

Introduction to Computational Tools

SACATM Meeting

September 2-3, 2020





Computational Toxicology Tools

- Computational tools and resources play a critical role in chemical evaluations such as:
 - Data aggregation
 - Exploring chemical properties
 - In vitro to in vivo extrapolation
 - Mapping high-content data to biological systems
 - Generating predicted values



Integrated
Chemical
Environment





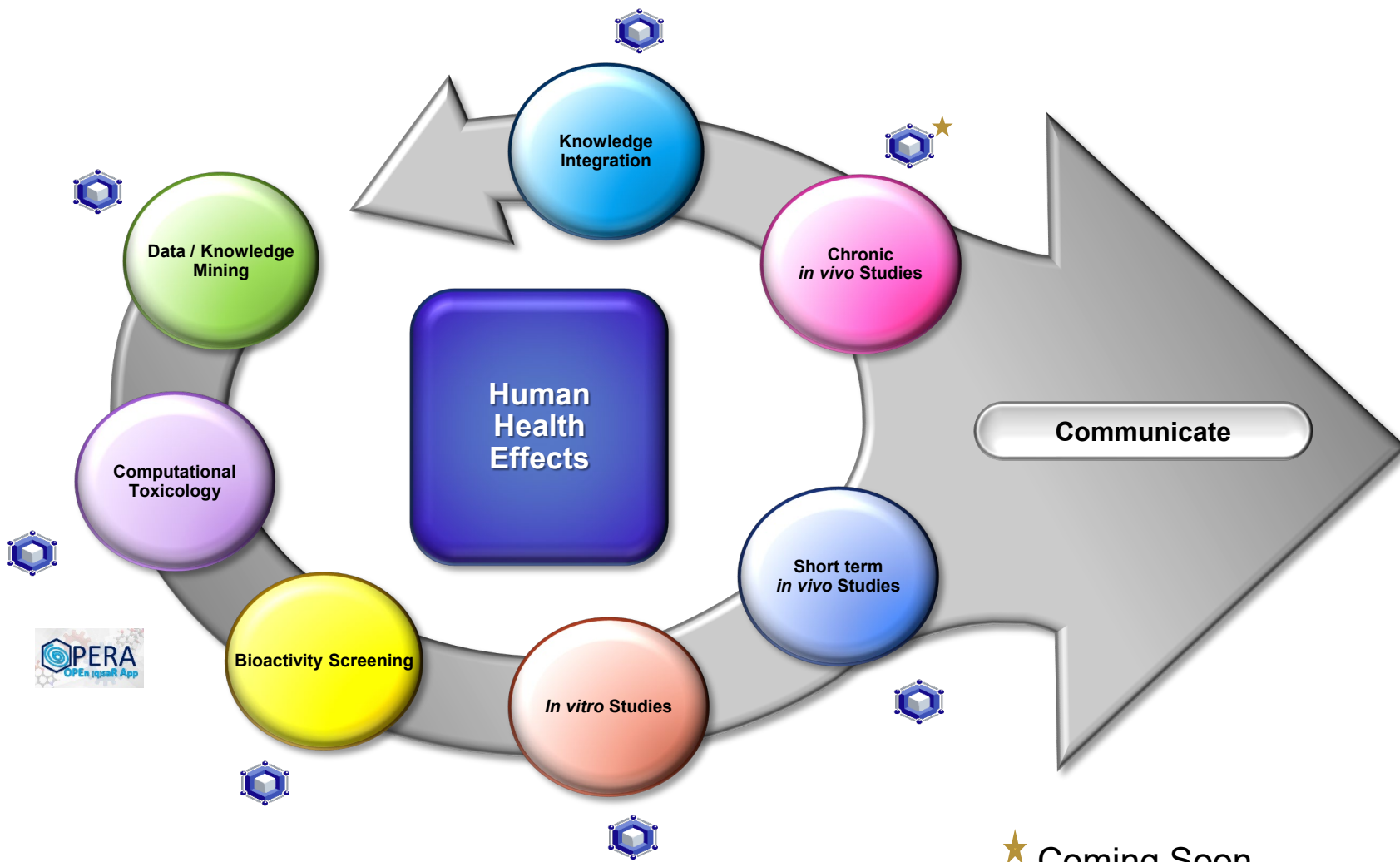
Feedback from SACATM 2019

- Increase accessibility, transparency, and utility of datasets
- Allow users to upload their own data to IVIVE workflow
- Increase documentation for tools, data, and search function
- Form ICE Advisory Group to provide timely feedback on:
 - new features/needs to serve ICCVAM, NICEATM and NTP stakeholders
 - the usability of ICE UI and tools
 - proposed changes to functionality or the user interface
- Increase chemical structural support for both input and output
- Curate and integrate human data and engage biomedical research community
- Engage with CROs to generate data on environmental chemicals



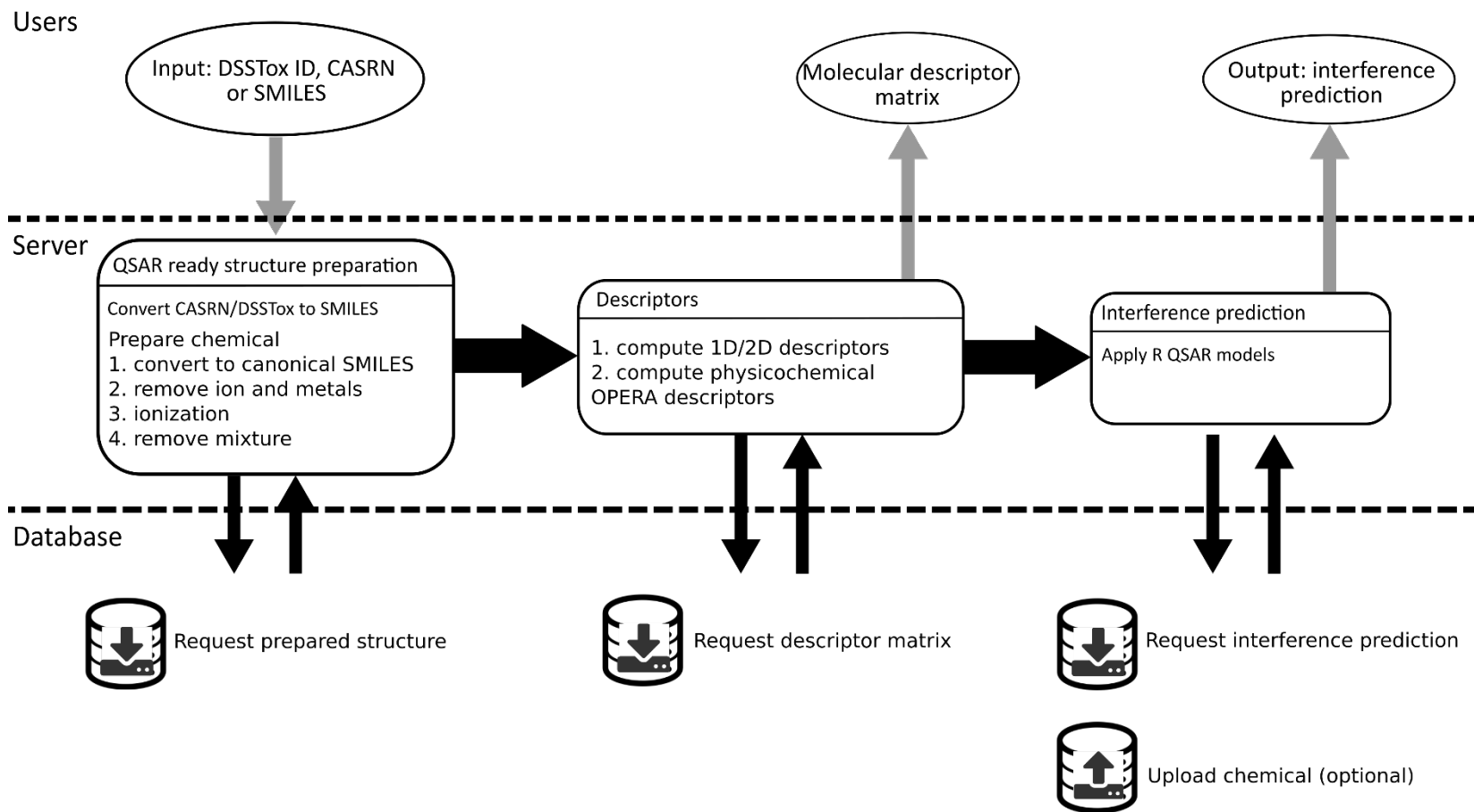


NTP Translational Toxicology Pipeline





InterPred: Assay Interference Prediction

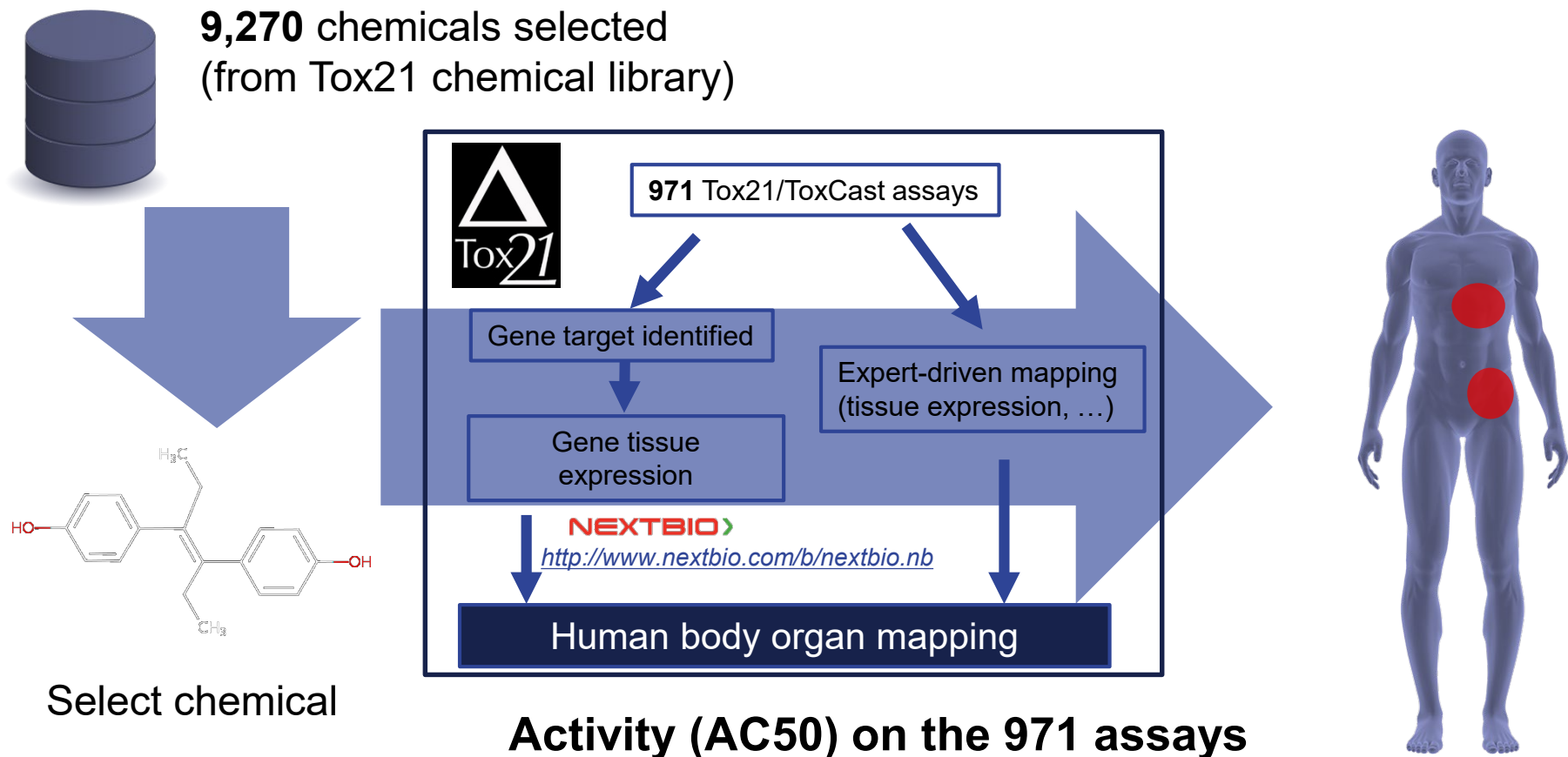


<https://sandbox.ntp.niehs.nih.gov/interferences/>



Tox21 BodyMap: Hypothesis Generation

- Knowledge-mapping exercise to visualize where a chemical may produce effects in the body

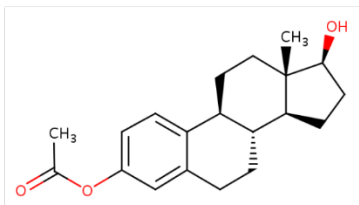


<https://sandbox.ntp.niehs.nih.gov/bodymap/>



Tox21 BodyMap: Hypothesis Generation

Chemical information



CASRN: 4245-41-4

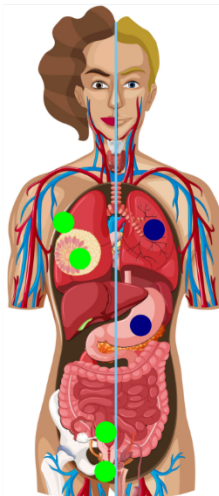
Name: Estradiol acetate

DSSTOX ID: DTXSID7045867

SMILES: CC(=O)OC1=CC=C2[C@H]3CC[C@]4(C)[C@@H](O)CC[C@H]4[C@@H]3CCC2=C1

[C@@H](O)CC[C@H]4[C@@H]3CCC2=C1

Body mapping



AC50 cutoff: 20 μ M

Tissue expression threshold: 10*folds control

List of organ: Uterus; Vagina;

Peritoneum; Mammary gland;

Immune System; Stomach; Lung

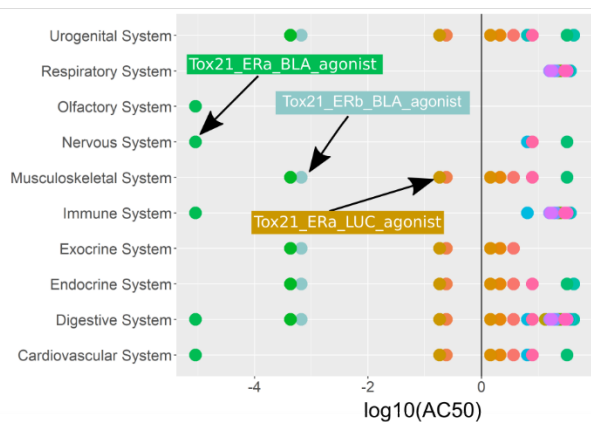
Immune System; Stomach; Lung

● mapped using assay gene target

● mapped using assay tissue

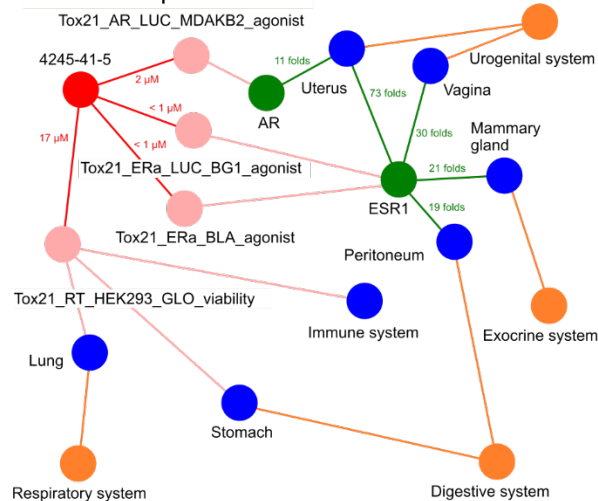
Input: Chemical name or CASRN, set assay activity and gene expression thresholds

Assay mapping



Visualisation of the log₁₀(AC₅₀) by assay grouped by organ system.

Network representation



Output: visualization including body mapping, assay mapping and a results network



ChemMaps: Visualizing the Chemical Universe

<https://sandbox.ntp.niehs.nih.gov/chemmaps/>



National Toxicology Program
U.S. Department of Health and Human Services

[Calendar & Events](#) | [News & Media](#) | [Get Involved](#) | [Support](#)

SEARCH

[ChemMaps.com](#) [DrugMap](#) [DSSToxMap](#) [Tox21Map](#) [PFASMap](#) [Help](#)

ChemMaps.com (v2.0)

ChemMaps.com is a webserver developed to navigate in the chemical space. In the version 1 the navigation was limited to the DrugBank database. Now with the version 2. It is available for the drug space and for extended universe in the environmental chemical space.

ChemMaps.com is a collaboration work between the National Institute of Health and the Fourches' lab in North Carolina State University.

Please cite: [A. Borrel, N. C. Kleinstreuer, & D. Fourches. \(2018\) Exploring drug space with ChemMaps.com. Bioinformatics, \(1\), 1-3.](#)

Available maps

The current version allows user to navigate in drug space (DrugMap) as well in three maps to navigate in the environmental chemicals space built from the *DSSTox database*.

DrugMap

Drugbank Version 5.1.2,
release 2018-12-20
~12,000 entries

DSSToxMap

DSSTox Release 2019-3-09
> 800,000 entries

Tox21Map

Tox21 included in the DSSTox
database
~ 9,000 entries

PFASMap

PFAS included in the DSSTox
database
~ 5,000 entries

Visualization

ChemMaps.com allows user to navigate in the space using different navigation tools.

[Navigate in a 3D space](#)

[Select chemicals on the fly](#)

[Explore neighborhood](#)

[Draw chemicals](#)



ChemMaps: Visualizing the Chemical Universe



National Toxicology Program
U.S. Department of Health and Human Services

Calendar & Events | News & Media | Get Involved | Support

Search the NTP Website

SEARCH

ChemMaps.com DrugMap DSSToxMap Tox21Map **PFASMap** Help

Generate the PFASMap

Select up to 5 features you would like put on the map:

Chemical classification

- EPA category
- LD50 (mg/kg)

Toxicology prediction

- Acute Tox (very toxic)
- Acute Tox (no toxic)
- Acute Tox (EPA)
- Acute Tox (GHS)
- Acute Tox (LD50)
- Estrogen Receptor activity (Agonist)
- Estrogen Receptor activity (binding)
- Hepatic clearance

- Androgen Receptor Activity (Antagonist)
- Androgen Receptor Activity (binding)

Physicochemical prediction

- Plasma fraction unbound
- Henry's Law constant (atm-mol3/mole)
- KM (biotransformation rate)
- Log Octanol/air partition coefficient
- Log Soil adsorption coefficient (L/Kg)
- Log Fish bioconcentration factor
- LogD
- LogP

- Melting Point (C)
- Pka acid
- Pka basic
- Biodegradability
- HPLC retention time
- Log vapor pressure (mmHg)
- Log Water solubility
- Log Atmospheric constant (cm3/molsec)
- Biodegradation half-life
- Boiling Point

Descriptors

- MW
- Lipinski Failures

Generate PFASMap

Optional - Upload your list of chemicals (< 100 chemicals)

- Choose up to 5 properties to put on the map
 - Toxicity values/predictions
 - Physicochemical properties



ChemMaps: Visualizing the Chemical Universe

National Toxicology Program
U.S. Department of Health and Human Services

Search bar, using DTXSID

Panel to manage the view
(color, axes, ...)

Interactive information panel

ChemMaps.com

Hide Chemicals
Colors by
Axes
Set a pivot point
Reset view
Reset map
Help
Close Controls

Compound ID: **DTXSID3047558**
GHS category: 5
EPA category:
LD50 (mg/kg): 0
Acute Tox (very toxic): 0
LogP: 4.3
MW: 432

Connect 1
Extract 1
Draw chemical
Download neighbors

- Chemicals are represented using a planet (default) or a star (based on tox/property information)



ChemMaps: Project New Chemicals

Optional - Upload your list of chemicals (< 100 chemicals)

From a list including SMILES, DrugBankID, DTXSID or CAS (not recommended):

Content:

```
DTXSID60200549
NC(=O)C1(CCN(CCC(C#N)(C2C=CC=CC=2)C2C=CC=CC=2)CC1)N1CCCCC1
CCCCNC1CCCCC1
CCOP(=S)(OC1C=CC(=CC=1)[N+][O-])=O)OCC
CC(N)CC(C)(C)N
.alpha.
1135-66-6
111-14-8
```

Upload SMILES, CASRN or DTXSID

Submit chemicals

From a file:

Choose File No file chosen

Upload list of chemicals

Example of input: [Test input](#)



ChemMaps: Project New Chemicals



National Toxicology Program
U.S. Department of Health and Human Services

Calendar & Events | News & Media | Get Involved | Support

Search the NTP Website

SEARCH

ChemMaps.com DrugMap DSSToxMap Tox21Map **PFASMap** Help

Descriptor computation

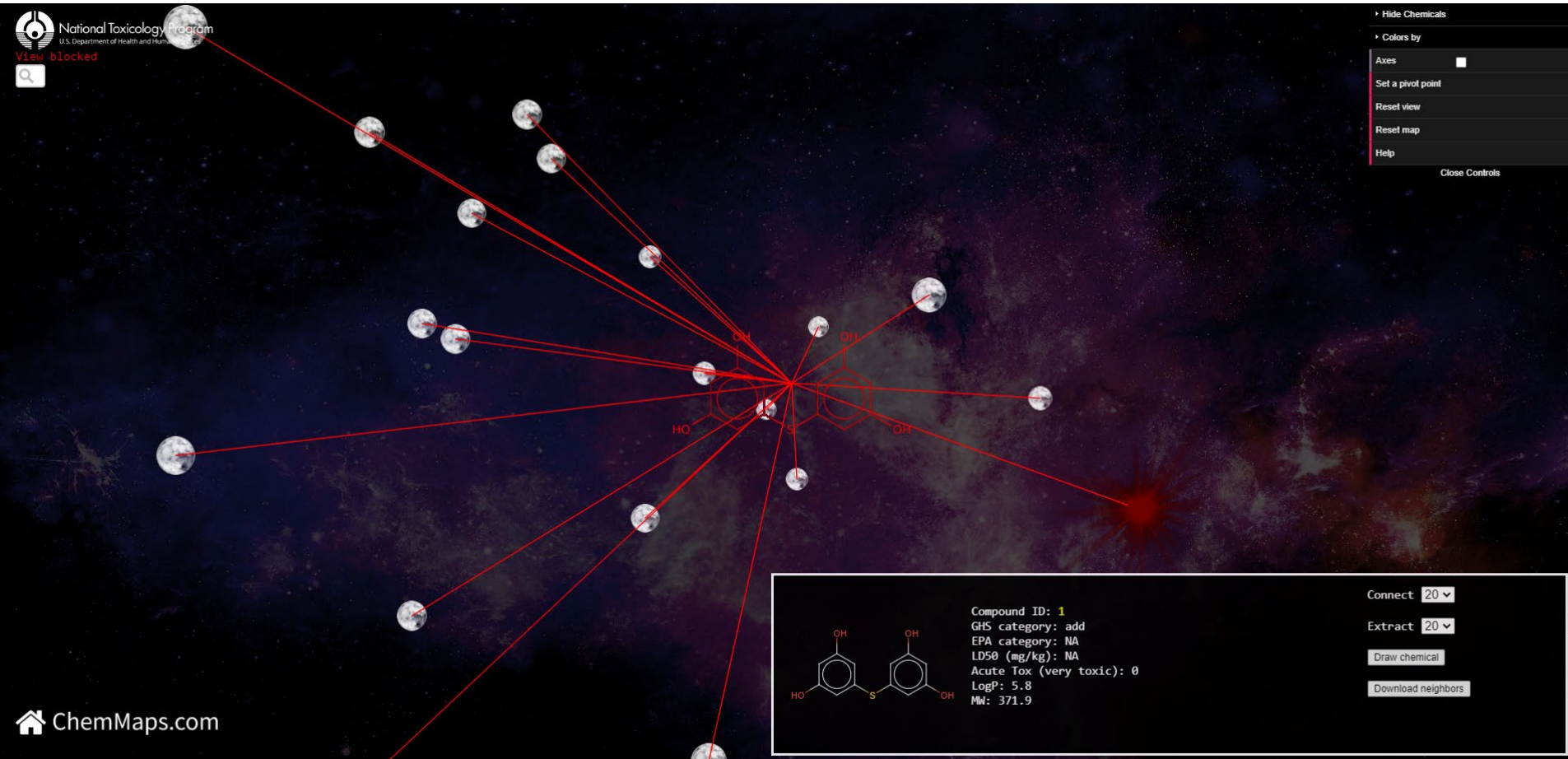
Inputs		QSAR-ready SMILES		Descriptor	
ID	Input	ID	SMILES	ID	Descriptor
1	DTXSID60200549	1	<chem>Oc1cc(O)cc(Sc2cc(O)cc(O)c2)c1</chem> ✓	1	OK ✓
2	<chem>NC(=O)C1(CCN(CCC(C#N)(C2C=CC=CC=2)C2C=CC=CC=2)CC1)N1CCCCC1</chem>	2	<chem>N#CC(CCN1CCC(C(N)=O)(N2CCCCC2)CC1)(c1ccccc1)c1ccccc1</chem> ✓	2	OK ✓
3	<chem>CCCCNC1CCCCC1</chem>	3	<chem>CCCCNC1CCCCC1</chem> ✓	3	OK ✓
4	<chem>CCOP(=S)(OC1C=CC(=CC=1)[N+](=[O-])=O)OCC</chem>	4	<chem>CCOP(=S)(OCC)Oc1ccc([N+](=O)[O-])cc1</chem> ✓	4	OK ✓
5	<chem>CC(N)CC(C)(C)N</chem>	5	<chem>CC(N)CC(C)(C)N</chem> ✓	5	OK ✓
6	.alpha.	6	0 ✗	6	Error ✗
7	1135-66-6	7	<chem>CC1(C)C2=CCCC(C)(C)[C@]23CC(C@H)1C3</chem> ✓	7	OK ✓
8	111-14-8	8	<chem>CCCCCCC(=O)O</chem> ✓	8	OK ✓

[Download 2D descriptor table](#)
[Download 3D descriptor table](#)

- Automated structure preparation
 - Clean structures
 - Prepare SMILES in QSAR ready form
 - Compute descriptors (downloadable)



ChemMaps: Project New Chemicals



- Analyze new chemical neighborhood



ChemMaps: Project New Chemicals

National Toxicology Program
U.S. Department of Health and Human Services

Project chemical structures

Hide Chemicals

- Classified
- No classified
- Added chemicals
- Draw structures

Colors by

Axes

Set a pivot point

Reset view

Reset map

Help

Close Controls

Compound ID: 1
GHS category: add
EPA category: NA
LD50 (mg/kg): NA
Acute Tox (very toxic): 0
LogP: 5.8
MW: 371.9

Connect: 20
Extract: 20
Draw chemical
Download neighbors

ChemMaps.com

- Analyze new chemical neighborhood