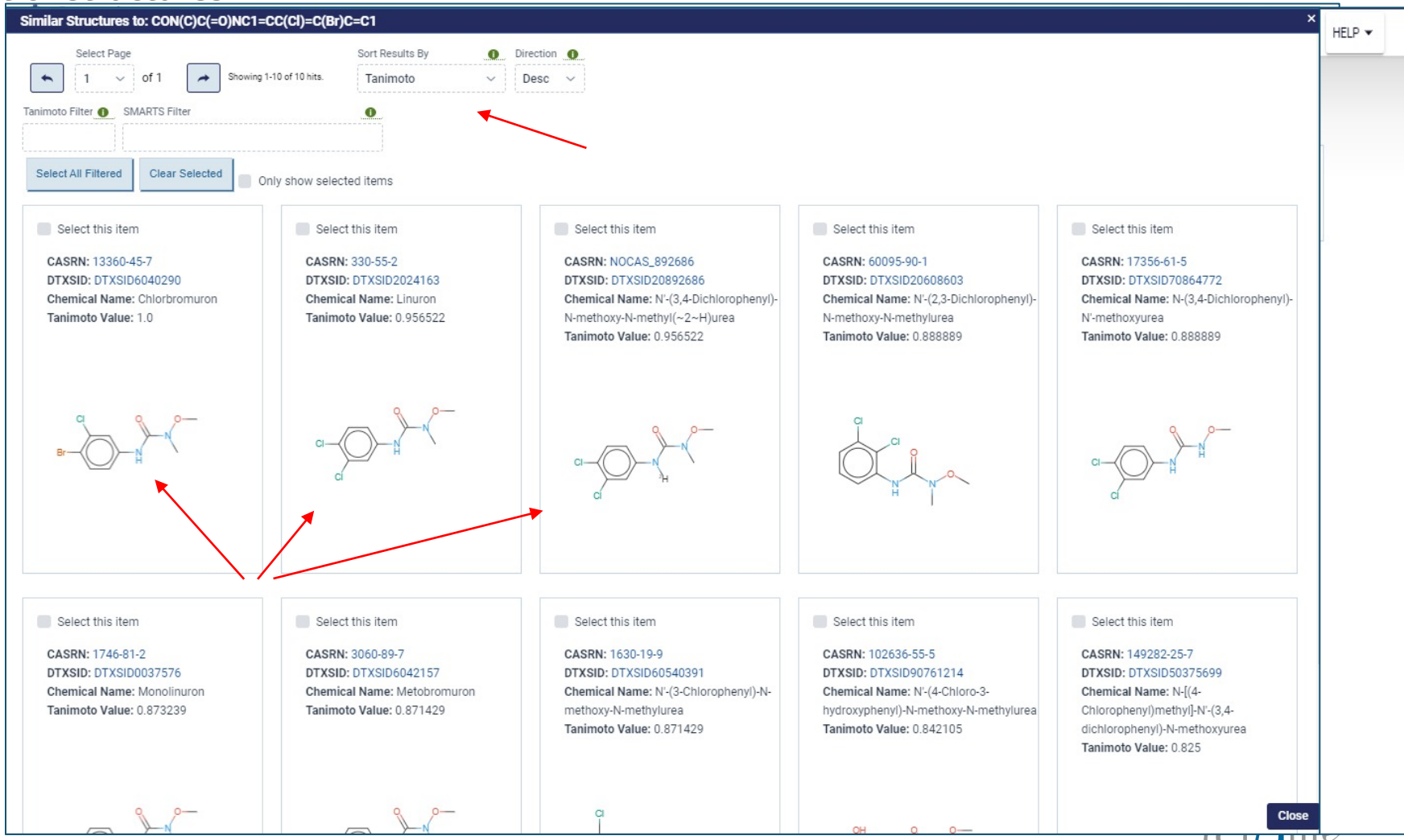
Chemical Characterization

- Chemical Characterization - view and compare one or two chemical lists based on their physicochemical properties
- Input 2 different lists for comparison
- Output
  - Chemical Properties Summ
  - Visualization of Chemical Properties
  - Interactive PCA
  - Consumer Use Explorer
    - Zoom in



Chemical Quest

- Chemical Quest tool uses fingerprints to predict structure similarity
- Input a chemical list and list of structures
  - Draw structures
  - add smiles to input list
- Output Results
  - Tanimoto threshold
  - Saagar
  - Downloaders
    - Text
    - Excel
    - SDF
  - Chemical Structures
  - Filter Chain



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Cheminformatics Scientist

Vijay.Gombar@sciome.com

OPERA – OPEn (q)saR App: Introduction

Credits to: Dr. Kamel Mansouri

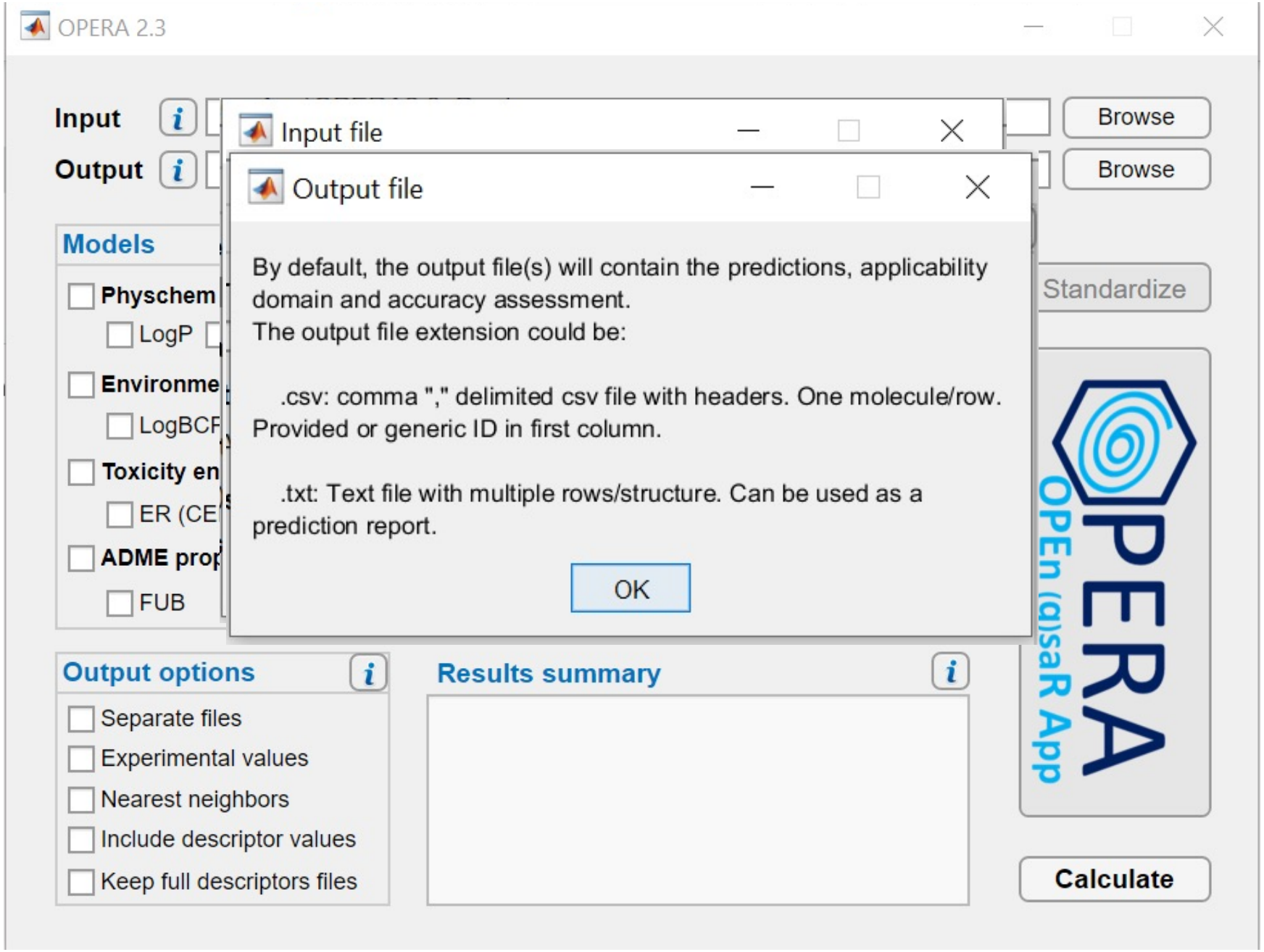
Computational Chemist at National Institute of Environmental Health Sciences (NIEHS), RTP, NC

- Developed by US (National Center for Computational Toxicology (Mansouri et al. 2018)[1].
- OPERA can be downloaded from the National Institute of Environmental Health Sciences GitHub repository (https:// github.com/NIEHS/OPERA) or https://github.com/kmansouri/OPERA

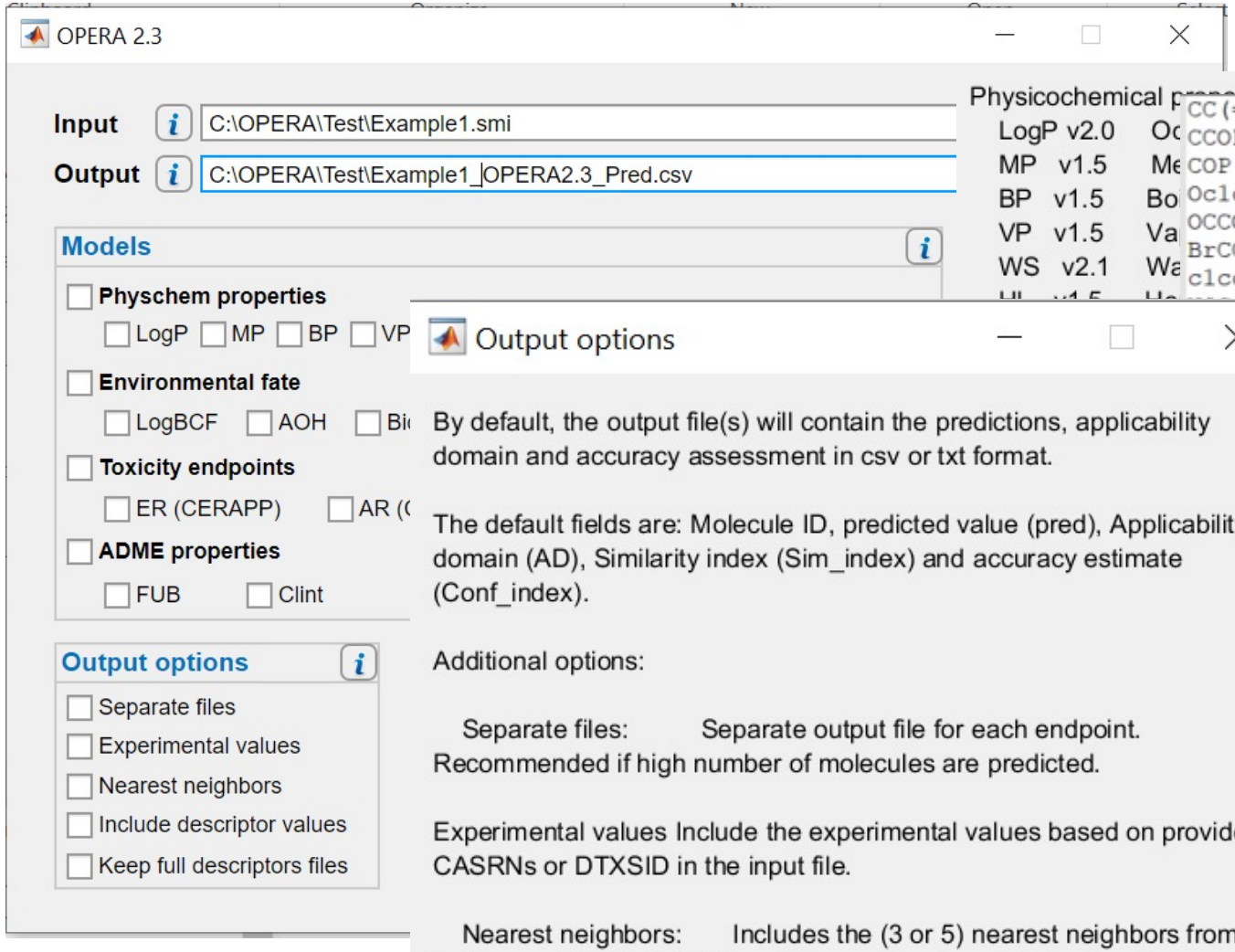
  Both a command-line version and user-friendly graphical user interface versions are available for Windows and Linux operating systems

[1]Mansouri K, Grulke CM, Judson RS, Williams AJ (2018). OPERA models for predicting physicochemical properties and environmental fate endpoints. J Cheminform 10(1):10, PMID: 29520515, https://doi.org/10.1186/s13321-018-0263-1.

OPERA – OPEn (q)saR App: Interface



OPERA – OPEn (q)saR App: Models



OPERA – OPEn (q)saR App: Models

1. Physicochemical properties such as acid dissociation constant (pKa) and octanol-water dissociation coefficient (logD) and partition coefficient (logP), water solubility, melting and boiling point (Mansouri et al. 2019)[2].
2. Ecotoxicity parameters such as fish bioconcentration factor, soil adsorption coefficient, and biodegradability.
3. Parameters for inputs into pharmacokinetic models, such as hepatic clearance and plasma fraction unbound.
4. Estrogenic activity from the Collaborative Estrogen Receptor Activity Prediction Project (CERAPP) (Mansouri et al. 2016)[3].
5. Androgenic activity from the Collaborative Modeling Project for Androgen Receptor Activity (CoMPARA) (Mansouri et al. 2020)[4].
6. Acute oral systemic toxicity from the Collaborative Acute Toxicity Modeling Suite (CATMoS) (Mansouri et al. 2021)[5].

All OPERA models were built on curated data and QSAR-ready chemical structures standardized using an open-source workflow (Mansouri et al. 2016)[6].

[2]Mansouri *et al.* Open-source QSAR models for pKa prediction using multiple machine learning approaches. *J Cheminform (2019) 11:60,* https://doi.org/10.1186/s13321-019-0384-1

[3]Mansouri, el (2016) CERAPP: Collaborative Estrogen Receptor Activity Prediction Project. Environ. Health Perspect. 2016, 124 (7), 1023−1033.

[4]Mansouri, et al (2020) CoMPARA: Collaborative Modeling Project for Androgen Receptor Activity. Environmental Health Perspectives, 128 (2). CID: 027002, https://doi.org/10.1289/EHP5580

[5]Mansouri et al. (2021) CATMoS: Collaborative Acute Toxicity Modeling Suite. Environmental Health Perspectives, 129 (4). CID: 047013, https://doi.org/10.1289/EHP8495

[6]Mansouri et al (2016) An automated curation procedure for addressing chemical errors and inconsistencies in public datasets used in QSARmodelling.SARQSAREnvironRes27(11):911–937, PMID: 27885862, https://doi.org/10.1080/1062936X.2016.1253611.

OPERA – OPEn (q)saR App: Models' Relevance

Properties like partition coefficient, boiling point, vapor pressure, and melting point also have great environmental impact.

LogP (Partition coefficient):

Is an important physical property of a substance and, thereby, a predictor of its behavior in different environments.

Is the first indicator on whether a substance will be absorbed by plants, animals, humans, or other living tissue; or be easily carried away and disseminated by water.

Vapor pressure:

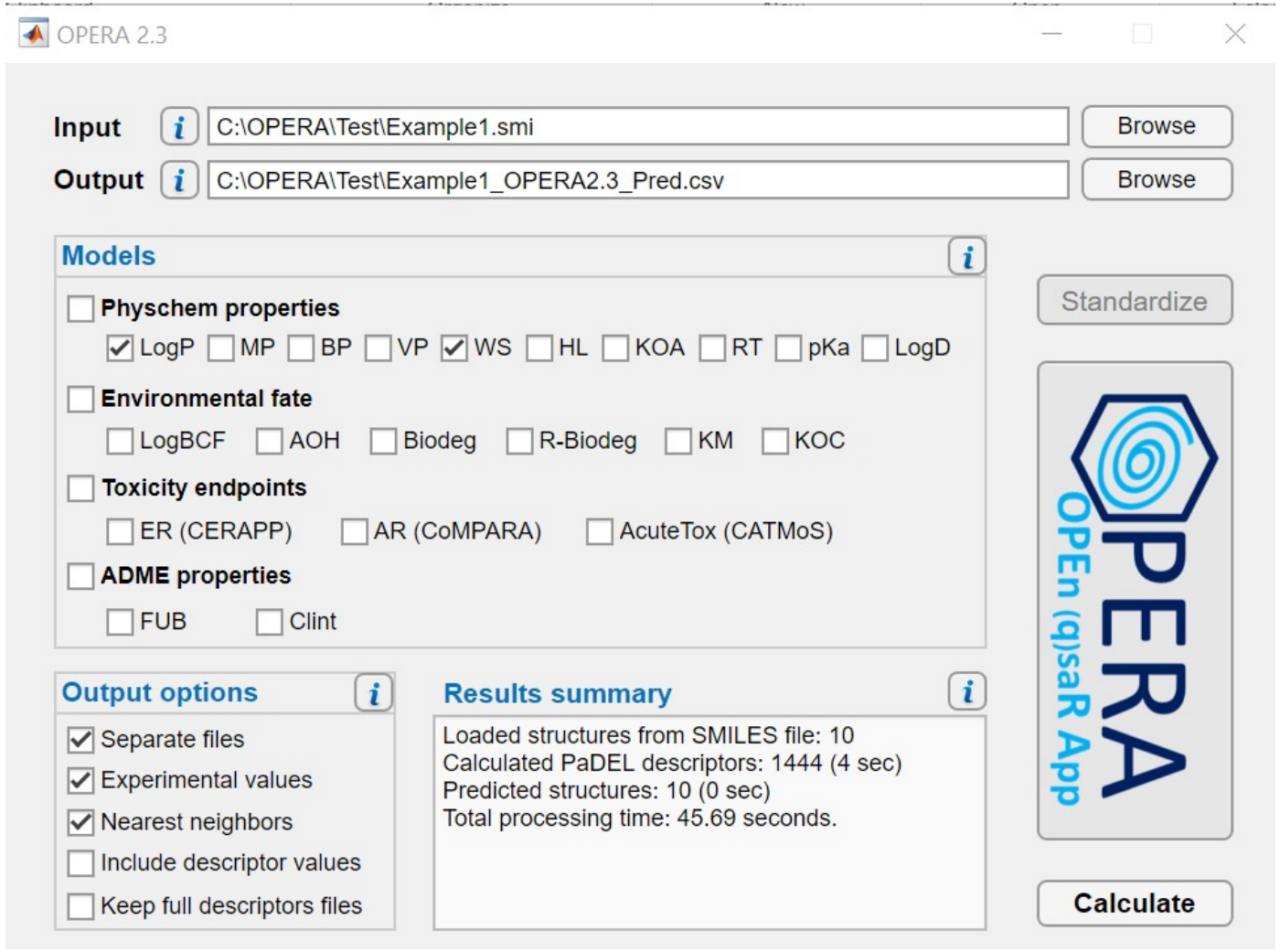
Affects a chemical's residence time in soil and in water and is a significant factor in its distribution and transport in the environment.

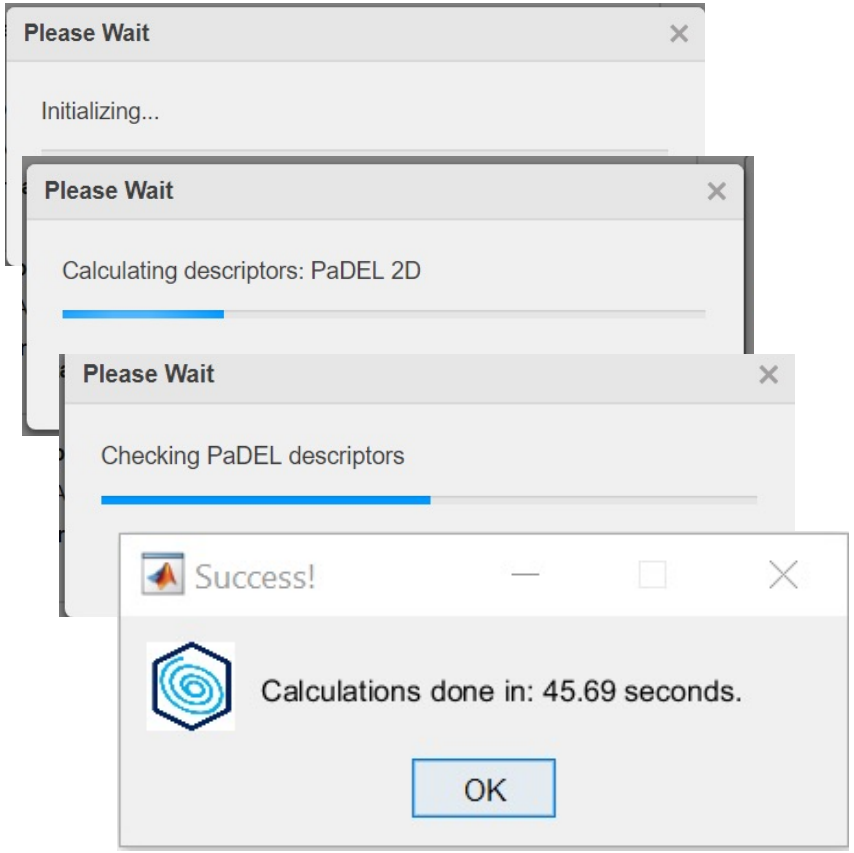
Melting point/boiling point:

Indicate the physical state of the chemical at ambient temperatures, which will dictate how the chemical is handled and treated.

Kamel Mansouri, Chris M. Grulke, Richard S. Judson & Antony J. Williams. OPERA models for predicting physicochemical properties and environmental fate endpoints. Journal of Cheminformatics volume 10, Article number: 10 (2018)

OPERA – OPEn (q)saR App: Running





OPERA – OPEn (q)saR App: Output

- MoleculeID
- LogWS_exp
- LogWS_pred
- AD_WS
- AD_index_WS
- Conf_index_WS
- LogWS_CAS_neighbor_1
- LogWS_CAS_neighbor_2
- LogWS_CAS_neighbor_3
- LogWS_CAS_neighbor_4
- LogWS_CAS_neighbor_5
- LogWS_InChiKey_neighbor_1
- LogWS_InChiKey_neighbor_2
- LogWS_InChiKey_neighbor_3
- LogWS_InChiKey_neighbor_4
- LogWS_InChiKey_neighbor_5
- LogWS_DTXSID_neighbor_1
- LogWS_DTXSID_neighbor_2
- LogWS_DTXSID_neighbor_3
- LogWS_DTXSID_neighbor_4
- LogWS_DTXSID_neighbor_5
- LogWS_DSSTOXMPID_neighbor_1
- LogWS_DSSTOXMPID_neighbor_2
- LogWS_DSSTOXMPID_neighbor_3
- LogWS_DSSTOXMPID_neighbor_4
- LogWS_DSSTOXMPID_neighbor_5
- LogWS_Exp_neighbor_1
- LogWS_Exp_neighbor_2
- LogWS_Exp_neighbor_3
- LogWS_Exp_neighbor_4
- LogWS_Exp_neighbor_5
- LogWS_pred_neighbor_1
- LogWS_pred_neighbor_2
- LogWS_pred_neighbor_3
- LogWS_pred_neighbor_4
- LogWS_pred_neighbor_5

Example1_OPERA2.3_Pred_LogP.csv

Example1_OPERA2.3_Pred_WS.csv

Example1_OPERA2.3_Pred_StrP.csv

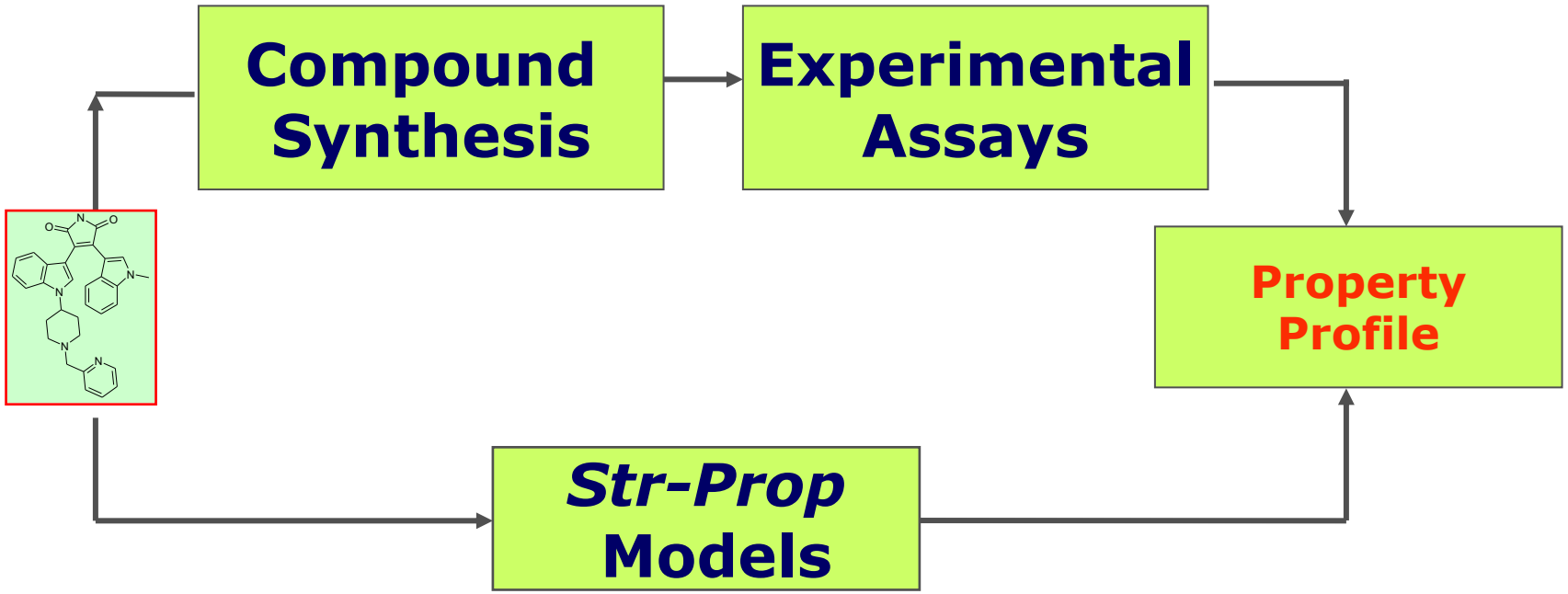
MoleculeID	LogWS		AppDom (AD)	AD_index	Conf_index	Neighbor 1		Neighbor 2		Neighbor 3		Neighbor 4		Neighbor 5	
	Exp	Pred				Exp	Pred	Exp	Pred	Exp	Pred	Exp	Pred	Exp	Pred
DTXSID1025853	1.119	1.090	1	0.856	0.841	1.119	0.920	0.983	0.641	1.119	1.049	0.527	0.587	0.935	0.508
DTXSID7021100	NaN	3.569	1	0.559	0.550	3.844	3.378	3.863	3.343	4.746	-3.868	-2.826	-3.384	-2.188	-3.800
DTXSID5020449										11	-1.569	-1.754	-1.490	-2.280	-1.498
DTXSID6020690										53	-4.143	-4.505	-4.750	-4.301	-4.743
DTXSID9021976										39	-0.964	-0.476	-0.987	-0.475	-1.712
DTXSID3020415										01	-2.073	-1.165	-1.461	-2.084	-2.106
DTXSID3039242	-1.640	-1.872	1	0.880	0.725	-1.640	-2.479	-2.790	-2.542	-2.075	-2.264	-2.727	-2.009	-2.625	-2.518
DTXSID6020319	-5.647	-5.541	1	0.864	0.712	-5.647	-4.972	-5.037	-5.223	-5.239	-5.494	-5.428	-2.864	-4.370	-4.760
DTXSID2021238	0.814	0.489	1	0.905	0.719	0.814	-0.153	-0.185	0.424	0.326	0.006	0.622	-0.687	-0.268	-0.998
DTXSID8022292	NaN	-6.202	1	0.546	0.427	-7.217	-4.776	-6.320	-6.199	-8.161	-4.906	-3.226	-6.167	-6.014	-5.734

Structural properties (StrP v2.0) included by default.
MolWeight, nbAtoms, nbHeavyAtoms, nbC, nbO, nbN, nbAromAtom, nbRing, nbHeteroRing, Sp3Sp2HybRatio, nbRotBd, nbHBdAcc, ndHBdDon, nbLipinskiFailures, TopoPolSurfAir, MolarRefract, CombDipolPolarizability

More details: QMRF registered in the European Commission's Joint Research Center (JRC) QMRF Inventory

https://www.researchgate.net/publication/316789777_QMRF_-_Title_WS_model_for_water_solubility_prediction_from_OPERA_models?channel=doi&linkId=59e624b50f7e9b4f49a97116&showFulltext=true

Experiments are too hard: Wet vs In Silico



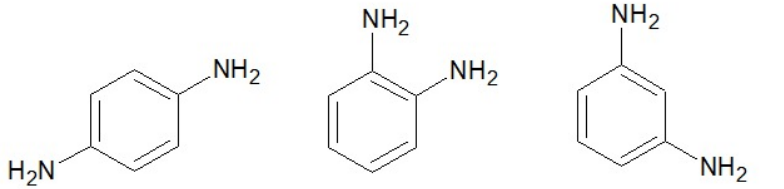
Experience

**"Experience is not what happens to you;
it's what you do with what happens to you."**

Aldous Huxley (1894-1963)

Models as In Silico Instruments

$$P = f(S)$$



Noncarcinogen Carcinogen Noncarcinogen

Structure	Name	Boiling point (°C)
	pentane	36.0
	2-methylbutane	27.9
	2,2-dimethylpropane	9.5

P: Property (Physchem, toxicity endpoint, ADME)

f: Mathematical function

S: Structure quantifier(s)

- Inexpensive
- Extremely fast
- Reduce animal use
- Rationalize synthesis and testing
- Help design safer compounds

Structure Quantification: Molecular E-State

$$\delta^v = (Z^v - H) / (Z - Z^v - 1)$$

$$I_i = (\delta^v + 1) / \delta$$

$$\Delta I_i = \Sigma [(I_i - I_j)] / r^2_{ij}$$

$$E_i = I_i + \Delta I_i$$

LB Kier and LH Hall, *Molecular Structure Description –The Electrotopological State,* Academic Press, 1999.

Models as iHTS: Minimizing Assays (Permeability)

Caco-2 (% Transport Distributions)				
Transport (%)	Category	ESMol < 55	ESMol < 50	ESMol < 45
< 4	Low	324	153	68
> 4	Not Low	2989	2002	1226
Total		3313	2155	1294
% Not Low		90.2%	92.9%	94.7%

Models as iHTS: Minimizing Assays (Solubility)

Kinetic Solubility Distributions				
Solubility	Category	ESMol < 50	ESMol < 45	ESMol < 40
< 120	Low	541	235	65
> 120	High	3641	2343	1197
Total		4182	2578	1262
% High Sol		87.1%	90.9%	94.8%

Models as iHTS: Well-known "Rules"

Lipinski's rule of 5 for orally active drugs:

- No more than 5 hydrogen bond donors (the total number of nitrogen–hydrogen and oxygen–hydrogen bonds)
- No more than 10 hydrogen bond acceptors (all nitrogen or oxygen atoms)
- A molecular mass less than 500 daltons
- An octanol-water partition coefficient (log *P*) that does not exceed 5

Veber's Rule for orally active compounds:

- 10 or fewer rotatable bonds and
- Polar surface area no greater than 140 $Å^2$

Rule of three (RO3) for defining lead-like compounds:

- Octanol-water partition coefficient log *P* not greater than 3
- Molecular mass less than 300 daltons
- Not more than 3 hydrogen bond donors
- Not more than 3 hydrogen bond acceptors
- Not more than 3 rotatable bonds

Ghose Filter for druglikeness:

- Partition coefficient log *P* in −0.4 to +5.6 range
- Molar refractivity from 40 to 130
- Molecular weight from 180 to 480
- Number of atoms from 20 to 70 (includes H-bond donors and H-bond acceptors)

- As with many other rules of thumb, there are many *exceptions*.

Detailed Structure Quantification: Packages

Yap, C. W. (2011) PaDEL-descriptor: An open-source software to calculate molecular descriptors and fingerprints. J. Comput. Chem. 32, 1466.

Hong, H., Slavov, S., Ge, W., Qian, F., Su, Z., Fang, H., … Tong, W. (2012). Mold2Molecular Descriptors for QSAR. Statistical Modelling of Molecular Descriptors in QSAR/QSPR, 65–109. doi:10.1002/9783527645121.ch3

Moriwaki, H., Tian, Y.-S., Kawashita, N., and Takagi, T. (2018) Mordred: a molecular descriptor calculator. J. Cheminf. 10, 4.

… and there are several commercial packages

Predictive Model: A Computational Instrument

$$P = f(S)$$

P: Property (Physchem, tox., ADME)

f: Mathematical function

S: Structure quantifier(s)

Copyright © 2000 Eli Lilly and Company

Black boxes vs Interpretable Models

$$\log P = -1.167 \times 10^{-4} S^2 - 6.106 \times 10^{-2} S + 14.87 Ov^2 - 43.67 Ov + 0.9986 I_{alkane} + 9.57 \times 10^{-3} Mw - 0.13 D - 4.929 Q_{ON} - 12.17 Q_N^4 + 26.81 Q_N^2 - 7.416 Q_N - 4.551 Q_O^4 + 17.92 Q_O^2 - 4.03 Q_O + 27.273$$

$n = 118$, $r = 0.9388$, $F = 115.1$

S:	Molecular surface
Ov:	Ovality of the molecule*
I_{alkane}:	Indicator variable for alkanes
Mw:	Molecular weight
D:	Calculated dipole moment
Q_{ON}:	Sum of absolute values of atomic charges on nitrogen an oxygen atoms
Q_N:	Square root of the sum of the squared charges on nitrogen atoms
Q_O:	Square root of the sum of the squared charges on oxygen atoms (AM1)

**J. Am. Chem. Soc.* 1989, 111, 3783.

Models with Structural Features as Descriptors

Can point out to a toxicologist:

a substructure potentially rendering a molecule toxic/nontoxic

May indicate to a pharmacologist:

the structural moiety required for certain pharmacological action

May help a biochemist:

generate hypothesis for a possible mode of action

Can guide a chemist:

in designing “better” compounds by combining substructures

Saagar - A new, extensible set of molecular substructures for interpretable QSARs and read-across applications

Sedykh AY; Shah RR; Kleinstreuer NC; Auerbach SS; Gombar VK (2021). “Saagar-A New, Extensible Set of Molecular Substructures for QSAR/QSPR and Read-Across Predictions.” Chemical Research in Toxicology 34(2):634-640

Saagar Features as Structure Descriptors

- A parsimonious but extensible set of chemistry-aware and chemically viable functional groups and moieties - *Saagar*

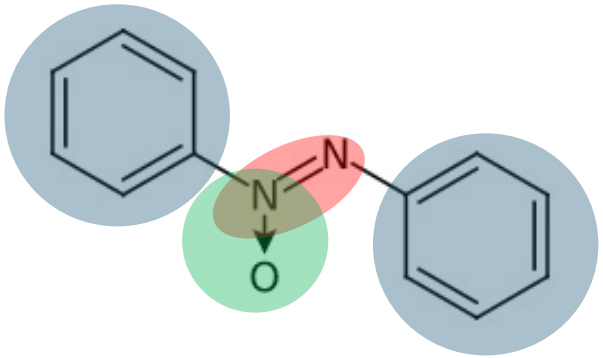
- Systematically gathered by studying and reviewing available open-source literature that highlights relationships between substructural moieties and a variety of physico-chemical, ADME, and toxicological properties

- The *Saagar* set encodes and enumerates salient molecular features like:
  - Hierarchical macro structural class (inorganic, aliphatic - acyclic or alicyclic, aromatic, fused or unfused carbo-aromatic and hetero-aromatic, and organometallic),
  - Elemental makeup,
  - Ring size, ring substituents and their positions,
  - Separation of certain hetero atoms to account for key interactions
  - Typical scaffolds for endogenous biochemicals (e.g., amino acids, lipids)
  - Scaffolds present in common medicinal and industrial chemicals
- *Saagar* version SGR-v0120 has 834 features coded as SMARTS strings
- Provide sufficient coverage of chemicals in Drugbank, ChEMBL, and Tox 21 sets

Example: *Saagar* v1 Collection

834 Saagar features are coded them as SMARTS* (SMILES ARbitrary Target Specification)

DSSTox_CID4555

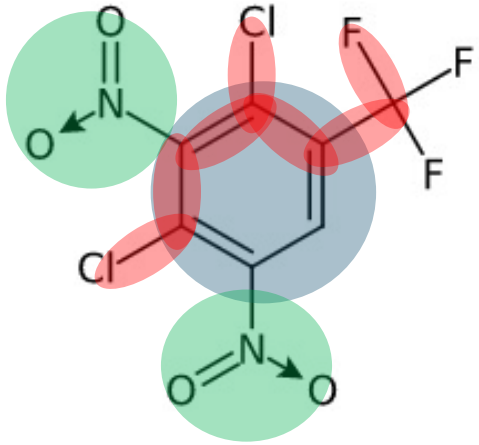


[R] 12

[N!r]=[N!r]

[N+!$(N=O)][O-X1]

DSSTox_CID24639

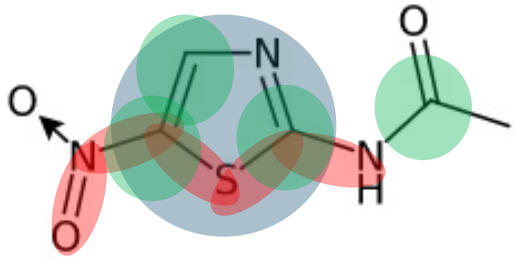


6

[F,Cl,Br,I]~*~*~*~[F,Cl,Br,I]

AR2NO2_META

DSSTox_CID26391



5

[O]~*~*~*~*~[NX3;NH2,$([NH][#6]),
$([N]([#6])[#6])]

[#6;X3]

How good is the *Saagar* Feature Set?

Experiment 1:

How effective *Saagar* features can be for read-across applications?

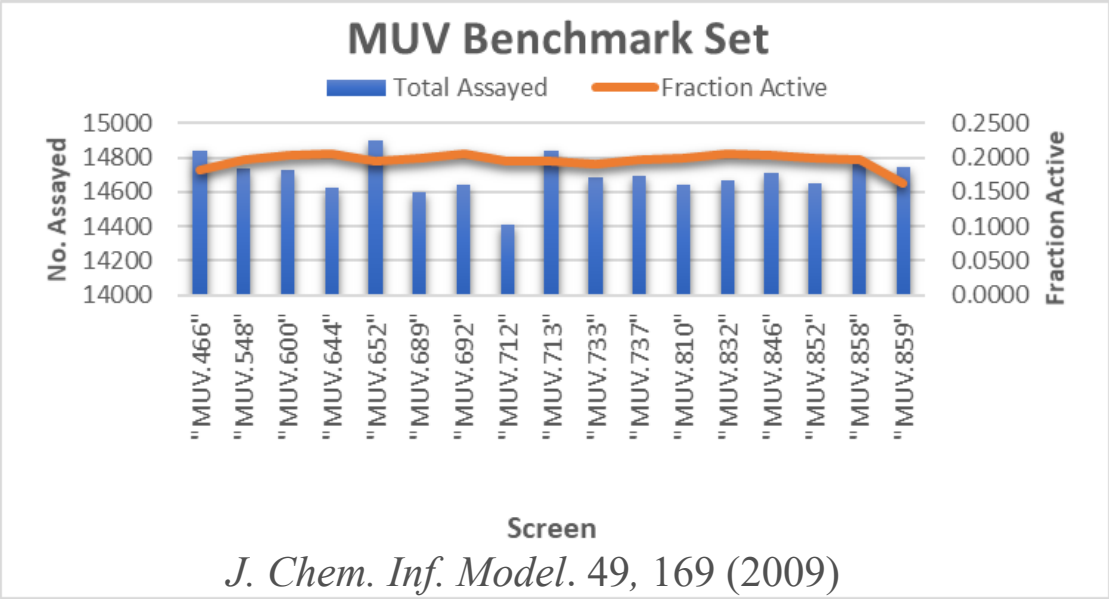
By comparing their active extraction efficiency with other fingerprints

Experiment 2:

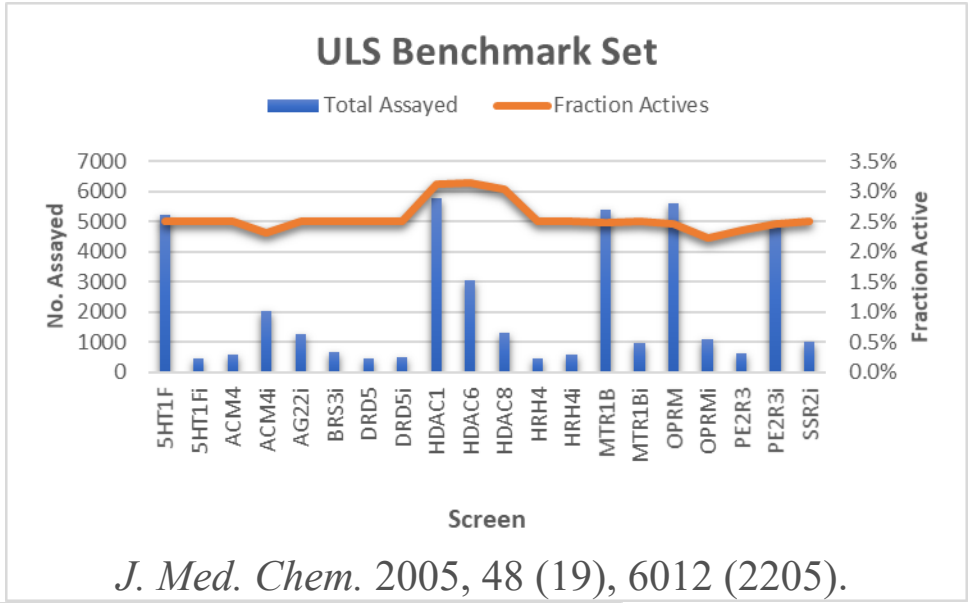
How good and interpretable QSAR models *Saagar* features will yield?

By comparing performance of QSAR models developed with *Saagar* features and with other descriptors.

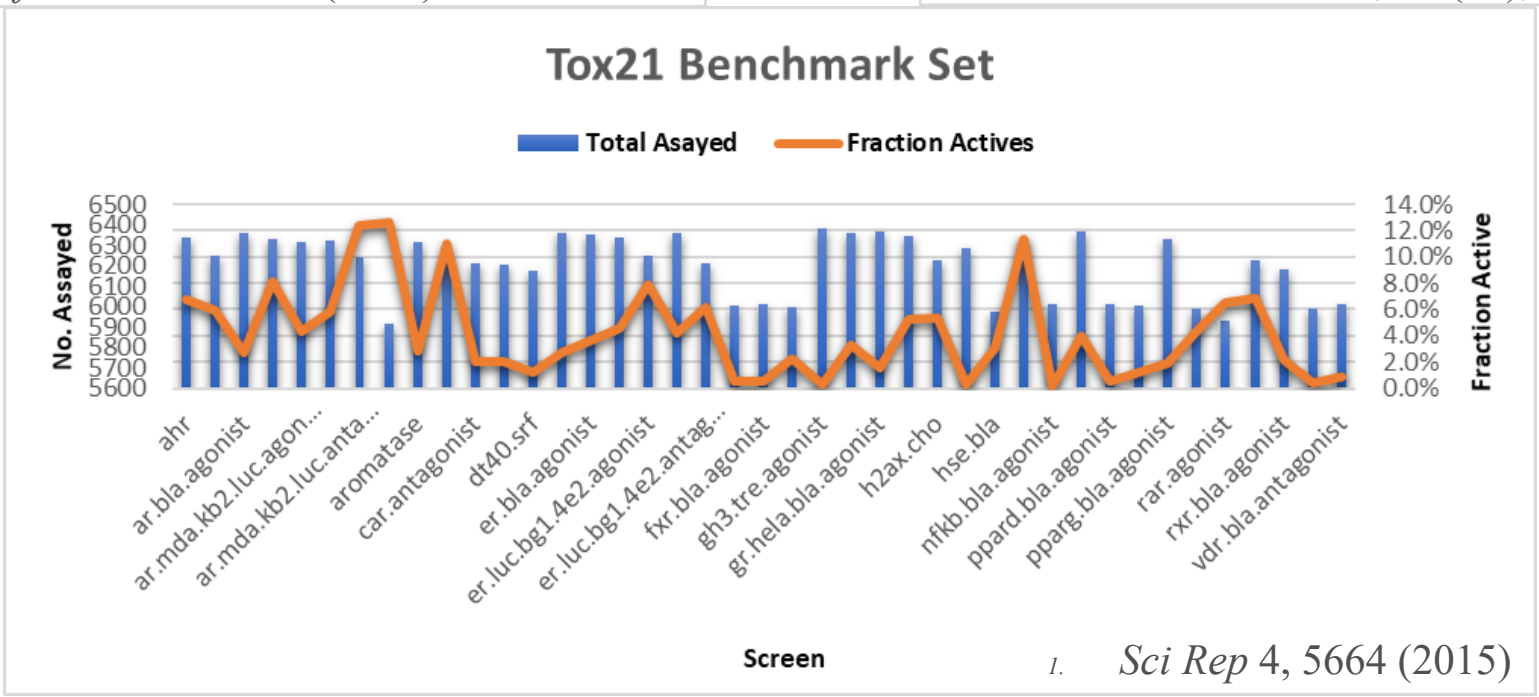
Analogue Extraction with *Saagar* Features



J. Chem. Inf. Model. 49, 169 (2009)

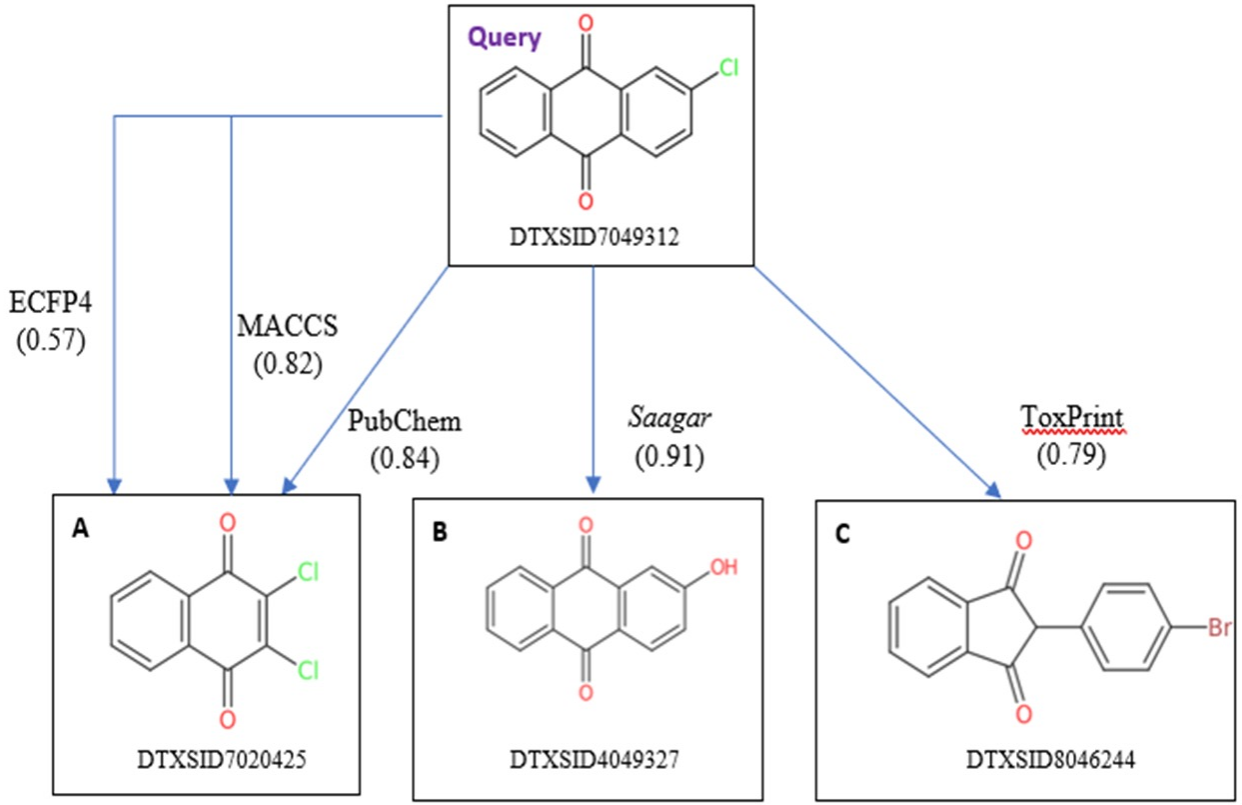


J. Med. Chem. 2005, 48 (19), 6012 (2205).



1. *Sci Rep* 4, 5664 (2015)

Chemistry-aware Analogues and Similarity with *Saagar*

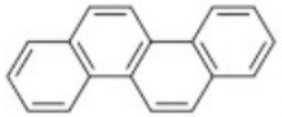


*For more information see www.sciome.com/saagar

Sedykh AY; Shah RR; Kleinstreuer NC; Auerbach SS; Gombar VK (2021). "Saagar-A New, Extensible Set of Molecular Substructures for QSAR/QSPR and Read-Across Predictions." Chemical Research in Toxicology 34(2):634-640

Structure Resolution with *Saagar*

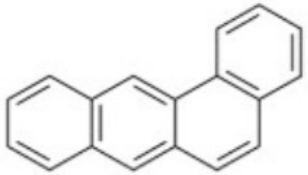
Query



Chrysene
DTXSID:DTXSID0022432
CASRN:218-01-9

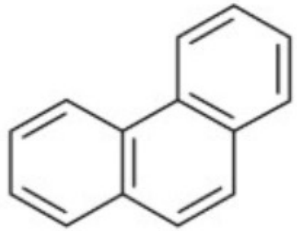
	A	B	C	D	E
ToxPrint	0.50	0.75	0.50	0.60	0.43
ECFP4	0.60	0.86	0.67	0.39	0.67
Pubchem	1.00	0.94	0.97	1.00	0.93
MACCS	1.00	1.00	1.00	1.00	0.88
Saagar	0.98	0.76	0.81	0.88	0.72

A



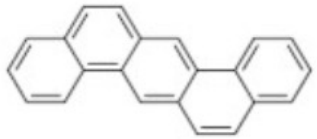
Benz(a)anthracene
DTXSID:DTXSID5023902
CASRN:56-55-3

B



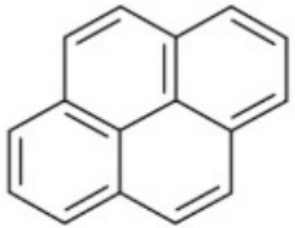
Phenanthrene
DTXSID:DTXSID6024254
CASRN:85-01-8

C



Dibenz(a,h)anthracene
DTXSID:DTXSID9020409
CASRN:53-70-3

D

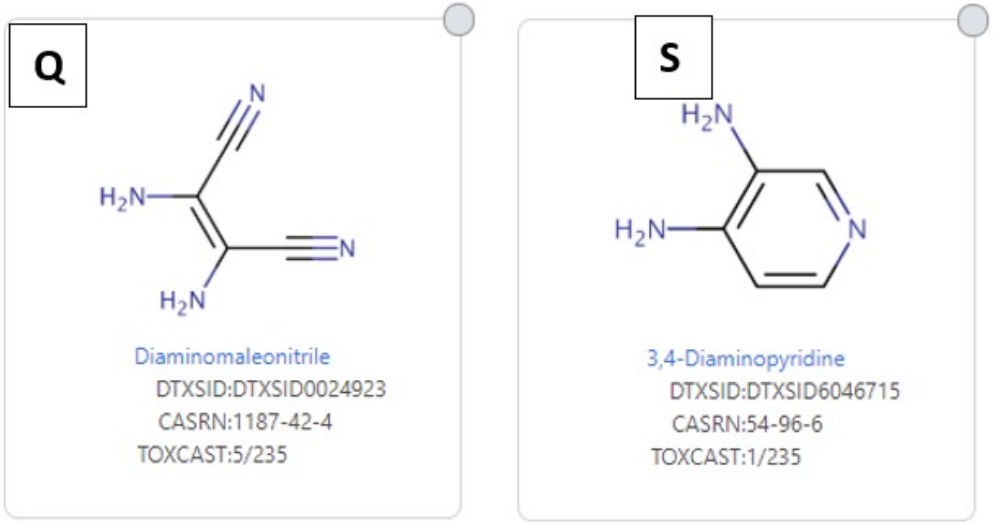


Pyrene
DTXSID:DTXSID3024289
CASRN:129-00-0

E

1-Methyl phenanthrene
DTXSID:DTXSID6025648
CASRN:832-69-9

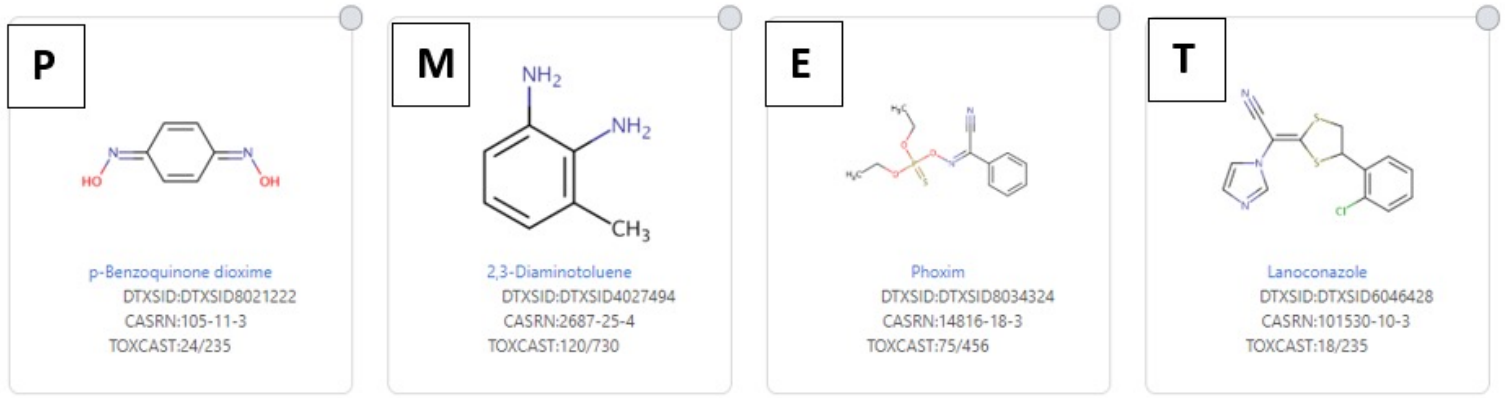
Extensibility of *Saagar*



Fingerprint	Window	Similarity to Query
ToxPrint	T	0.29
ECFP	E	0.12
PubChem	P	0.31
MACCS	M	0.41
Saagar	S	0.33

[N;H2][C;!R]=[C;!R] and/or

N#C[C;!R]=[C;!R].



Saagar Performance vs Mordred in Predictive Models

- Developed predictive models for outcomes in 41 Tox21 Assays using *Saagar* and Mordred

- In 5-fold cross validation test, the average absolute difference in AUROC between *Saagar* and Mordred models was just 0.02

- In a detailed analysis comparing accuracy, NPV, PPV, and AUROC for five representative sets of the 41 Tox21 data sets,

    - *Saagar* performed better than Mordred in 14 of the 20 comparisons,
    - *Saagar* performed as good as Mordred in 3 of the 20 comparisons, and
    - *Saagar* performed a bit inferior to Mordred in 3 of the 20 comparisons.

Saagar descriptors yield models better than or as good as the models using Mordred descriptors – and chemistry-backed reasoning for prediction

Methods to Develop Predictive Models

$$P = f(S)$$

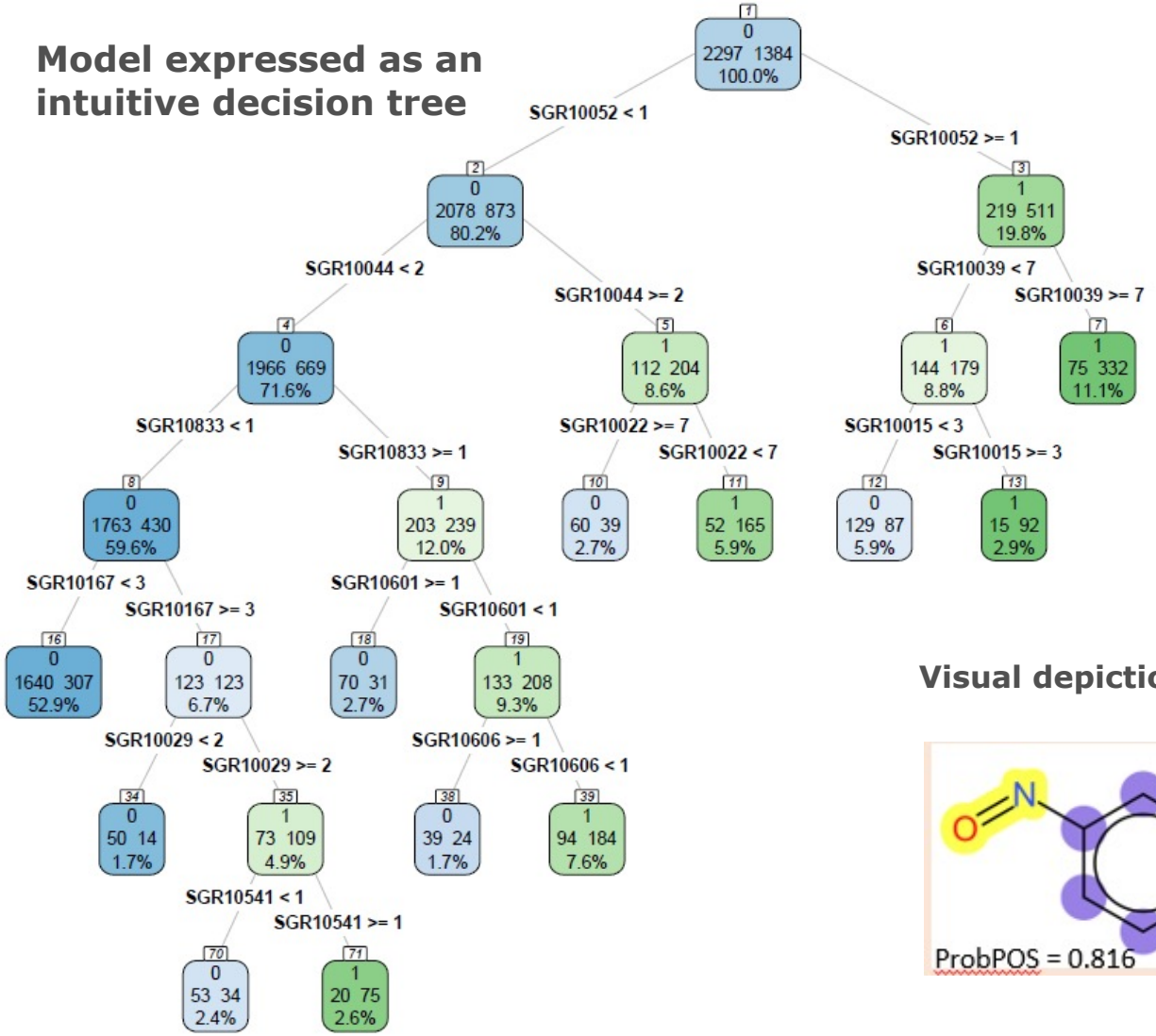
Modeling Methods:

- Regression Analysis
- Linear and Canonical Discriminant Analysis
- Partial Least Squares
- Principal Component Regression
- Nearest Neighbor Analysis
- Neural Networks
- Inductive Logic
- Support Vector Machines
- Recursive Partitioning and Random Forest

QSAR Methods, Giuseppina Gini. In *In Silico Methods for Predicting Drug Toxicity* *Volume 1425 of the series Methods in Molecular Biology* pp 1-20, 17 June 2016

Saagar-RP Model: Ames Test (-S9)

Model expressed as an intuitive decision tree



Model expressed as structure-based rules

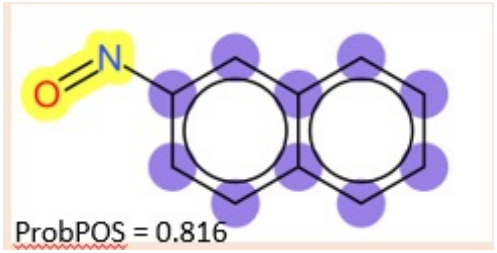
Prob_POS	Rule Hits											R
0.816	407	SGR10052	>=	1	&	SGR10039	>=	7				
0.860	107	SGR10052	>=	1	&	SGR10039	<	7	&	SGR10015	>=	3
0.403	216	SGR10052	>=	1	&	SGR10039	<	7	&	SGR10015	<	3
0.760	217	SGR10052	<	1	&	SGR10044	>=	2	&	SGR10022	<	7
0.394	99	SGR10052	<	1	&	SGR10044	>=	2	&	SGR10022	>=	7

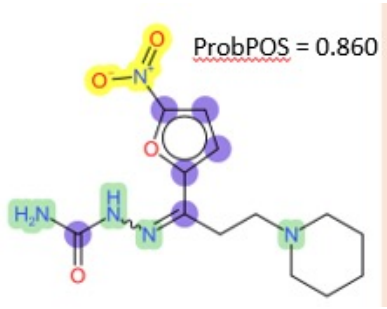
7 more rows

Saagar Code	Hit Freq (3681)	Positive/Negative	Feature Description
SGR10015	2320	972/1348	[#7]
SGR10022	2837	1024/1813	[CX4]
SGR10029	3599	1376/2223	[!#6]
SGR10039	3266	1249/2017	[#6;X3]
SGR10044	325	211/114	[r3,r4]
SGR10052	731	512/219	[OH0]~N

5 more rows

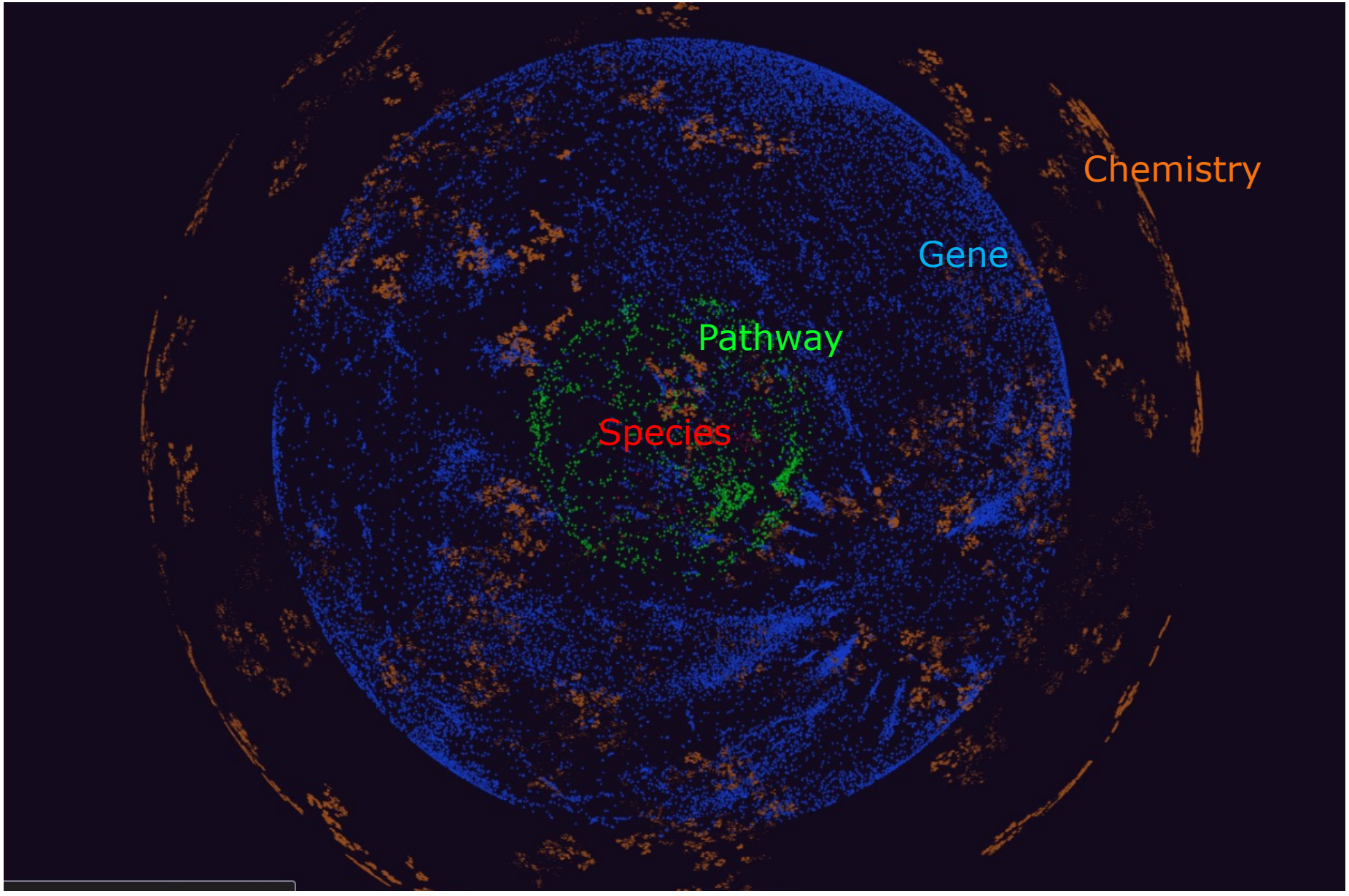
Visual depiction for chemistry-backed reasoning





OrbiTox – An integrated framework for concerted view and connectivity among multi-domain data, predictive models, and cheminformatics tools

OrbiTox Big Data Organization



OrbiTox Content Status

Chemistry Orbit:

~ 900,000 chemical substances (name, structure, DSSTOX ID, macro class, *etc.*)

~ 1,400 chemicals with carcinogenic potency data (CPDB)

~400 chemicals with human carcinogenicity group (IARC)

~ 600 chemicals with sex/species-specific carcinogenicity evidence (NTP Technical Reports)

~4,000 chemicals with bacterial mutagenicity calls (ToxNet)

Gene Orbit

~25,000 annotated human genes:

GO Terms, Synonyms, Name, Chromosome, Location, etc.

Pathway Orbit

~2,000 annotated pathways

Name, Size, Set, DB

~40,000 connections with genes

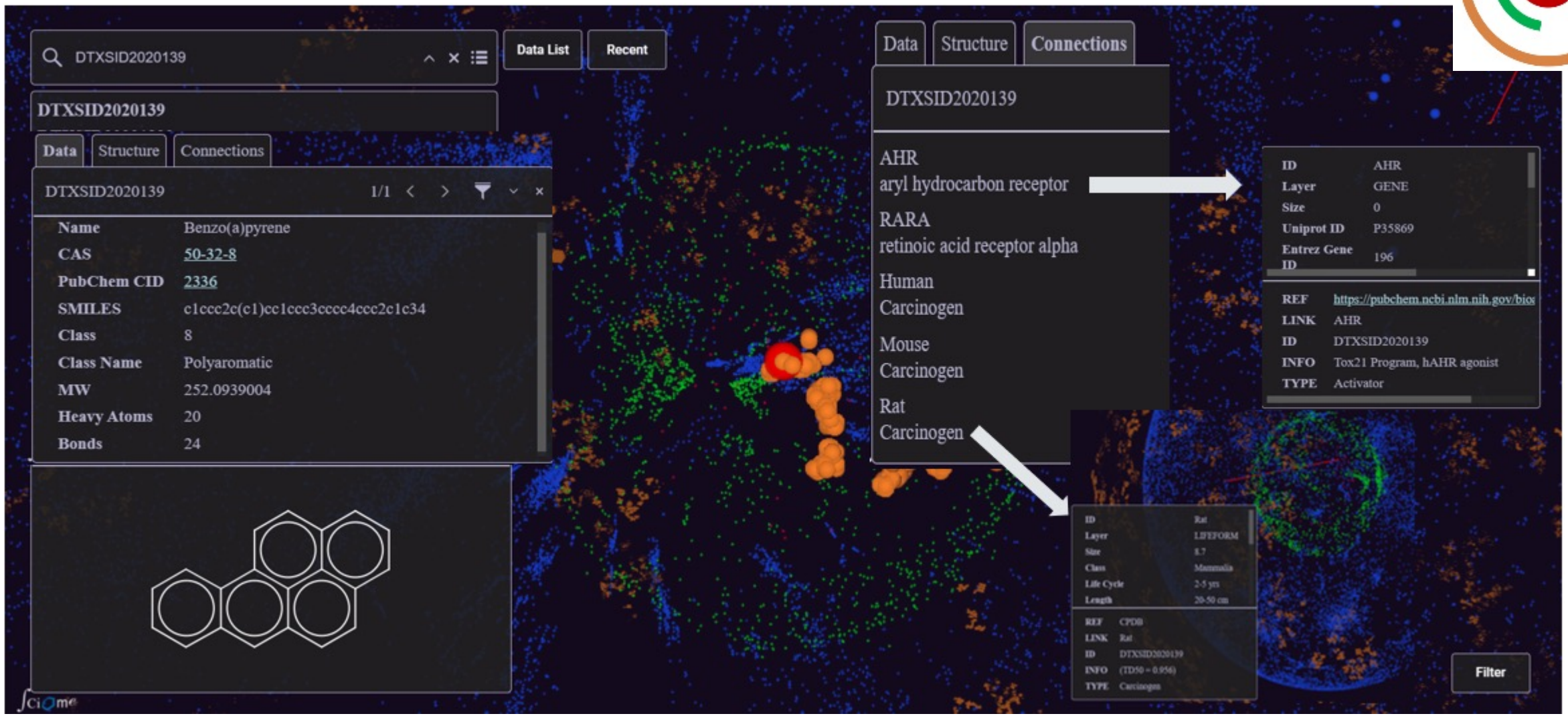
Species Orbit

~200 organisms with life cycle information

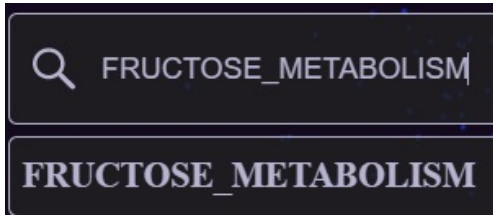
Genus, family, class, genome, life span, weight, *etc.*

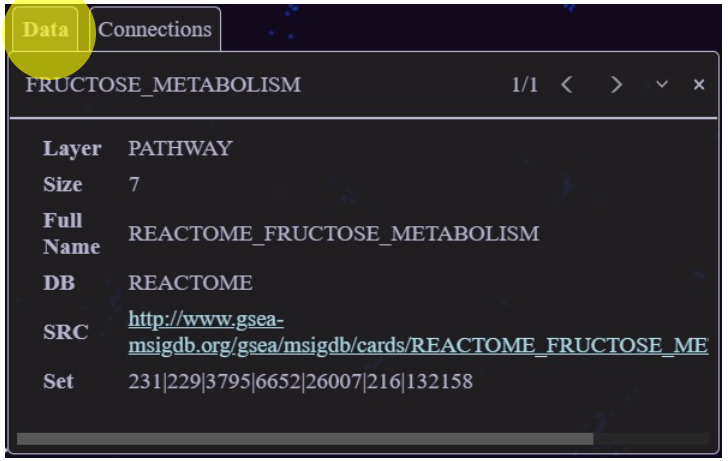
~1,800 Connections with carcinogenicity

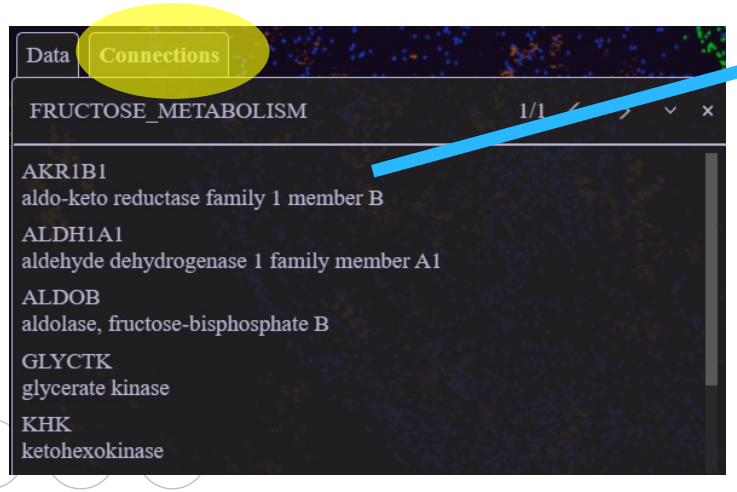
OrbiTox Data Connectivity (Chemical Query)

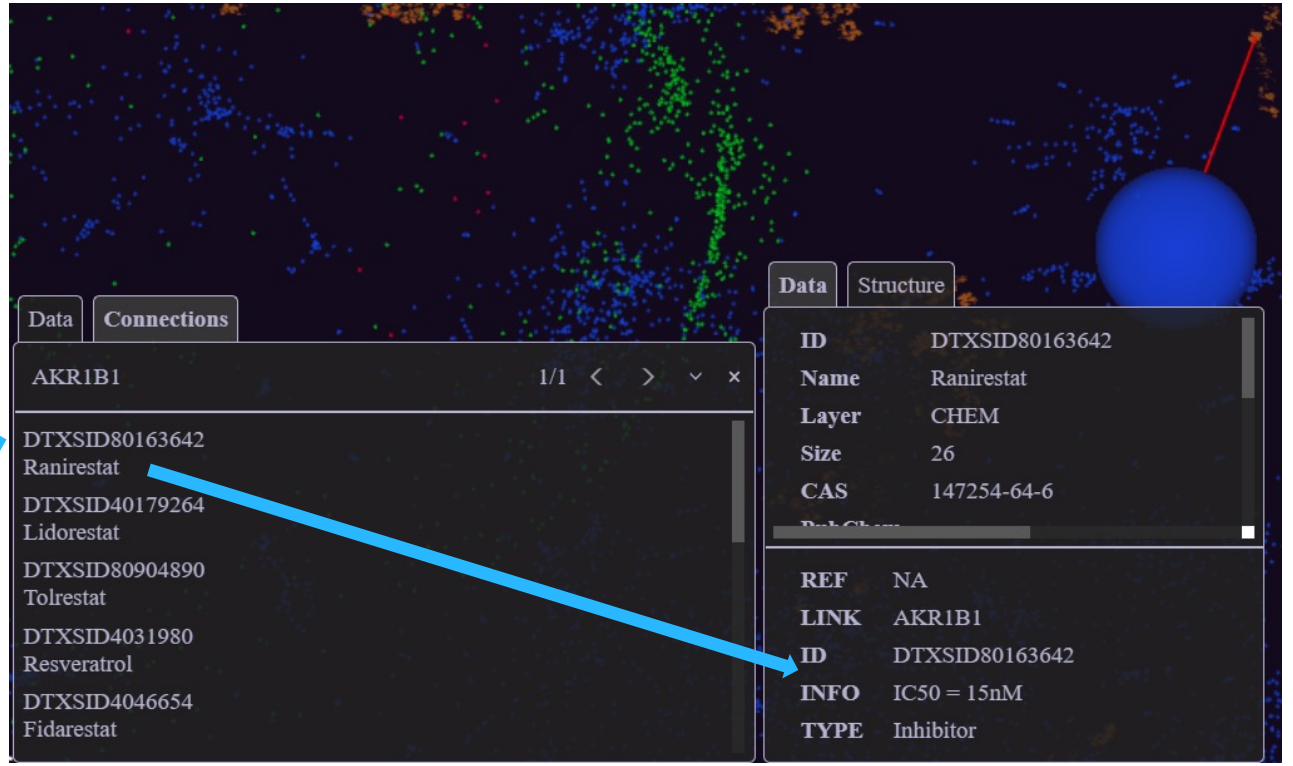


OrbiTox Data Connectivity (Pathway Query)

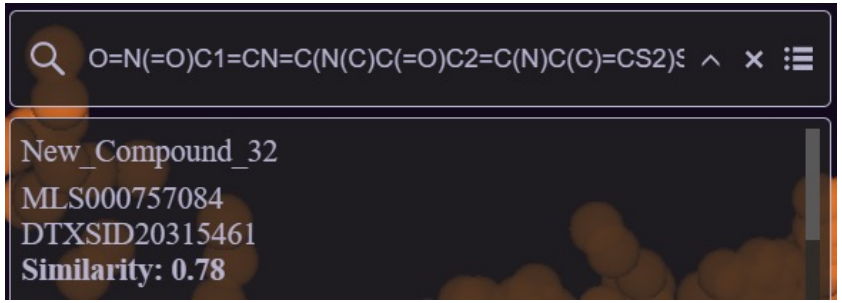


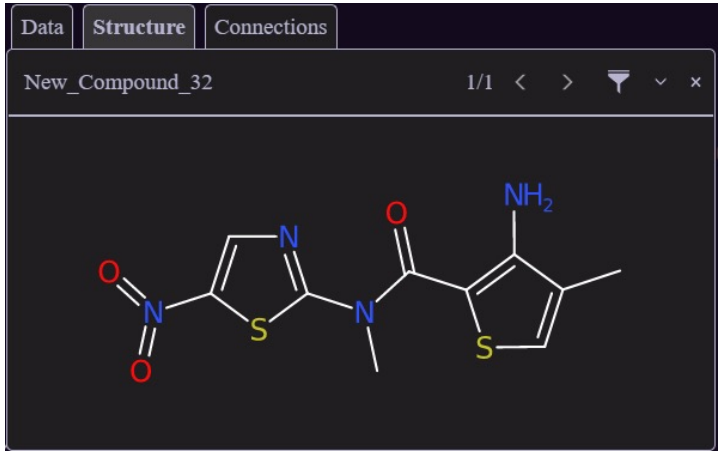


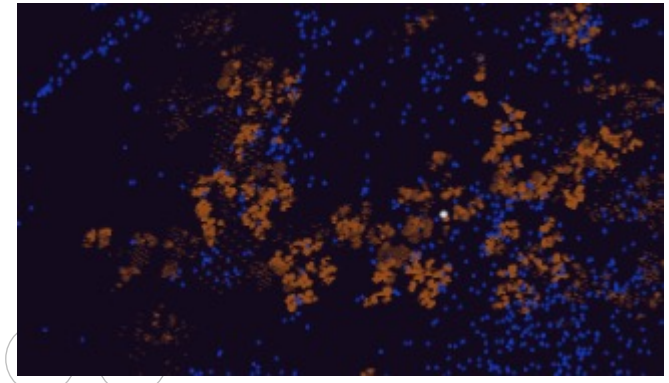


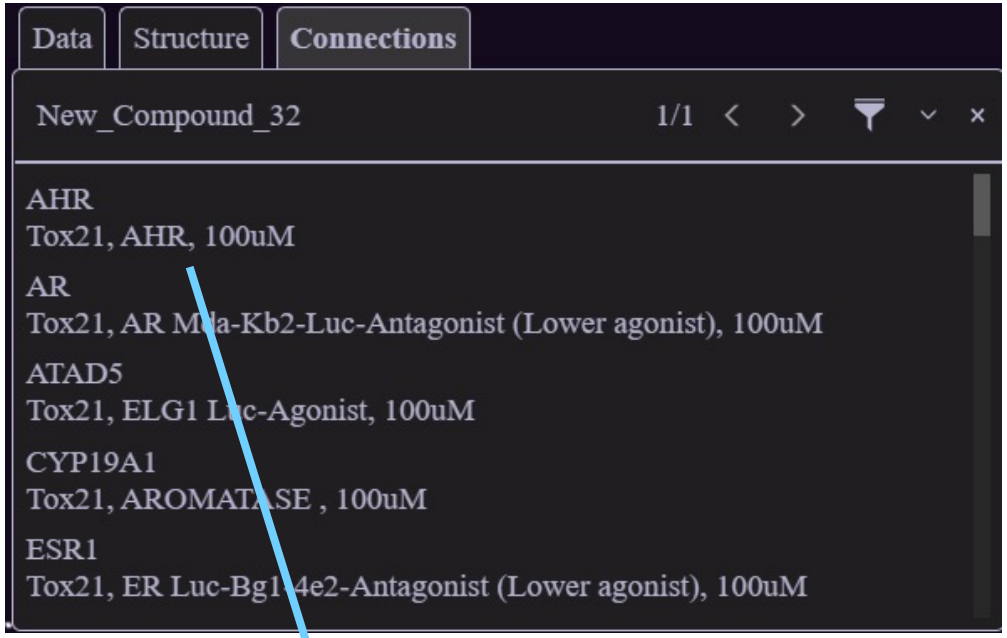


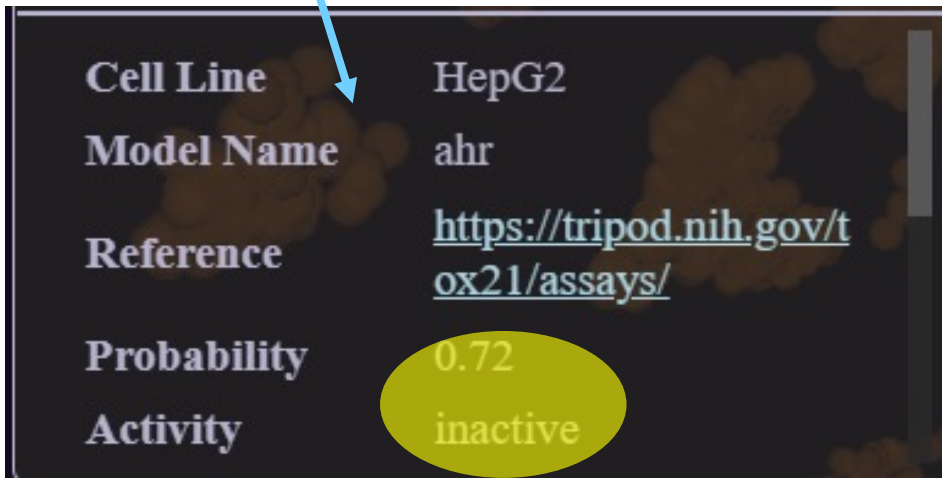
OrbiTox Toxicity Prediction Models











OrbiTox In Action

Austin Ross

Software Developer

Austin.Ross@sciome.com

Sciome

How to access OrbiTox

https://apps.sciome.com/orbitox/

Username:
guest

Password:
guest

Why Develop Predictive Models?

Toxicity Tests for Regulatory Acceptance (OECD)

- Acute Oral, inhalation, and dermal toxicity
- Genotoxicity (*in vitro, in vivo*)
- Reproductive Toxicity
- Developmental Toxicity
- Organ Toxicity (hepato-, cardio-, and nephrotoxicity)
- Skin and eye irritation and skin sensitization
- Carcinogenicity
- Bioaccumulation and biodegradation
- Acute aquatic toxicity (fish, daphnia, algae)

Safety Tests for Chemicals Entering Commerce:

- Industrial chemicals
- Pesticides and Insecticides
- Cosmetics
- Drugs
- Food additives, etc.

TSCA list alone contains 67,385 chemicals

HPV (> 1mil lbs/yr) list has over 2200 chemicals

EU's COSMOS project has 5500 cosmetic ingredients

Why Develop Predictive Models?

Regulatory bodies are requiring it

- The ICH M7 guidelines state: "Two (Q)SAR prediction methodologies that complement each other should be applied. One methodology should be expert rule-based and the second methodology should be statistical-based."

- One of the aims of REACH (**R**egistration, **E**valuation, **A**uthorisation and Restriction of **Ch**emicals) regulations is to: "…Promote alternative methods for the assessment of hazards of substances "

- Fund for the Replacement of Animals in Medical Experiments (FRAME) …to assess the prospects of developing *in vitro*, target organ, and theoretical model systems which would lead to reduction in studies on live animals (3Rs):

- Reduction of the number of animas used, Refinement of the endpoints of animal experiments, Replacement of animals by other techniques

Experimental Assessment is Costly

Estimated External Costs for Representative Nonclinical Safety Studies

Study type	Approximate external costs[a] (U.S. $)			Approximate duration[b] (wk)
	Rats	Dogs	Monkeys	
Single-dose and range-finding				
Single dose	6000–25,000	20,000–50,000	20,000–70,000	10–12
Combined Single and 7-d repeat dose	20,000–80,000	40,000–90,000	80,000–120,000	10–12
Combined single and 10-d repeat dose	35,000–67,000	45,000–75,000	85,000–125,000	10–12
Repeat dose toxicology				
7-d	20,000–35,000	34,000–70,000	55,000–75,000	14–16
14-d	40,000–115,000	90,000–130,000	100,000–190,000	14–16
28-d	70,000–150,000	80,000–195,000	150,000–300,000	16–18
3-mo	110,000–270,000	165,000–200,000	240,000–500,000	30–34
6-mo	215,000–350,000	190,000–300,000	350,000–500,000	40–44
9-mo	275,000–375,000	250,000–500,000	400,000–620,000	52–56
12-mo	320,000–490,000	320,000–470,000	500,000–840,000	68–74
Genetic toxicity				
Ames test		5000–10,000		8–12
In vitro chromosomal aberration assay		10,000–35,000		12–16
In vivo micronucleus test (mice/rats)		10,000–30,000		12–16

Anticancer Drug Development Guide: Preclinical Screening, Clinical Trials, and Approval, Editors: **Teicher**, Beverly A., **Andrews**, Paul A. (Eds.)

Predictive Models:
For Increased Efficiency and Saving Animal Lives

Cost in $:

Cost/cmpd of typical HT ADME assays: ~$250, 20min
Number of compounds assayed/year: 12000
Cost/year: $3,000,000

If we could eliminate just ~15% assays, i.e., assays for 1800 compounds

Savings: 600 hrs of screening time, ~ $450,000

Cost in animal sacrifice:

According to the Humane Society of the United States:

In total, an estimated 25 million animals are used annually in research, testing, and education in the United States (over 1 million un-bred, mainly for toxicity evaluation)

Conclusions

- In silico experiments are experiments too.
- In silico models or computational instruments save, time, money, and animal lives.
- Tools like EPA's CompTox Chemicals Dashboard, ICE, OPERA, and **OrbiTox** are great resources for bioassay data and predictive models.
- *Saagar* set is an extensible, endpoint-agnostic set of substructures for cheminformatics applications.
- In an elaborate benchmark study, *Saagar* performed better than commonly used fingerprints in extracting analogues for read-across studies.
- **OrbiTox** is one-of-a-kind interactive, translational discovery platform that gives concerted view of large amounts of multi-domain data, connectivity among data, and predictive models.
- Predictive models in **OrbiTox** provide chemistry-backed reasoning for every prediction.
- **OrbiTox** is extensible to add proprietary data, custom models, and new data domains.

Thank you for joining us !

This concludes the Big Data in Environmental Science and Toxicology series

But on-line data science training continues on . . .

https://training.tamids.tamu.edu/