National Institute of Environmental Health Sciences
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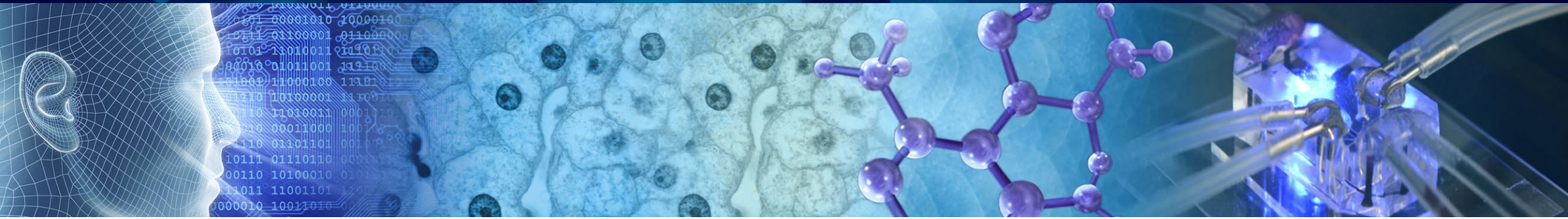


Open-access Data and Computational Tools to Investigate Chemical Bioactivity

12th ASCCT Annual Meeting
2023-10-25

Aswani Unnikrishnan, Victoria Hull, Alexandre Borrel, Kim T To, James T Auman

Inotiv, contractor's supporting NICEATM

Disclaimer: Inotiv staff provide technical support for NICEATM,
but do not represent NIEHS, NTP, DTT, or the official positions of any federal agency.

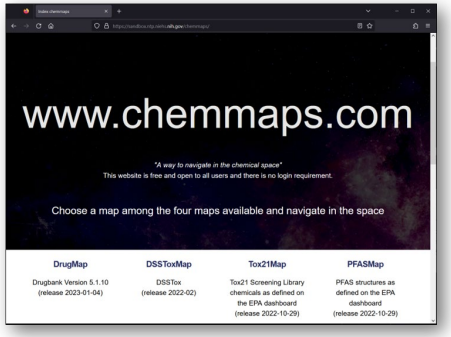
Session Objectives

- Gain an understanding of the data within ICE and how to use ICE tools for data interpretation and exploration.

Integrated Chemical Environment

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

- Discover the utility of ChemMaps.com for supporting read-across analysis, risk assessment, and the exploration of unknown chemicals.



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

- Understand the purpose and functionality of the DASS App.

https://ntp.niehs.nih.gov/go/952311

Session Agenda

1. **First Presentation: (30 mins)**
   - Title: Overview of NICEATM's Integrated Chemical Environment (ICE) with detailed insight into its Search and structural similarity prediction tools.
   - Speaker: Aswani Unnikrishnan
2. **Second Presentation**: **(30 mins)**
   - Title: Using the Integrated Chemical Environment (ICE) to access interoperable computational tools and inform chemical hazard.
   - Speaker: Victoria Hull
3. **ICE Q & A (10 mins)**
4. **Recess: (10 mins)**
5. **Third Presentation: (30 mins)**
   - Title 1: ChemMaps.com v2.0 – Exploring the Environmental Chemical Universe
   - Title 2: DASS App: A Web Application for Applying Defined Approaches for Skin Sensitization to Predict Hazard and Potency Categorization.
   - Speaker: Kim To
6. **ChemMaps & Dass App Q & A (5 mins)**

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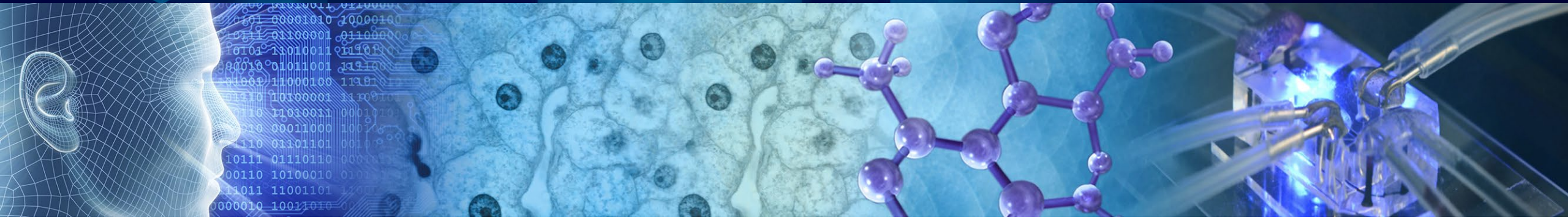

Overview of NICEATM's Integrated Chemical Environment (ICE) with detailed insight into its Search and structural similarity prediction tools

12th ASCCT Annual Meeting
2023-10-25

Presented by Aswani Unnikrishnan, Inotiv, contractor supporting NICEATM
ICE-support@niehs-nih.gov

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but do not represent NIEHS, NTP, DTT, or the official positions of any federal agency.

Agenda

1. Introduction to ICE
2. ICE Data
   - In Vivo and In Vitro
   - In Silico Models/Integrated Approaches
     - OPERA Predictions in ICE
3. ICE Chemical Quick Lists
4. Accessing ICE Data
5. Accessing ICE Tools
6. ICE Tools Workflow
7. **Demo** – ICE Walkthrough
8. Search Tool Overview
9. **Demo** – Search Tool
10. Search Tool Summary
11. Chemical Quest Tool Overview
12. **Demo** – Chemical Quest Tool
13. Chemical Quest Tool Summary

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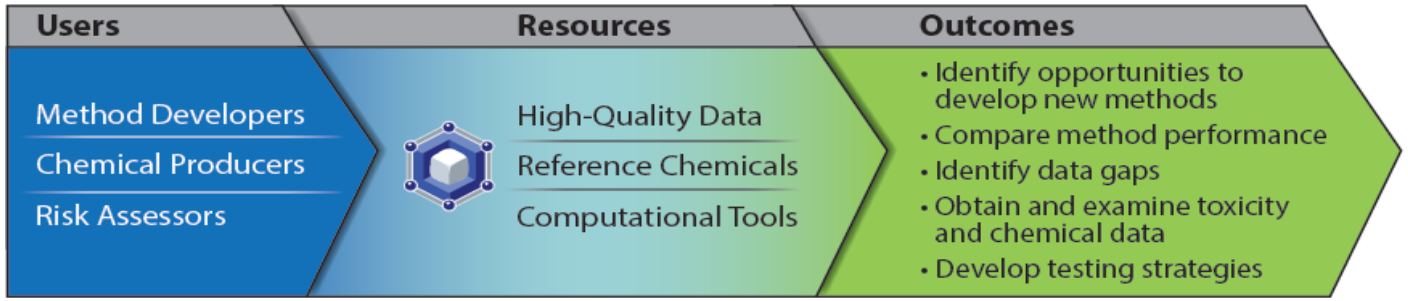
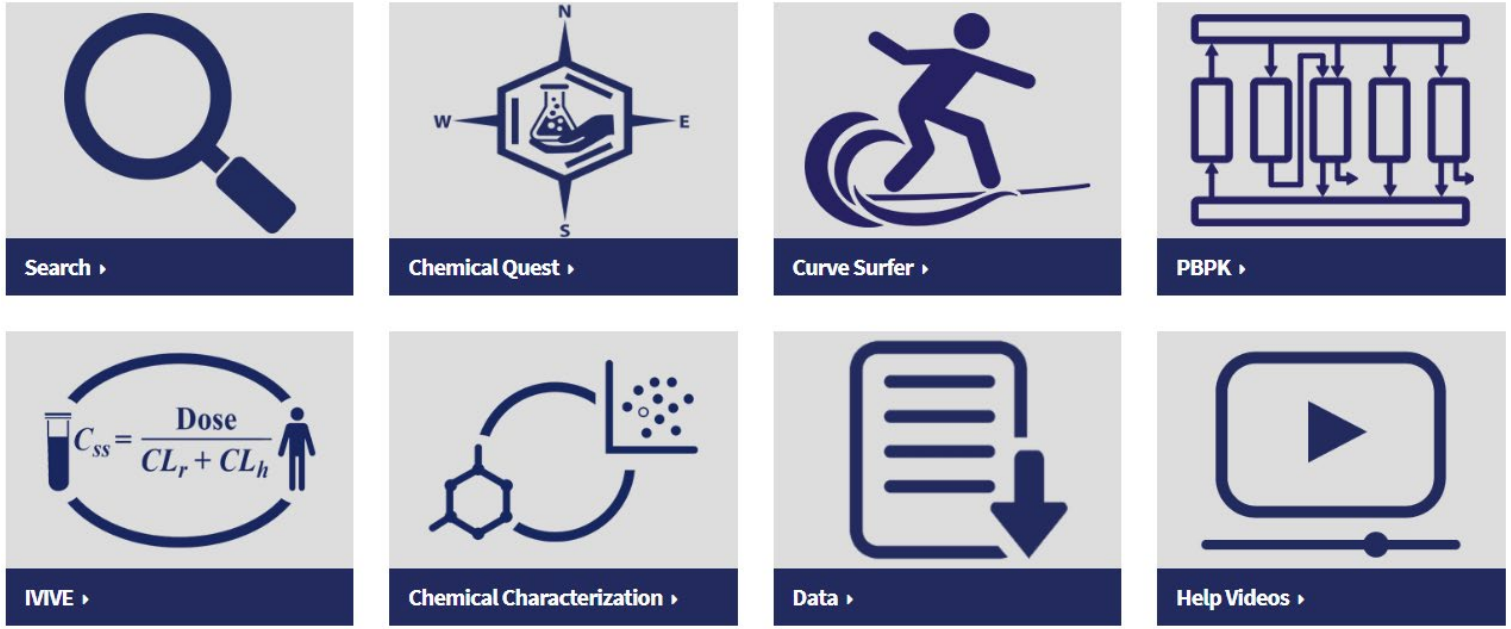
ICE: Integrated Chemical Environment

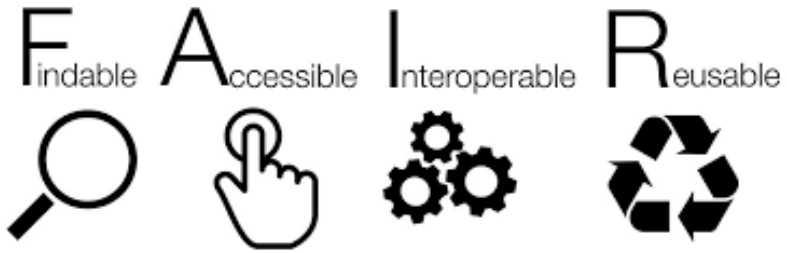
Integrated Chemical Environment



Releases in 2023:

ICE v4.0 (March)
ICE v4.0.1 (August)





Bell et al. 2017 EHP
Bell et al. 2020 Tox In Vitro
Abedini et al. 2021 Comp Tox
Daniel et al. 2022 Front Toxicol

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

ICE: Site Visits January 2023 – October 2023

Duration	Users	New Users
January 2023 – October 2023	3,342	706

Users From Around The World

AMERICAS (1,365)

EUROPE (1,035)

ASIA (847)

AFRICA (47)

Data organized by Toxicity Endpoint (TE) based on outcomes of regulatory concern.

Toxicity Endpoints
Chemical Parameters
ADME Parameters
Acute Toxicity
Cancer
DART

Toxicity Endpoints
Skin Sensitization
Skin Irritation
Eye Irritation
Endocrine
cHTS
Exposure

Example: cHTS data sourced from US Federal Tox21 and ToxCast, EPA's InvitroDB pipeline and annotated using controlled vocabularies.

			MOA		TE		MT			
	A	B	C	D	E	F	G	H	I	
1	AssayEndpointName	Assay_MOA	ModeofAction	MOA_ToxicityEndpoint	ToxicityEndpoint	Assay_MechanisticTarget	MechanisticTarget	MT_NCIm_term	MT_NCIm_term_ID	
2	APR_HepG2_MicrotubuleCSK_1h_dn	mayInformOn	AcuteTox - Cytotoxicity	mayContributeTo	Acute Lethality	throughMechanisticTarget	Cell Morphology	Cell Viability Process	CUI:C1516362	
3	APR_HepG2_MicrotubuleCSK_1h_up	mayInformOn	AcuteTox - Cytotoxicity	mayContributeTo	Acute Lethality	throughMechanisticTarget	Cell Morphology	Cell Viability Process	CUI:C1516362	
4	APR_HepG2_MitoMass_1h_dn	mayInformOn	AcuteTox - Energy Metabolism Process	mayContributeTo	Acute Lethality	throughMechanisticTarget	Mitochondrial Function	Energy Metabolism Process	CUI:C0014272	
5	APR_HepG2_MitoMass_1h_up	mayInformOn	AcuteTox - Energy Metabolism Process	mayContributeTo	Acute Lethality	throughMechanisticTarget	Mitochondrial Function	Energy Metabolism Process	CUI:C0014272	
6	APR_HepG2_MitoMembPot_1h_dn	mayInformOn	AcuteTox - Energy Metabolism Process	mayContributeTo	Acute Lethality	throughMechanisticTarget	Mitochondrial Function	Energy Metabolism Process	CUI:C0014272	
7	APR_HepG2_MitoMembPot_1h_up	mayInformOn	AcuteTox - Energy Metabolism Process	mayContributeTo	Acute Lethality	throughMechanisticTarget	Mitochondrial Function	Energy Metabolism Process	CUI:C0014272	
8	APR_HepG2_p53Act_1h_dn	mayInformOn	AcuteTox - p53 Signaling Pathway	mayContributeTo	Acute Lethality	throughMechanisticTarget	p53 Modulation	p53 Signaling Pathway	CUI:C2984306	
9	APR_HepG2_p53Act_1h_up	mayInformOn	AcuteTox - p53 Signaling Pathway	mayContributeTo	Acute Lethality	throughMechanisticTarget	p53 Modulation	p53 Signaling Pathway	CUI:C2984306	
10	APR_HepG2_CellLoss_24h_dn	mayInformOn	AcuteTox - Cytotoxicity	mayContributeTo	Acute Lethality	throughMechanisticTarget	Cell Viability	Cell Viability Process	CUI:C1516362	
11	APR_HepG2_MicrotubuleCSK_24h_up	mayInformOn	AcuteTox - Cytotoxicity	mayContributeTo	Acute Lethality	throughMechanisticTarget	Cell Morphology	Cell Viability Process	CUI:C1516362	

Data

ICE Data (In Vivo and In Vitro)

Toxicity endpoint	Assays	# of chemicals
Chemical Parameters	Experimental physicochemical properties	~20000
ADME Parameters	Fu, intrinsic clearance, Caco2 permeability	~3000
Acute Toxicity	In vivo acute oral, dermal, and inhalation toxicity	~10000
Cancer	In vivo and in vitro cancer, and Weight of Evidence	3038
DART	In vivo and in vitro DART	628
Skin Sensitization	In vivo and in vitro skin sensitization	1771
Skin Irritation	In vivo and in vitro skin irritation/corrosion	595
Eye Irritation	In vivo and in vitro eye irritation/corrosion	455
Endocrine	In vivo and low throughput in vitro data on AR and ER agonist and antagonist activity	384
cHTS	Curated US EPA's ToxCast and Federal Tox21 assays (In vitro)	~10000

Harmonized and updated datasets!

Data

ICE Data (In Silico Models/Integrated Approaches)

Endpoint	Model	# of chemicals
Physicochemical Properties	OPEn (q)saR App (OPERA) Mansouri et al. J Cheminform 2018	1M+
Structural Properties	OPEn (q)saR App (OPERA) Mansouri et al. J Cheminform 2018	1M+
Predicted ADME Properties	OPEn (q)saR App (OPERA) Mansouri et al. J Cheminform 2018	1M+
Environmental Fate	OPEn (q)saR App (OPERA) Mansouri et al. J Cheminform 2018	1M+
Acute Oral Toxicity	Collaborative Acute Toxicity Modeling Suite (CATMoS) - Rat acute oral toxicity. Mansouri et al. EHP 2021	1M+
Endocrine	Estrogen Receptor pathway Model. Browne et al. ES&T 2015	1812
	Androgen Receptor Pathway Model. Kleinstreuer et al. Chem Res Tox 2017	1855
	Collaborative Estrogen Receptor Activity Prediction Project (CERAPP). Mansouri et al. EHP 2016	1M+
	Collaborative Modeling Project for Androgen Receptor Activity (COMPARA). Mansouri et al. EHP 2020	1M+
Exposure Predictions	Systematic Empirical Evaluation of Models (US EPA'S SEEM3). Ring et al. Environ Sci Technol 2019	475,000+

New exposure predictions!

OPERA Predictions in ICE

Search

Chemical characterization

Data

Research article | Open access | Published: 08 March 2018

OPERA models for predicting physicochemical properties and environmental fate endpoints

Kamel Mansouri, Chris M. Grulke, Richard S. Judson & Antony J. Williams

Journal of Cheminformatics **10**, Article number: 10 (2018) | Cite this article

20k Accesses | **261** Citations | **25** Altmetric | Metrics

Open Structure-Activity/Property Relationship App (OPERA)

- OPERA is a free and open-source quantitative structure-activity relationship (QSAR) tool.
- OPERA predictions include:
  - Physicochemical Properties
  - Structural Properties
  - Environmental Fate Properties
  - ADME properties
  - Models for Toxicity Endpoints
    - CERAPP: Collaborative Estrogen Receptor Activity Prediction Project
    - CoMPARA: Collaborative Modeling Project for Androgen Receptor Activity
    - CATMoS: Collaborative Acute Toxicity Modeling Suite

https://github.com/NIEHS/OPERA

https://ntp.niehs.nih.gov/go/opera

https://doi.org/10.1186/s13321-018-0263-1

ICE Chemical Quick Lists

Reference Chemical List
AR In Vitro Agonist
AR In Vitro Antagonist
ER In Vivo Agonist
ER In Vitro Agonist
Eye Irritation-Corrosion
Genotoxicity
OECD Defined Approach to Skin Sensitization: Human
OECD Defined Approach to Skin Sensitization: LLNA
Skin Corrosion

Non-reference Chemical List
AR In Vivo Agonists
AR In Vivo Antagonists
EPA Pesticide Active Ingredients
EPA Pesticide Inert Ingredients, Food and Nonfood Use
EPA IRIS Cancer Assessment
EPA IRIS Non-Cancer Assessment
IARC Classifications
Mixtures and Formulations in ICE
NTP Cancer Bioassay Chemicals
RoC Classifications
Steroidogenesis - Androgen
Steroidogenesis - Estrogen
Thyroid
Tox21
ToxCast Phase I, Phase II, and e1k

New quick lists!

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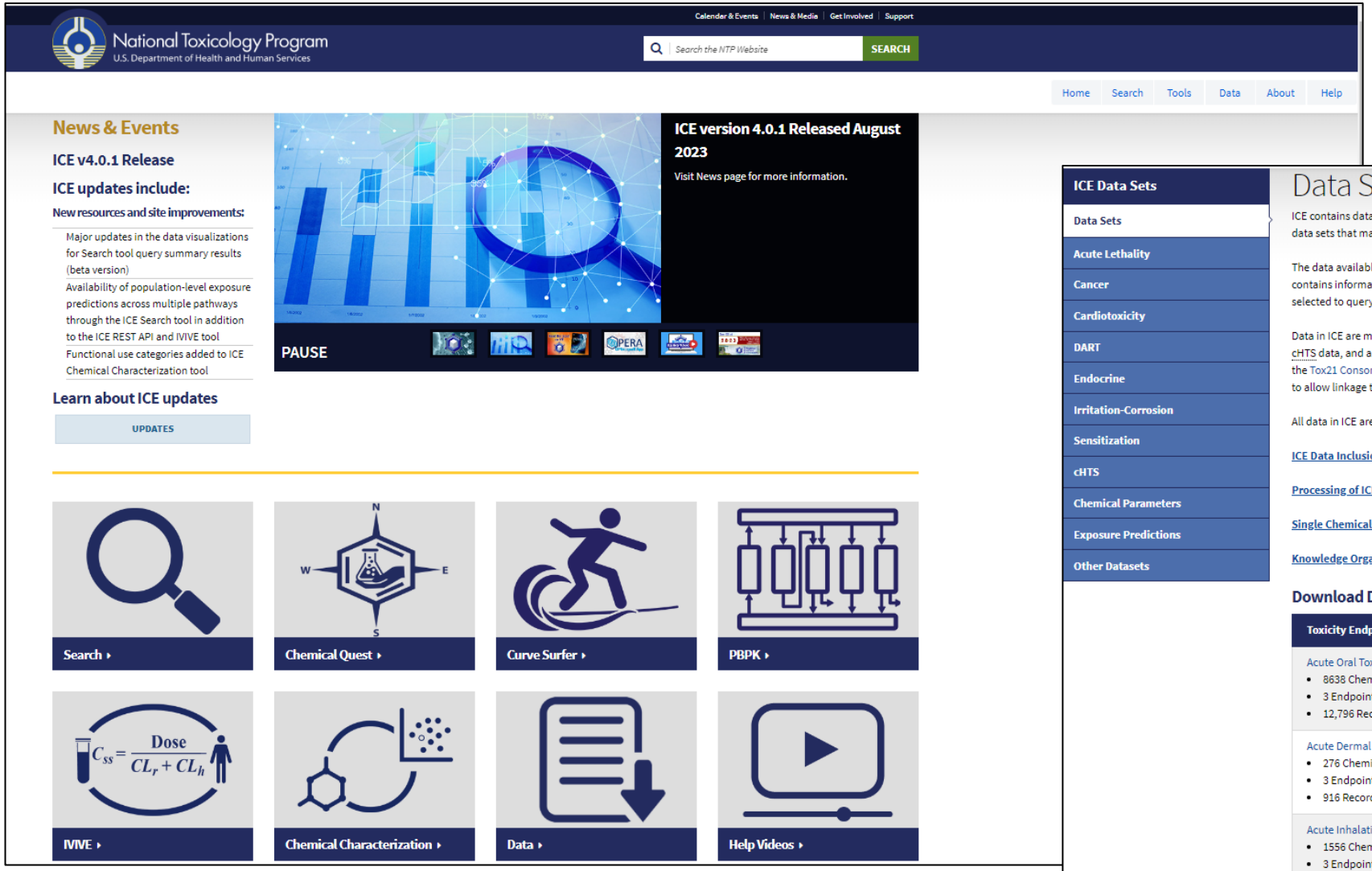
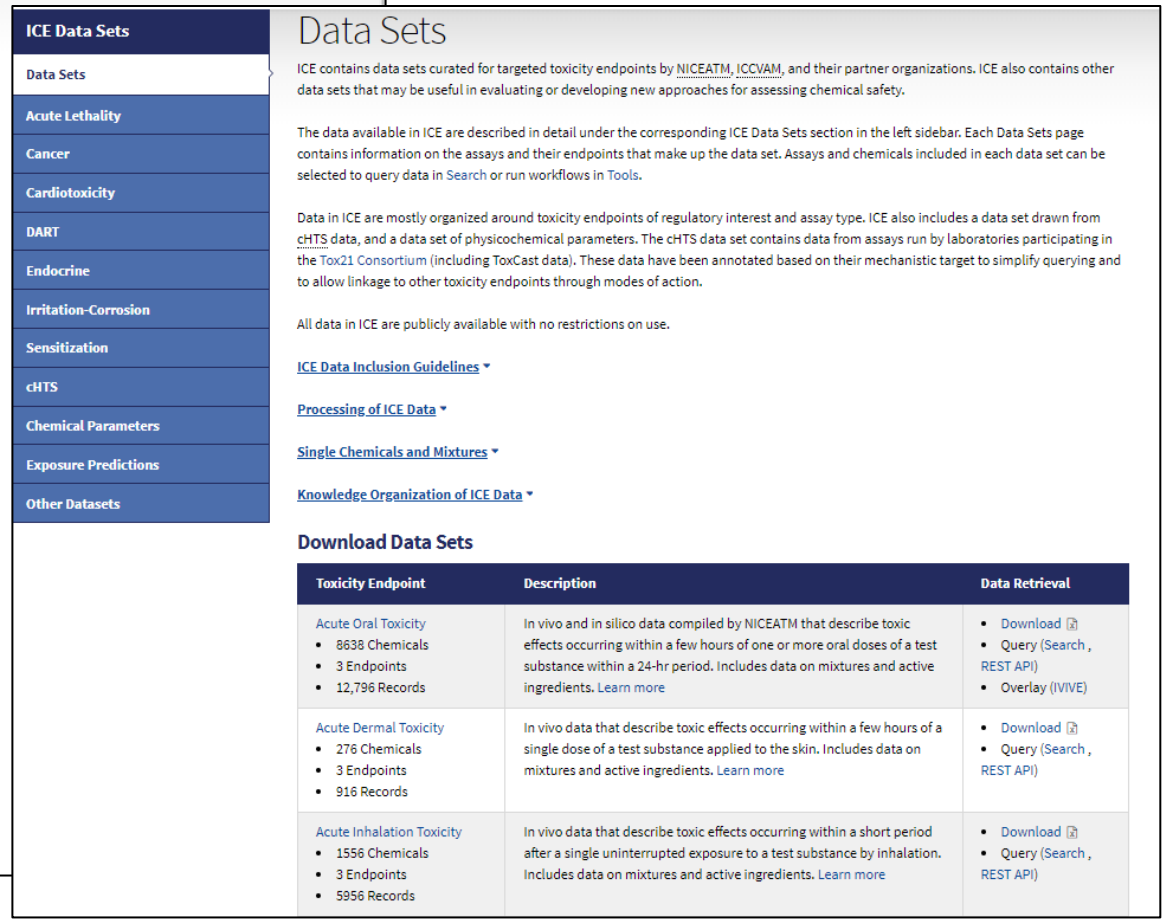
Accessing ICE Data

Data

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





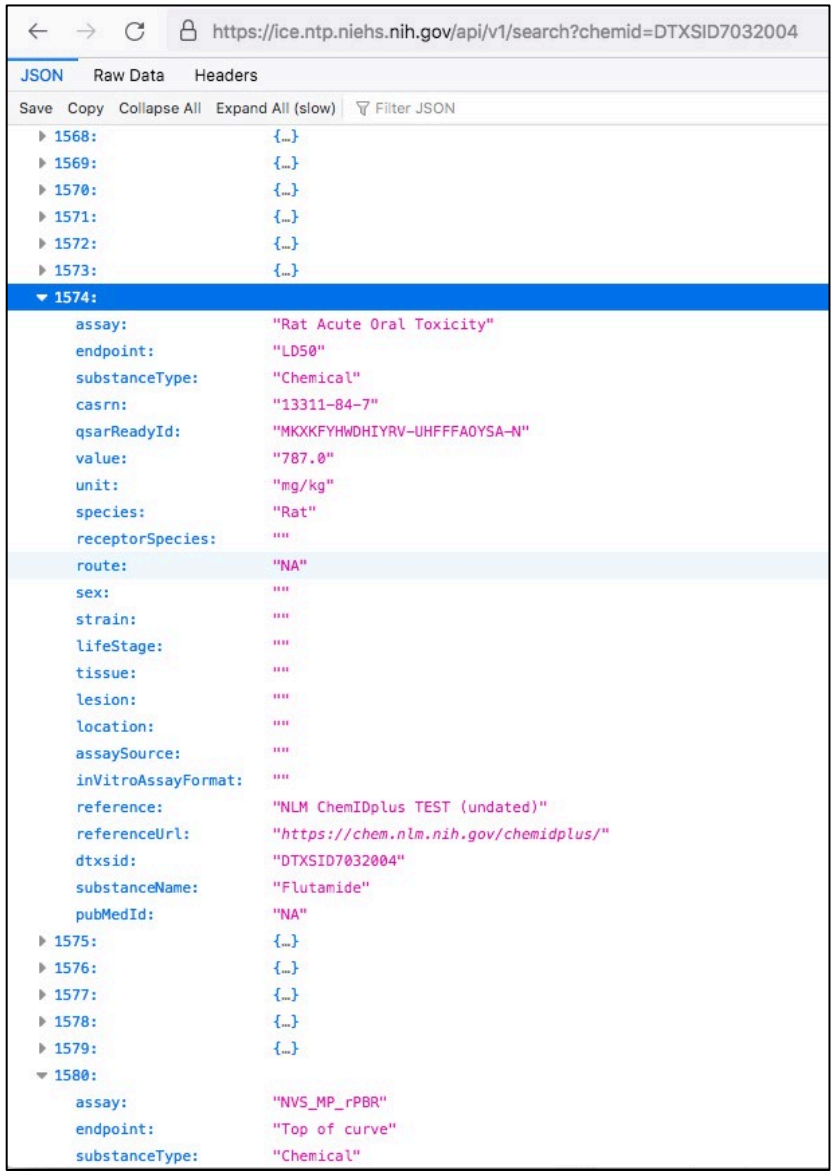
ICE Data Access via REST API

Data

- For one or more chemical ids, return a list of Assay/Endpoint objects.
  - Query one chemical id using GET
  - Query multiple chemicals using POST
- Results are formatted in JSON
  - Same data structure for POST and GET REST requests.
  - Array of Assay/Endpoint objects per chemical.

https://ice.ntp.niehs.nih.gov/api/v1/search

Newly added Rest API User guide provides more details and example codes!!



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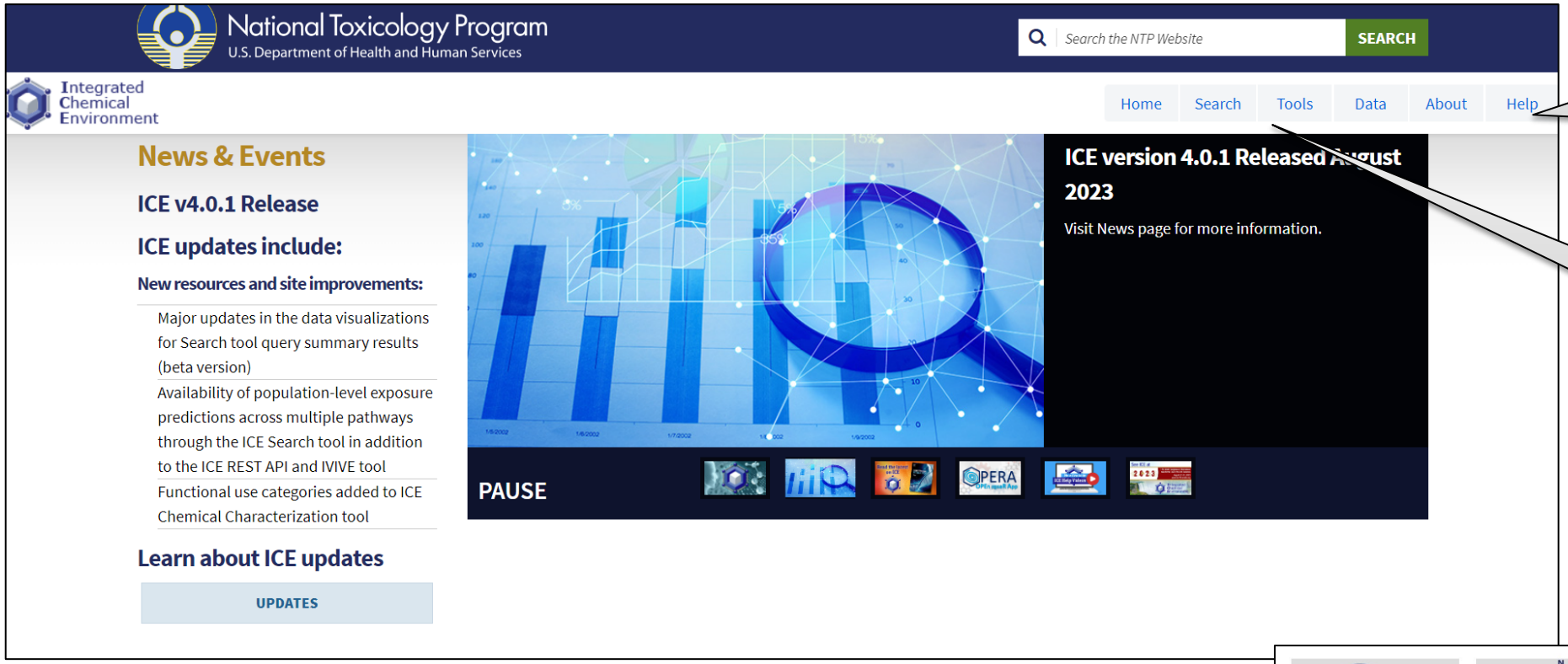
Accessing ICE Tools

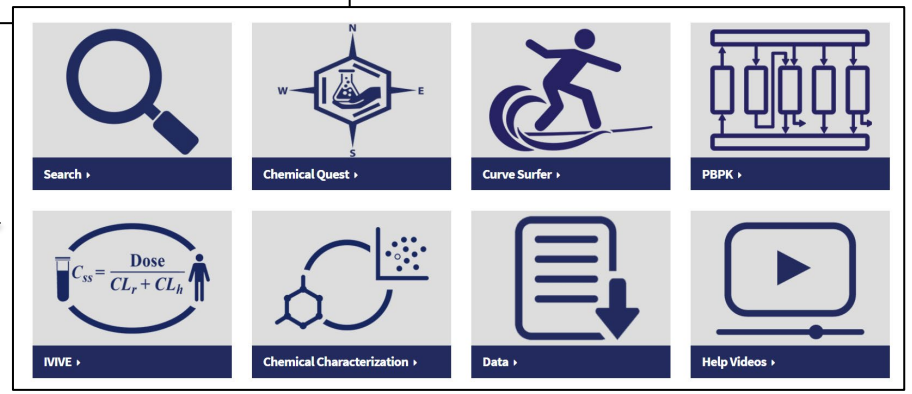


Detailed information on each tool is available as individual user guides and videos through the help tab.

Search and other tools can also be accessed through the search tab and tools tab, respectively.

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

The tools can be accessed through ICE homepage by clicking the respective icons.



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ICE Tools Workflow

Integrated Chemical Environment

Perform a search	Expand inventory: Identify similar chemicals	Characterize chemical inventory	Review in vitro data details	Generate chemical concentration predictions	Predict equivalent administered dose from in vitro data
Search	Chemical Quest	Chemical characterization	Curve Surfer	PBPK	IVIVE

Demo

Exploring ICE

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

ICE Tools Workflow - Search

Integrated Chemical Environment

ICE Search tool allows integration of data from different models and testing systems to provide an overall view of chemical bioactivity for regulatory endpoints of interest.

Perform a search

Search

Expand inventory: Identify similar chemicals

Chemical Quest

Characterize chemical inventory

Chemical characterization

Review in vitro data details

Curve Surfer

Generate chemical concentration predictions

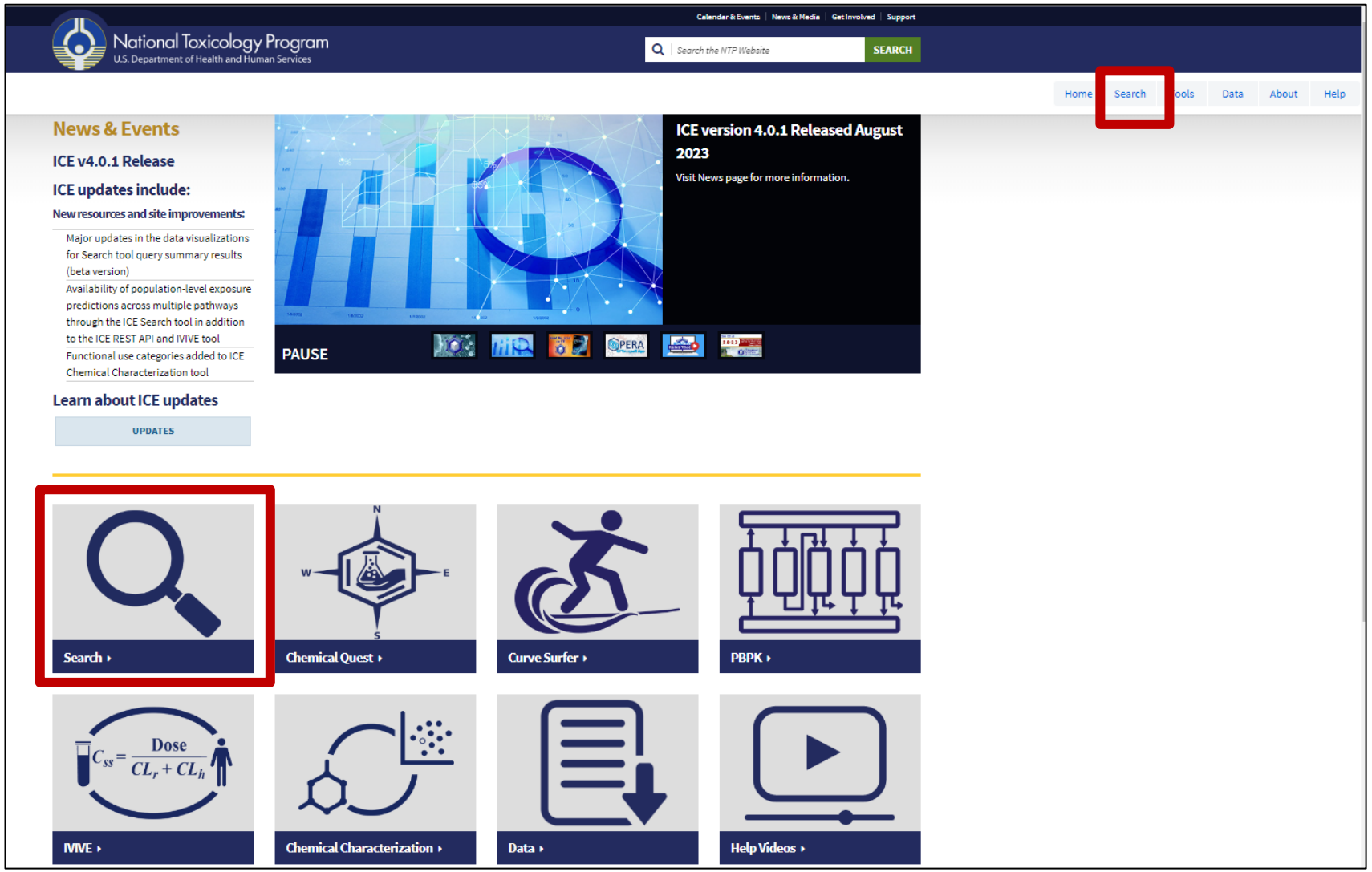
PBPK

Predict equivalent administered dose from in vitro data

$C_{ss} = \frac{Dose}{CL_r + CL_h}$

IVIVE

Search - Access



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

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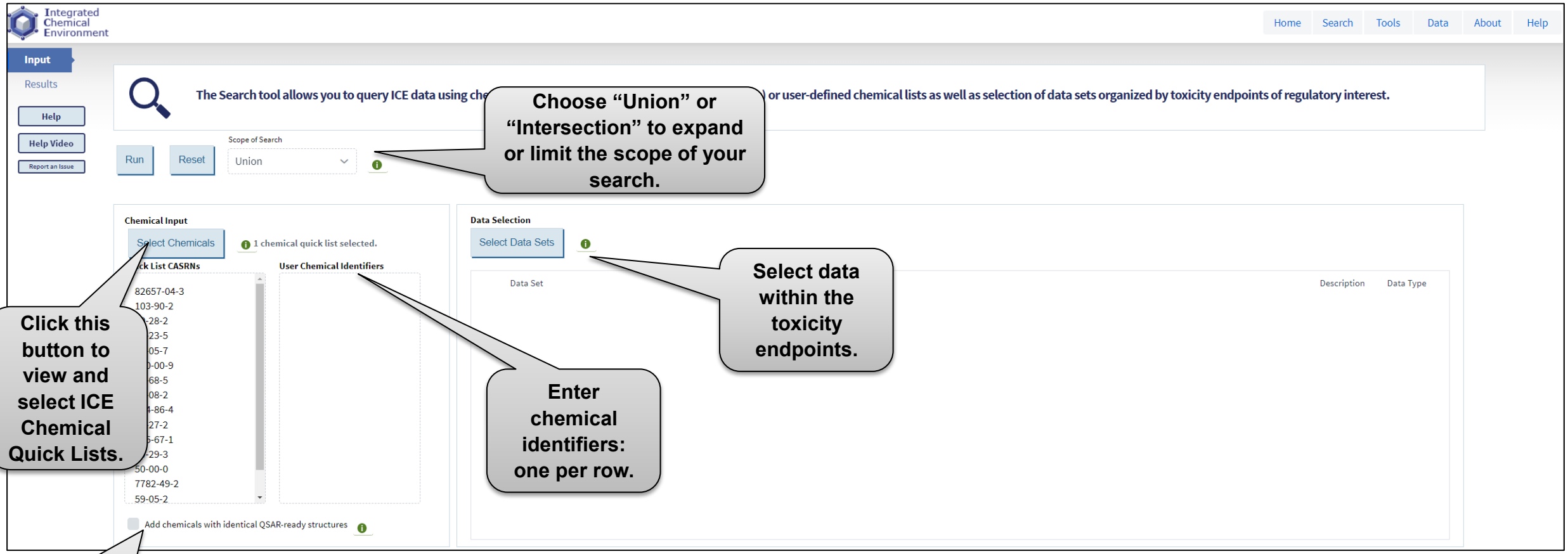
Search Input View



Choose "Union" or "Intersection" to expand or limit the scope of your search.

Click this button to view and select ICE Chemical Quick Lists.

Select data within the toxicity endpoints.

Enter chemical identifiers: one per row.

Add chemicals available in ICE to your query that have the same QSAR structure as a chemical you have specified.

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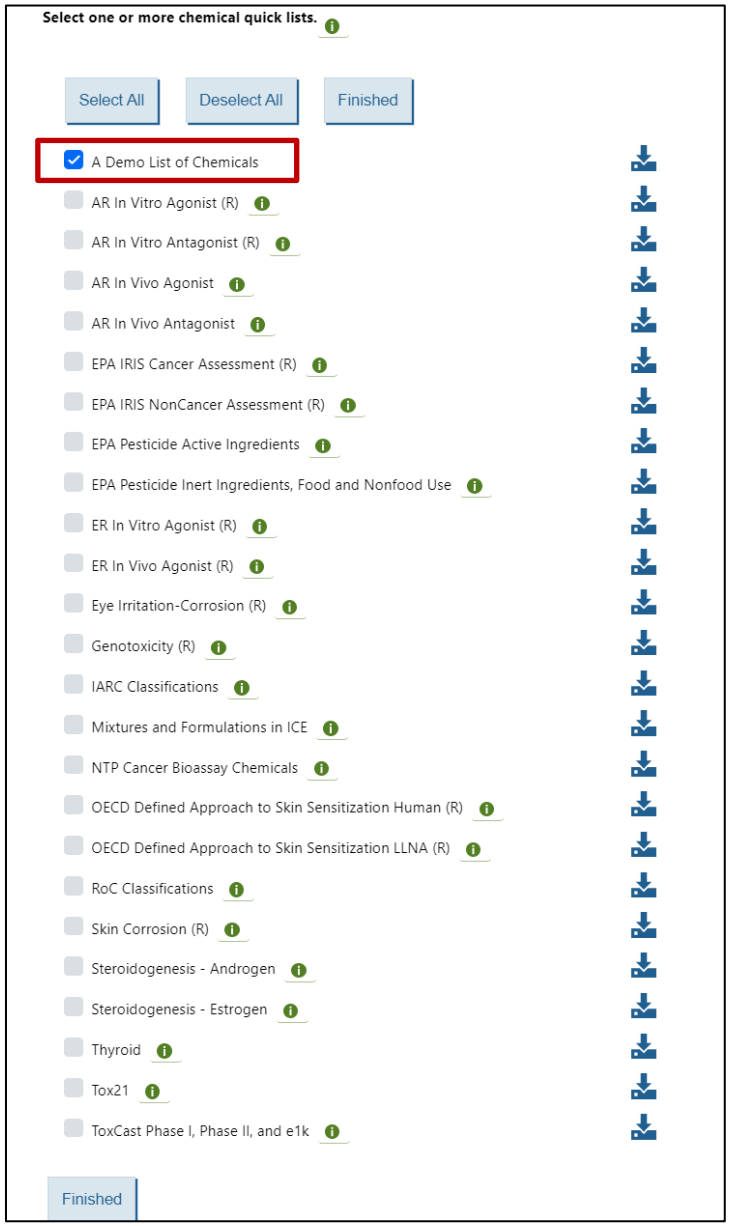
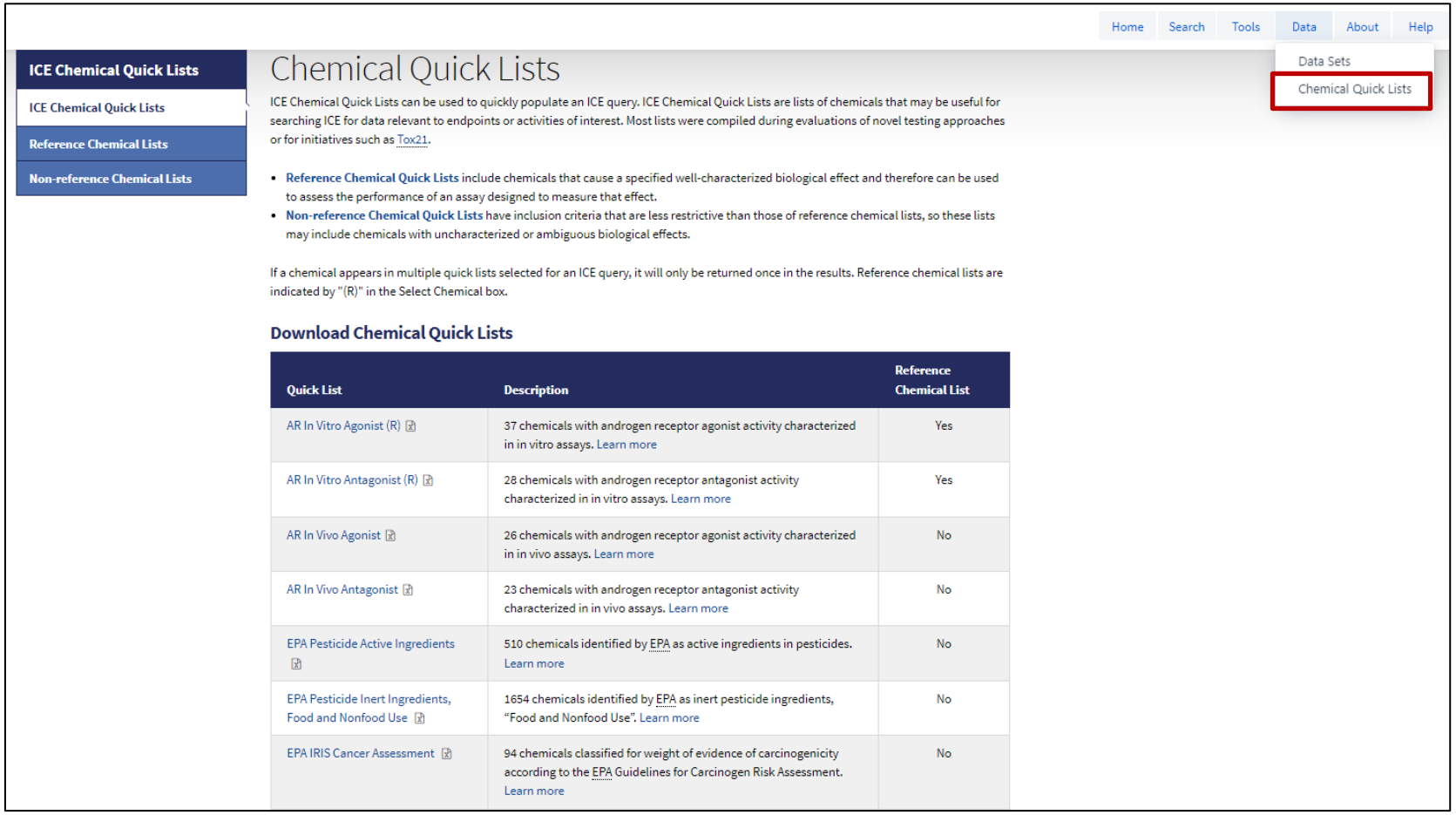
ICE Chemical Quick Lists





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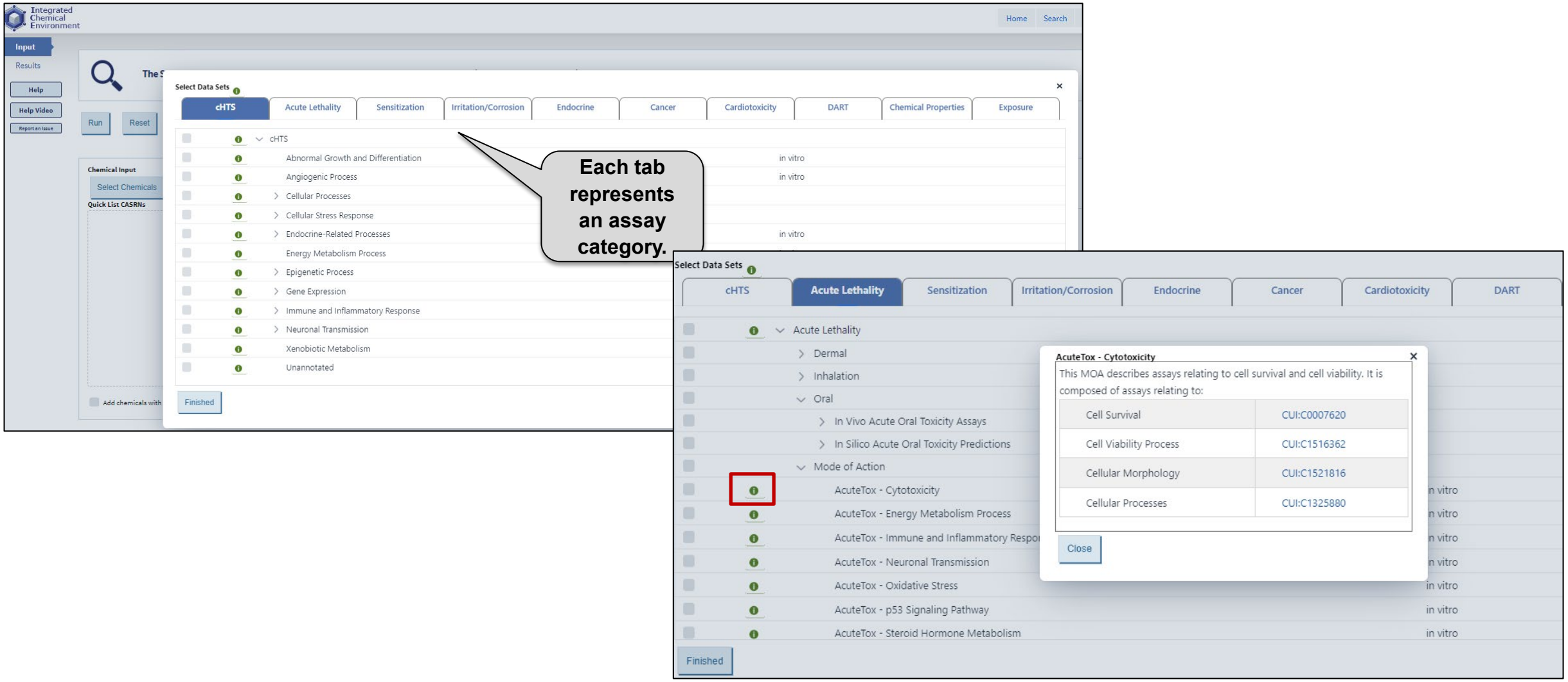
Search

Search organized by Toxicity Endpoint



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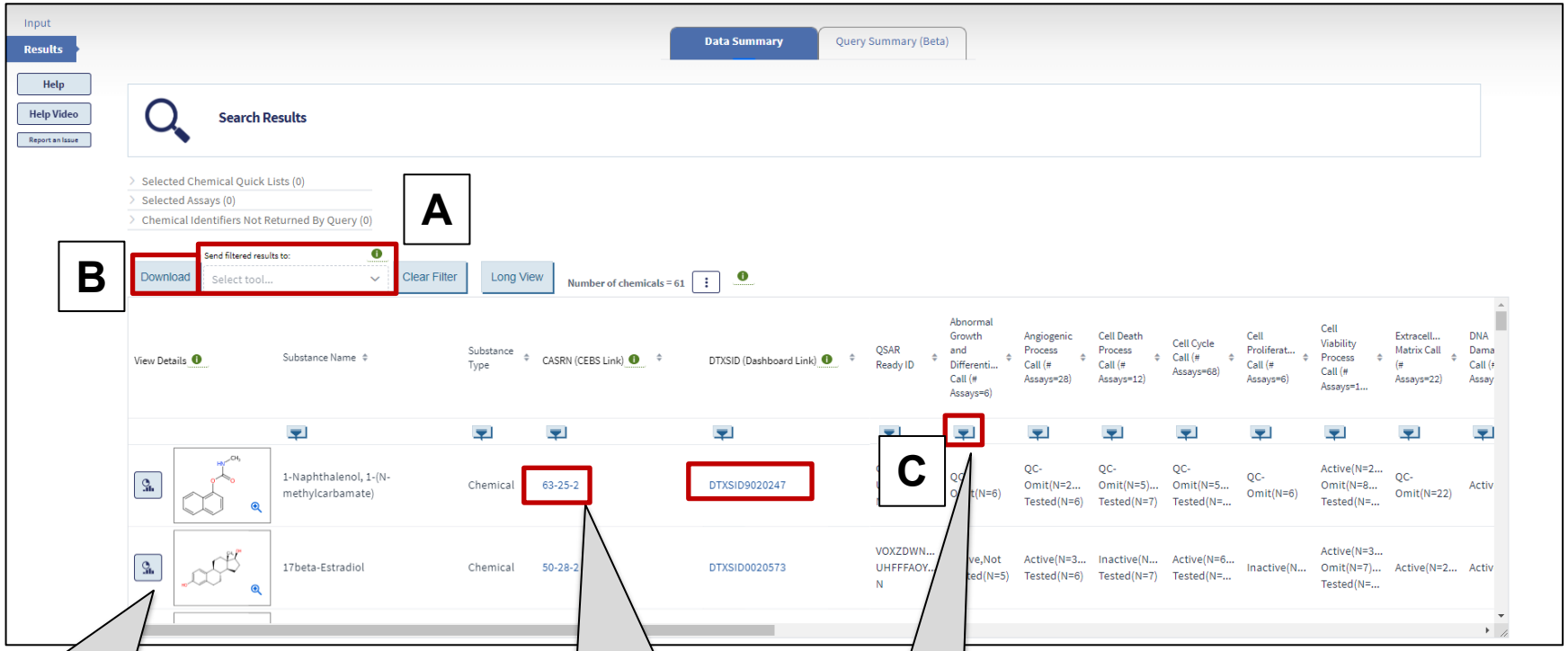
Search

Search Results - Summary Table



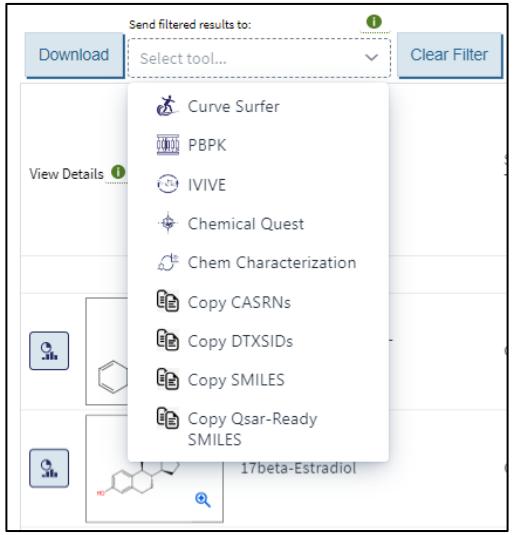
Click icons to view substance details.

CASRN links to NIEHS CEBS and DTXSID links to U.S. EPA's CompTox Chemicals Dashboard

Click icons to filter results.

https://cebs.niehs.nih.gov/cebs/
https://comptox.epa.gov/dashboard/

A



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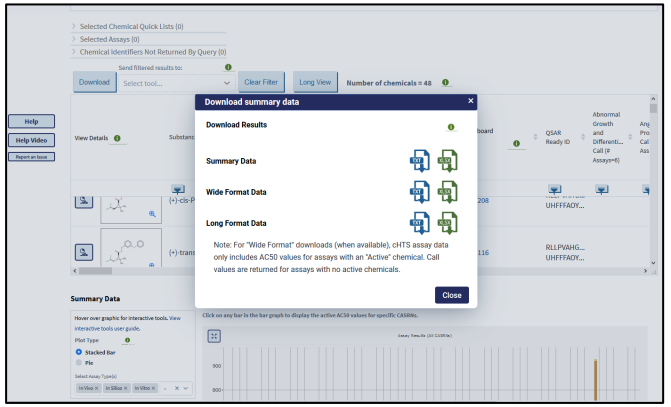
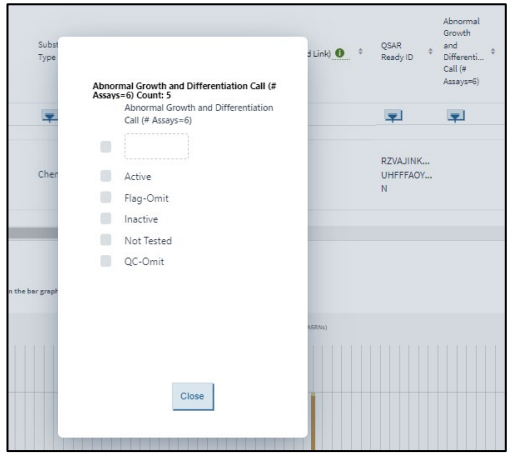


C



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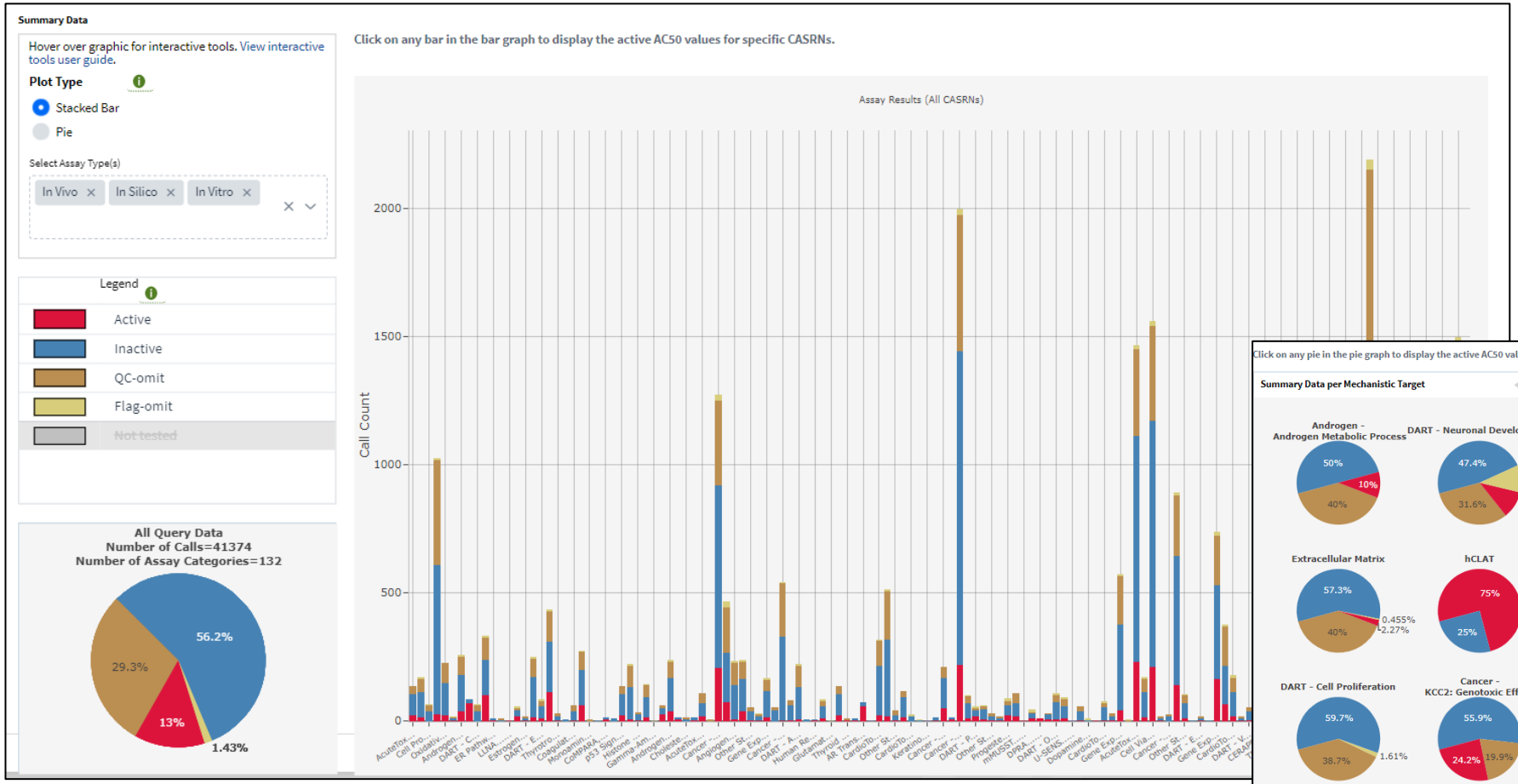
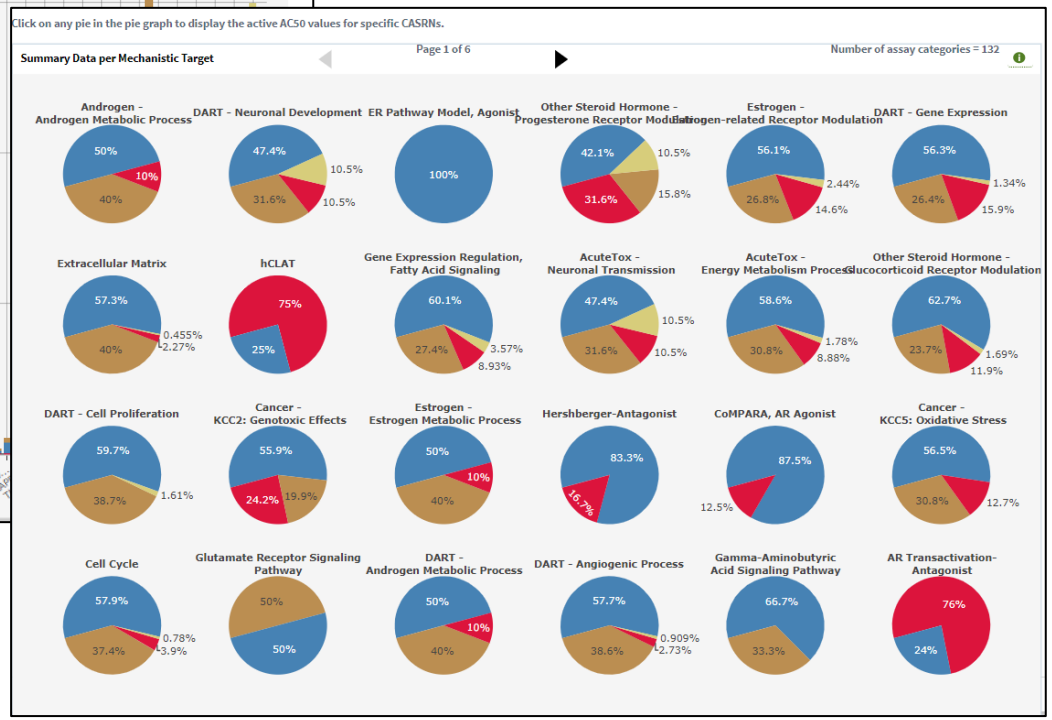
Search

Search Results – Bioactivity Summary





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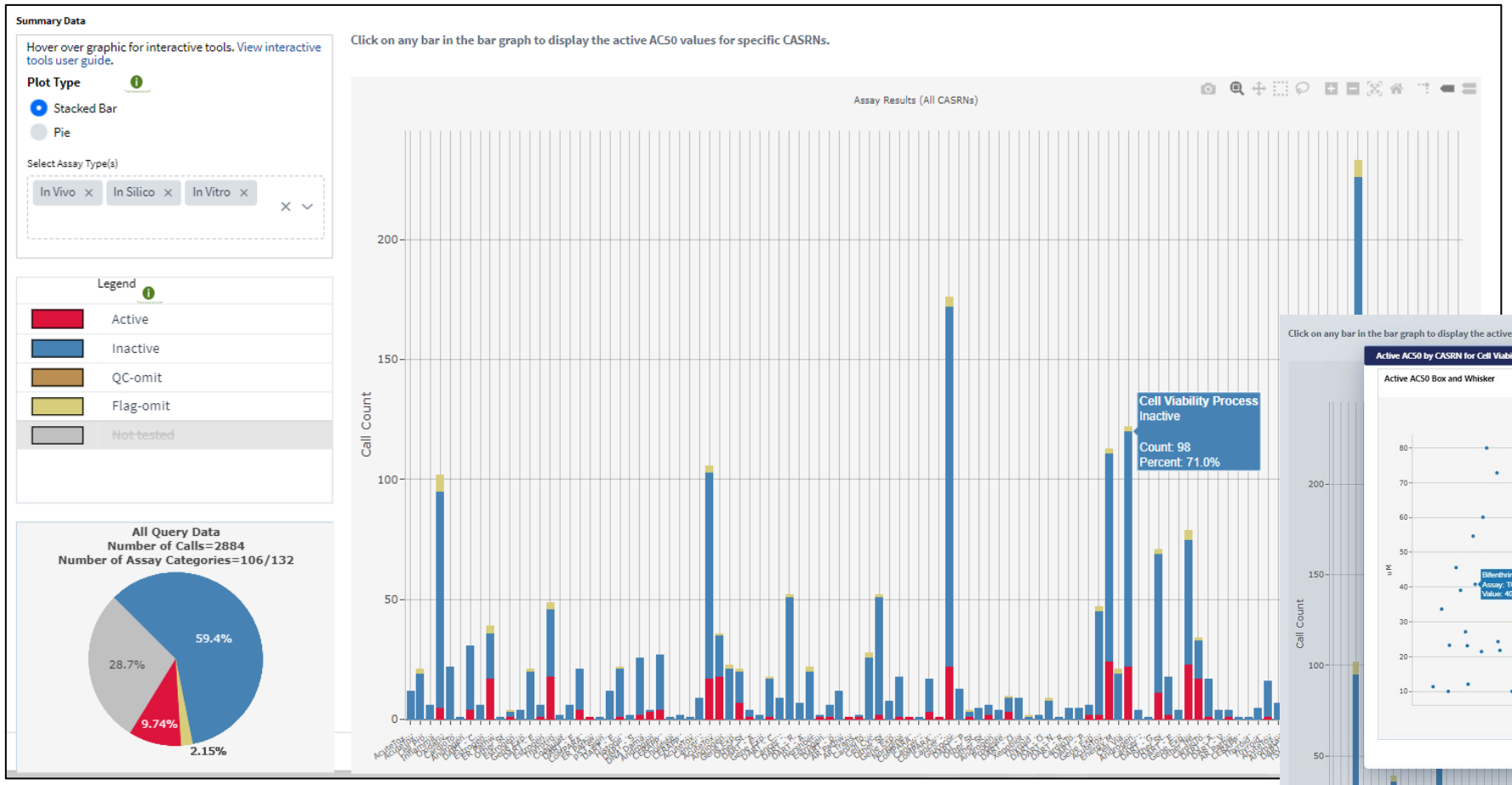
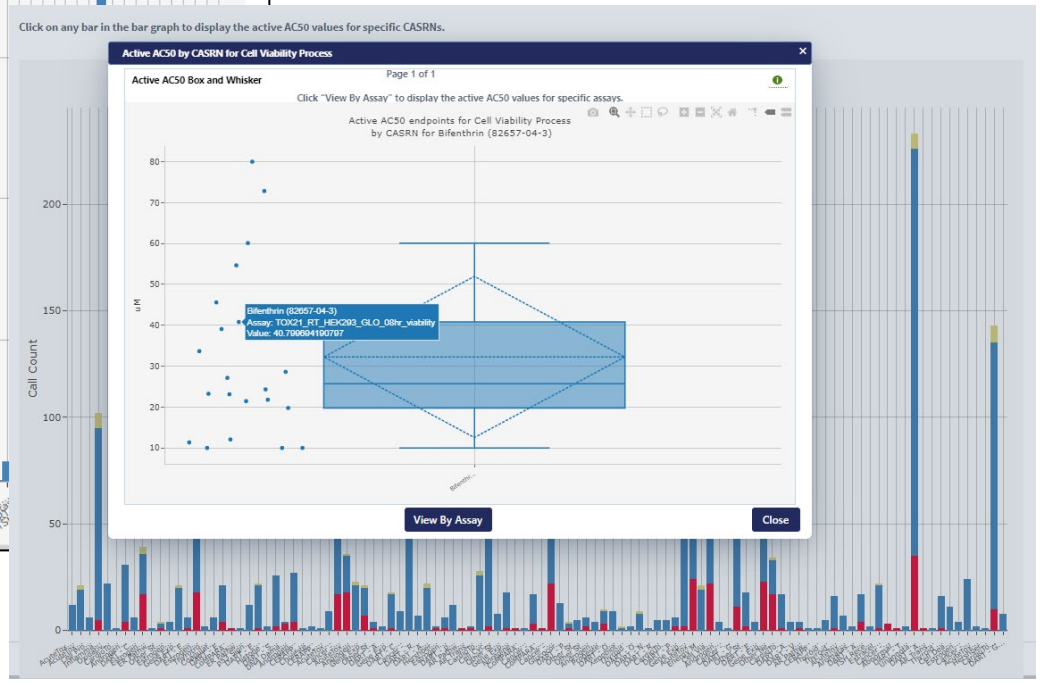
Search

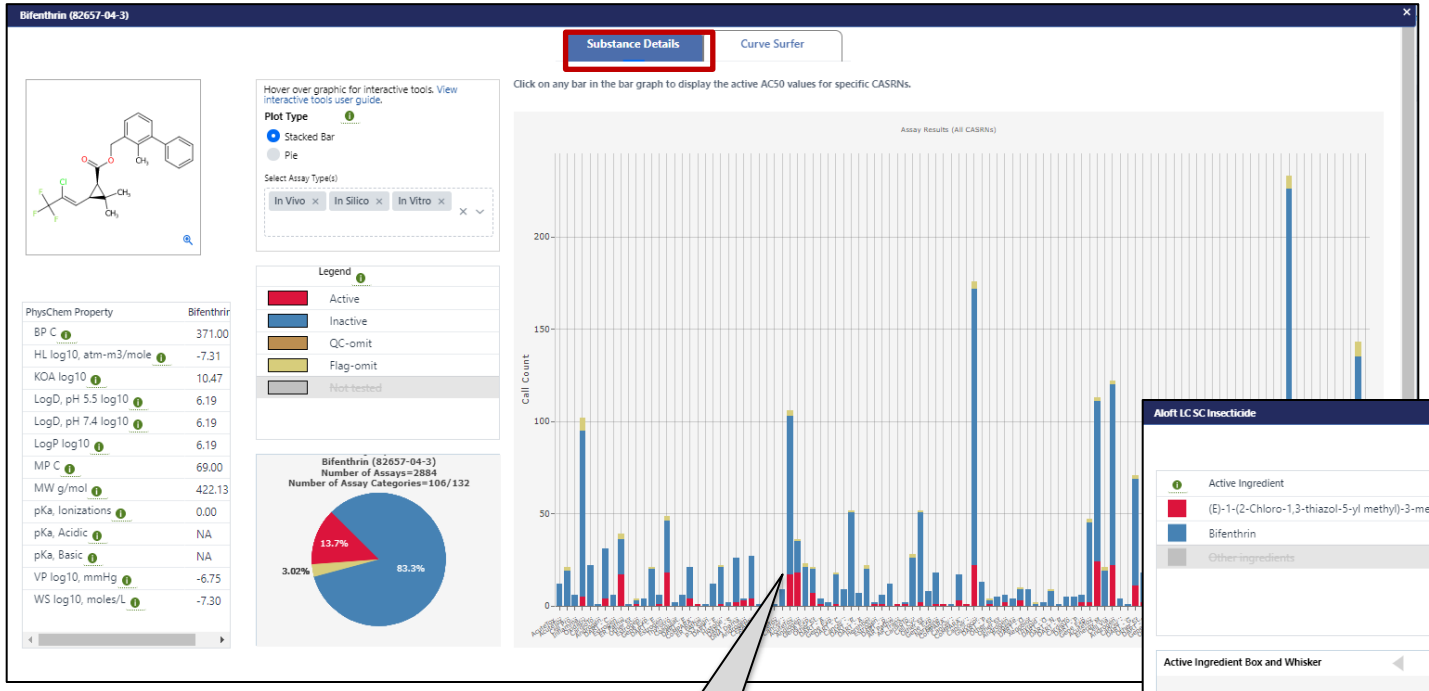
Search Results – Bioactivity Summary (Single Chemical)





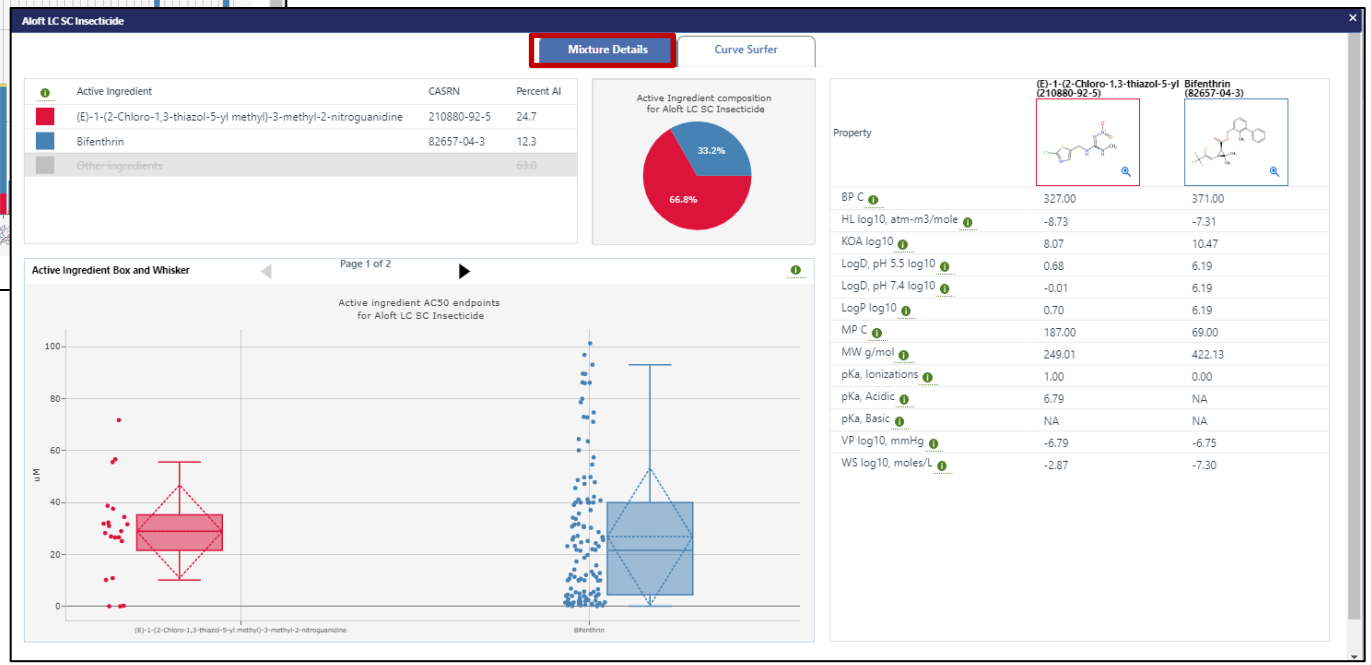
Active AC50 Plot for Assay Chemical Combo

Detail View for Single Chemical



Assay call count for each cHTS assay

Detail View for Mixtures



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Dose Response Curves

Bifenthrin (82657-04-3)

Substance Details | **Curve Surfer**

100%

Select Filter to add to chain:

- Mechanistic Targets
- Call
- Assay Text
- Assay
- CASRN
- Chemical Name
- DTXSID
- Assay Format
- Normalized Data Type
- AC50
- Top of Curve

Select All Filtered

Only show selected

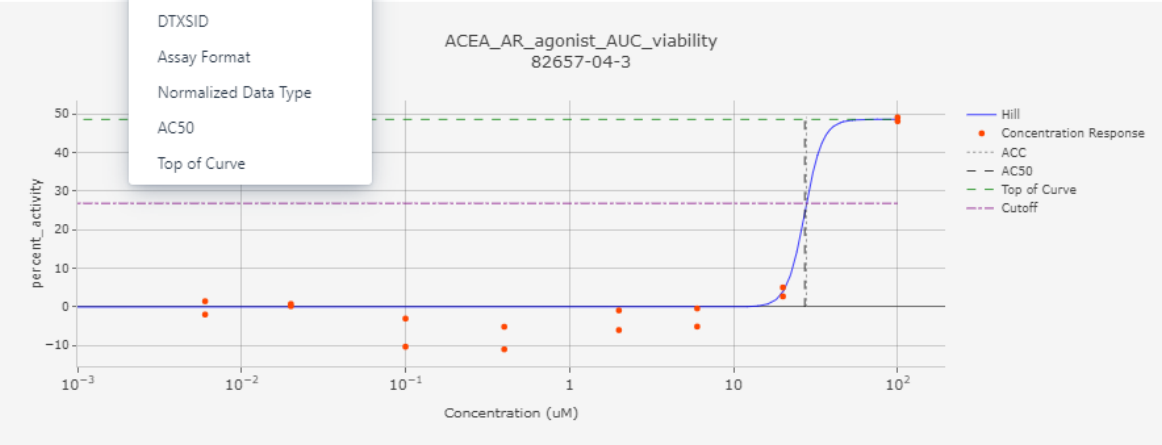
Select Page 1 of 34

Showing 1-10 of 338 curves.

Sort Results By: Chemical Name | Direction: Asc

Overlay Selected | Overlay Filtered

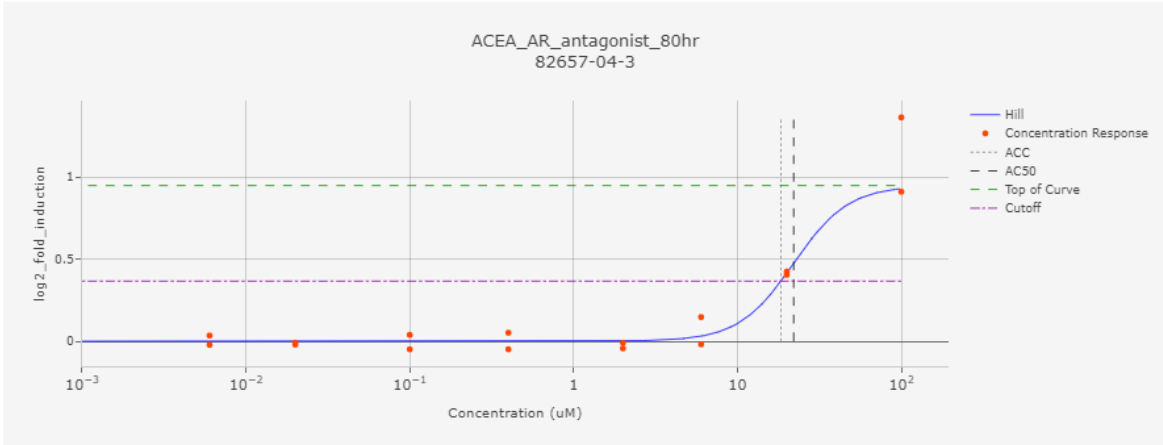
Select this item



Assay: ACEA_AR_agonist_AUC_viability
CASRN: 82657-04-3
Chemical Name: Bifenthrin
AC50 (uM): 27.14
Top of Curve: 48.66

Mechanistic Target: Cell Viability Process
DTXSID: DTXSID9020160
Winning Curve-Fit Model: Hill
ACC (uM): 27.86
Call: Active

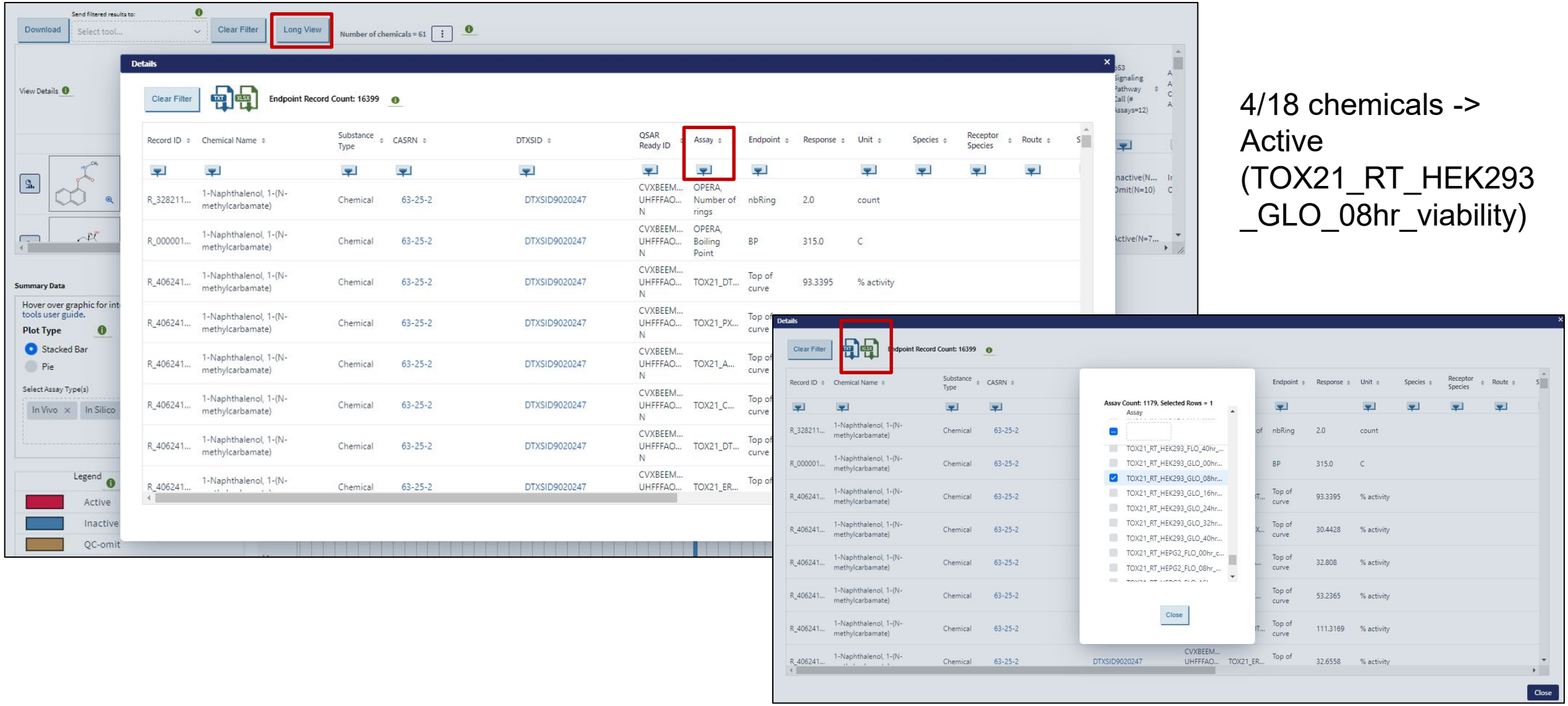
Select this item



Assay: ACEA_AR_antagonist_80hr
CASRN: 82657-04-3
Chemical Name: Bifenthrin
AC50 (uM): 22.02
Top of Curve: 0.95

Mechanistic Target: Androgen Metabolic Process,Gene Expression Regulation, Steroid Hormone Nuclear Receptor
DTXSID: DTXSID9020160
Winning Curve-Fit Model: Hill
ACC (uM): 18.43
Call: Active

Search Results – Long View (Single Assay)



4/18 chemicals -> Active (TOX21_RT_HEK293_GLO_08hr_viability)

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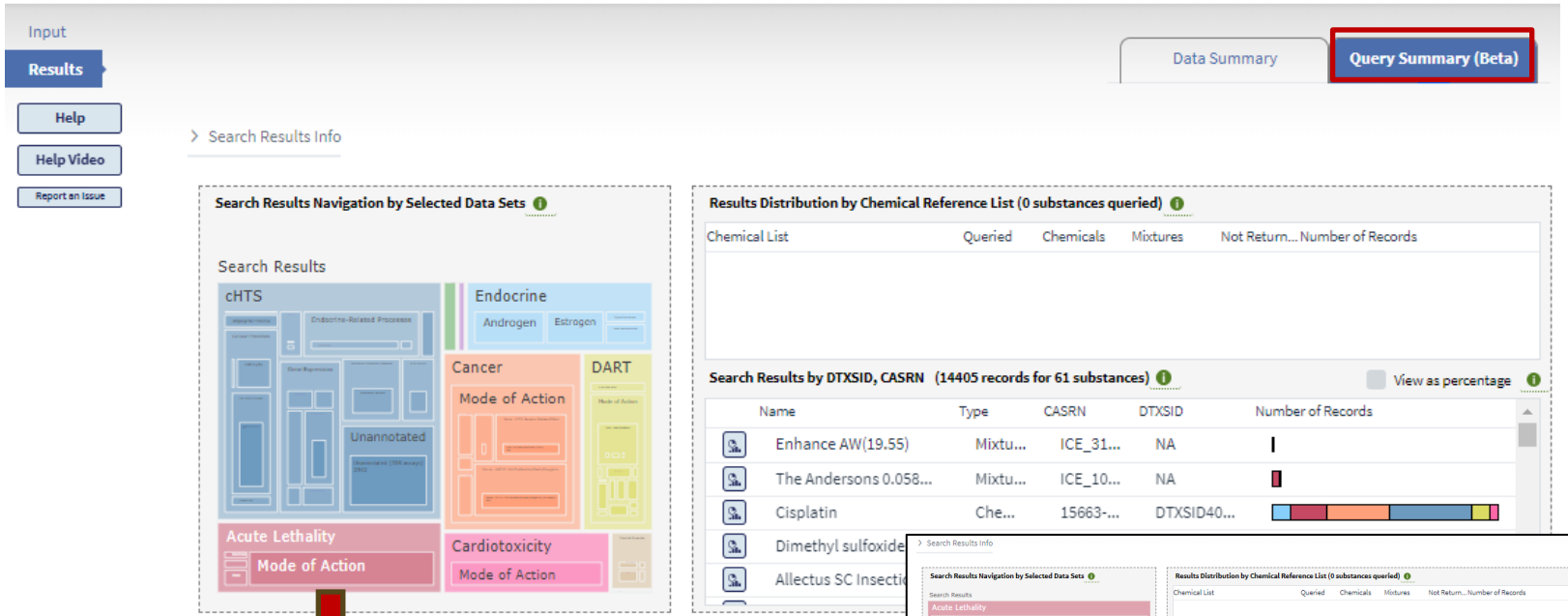
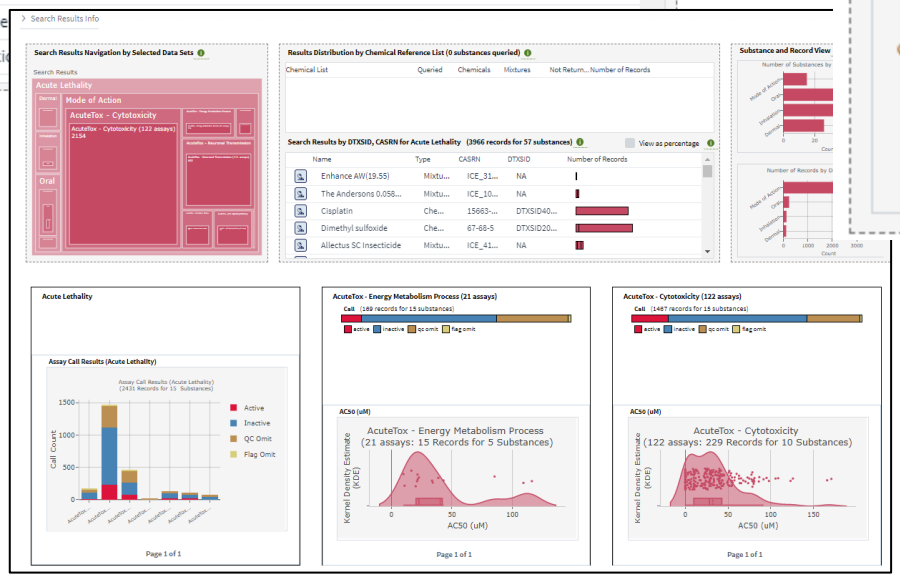
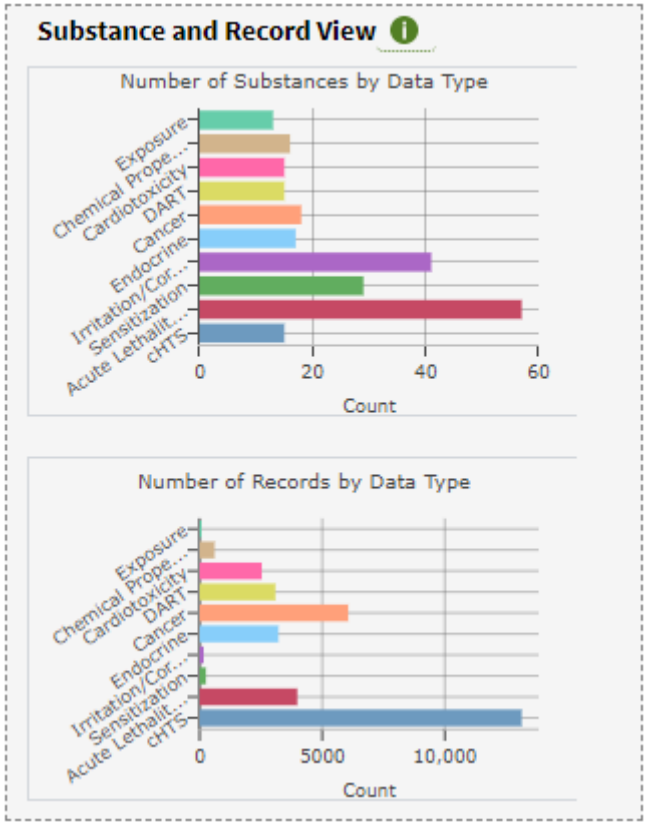
Search

Search Query Summary Results







Demo

Exploring ICE Search using “A Demo List of Chemicals”

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

Search Summary

- Identify information on a set of chemicals regarding their toxicity and biological effects.
  - Users can query by CASRN, DTXSID, Chemical Name, InChiKey or SMILES.
  - Option to query on the parent structure as opposed to a specific salt form.
  - Detailed view of single chemicals and mixtures.
  - Explore all data from both animal and non-animal tests.
  - Interactive graphs visualize substance bioactivity in an assay.
  - AC50 plots for Active chemicals.
  - Downloadable results and graphs.
  - Sending results to other tools to run further queries and analysis.

ICE Tools Workflow - Chemical Quest

Integrated Chemical Environment

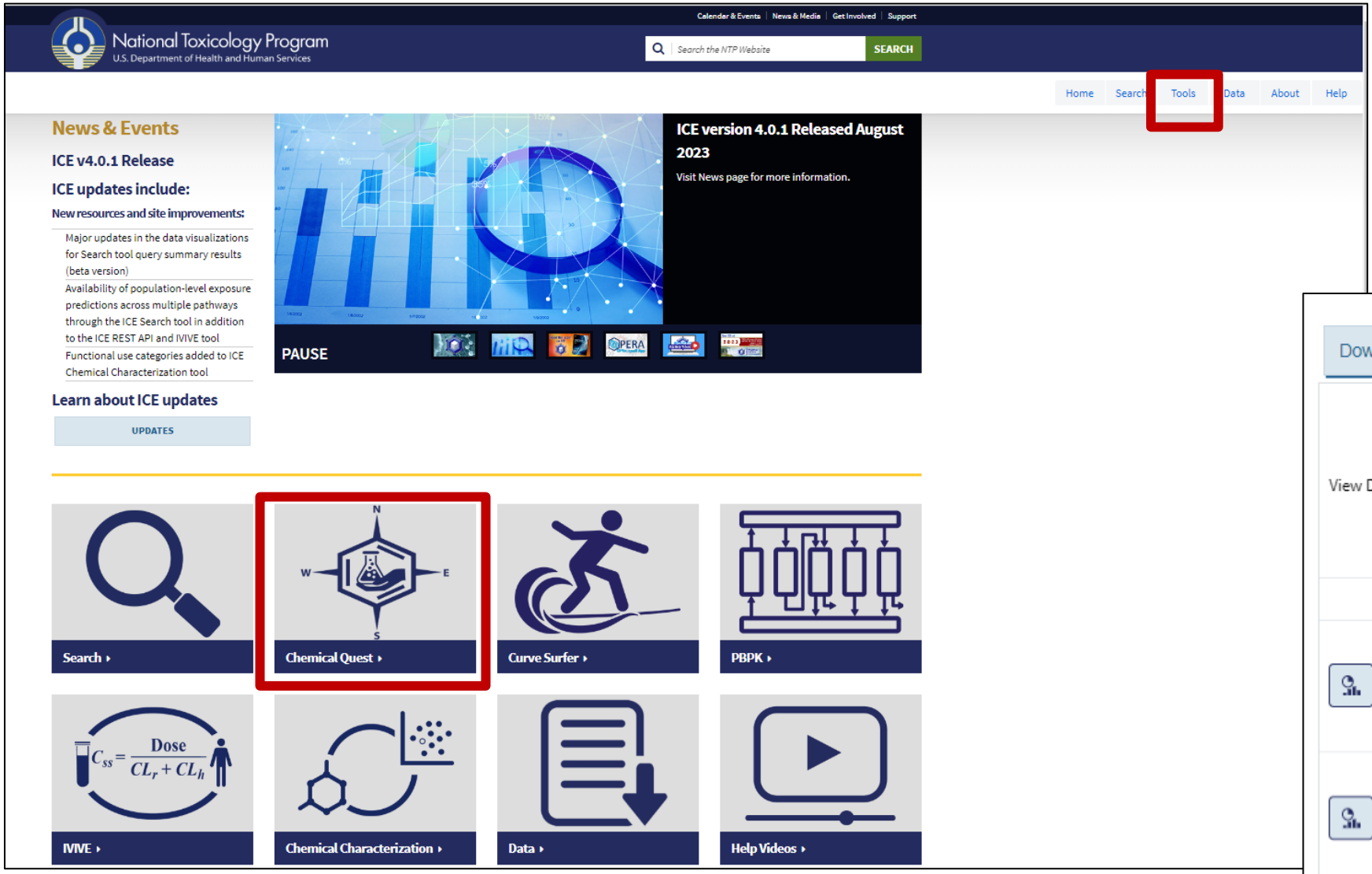
The Chemical Quest tool allows for identification of structurally similar chemicals for potential property and biological interactions.

Perform a search	**Expand inventory: Identify similar chemicals**	Characterize chemical inventory	Review in vitro data details	Generate chemical concentration predictions	Predict equivalent administered dose from in vitro data
Search	Chemical Quest	Chemical characterization	Curve Surfer	PBPK	IVIVE

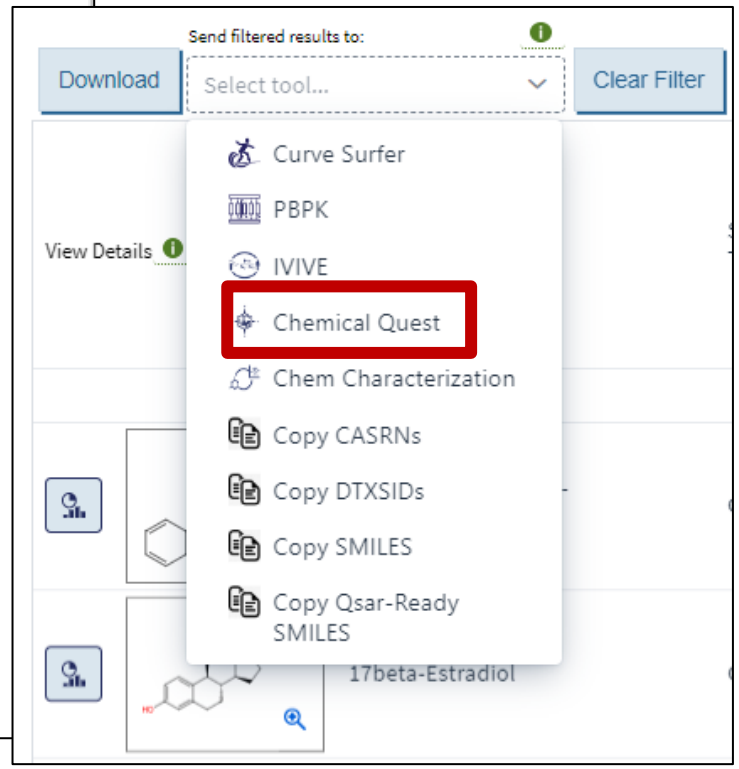
Chemical Quest - Key Terms

- Molecular Descriptors
  - Mathematical representations of the chemical structure.
    - Molecular weight, LogP, Bond Count
- Molecular Fingerprints
  - Code representation of molecular descriptors typically binary digits (bits).
- Saagar
  - Specific set of molecular fingerprints focused on ADME (absorption, distribution, metabolism and excretion) and toxicological properties.
- Tanimoto Value
  - Compare the molecular fingerprint bits for similarity.
  - Values range from 0 (not similar) to 1 (similar).

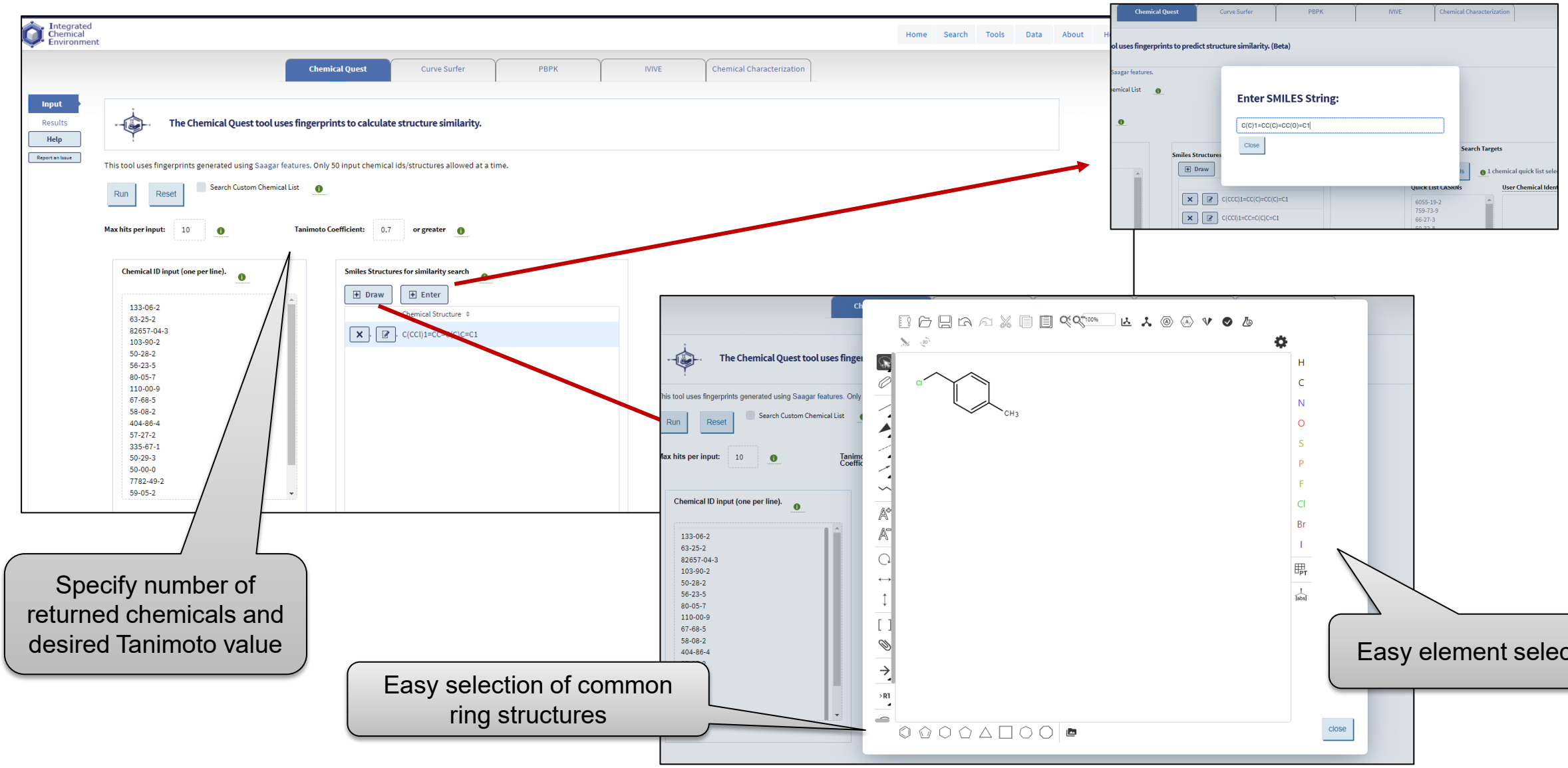
Chemical Quest - Access



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



Chemical Quest - Input



Specify number of returned chemicals and desired Tanimoto value

Easy selection of common ring structures

Easy element selection

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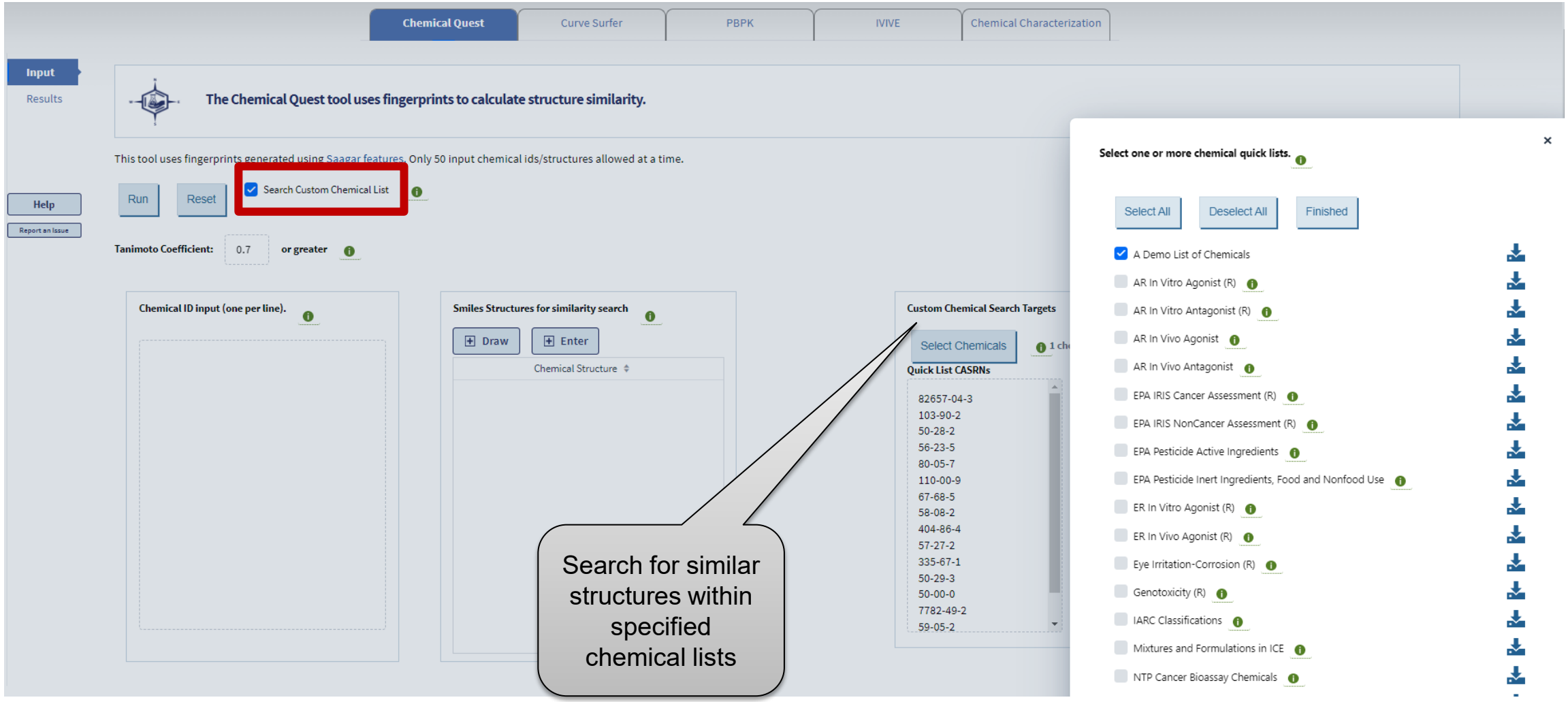
Chemical Quest - Specified Chemical Lists



Chemical Quest Output - Similar Structure Results

Input

Results

Help

Report an Issue

Chemical Quest Results

Send filtered results to:

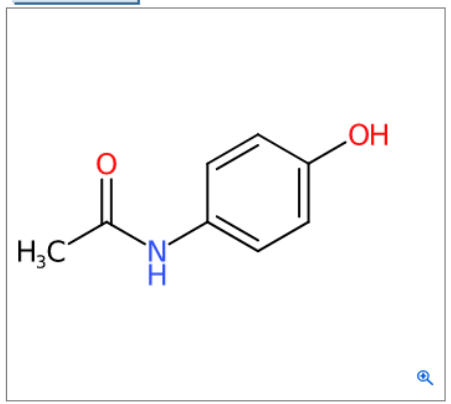
Select tool...

Clear Filter

All results can be sent to other tools for easy analysis or downloaded to be used in external workflows

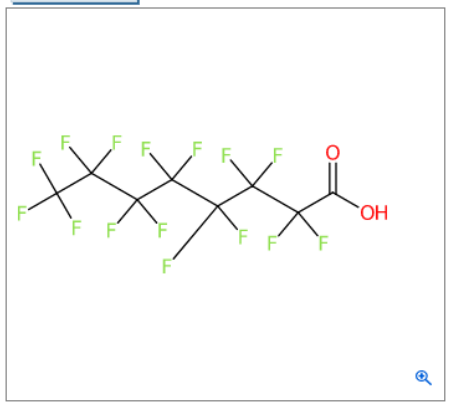
Chemical Name: Acetaminophen
CASRN: 103-90-2
DTXSID: DTXSID2020006
Tanimoto: top 10 hits and >0.7
Hit Count: 10
Passed Filter(s): 10/10
Selected Item(s): 0/10

View Results



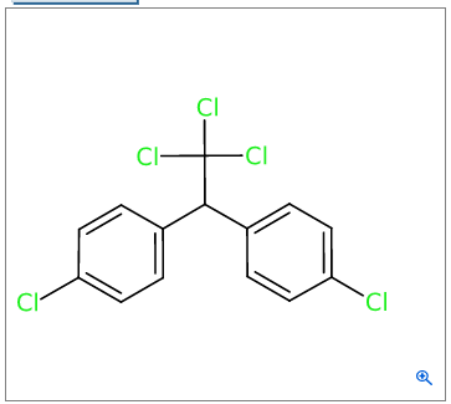
Chemical Name: Perfluorooctanoic acid
CASRN: 335-67-1
DTXSID: DTXSID8031865
Tanimoto: top 10 hits and >0.7
Hit Count: 10
Passed Filter(s): 10/10
Selected Item(s): 0/10

View Results



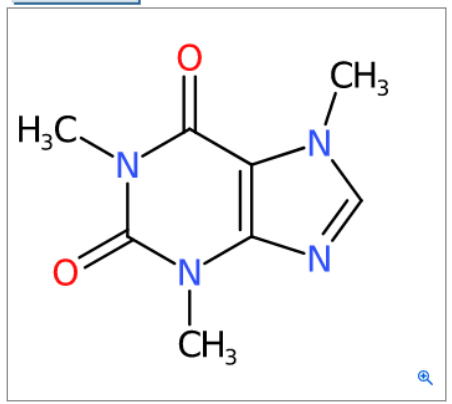
Chemical Name: DDT
CASRN: 50-29-3
DTXSID: DTXSID4020375
Tanimoto: top 10 hits and >0.7
Hit Count: 10
Passed Filter(s): 10/10
Selected Item(s): 0/10

View Results



Chemical Name: Caffeine
CASRN: 58-08-2
DTXSID: DTXSID0020232
Tanimoto: top 10 hits and >0.7
Hit Count: 10
Passed Filter(s): 10/10
Selected Item(s): 0/10

View Results



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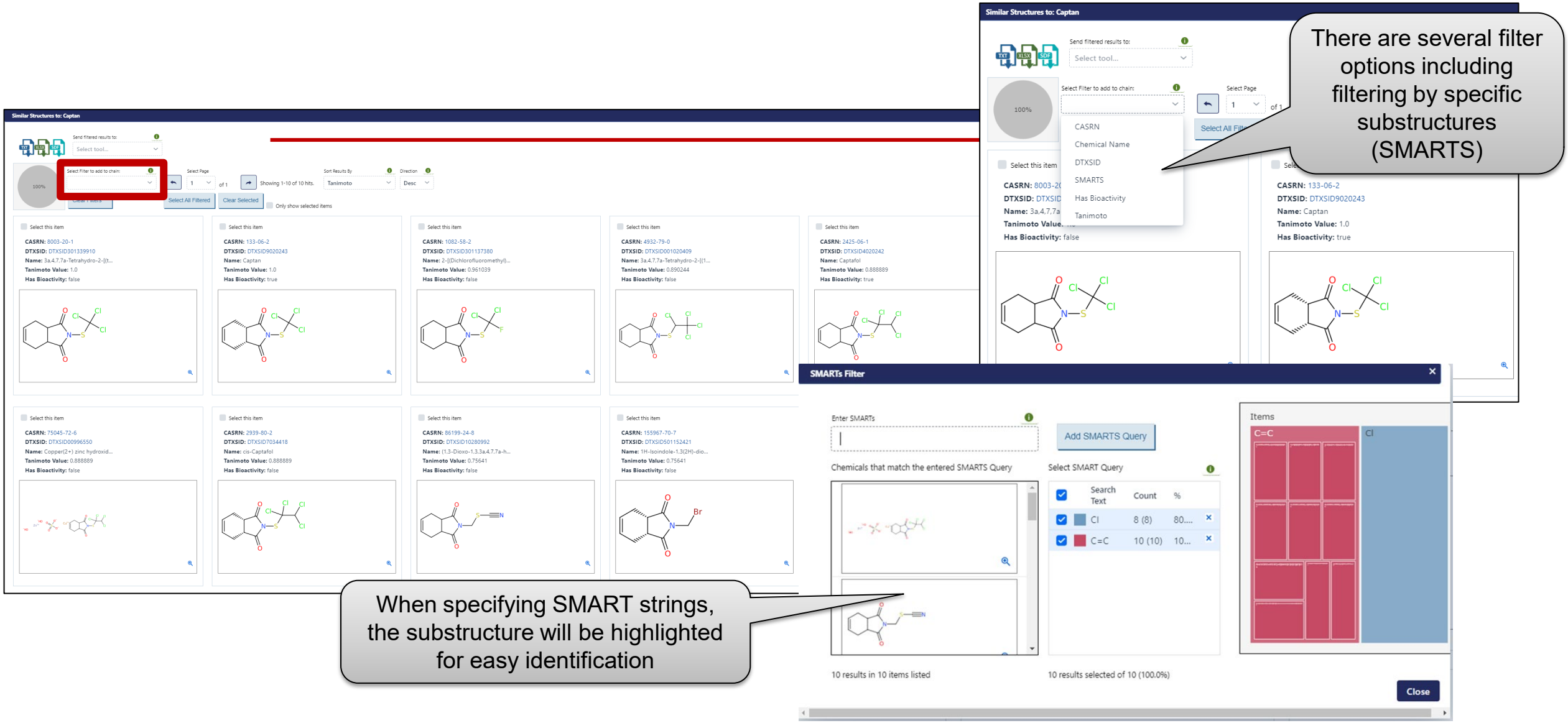
Chemical Quest Output - Filtering



Demo

Exploring ICE Chemical Quest using
“A Demo List of Chemicals”

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

Chemical Quest Summary

Supports identification of information for data poor chemicals

- Identify structurally similar chemicals within the ICE database or a specific list of chemicals
- Users to query chemicals by drawing and editing 2D chemical structures or by chemical identifiers (CASRN, DTXSID, Chemical Name, InChiKey or SMILES)
- Identifying structural features that may be driving factors in assay performance
- Sending all identified chemicals to other tools to understand potential links between structure and chemical characteristics or assay information

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Acknowledgments

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

The NICEATM Group

Integrated Chemical Environment

https://github.com/

OPERA OPEn (q)saR App

Sciome

https://www.sciome.com/

CEBS Chemical Effects in Biological Systems

https://cebs.niehs.nih.gov/cebs/

United States Environmental Protection Agency

https://comptox.epa.gov/dashboard

Subscribe to NICEATM News email list
https://list.nih.gov/cgi-bin/wa.exe?SUBED1=niceatm-l&A=1

United States ICCVAM Advancing Alternatives to Animal Testing

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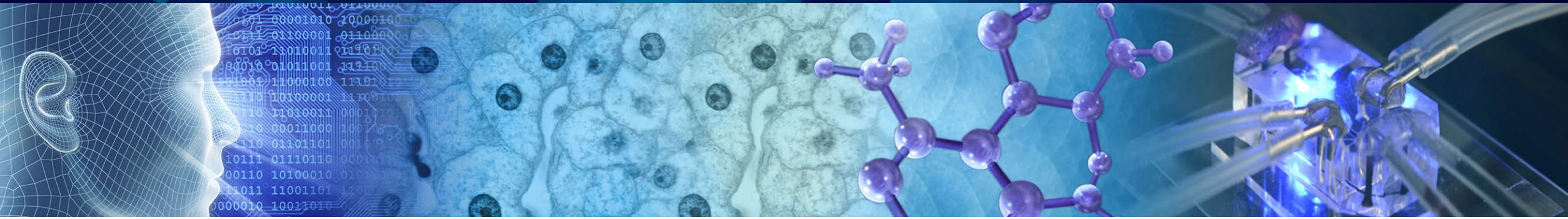


Using the Integrated Chemical Environment (ICE) to access interoperable computational tools and inform chemical hazard

12th ASCCT Annual Meeting
2023-10-25

Victoria Hull, Inotiv, Inc., Contractor Supporting the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)

Disclaimer: Inotiv staff provide technical support for NICEATM, but do not represent NIEHS, NTP, or the official positions of any federal agency.

Presentation Outline

1. Introduction
2. Chemical Characterization - Walkthrough and Demo
3. Curve Surfer - Walkthrough and Demo
4. PBPK - Walkthrough and Demo
5. IVIVE - Walkthrough and Demo
6. Summary
7. ICE Q&A

Introduction

- In the previous presentation, we introduced the ICE interface, explored ICE data sets, visualized various endpoints in Search, and used Chem Quest to expand chemical queries.
- Now we will explore interactive, interoperable tools in ICE that enable users to interpret large amounts of toxicologically relevant data and implement complex models through a user-friendly interface.
  - These tools include Chemical Characterization, Curve Surfer, Physiologically-based Pharmacokinetic models (PBPK), and In Vitro to In Vivo Extrapolation (IVIVE).
- We will build upon the case studies from the first presentation to demonstrate the use of these tools for exploring data and understanding potential chemical bioactivity.

ICE Tools Workflow

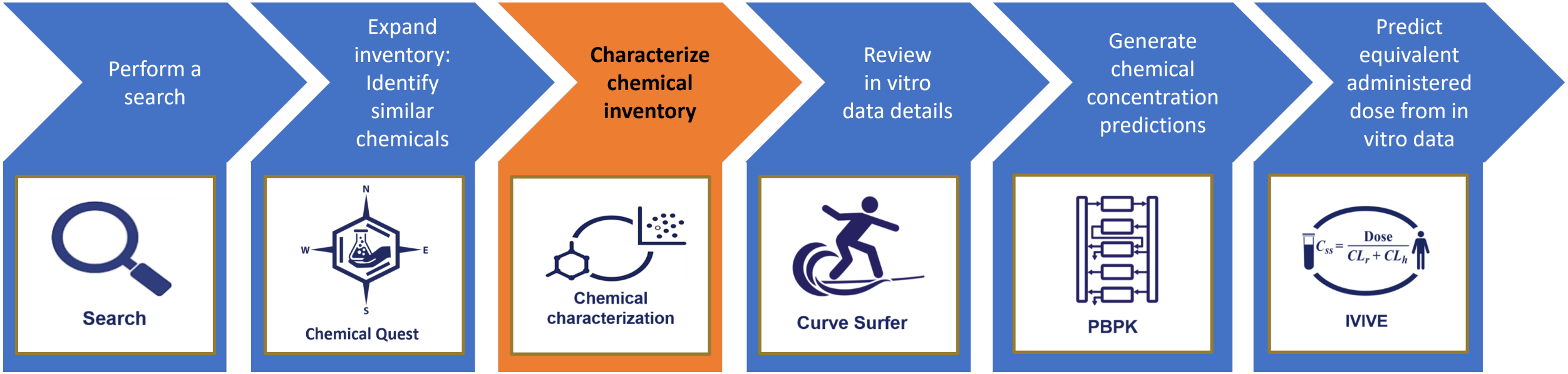
Integrated Chemical Environment

1. Perform a search
   - Search
2. Expand inventory: Identify similar chemicals
   - Chemical Quest
3. Characterize chemical inventory
   - Chemical characterization
4. Review in vitro data details
   - Curve Surfer
5. Generate chemical concentration predictions
   - PBPK
6. Predict equivalent administered dose from in vitro data
   - IVIVE

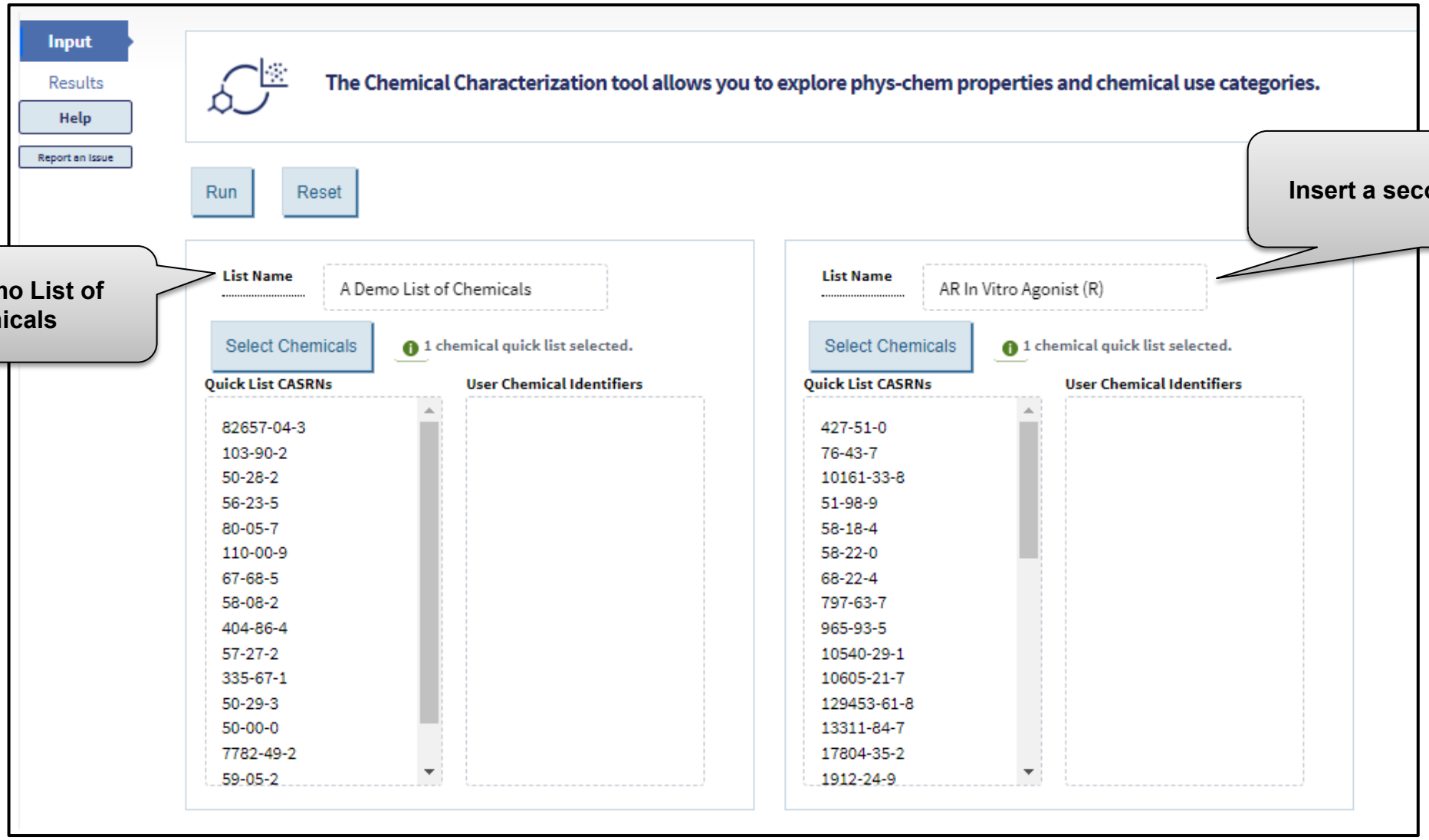
ICE Tools Workflow

Integrated Chemical Environment

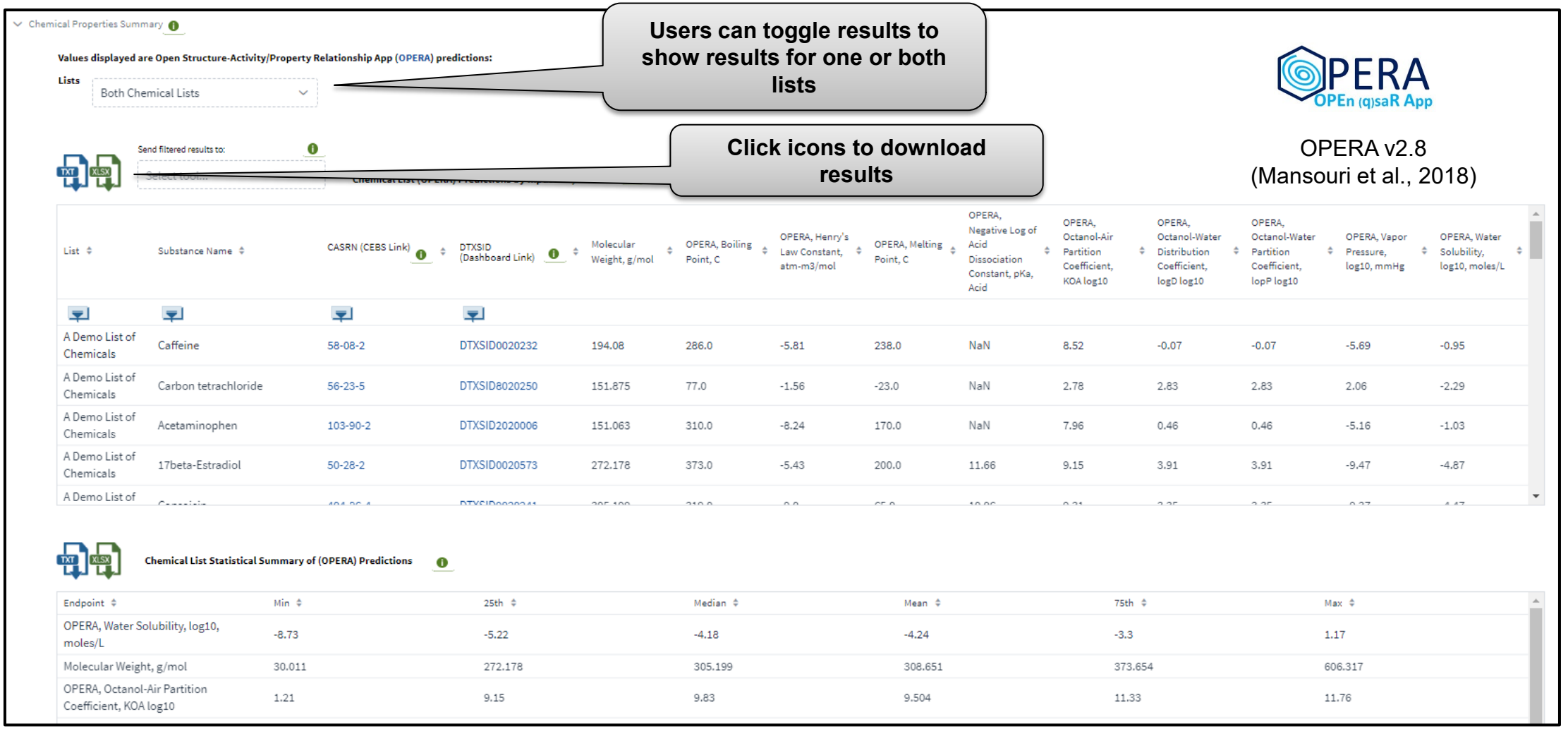
The Chemical Characterization tool can help compare chemical properties and chemical use categories.



Compare phys-chem properties and use categories of two chemicals lists



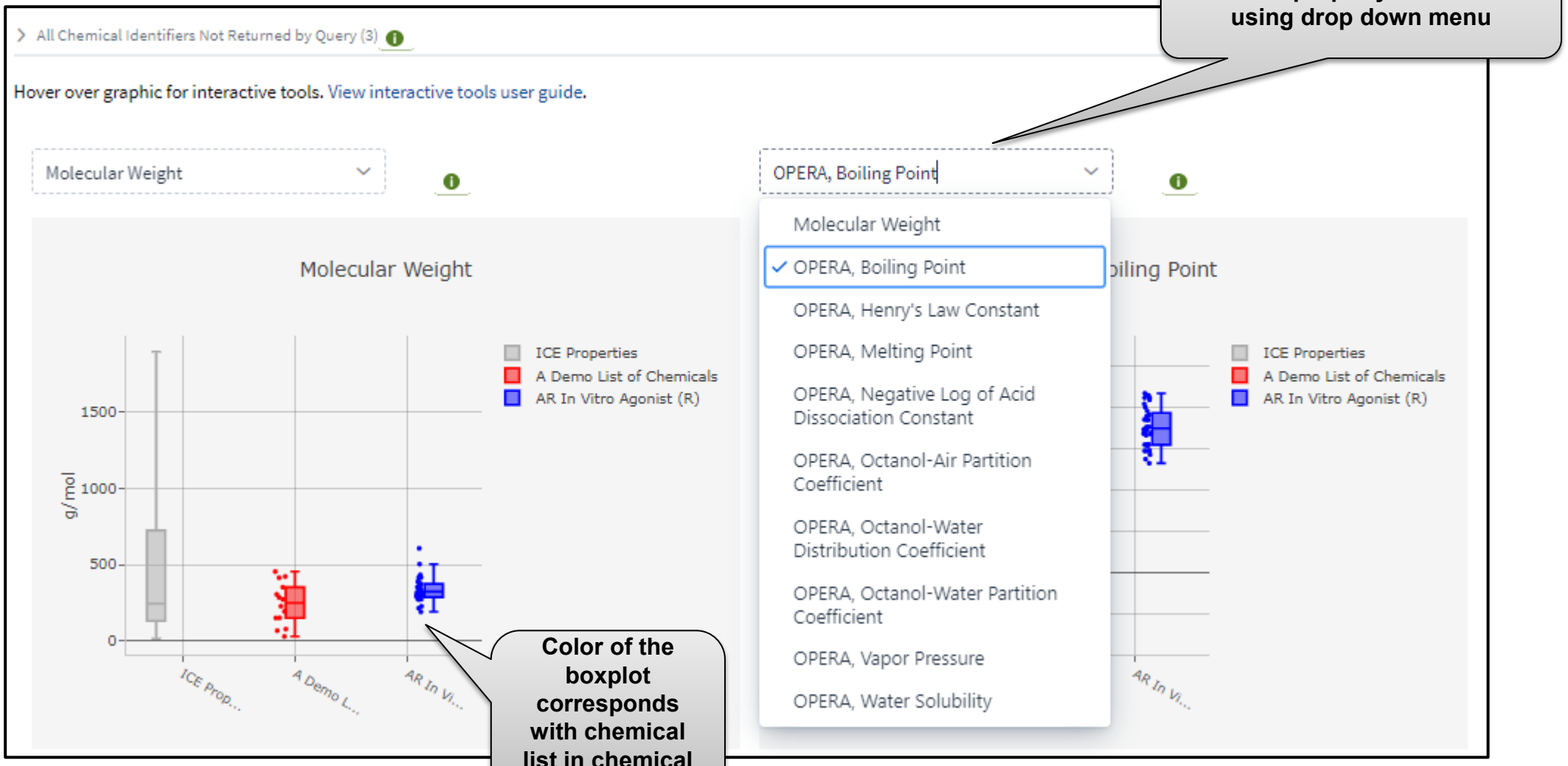
View and download chemical properties for individual chemicals or summarize chemical lists



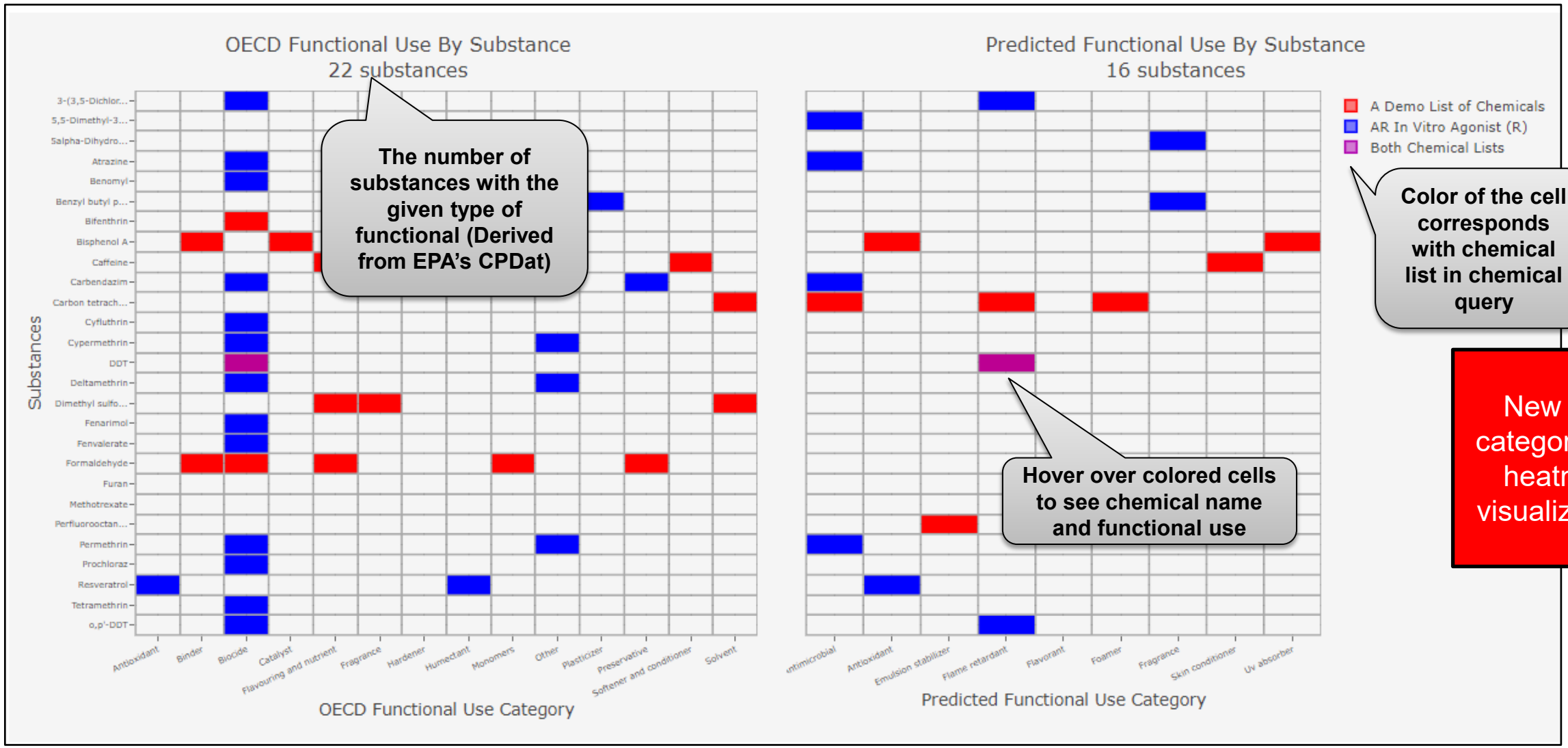
List	Substance Name	CASRN (CEBS Link)	DTXSID (Dashboard Link)	Molecular Weight, g/mol	OPERA, Boiling Point, C	OPERA, Henry's Law Constant, atm-m3/mol	OPERA, Melting Point, C	OPERA, Negative Log of Acid Dissociation Constant, pKa, Acid	OPERA, Octanol-Air Partition Coefficient, KOA log10	OPERA, Octanol-Water Distribution Coefficient, logD log10	OPERA, Octanol-Water Partition Coefficient, logP log10	OPERA, Vapor Pressure, log10, mmHg	OPERA, Water Solubility, log10, moles/L
A Demo List of Chemicals	Caffeine	58-08-2	DTXSID0020232	194.08	286.0	-5.81	238.0	NaN	8.52	-0.07	-0.07	-5.69	-0.95
A Demo List of Chemicals	Carbon tetrachloride	56-23-5	DTXSID8020250	151.875	77.0	-1.56	-23.0	NaN	2.78	2.83	2.83	2.06	-2.29
A Demo List of Chemicals	Acetaminophen	103-90-2	DTXSID2020006	151.063	310.0	-8.24	170.0	NaN	7.96	0.46	0.46	-5.16	-1.03
A Demo List of Chemicals	17beta-Estradiol	50-28-2	DTXSID0020573	272.178	373.0	-5.43	200.0	11.66	9.15	3.91	3.91	-9.47	-4.87
A Demo List of													

Endpoint	Min	25th	Median	Mean	75th	Max
OPERA, Water Solubility, log10, moles/L	-8.73	-5.22	-4.18	-4.24	-3.3	1.17
Molecular Weight, g/mol	30.011	272.178	305.199	308.651	373.654	606.317
OPERA, Octanol-Air Partition Coefficient, KOA log10	1.21	9.15	9.83	9.504	11.33	11.76

Visualize physicochemical properties

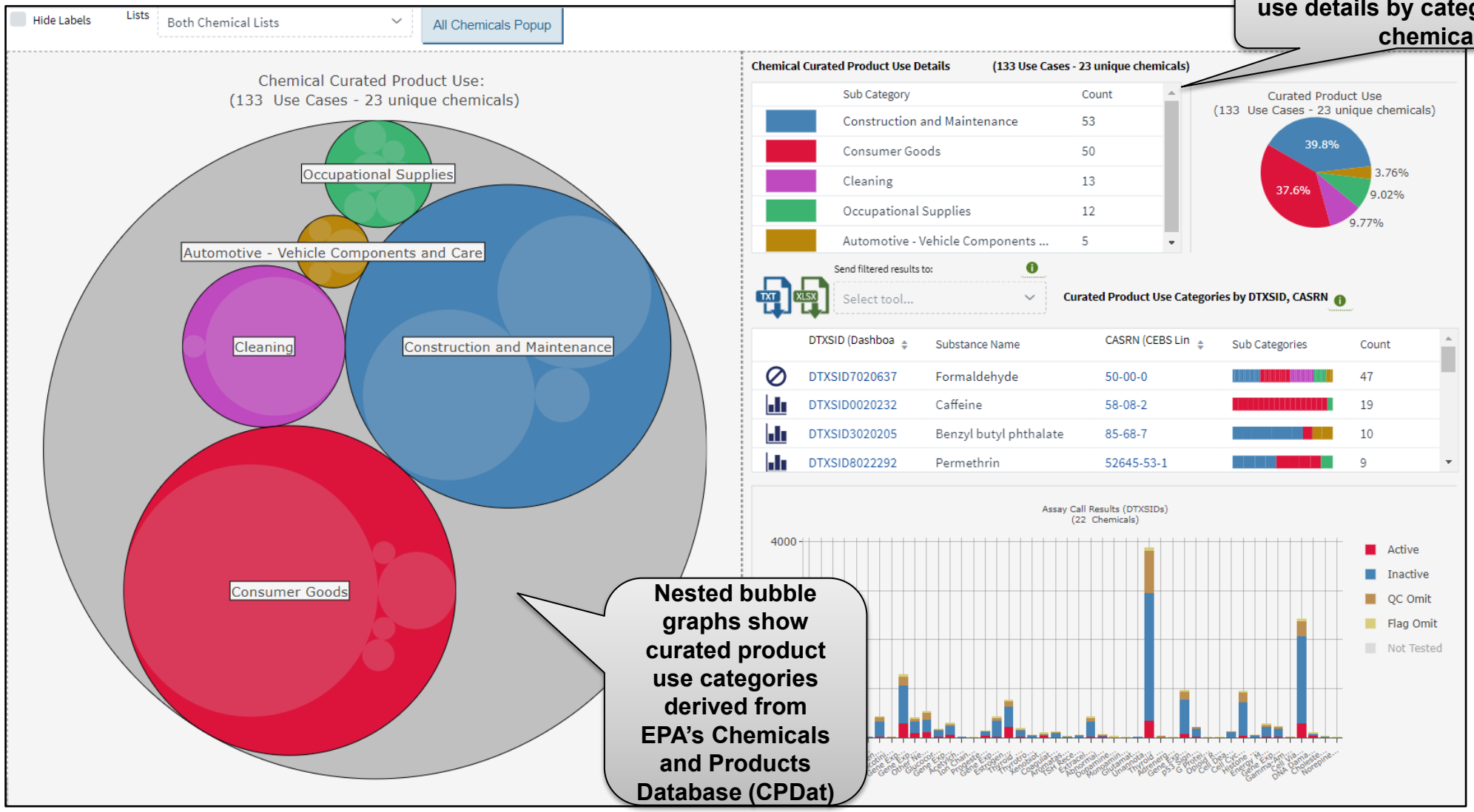


Explore Functional Use Categories



CPDat v3 (Williams, 2017)

Explore Curated Product Use Categories



Summary details show product use details by category and by chemical

Nested bubble graphs show curated product use categories derived from EPA's Chemicals and Products Database (CPDat)

Consumer use categories are now called curated product use categories!

CPDat v3
(Williams, 2017;
Philips et al. 2018)

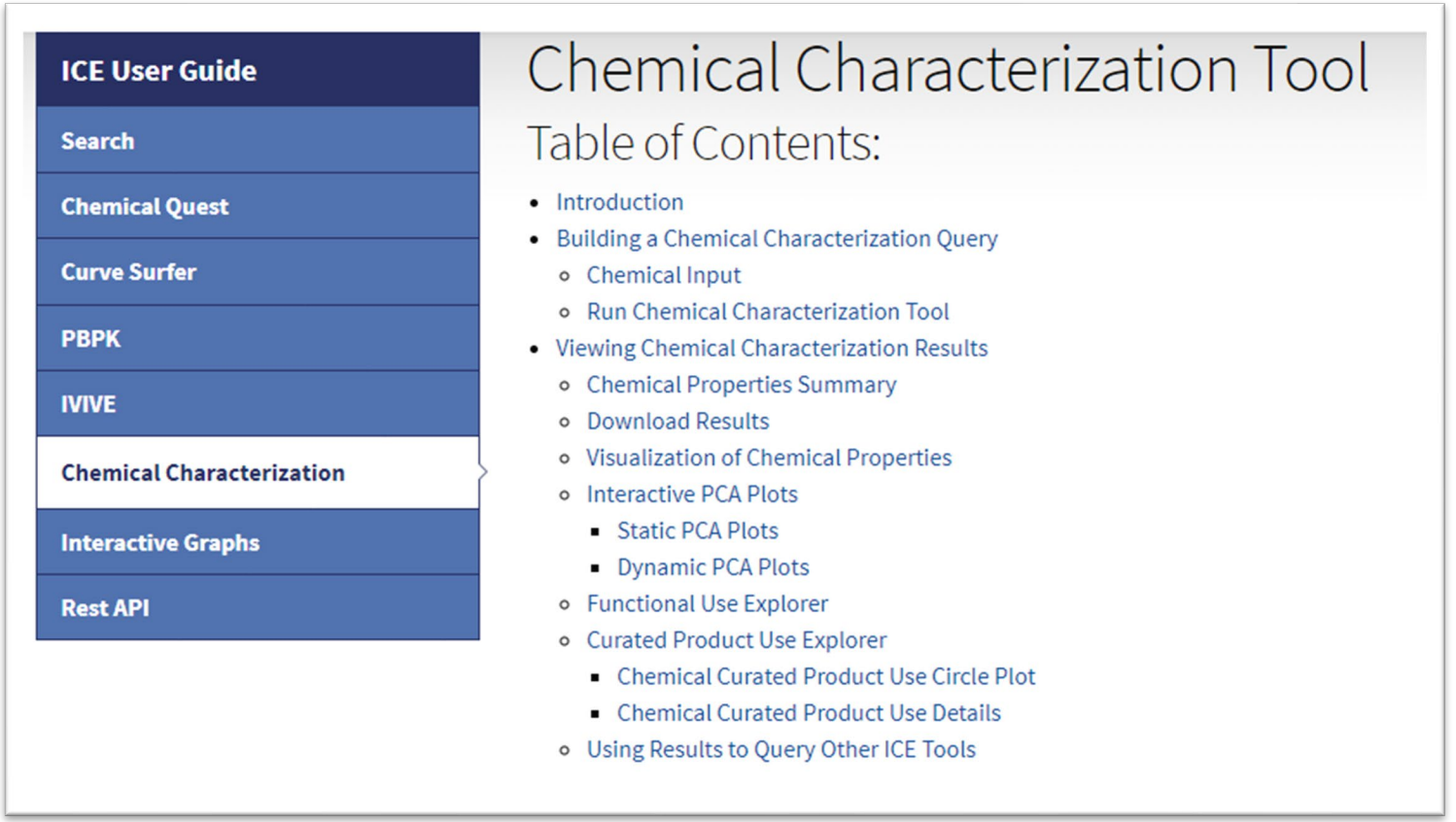
Demo

Chemical Characterization

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

Chemical Characterization Summary

- Comparison tool that allows users to look at the **property distribution and chemical use cases between one or two lists of chemicals**
- Examine what properties may be driving differences in performance of chemicals in assays
- Explore different the role a chemical may play in a product and what products a chemical has been found in
- Characterize the differences between lists to identify possible redundancy or define the range of property coverage in preparation for testing



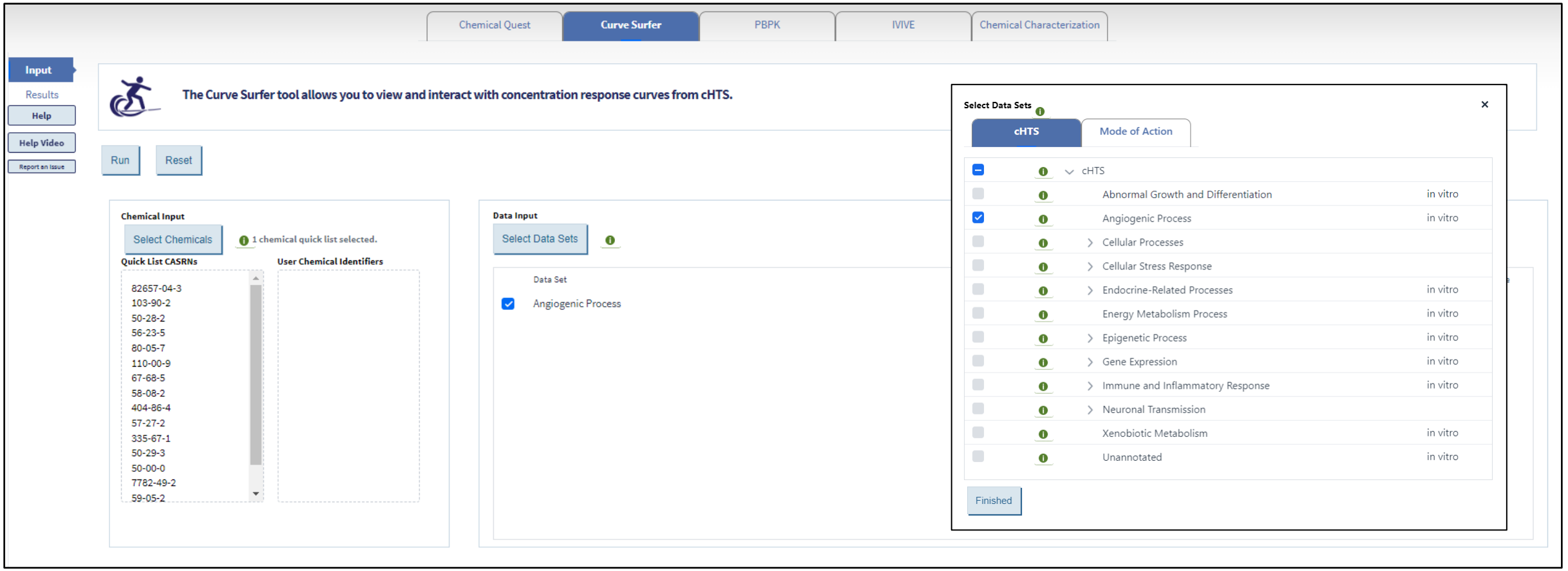
ICE Tools Workflow

Integrated Chemical Environment

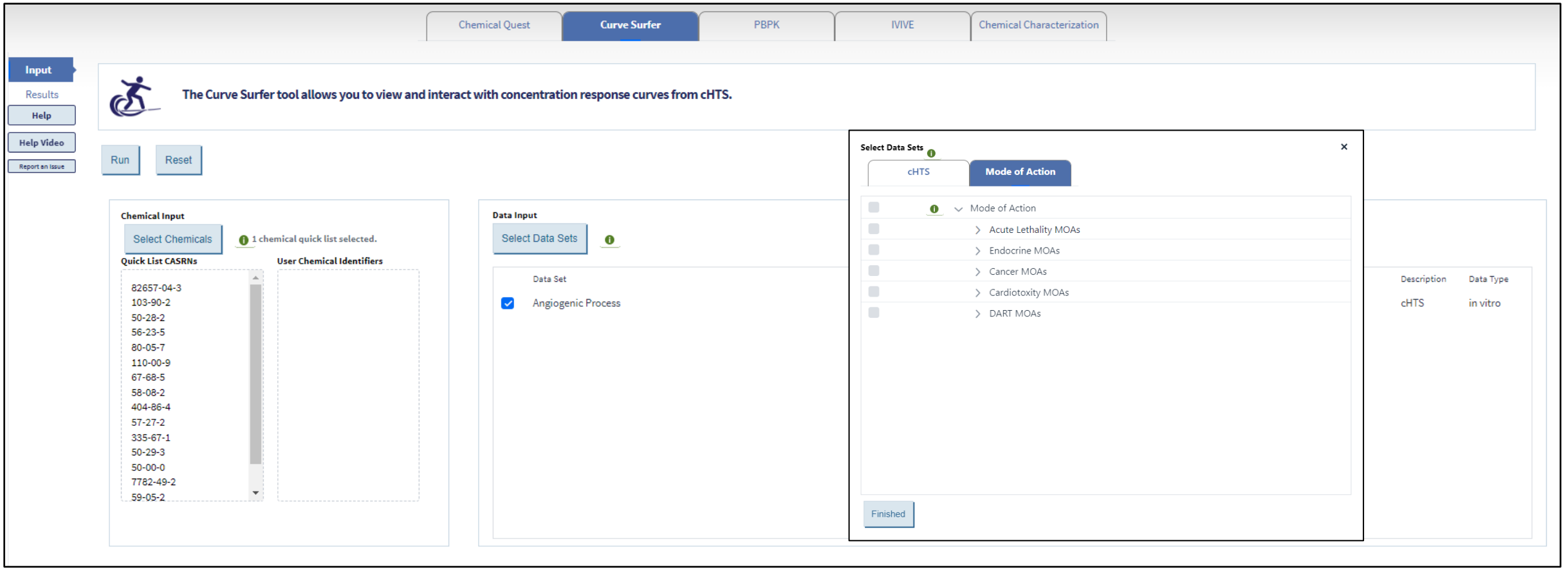
The Curve Surfer tool provides concentration-response curves for curated High Throughput Screening (cHTS) data, providing detailed information on EPA's ToxCast and Tox21 assays.

1. Perform a search
   - Search
2. Expand inventory: Identify similar chemicals
   - Chemical Quest
3. Characterize chemical inventory
   - Chemical characterization
4. **Review cHTS concentration-response curves**
   - Curve Surfer
5. Generate chemical concentration predictions
   - PBPK
6. Predict equivalent administered dose from in vitro data
   - IVIVE

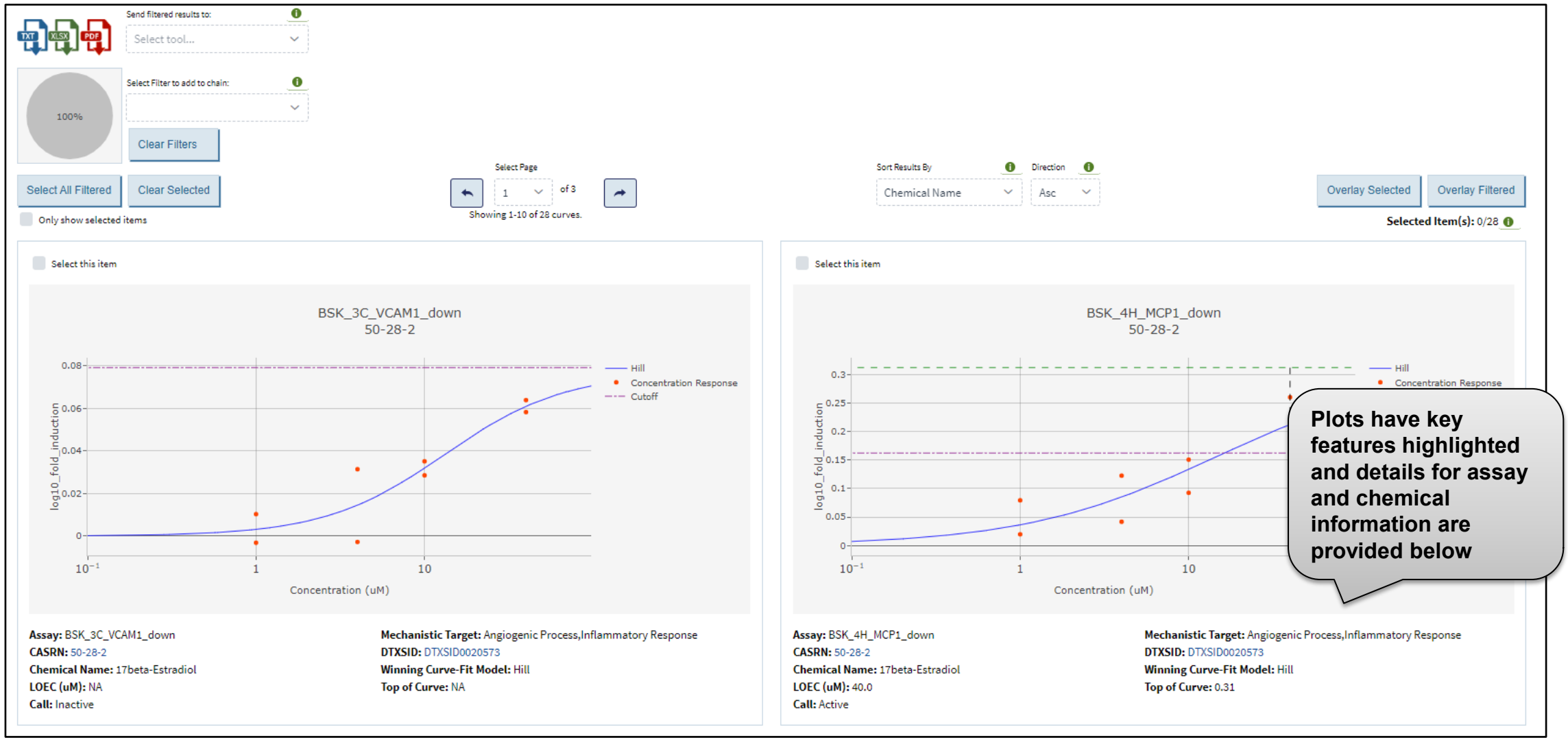
Select chemical list and assay mechanistic target



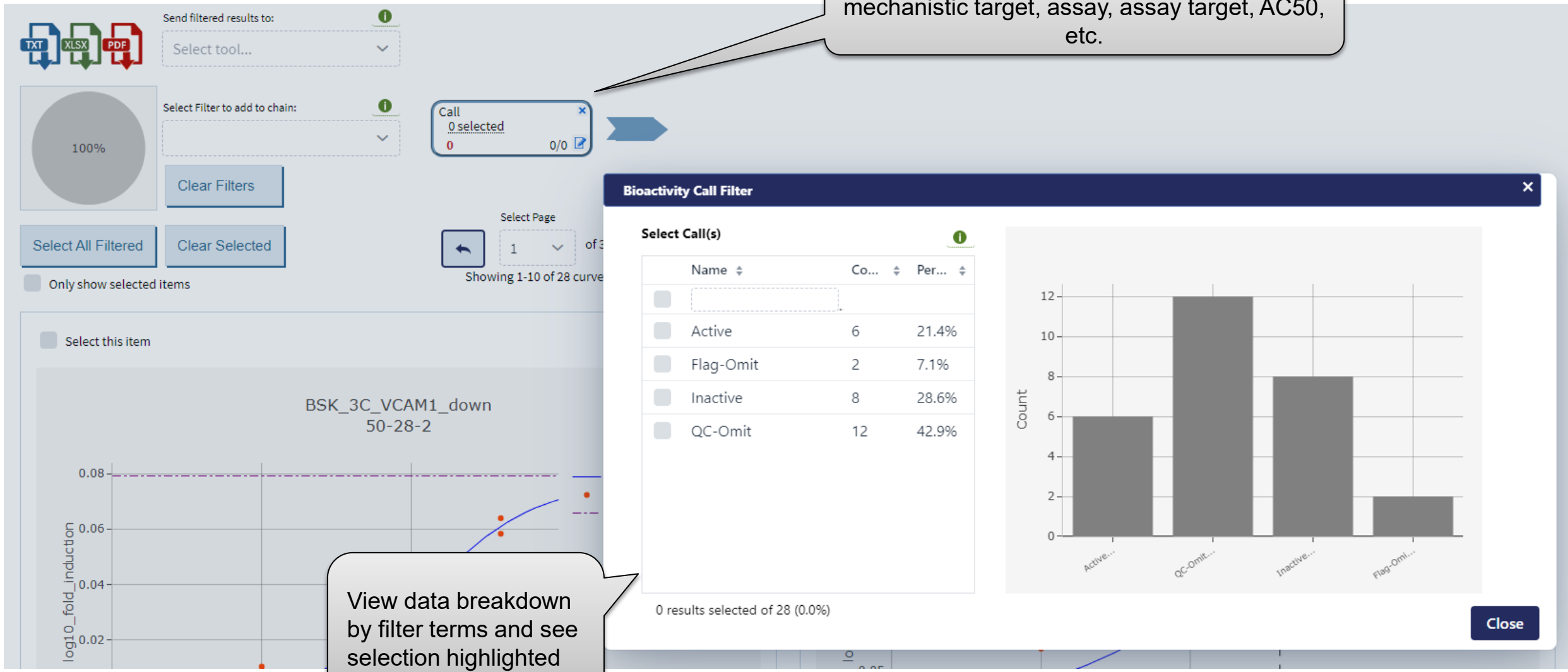
Select chemical list and assay mode of action



View concentration-response curves, bioactivity, and assay information for cHTS data



Filter chain allows users to filter based on call, mechanistic target, assay, assay target, AC50, etc.

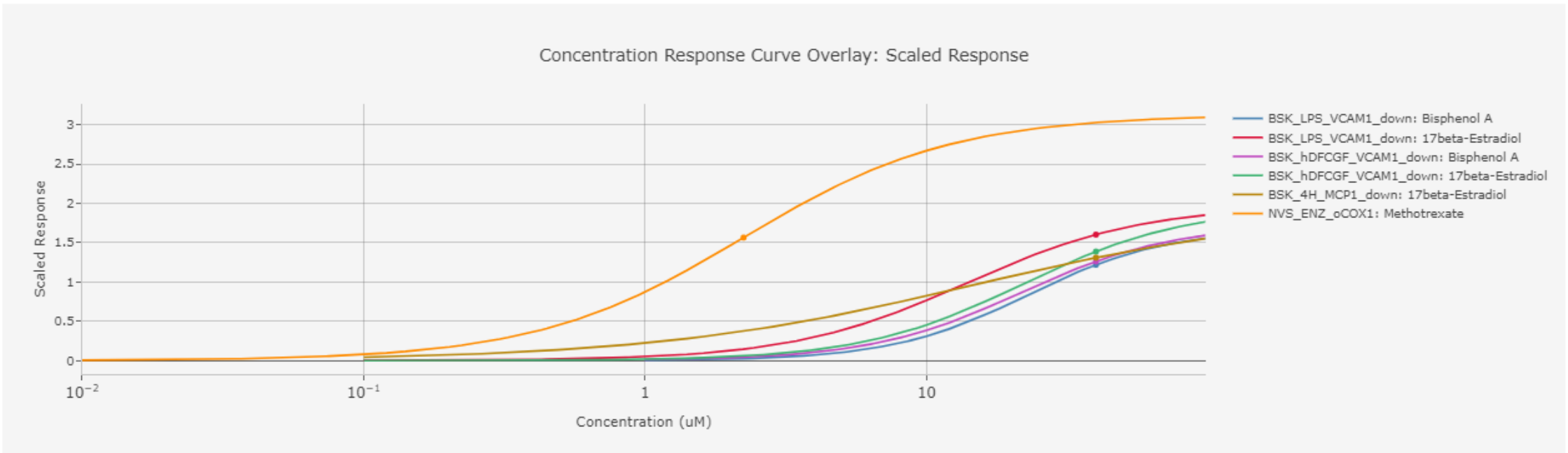


View data breakdown by filter terms and see selection highlighted

Select curves based on y-axis types including scaled response, percent activity and log2_fold_induction

Curve Overlay Plots

3-D | Show Actives | Select Normalized Data Type: Scaled Response



Close

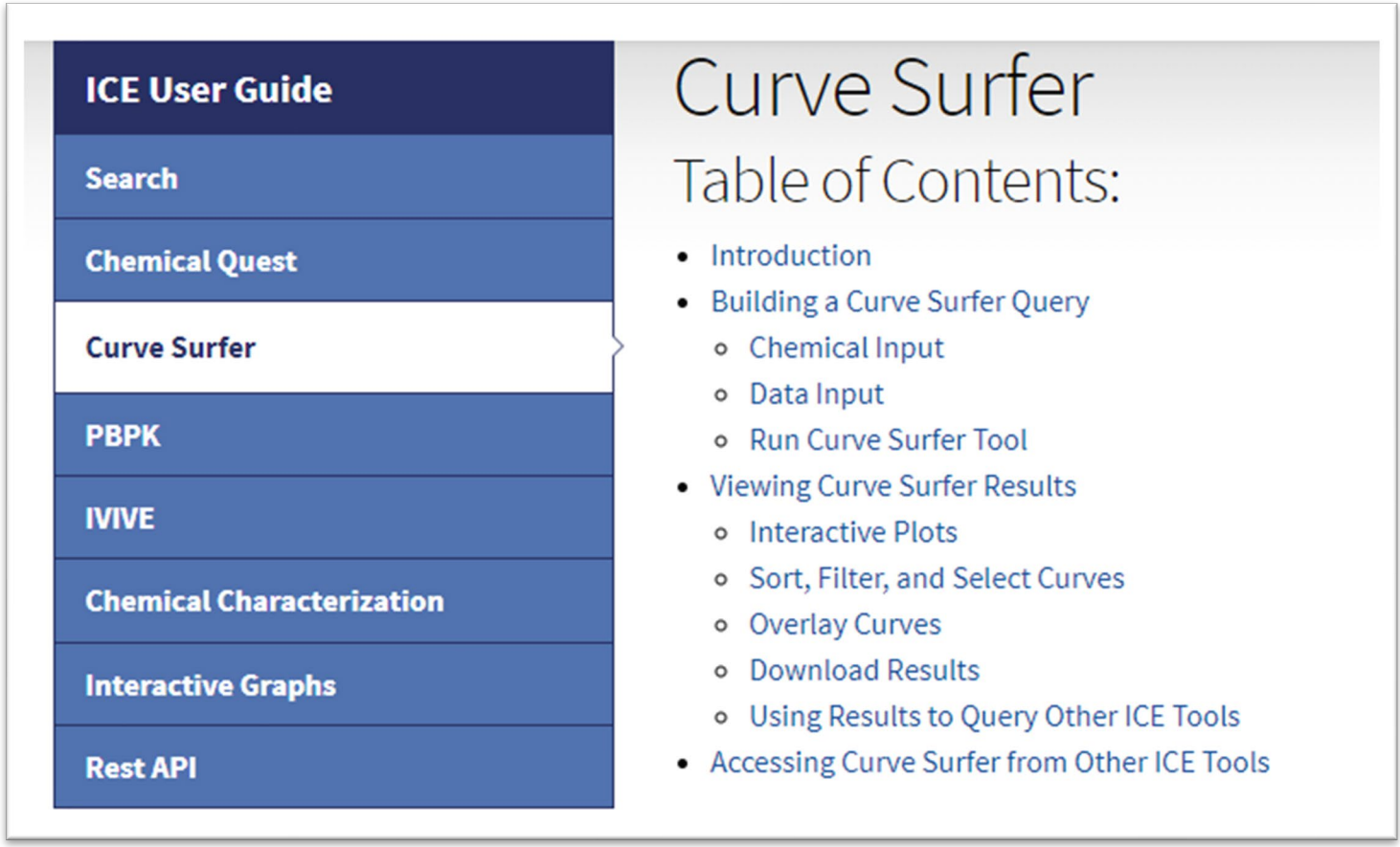
Demo

Curve Surfer

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

Curve Surfer Summary

- Visualize concentration response-curves for curated high-throughput screening (cHTS) data derived from ToxCast and Tox21
- Explore bioactivity calls, including actives, inactives, flag-omits, and QC-omits
- Relate assays to biological processes through annotations for mode of action and mechanistic target
- Use filtering to narrow down on assay data of interest for reviewing concentration-response curves



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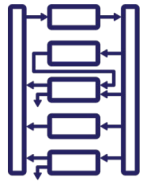
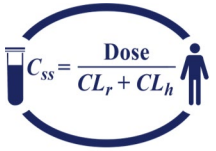
ICE Tools Workflow

Integrated Chemical Environment

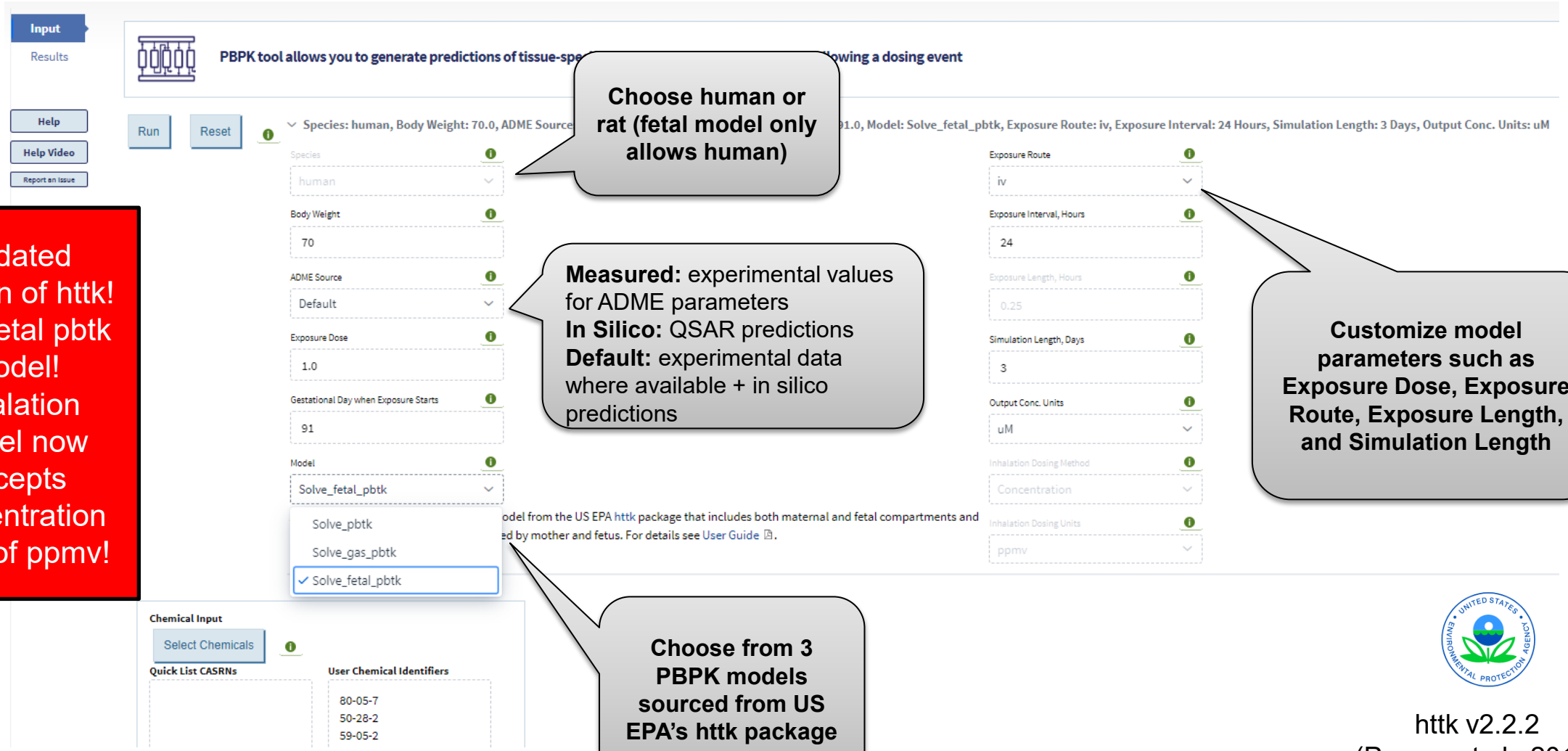
The Physiologically Based Pharmacokinetic (PBPK) tool provides predictions of tissue-specific chemical concentration profiles following a dosing event.

1. Perform a search
   - Search
2. Expand inventory: Identify similar chemicals
   - Chemical Quest
3. Characterize chemical inventory
   - Chemical characterization
4. Review in vitro data details
   - Curve Surfer
5. Generate chemical concentration predictions
   - PBPK
6. Predict equivalent administered dose from in vitro data
   - IVIVE





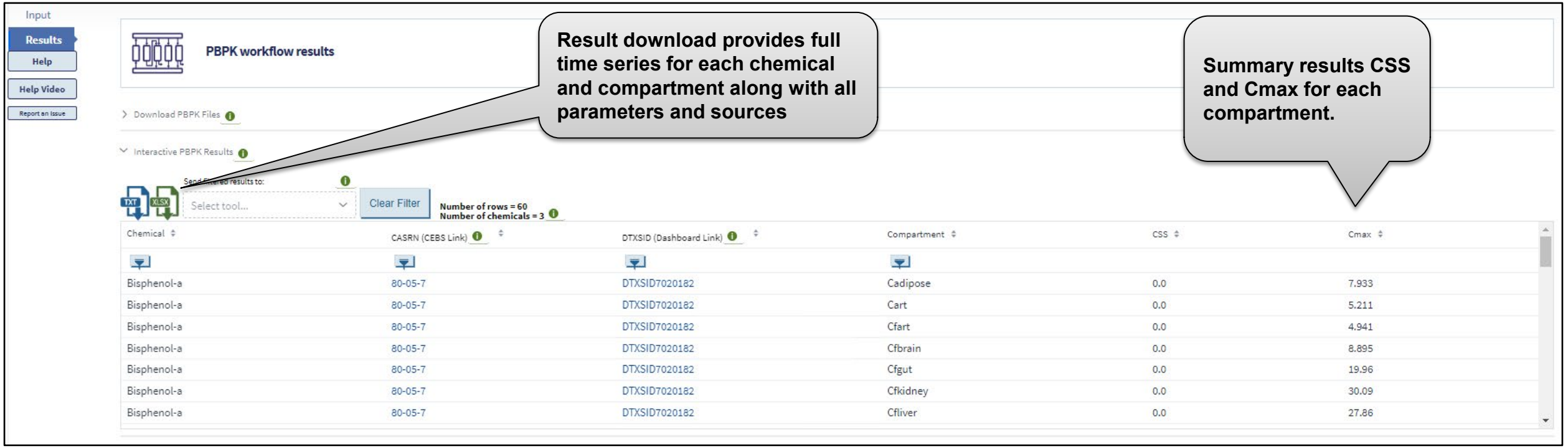
Parameterize PBPK models for a chemical list



Updated version of httk! New fetal pbtk model! Inhalation model now accepts concentration units of ppmv!

httk v2.2.2
(Pearce et al., 2017)

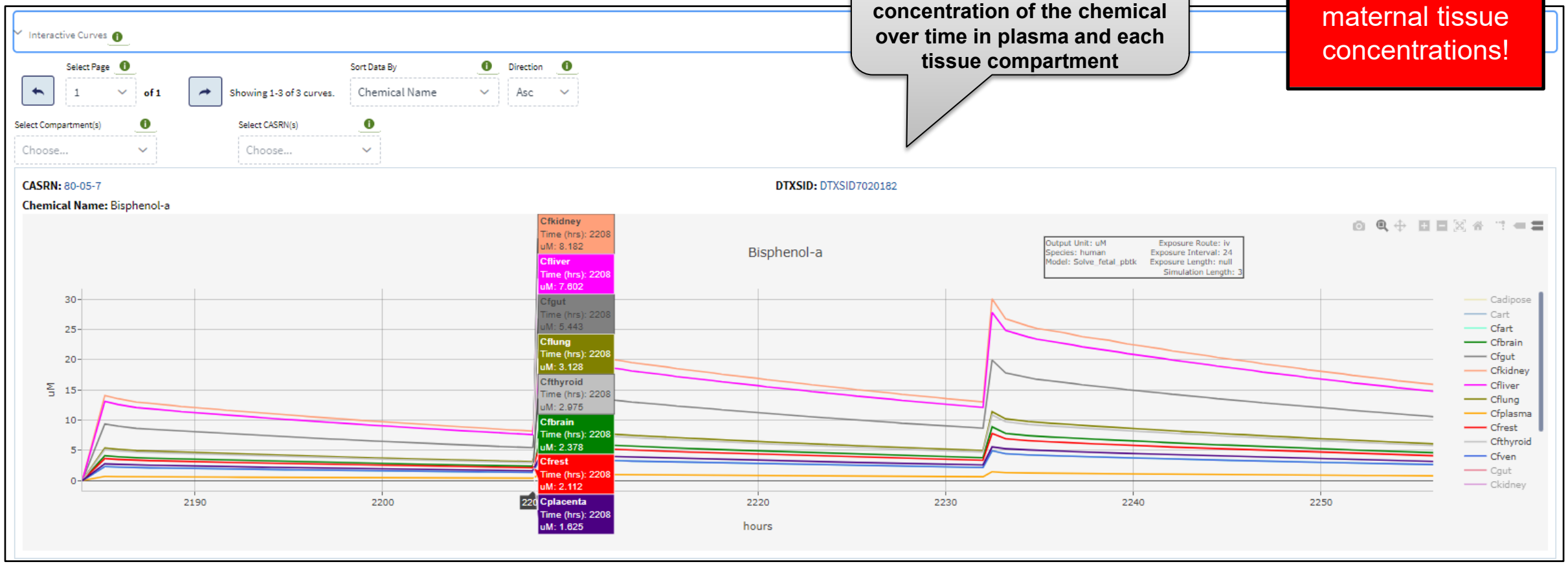
View PBPK results in an interactive table



Visualize PBPK results

For each input chemical, the results show the concentration of the chemical over time in plasma and each tissue compartment

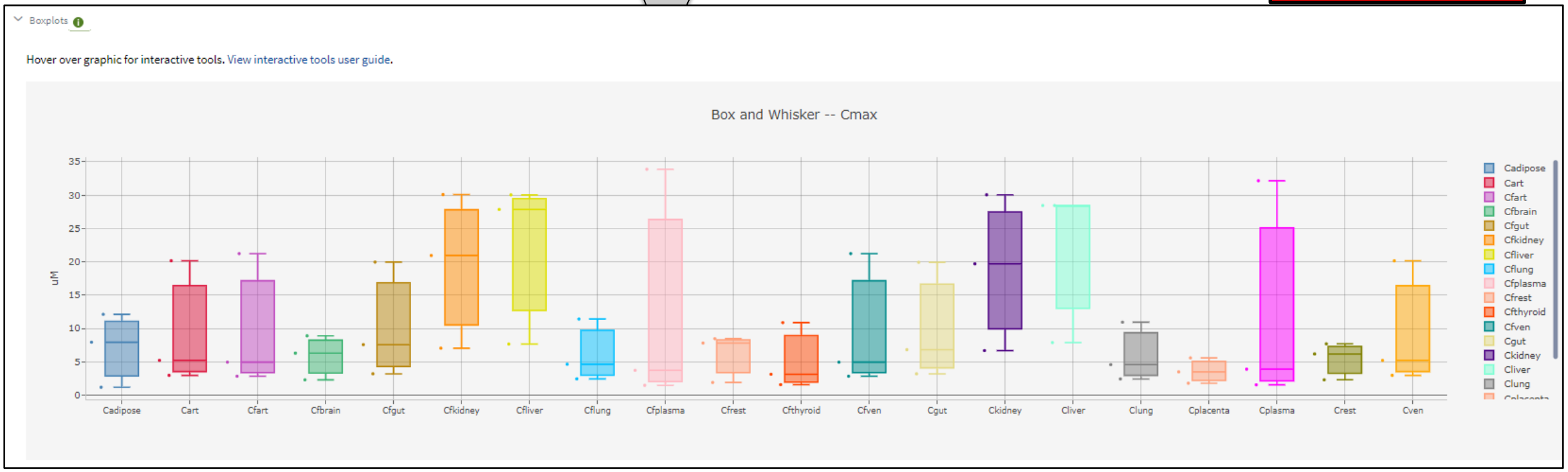
Visualize fetal and maternal tissue concentrations!



Visualize PBPK results

Boxplots show the Cmax distribution across all returned chemicals for each compartment

Visualize fetal and maternal tissue concentrations!



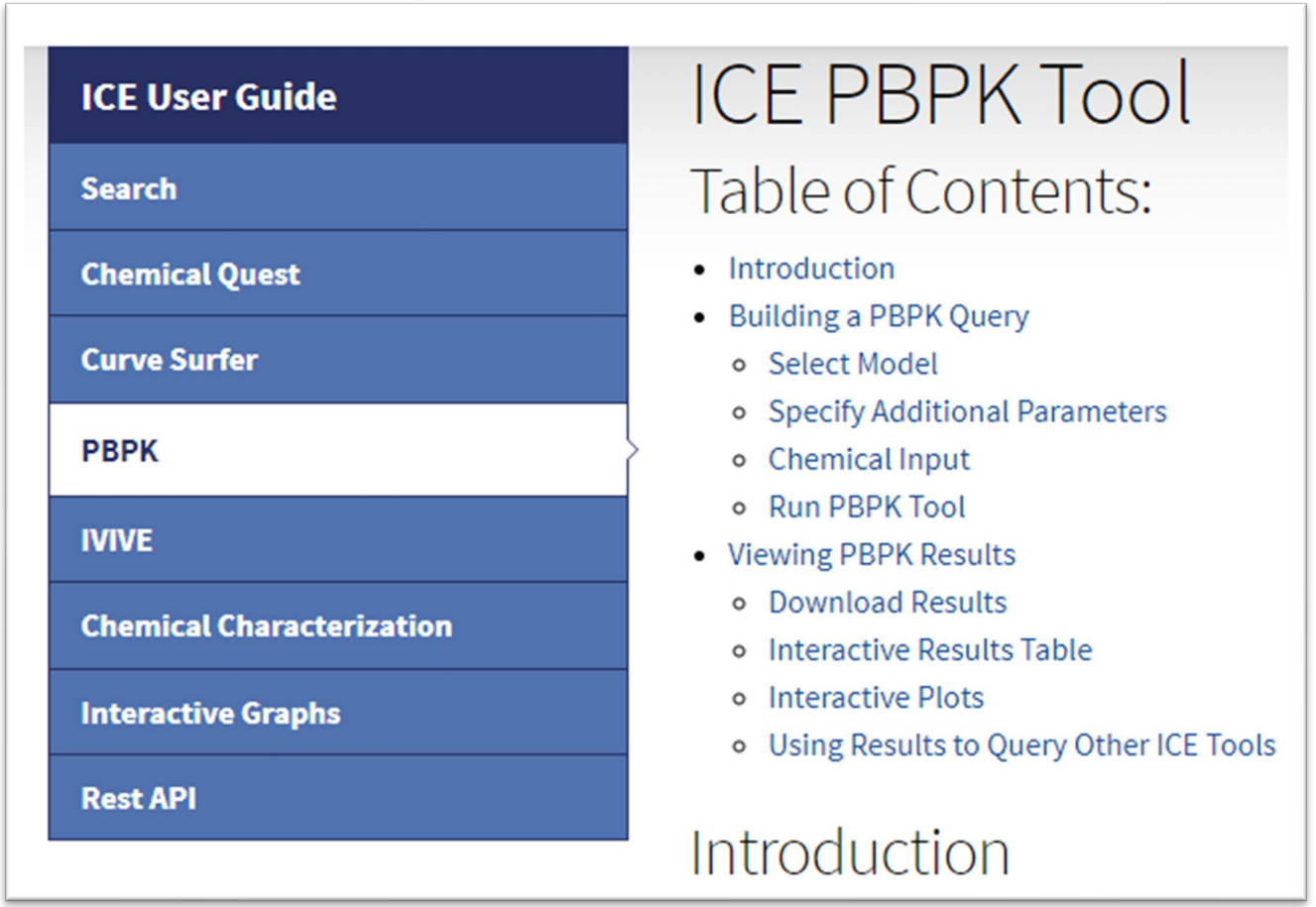
Demo

PBPK

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

PBPK Demo

- Physiologically Base Pharmacokinetic (PBPK) models describe:
  - Absorption, Distribution, Metabolism, and Excretion
- ICE PBPK tool uses multiple generalized models from U.S. EPA's httk R package
  - Includes 3 different exposure routes
- PBPK allows users to:
  - Relate external doses to internal concentrations
  - Screen for chemicals that may accumulate
  - Predict residence time for chemical/drug exposures



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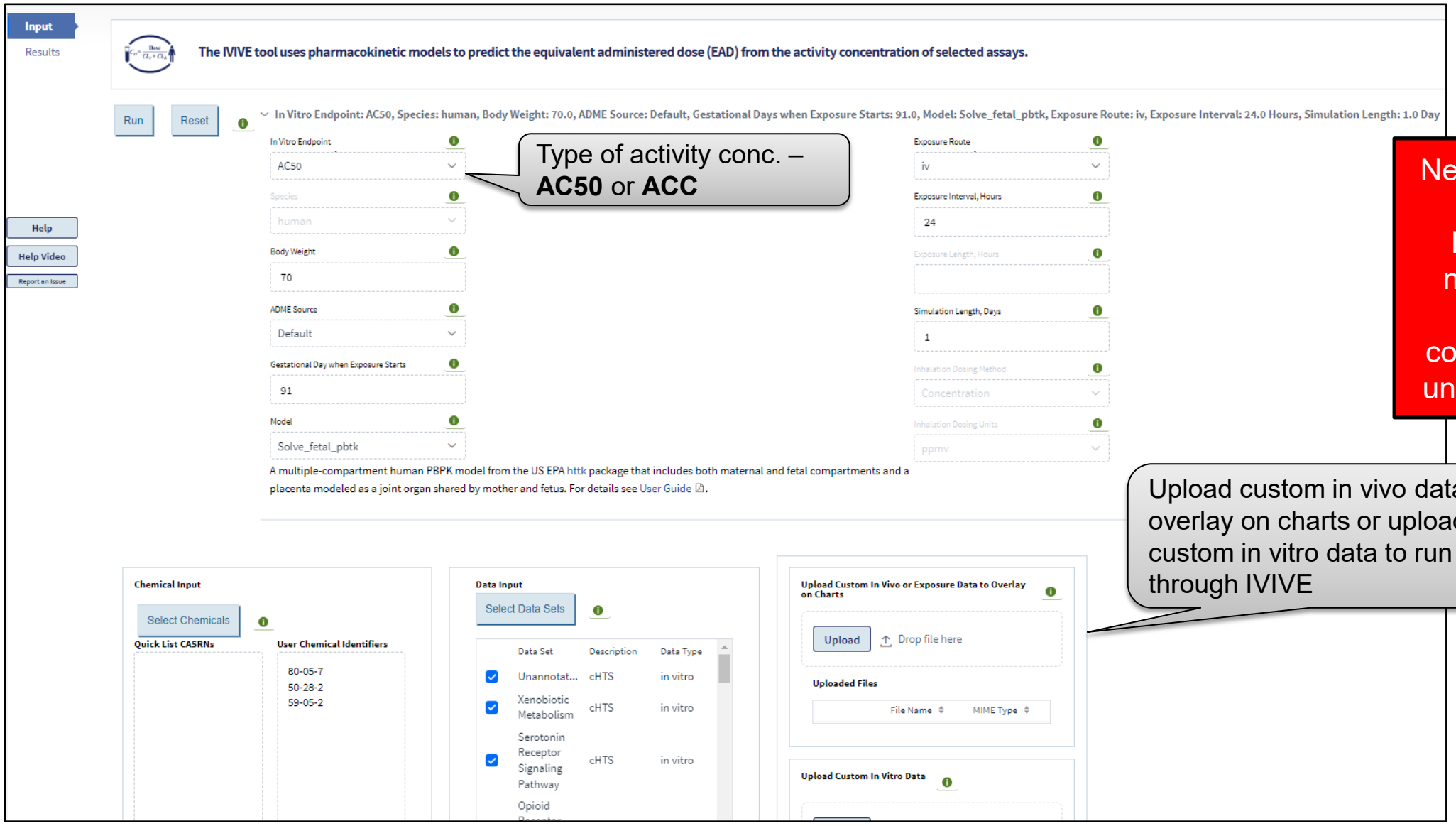
ICE Tools Workflow

Integrated Chemical Environment

IVIVE tool allows the estimation of daily equivalent administered dose (EAD) that would result in the plasma concentration of a chemical equal to the active concentration in a given in vitro assay.

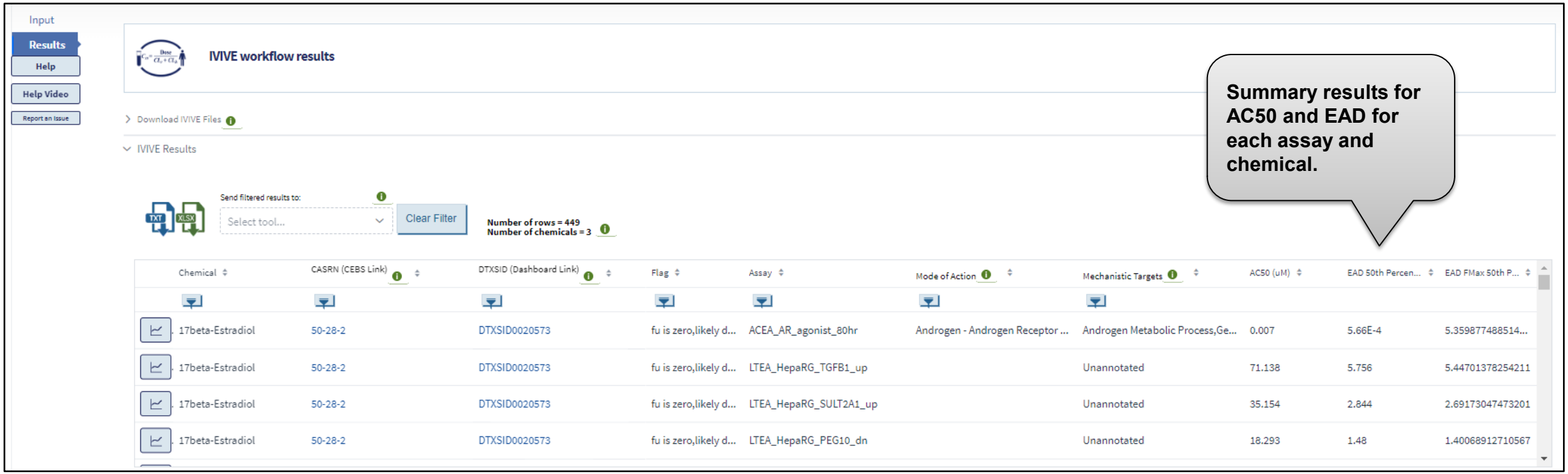
1. Perform a search
   - Search
2. Expand inventory: Identify similar chemicals
   - Chemical Quest
3. Characterize chemical inventory
   - Chemical characterization
4. Review in vitro data details
   - Curve Surfer
5. Generate chemical concentration predictions
   - PBPK
6. Predict equivalent administered dose from in vitro data
   - IVIVE

Parameterize IVIVE models for a chemical list



httk v2.2.2 (Pearce et al., 2017)

View and download IVIVE results



Chemical	CASRN (CEBS Link)	DTXSID (Dashboard Link)	Flag	Assay	Mode of Action	Mechanistic Targets	AC50 (uM)	EAD 50th Percen...	EAD FMax 50th P...
17beta-Estradiol	50-28-2	DTXSID0020573	fu is zero,likely d...	ACEA_AR_agonist_80hr	Androgen - Androgen Receptor ...	Androgen Metabolic Process,Ge...	0.007	5.66E-4	5.359877488514...
17beta-Estradiol	50-28-2	DTXSID0020573	fu is zero,likely d...	LTEA_HepaRG_TGFB1_up		Unannotated	71.138	5.756	5.44701378254211
17beta-Estradiol	50-28-2	DTXSID0020573	fu is zero,likely d...	LTEA_HepaRG_SULT2A1_up		Unannotated	35.154	2.844	2.69173047473201
17beta-Estradiol	50-28-2	DTXSID0020573	fu is zero,likely d...	LTEA_HepaRG_PEG10_dn		Unannotated	18.293	1.48	1.40068912710567

Visualize IVIVE results

Boxplot of EAD for input chemicals

Violin plot of in vitro input values showing distribution of bioactivity

National Institute of Environmental Health Sciences
Division of Translational Toxicology

IVIVE

IVIVE Results Visualizations

Select EAD to visualize: EAD 50th

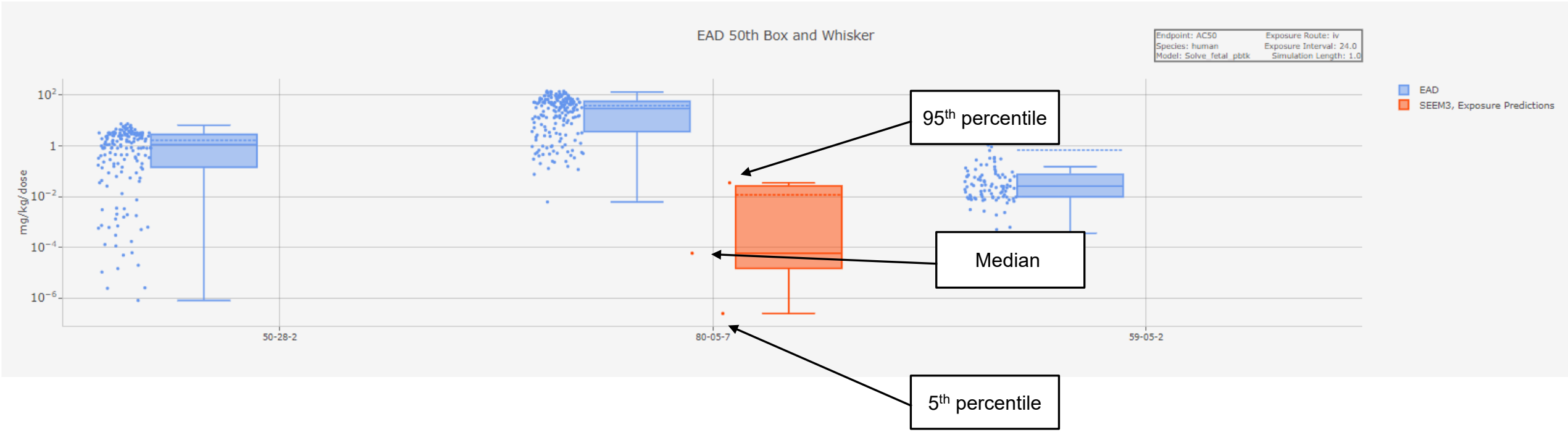
Select in vivo data or exposure data to display. Exposure Predictions

Log Axis Show Name

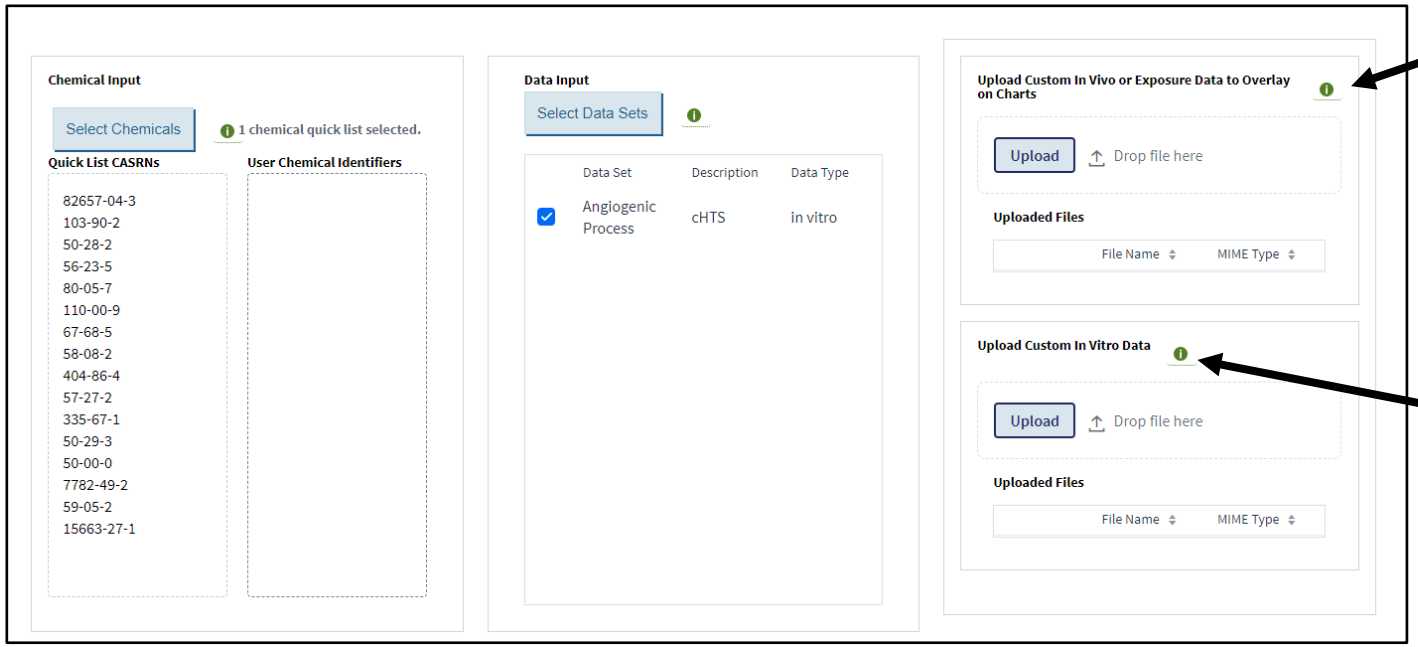
Select Page 1 of 1 Showing 1-3 of 3 chemicals.

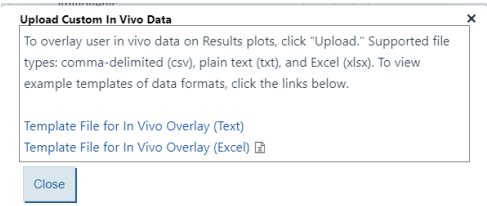
Hover over graphic for interactive tools. View interactive tools user guide.

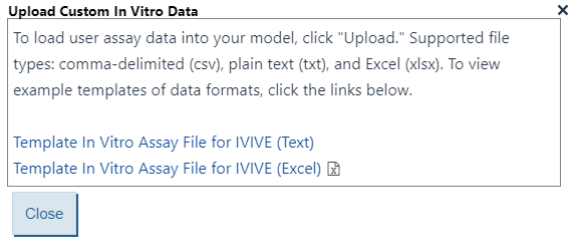
Overlay new exposure predictions from EPA's SEEM3!



Run IVIVE Using Custom Data







Custom In vitro data template

casrn	user assay1	user assay2	user assay3	user assay4
115-32-2	1.2	1.3	1.5	1.7
117-81-7	2.2	2.3	2.5	2.7
120-47-8	3.6	3.7	3.8	3.9
13311-84-7	4.1	4.2	4.3	4.4
140-66-9	5.1	5.2	5.3	5.4
57-85-2	1.2	1.3	1.5	1.7
10161-33-8	2.2	2.3	2.5	2.7
58-22-0	3.6	3.7	3.8	3.9
58-18-4	4.1	4.2	4.3	4.4
57-85-2	5.1	5.2	5.3	5.4
10161-33-8	3.6	3.7	3.8	3.9
58-22-0	4.1	4.2	4.3	4.4

Custom In vitro data template

casn	dxsid	chem name	dataset	assay1	assay2	assay3	assay4	assay5	assay6	assay7	assay8	assa9	assay10	assay11
115-32-2	dtxsid1	17-Methylte	dataset 1	1	23	4	213	8	9		98	9	9	
117-81-7	dtxsid2	Testosterone	dataset 1	55	65	55	4	3	466		66	88	8	986
120-47-8	dtxsid2	17beta-Trenl	dataset 1	788	887	997	778	997	997	56	7	76	677	2
13311-84-7	dtxsid2	Testosterone	dataset 1	9876	7687	877	679	547	123	234	45	456	67	56
140-66-9	dtxsid1	17-Methylte	dataset 2	987	76	987	4	54	54	556	456	567	778	23
57-85-2	dtxsid2	Testosterone	dataset 2	98		9	98			98			98	98
10161-33-8	dtxsid2	17beta-Trenl	dataset 2	123		2345	567	567			45		566	6
58-22-0	dtxsid2	Testosterone	dataset 2	876			87		6443	345		678		322
58-18-4	dtxsid1	17-Methylte	dataset 3	987	234	23	567	775	445	7878	123	456	8	6
57-85-2	dtxsid2	Testosterone	dataset 3	1	23	4	213	8	9		98	9	9	
10161-33-8	dtxsid2	17beta-Trenl	dataset 3	55	65	55	4	3	466		66	88	8	986
58-22-0	dtxsid2	Testosterone	dataset 3	788	887	997	778	997	997	56	7	76	677	2

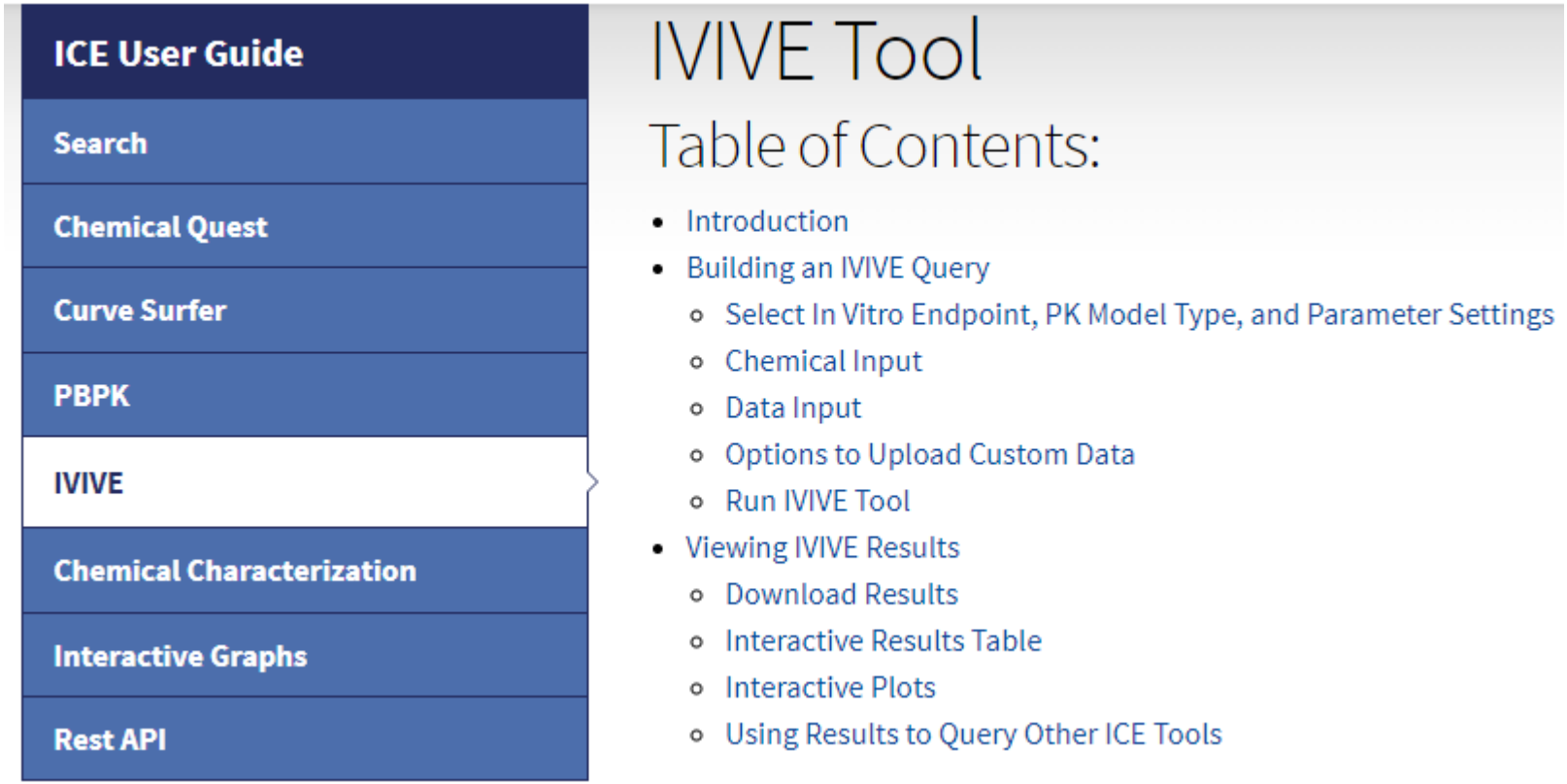
Demo

IVIVE

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

IVIVE Summary

- The In Vitro to In Vivo Extrapolation (IVIVE) tool estimates the administered dose needed to achieve in vitro bioactivity concentrations within the body
  - 4 models from EPA's httk, 1 in-house model from ICE
- Use in vivo and exposure overlays to place predictions in larger context



Summary

- ICE is an open-access computational tool with highly-curated data and interoperable computational tools intended to support the development, application, and evaluation of New Approach Methodologies
- ICE is continuously updated to address evolving stakeholder needs. This includes, but is not limited to, the following updates released in 2023:
  - The ability to search using chemical names and synonyms
  - Population-level exposure predictions from EPA's SEEM3 model
  - Gestational models from EPA's httk package (v2.2.2) in PBPK and IVIVE tools
  - Functional use categories derived from EPA's Chemical and Products Database
  - New quick lists for mixtures and ToxCast chemicals
- Let us know what you would like to see!

Integrated Chemical Environment

National Institute of Environmental Health Sciences
Division of Translational Toxicology

Acknowledgments

The NICEATM Group

NIEHS/DTT Contributors

Integrated Chemical Environment
https://ice.ntp.niehs.nih.gov/

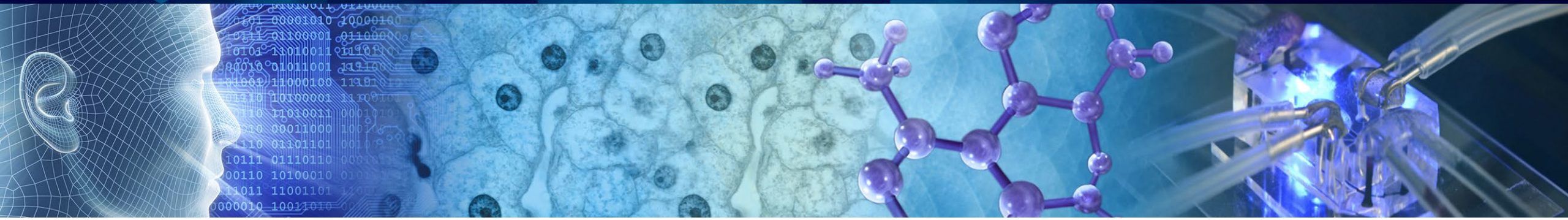
OPERA OPEn (q)saR App
https://github.com/NIEHS/OPERA

Subscribe to NICEATM News
https://list.nih.gov/cgi-bin/wa.exe?SUBED1=niceatm-l&A=1

Questions?

Contact: ICE-support@niehs.nih.gov

National Institute of Environmental Health Sciences
Division of Translational Toxicology



ChemMaps.com v2.0 – Exploring the Environmental Chemical Universe

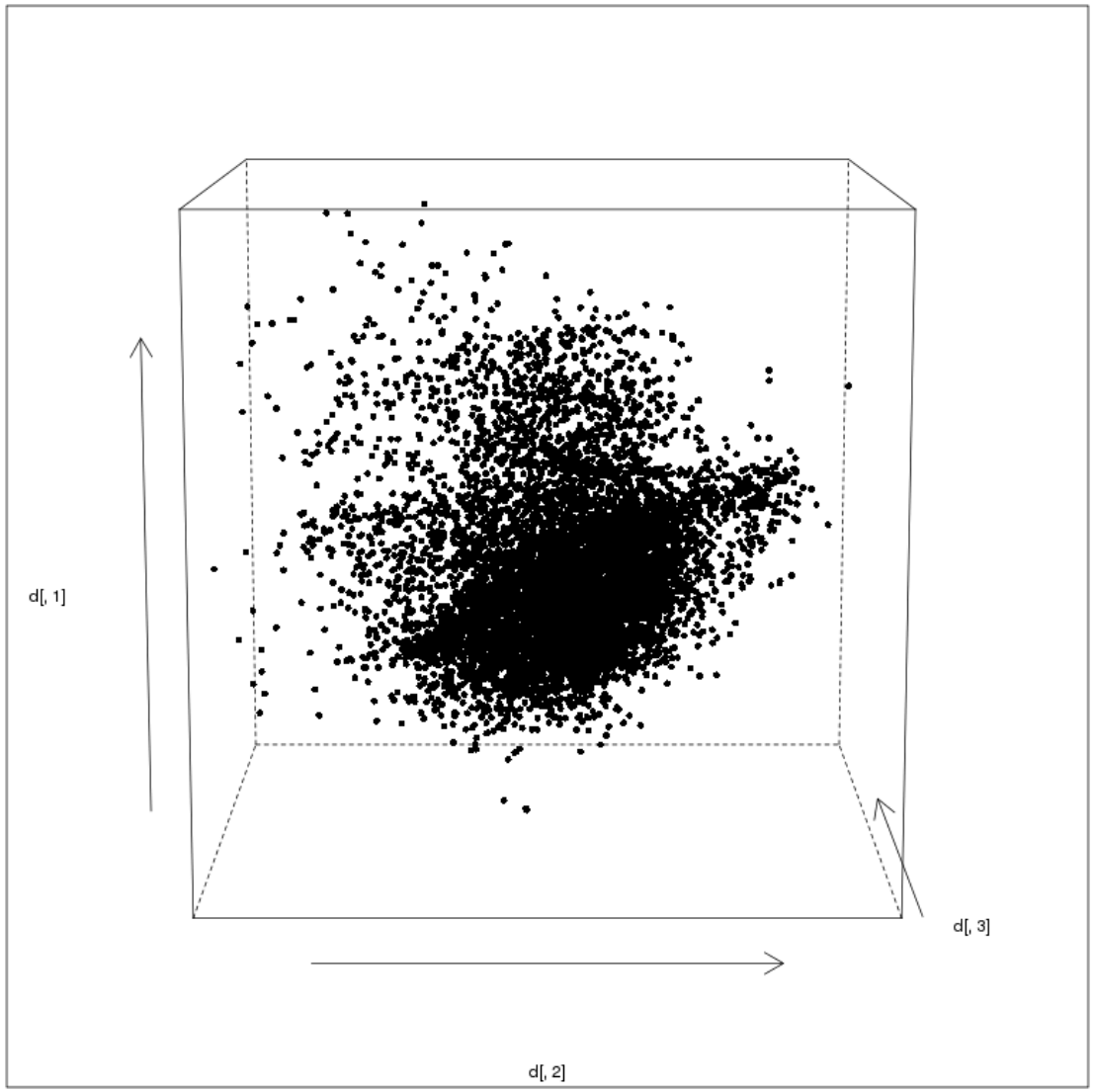
12th ASCCT Annual Meeting
2023-10-25

Alexandre Borrel, Inotiv, contractor supporting NICEATM
Presented by Kim To, Inotiv, contractor supporting NICEATM

Disclaimer: Inotiv staff provide technical support for NICEATM,
but do not represent NIEHS, NTP, DTT, or the official positions of any federal agency.

The Chemical Space

- The chemical space is a multi-dimensional space defined by a set of molecular descriptors, within which chemicals are projected.
- Defining the chemical space allows exploration of chemical properties and search for chemical analogues.



The Chemical Space

- Chemical biological databases provide large amounts of information that can be leveraged to define the chemical space.
- The rapid growth of such databases presents a challenge to researchers who wish to interpret large databases to contextualize their chemicals of interest.

DRUGBANK

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

CompTox
Chemicals Dashboard

Tox21

ChemMaps.com

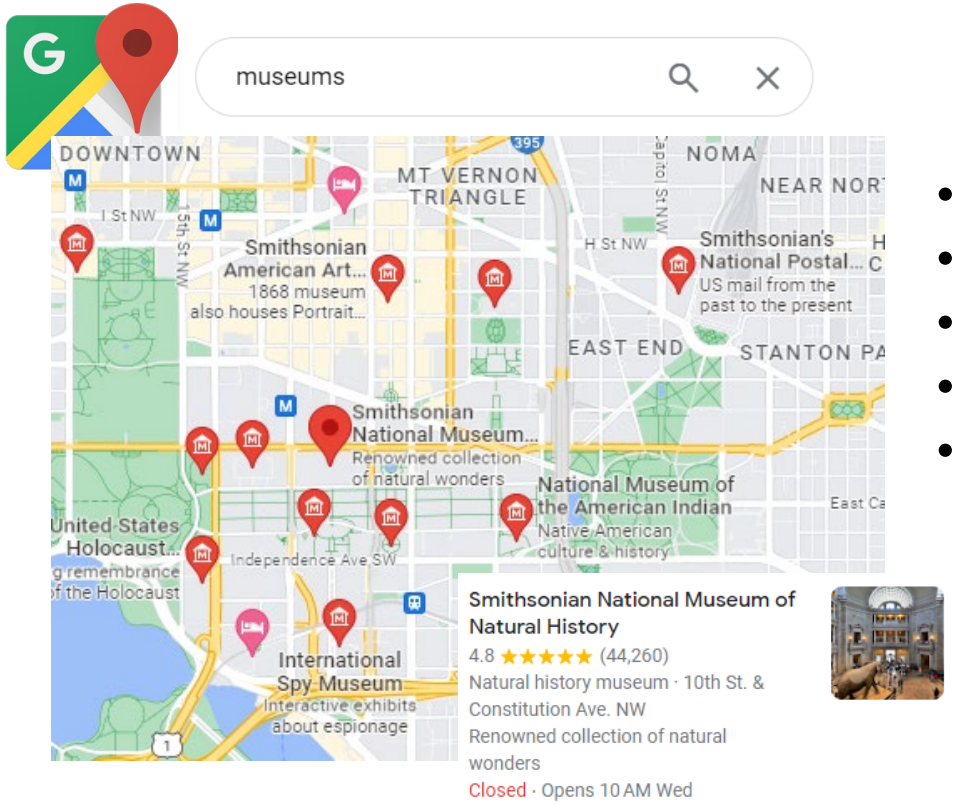
- ChemMaps.com was developed to support visual browsing and inspection of a given chemical space.
- ChemMaps.com v2.0 features four chemical space maps

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

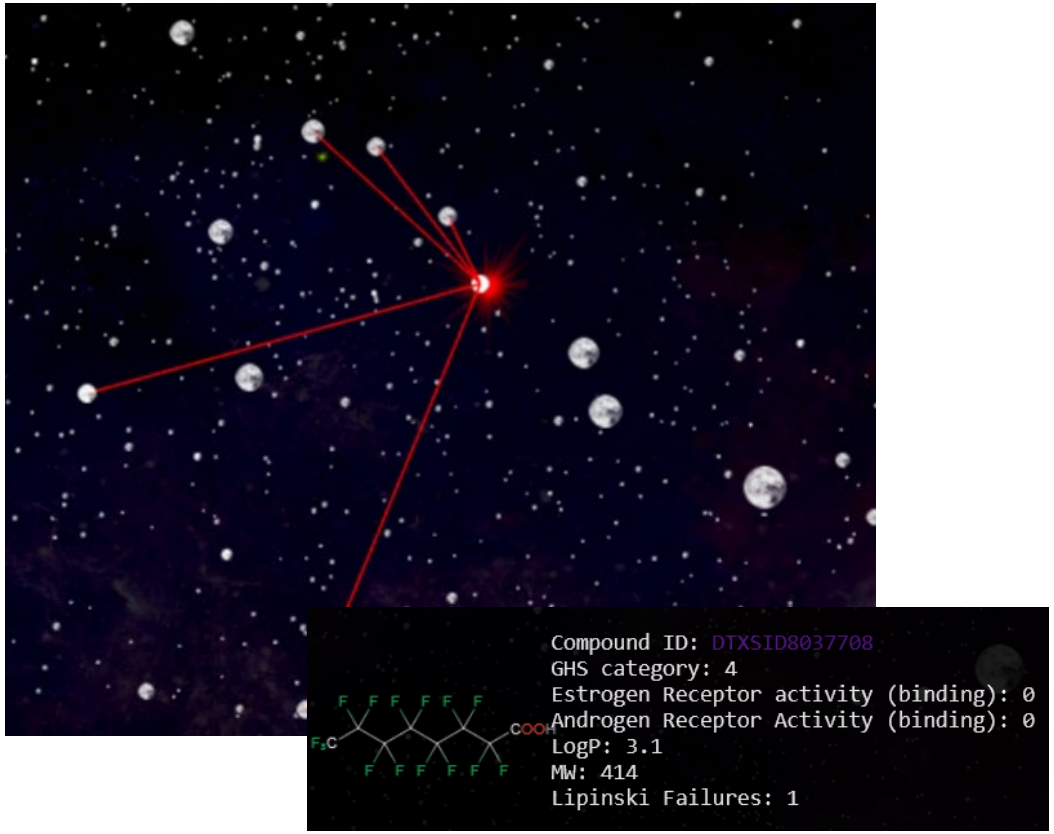
Borrel et al. 2018. Bioinformatics.
Borrel et al. 2023. Nucleic Acids Research.

ChemMaps.com

- ChemMaps applies a “Google Maps approach” to chemical space navigation.
- Users can easily explore the chemical space through an interactive interface.

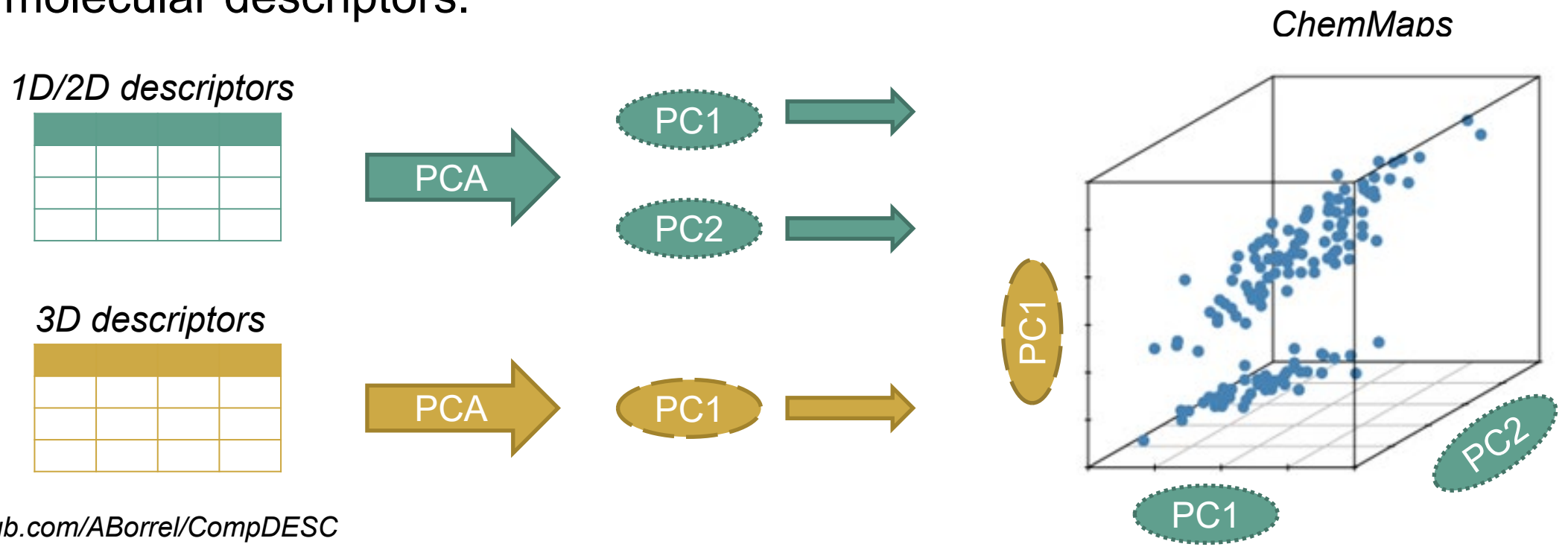


- Interactive
- Easy to use
- Informative
- Responsive
- ….



ChemMaps.com: Mapping chemicals

- For the chemicals in each data source, 1D, 2D, and 3D molecular descriptors are computed using RDKIT.
- Chemical coordinates are defined by principal components analysis of the molecular descriptors.



https://github.com/ABorrel/CompDESC

ChemMaps.com

DrugMap

- 10,805 drug entries from the DrugBank database
- Visualize experimental physicochemical properties

DRUGBANK

DSSToxMap

- ~1M chemicals from the DSSTox database
- Visualize predicted acute oral toxicity and physicochemical properties

PFASMap

- 14,629 PFAS chemicals identified in the EPA's PFAS master list

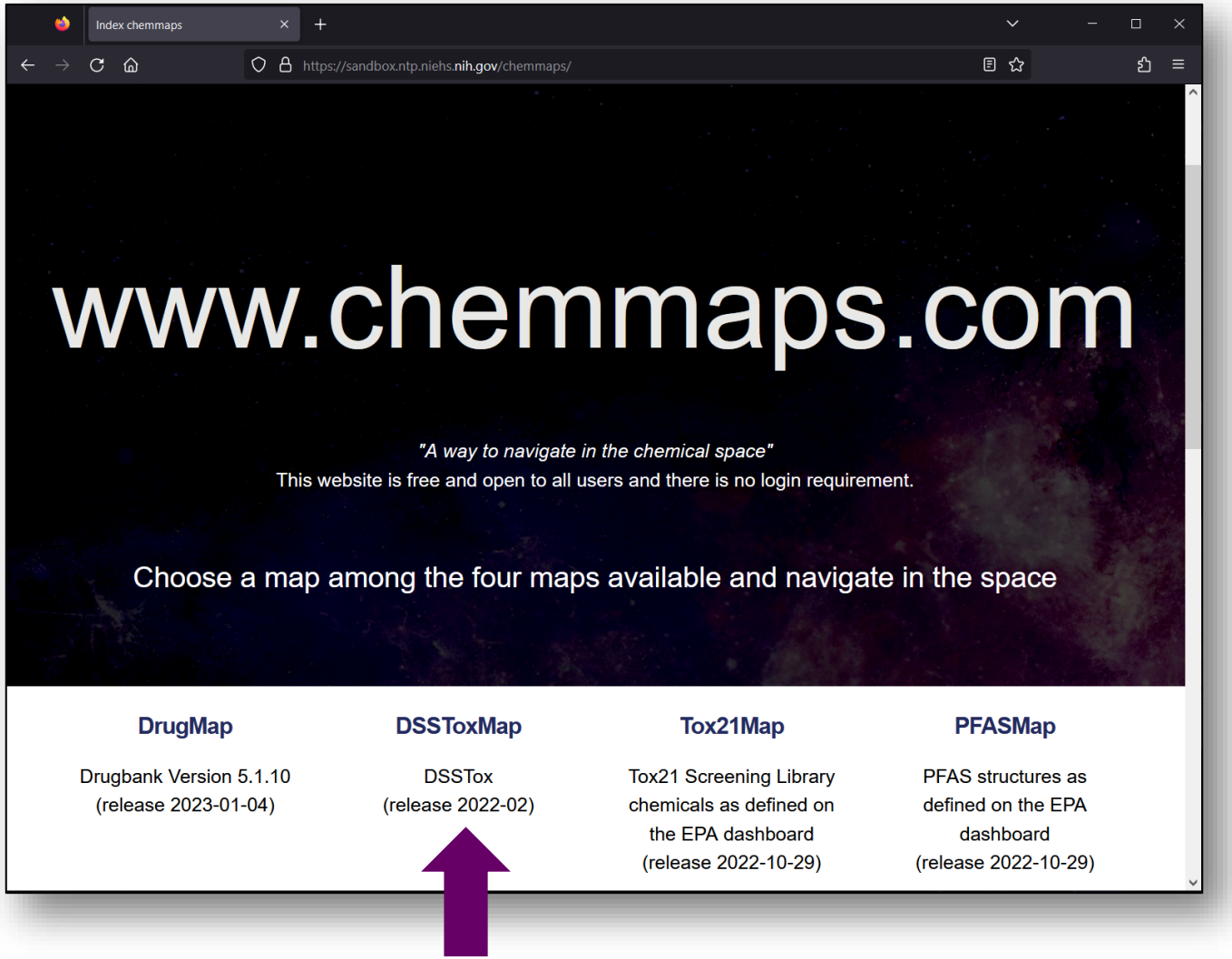
Tox21Map

- 8,236 chemicals that were tested in the Tox21 and ToxCast high-throughput screening programs
- Visualize chemical bioactivity

“Demo”

Exploring the PFOA chemical space

PFOA on DSSToxMap



National Institute of Environmental Health Sciences
Division of Translational Toxicology

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

PFOA on DSSToxMap

Generate the DsstoxMap

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)
- [x] Estrogen Receptor activity (binding)
- [ ] Hepatic clearance
- [ ] Androgen Receptor Activity (Antogonist)
- [x] 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
- [x] 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

- [x] MW
- [x] Lipinski Failures

Chemical in the center of the map (DTXSID):

DTXSID8031865

Generate DSSToxMap

ChemMaps.com

Center chemical: DTXSID8031865

DSSToxMap displays projections for 10,000 chemicals

Hide Chemicals

- Classified
- No classified
- Added chemicals
- Draw structures

Colors by

- GHS category
- Lipinski Failures
- Androgen Receptor Activity (binding)
- Estrogen Receptor activity (binding)
- MW
- LogP

- Axes
- Set a pivot point
- Reset view
- Reset map
- Help
- Save map view

Close Controls

9874 chemicals

Compound ID: DTXSID8031865
GHS category: NA
Lipinski Failures: 1
Androgen Receptor Activity (binding): 0
Estrogen Receptor activity (binding): 0
MW: 414
LogP: 3.1

Connect 1

Extract 1

Draw chemical

Download neighbors

Link to DSSTOXMap

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

ChemMaps.com

DTXSID8031865

Center chemical: DTXSID8031865

Chemicals are represented by planets or stars.

Stars indicate that the chemical has acute toxicity information available.

Hide Chemicals

- Classified ☑
- No classified ☑
- Added chemicals ☑
- Draw structures ☐

Colors by

- GHS category
- Estrogen Receptor activity (binding)
- Androgen Receptor Activity (binding)
- LogP
- MW
- Lipinski Failures

- Axes ☐
- Set a pivot point
- Reset view
- Reset map
- Help
- Save map view

Close Controls

9874 chemicals

Compound ID: DTXSID8031865
GHS category: NA
Estrogen Receptor activity (binding): 0
Androgen Receptor Activity (binding): 0
LogP: 3.1
MW: 414
Lipinski Failures: 1

Connect 1

Extract 1

Draw chemical

Download neighbors

Link to DSSTOXMap

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

ChemMaps.com

DTXSID8031865

Center chemical: DTXSID8031865

Search bar to locate specific chemicals

Navigation panel allows visualization of previously selected features or chemical structure

Information panel updates in real time while navigating the map

- Hide Chemicals
  - Classified
  - No classified
  - Added chemicals
  - Draw structures
- Colors by
  - GHS category
  - Estrogen Receptor activity (binding)
  - Androgen Receptor Activity (binding)
  - LogP
  - MW
  - Lipinski Failures
- Axes
- Set a pivot point
- Reset view
- Reset map
- Help
- Save map view
- Close Controls

9874 chemicals

Compound ID: DTXSID8031865
GHS category: NA
Estrogen Receptor activity (binding): 0
Androgen Receptor Activity (binding): 0
LogP: 3.1
MW: 414
Lipinski Failures: 1

Connect 1

Extract 1

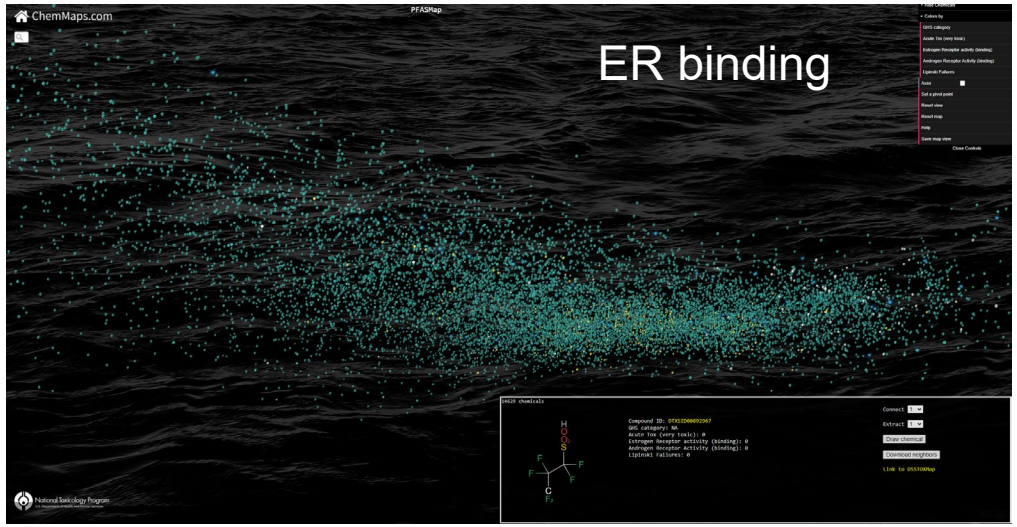
Draw chemical

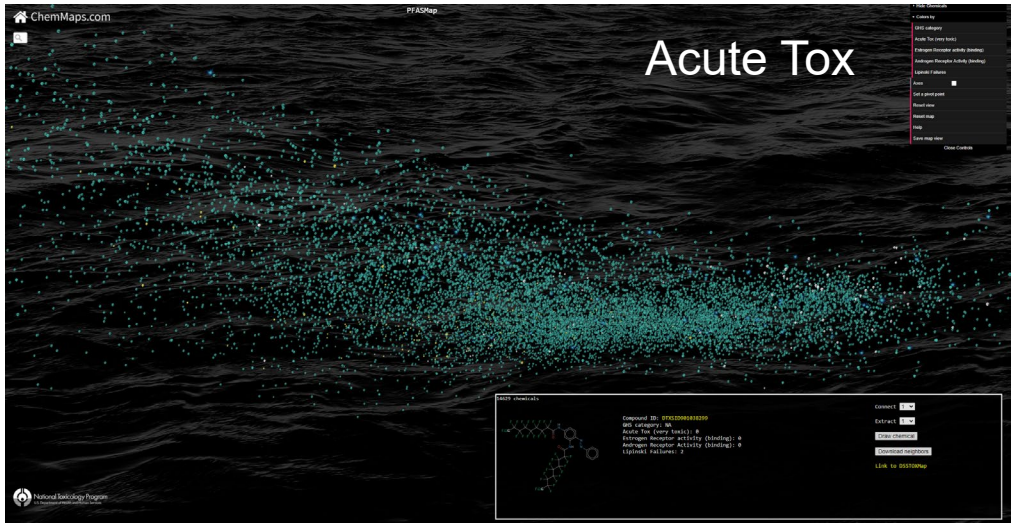
Download neighbors

Link to DSSTOXMap

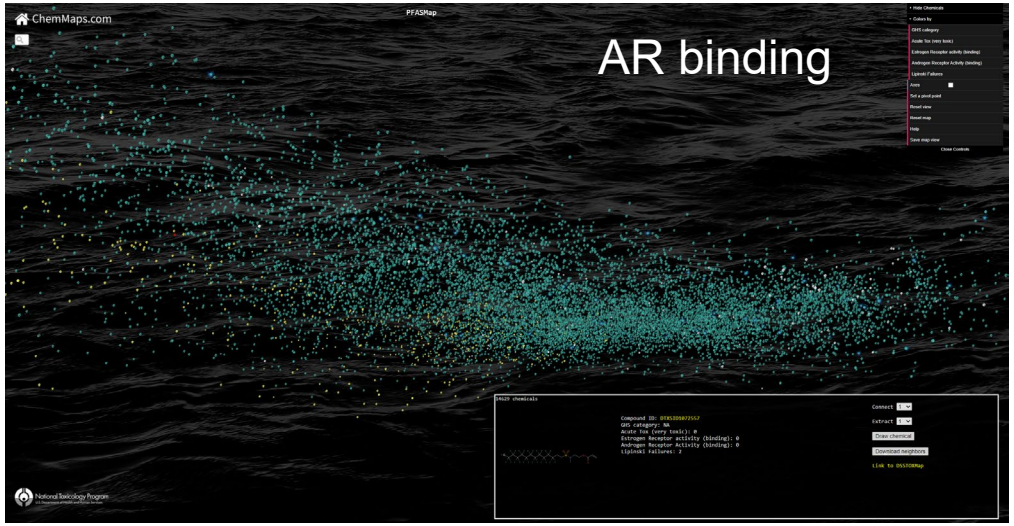
National Toxicology Program
U.S. Department of Health and Human Services

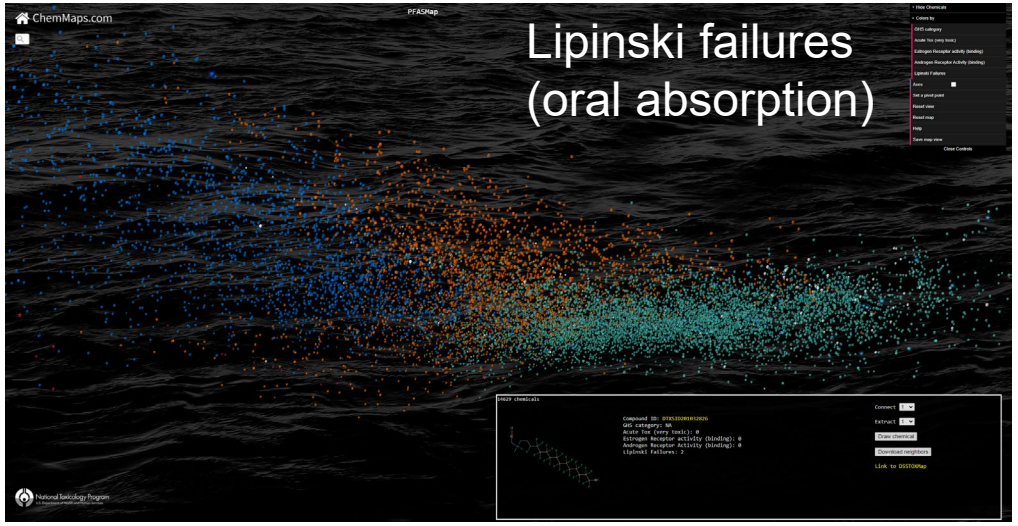
Visualizing Features





- Inactive
- Active





- 0 failures
- 1 failure
- 2 failures
- 4 failures

ChemMaps.com

Center chemical: DTXSID8031865

Hide Chemicals

- Classified
- No classified
- Added chemicals
- Draw structures

Colors by

- Axes
- Set a pivot point
- Reset view
- Reset map
- Help
- Save map view

Close Controls

Highlight closest PFOA neighbors

9874 chemicals

Compound ID: DTXSID50896576
GHS category: NA
Lipinski Failures: 1
Androgen Receptor Activity (binding): 0
Estrogen Receptor activity (binding): 0
MW: 414
LogP: 3.9

Connect 10

Extract 20

Draw chemical

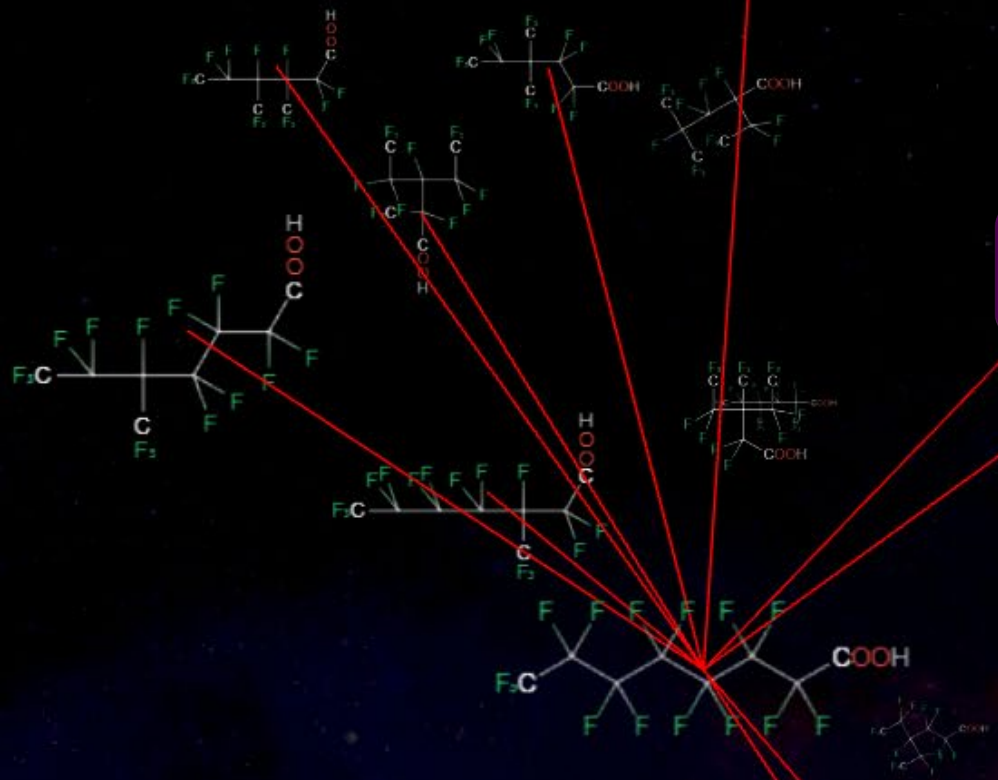
Download neighbors

Link to DSSTOXMap

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

ChemMaps.com

Center chemical: DTXSID8031865



Toggle visualization of chemical structures

- Hide Chemicals
  - Classified ☑
  - No classified ☑
  - Added chemicals ☑
  - Draw structures ☑
- Colors by
  - GHS category
  - Estrogen Receptor activity (binding)
  - Androgen Receptor Activity (binding)
  - LogP
  - MW
  - Lipinski Failures
- Axes ☐
- Set a pivot point
- Reset view
- Reset map
- Help
- Save map view
- Close Controls

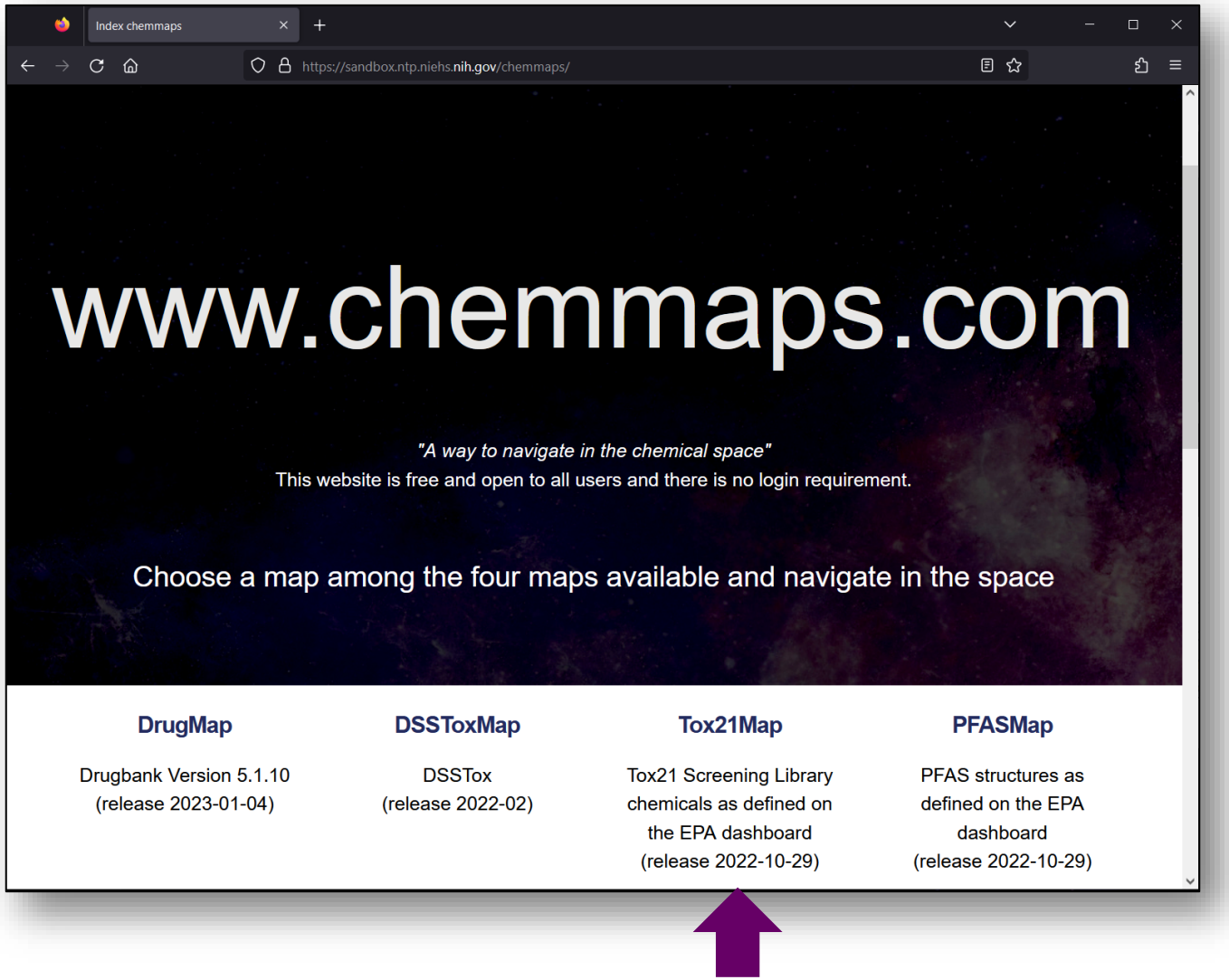
9874 chemicals

Compound ID: DTXSID70896654
GHS category: NA
Estrogen Receptor activity (binding): 0
Androgen Receptor Activity (binding): 0
LogP: 3.2
MW: 396
Lipinski Failures: 0

Connect 10
Extract 20
Draw chemical
Download neighbors
Link to DSSTOXMap

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

PFOA on Tox21Map



National Institute of Environmental Health Sciences
Division of Translational Toxicology

Tox21Map

Project Tox21 assay results

Choose a assay protocol or an assay target. Assay target will provide you a concensus of all Tox21 assays that target the same gene. Tox21 assay results have been extracted from the *Integrated Chemical Environement*.

Assay	Species	Tissue	Cell line	Gene	Mechanistic target
ACEA_ER_80hr	human	breast	cell line(T47D)	ESR1	CardioTox_ER Alpha,Estrogen Re...
APR_HepG2_MicrotubuleCSK_1h_dn	human	liver	cell line(HepG2)	TUBA1A	Cell Morphology
APR_HepG2_MicrotubuleCSK_1h_up	human	liver	cell line(HepG2)	TUBA1A	Cell Morphology
APR_HepG2_MitoticArrest_1h_dn	human	liver	cell line(HepG2)	H3F3A	Cell Cycle
APR_HepG2_MitoticArrest_1h_up	human	liver	cell line(HepG2)	H3F3A	Cell Cycle
APR_HepG2_P-H2AX_1h_dn	human	liver	cell line(HepG2)	H2AFX	Oxidative Stress
APR_HepG2_P-H2AX_1h_up	human	liver	cell line(HepG2)		Oxidative Stress
APR_HepG2_p53Act_1h_dn	human	liver	cell line(HepG2)		p53 Modulation
APR_HepG2_p53Act_1h_up	human	liver	cell line(HepG2)		p53 Modulation
APR_HepG2_StressKinase_1h_dn	human	liver	cell line(HepG2)		Oxidative Stress
APR_HepG2_StressKinase_1h_up	human	liver	cell line(HepG2)	JUN	Oxidative Stress
APR_HepG2_M...ubuleCSK_24h_dn	human	liver	cell line(HepG2)	TUBA1A	Cell Morphology

Project assays with the same target gene

Project a unique assay result

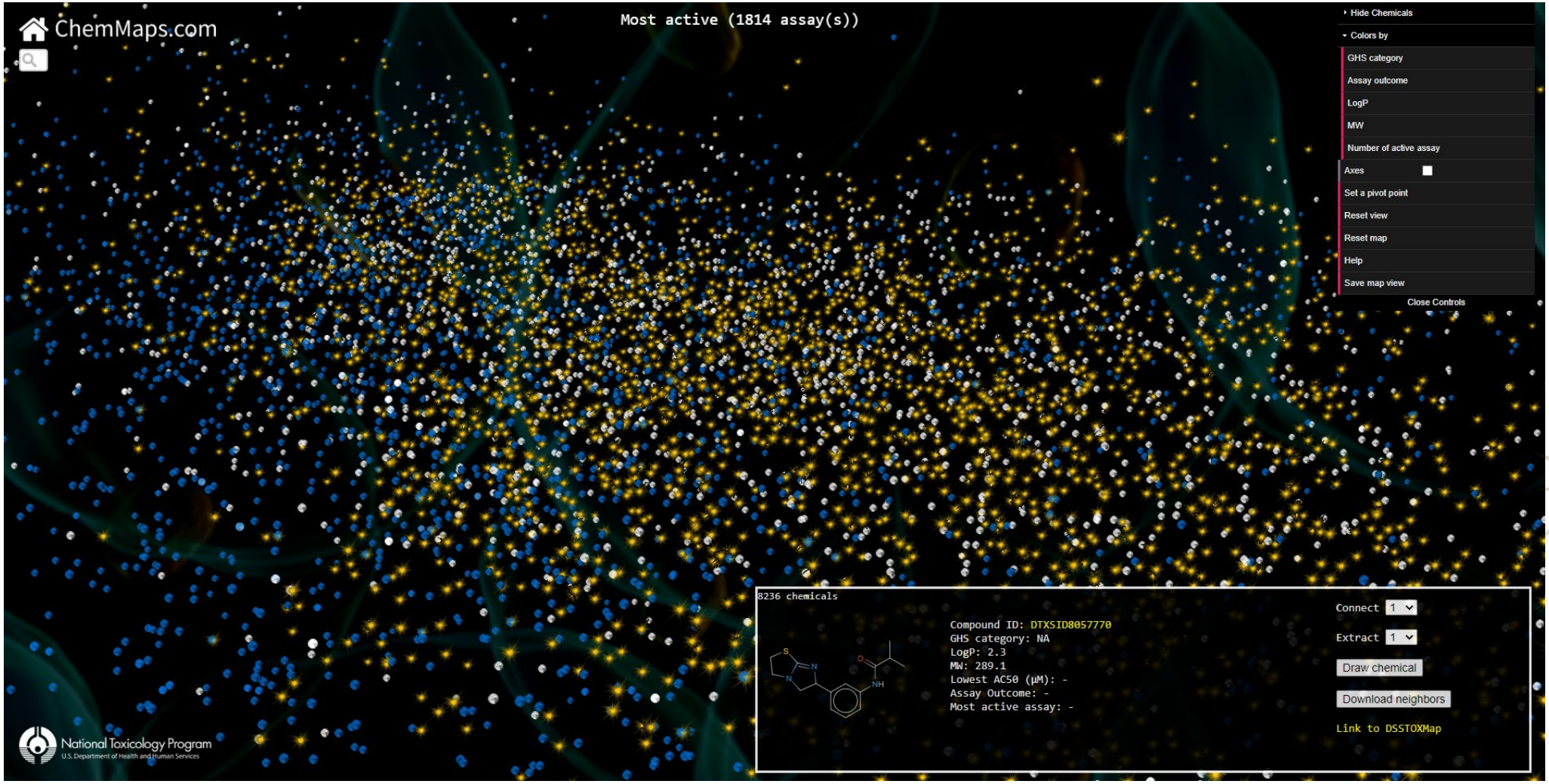
Project by chemical the most active assay

Only the most active assay result is projected for each chemical.

Tox21Map with lowest AC50 by chemicals

Project the assay result with the lowest AC50

Tox21Map – Lowest AC50

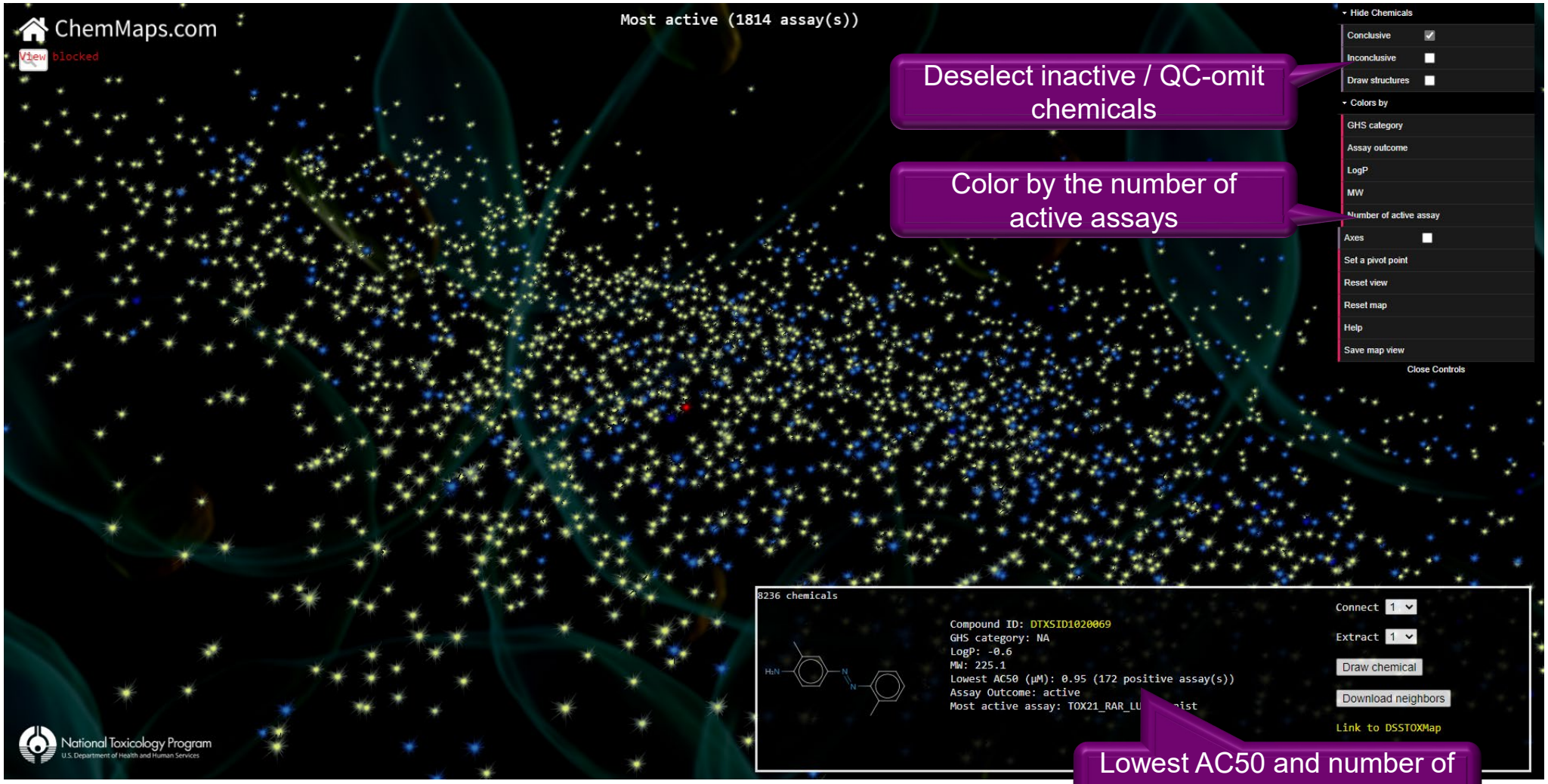


Inactive

QC omit

At least one assay active

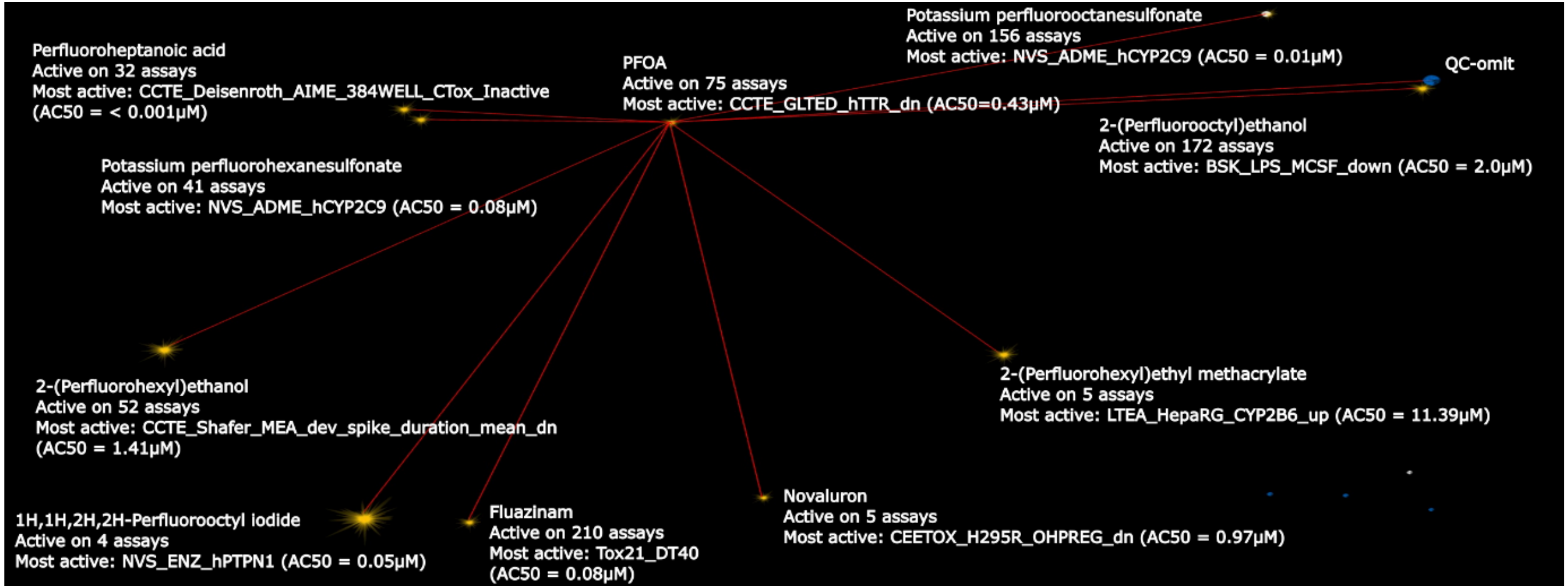
Tox21Map – Lowest AC50



600 assays

1 assay

PFOA on Tox21Map



Summary

- ChemMaps.com is an open-source tool that enables interactive exploration of large chemical spaces.
- ChemMaps v2.0 introduced DSSToxMap comprising an expanded library of environmental chemicals from the EPA's DSSTox database.
  - PFASMap and Tox21Map are subsets of DSSToxMap that allow exploration of specific data subsets.

For more information, contact:
Alexandre.Borrel@inotivco.com

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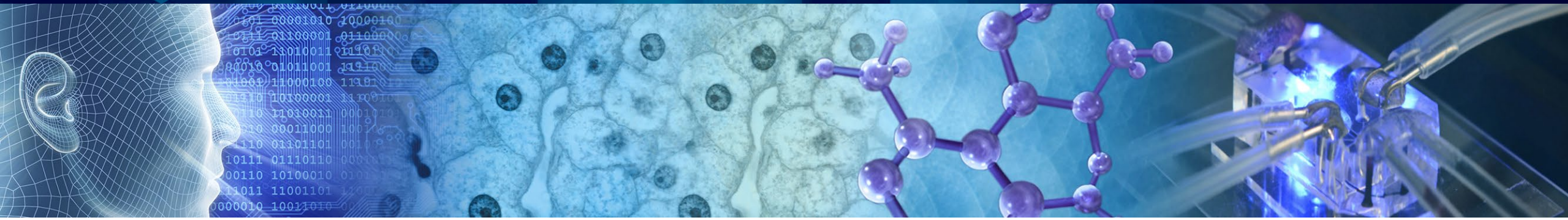
Division of Translational Toxicology



The DASS App: A Web Application to Predict Skin Sensitization Using Defined Approaches

12th ASCCT Annual Meeting
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Disclaimer: Inotiv staff provide technical support for NICEATM,
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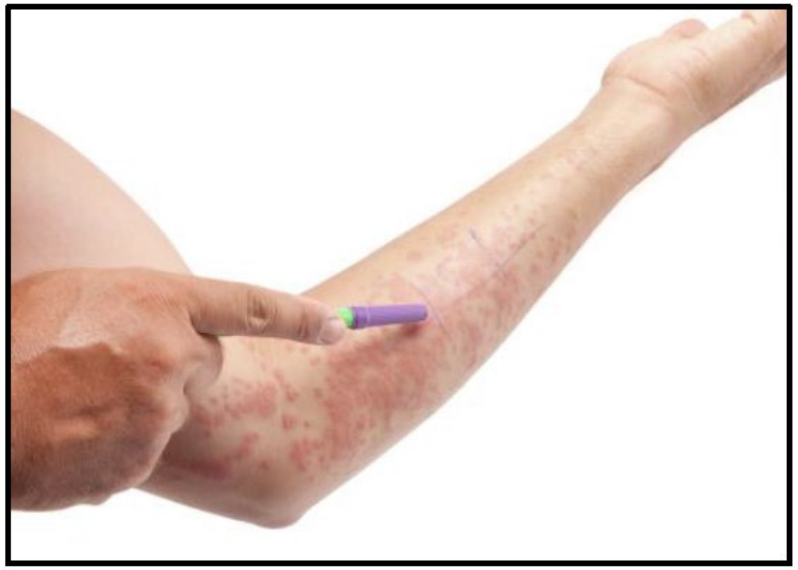
Skin Sensitization

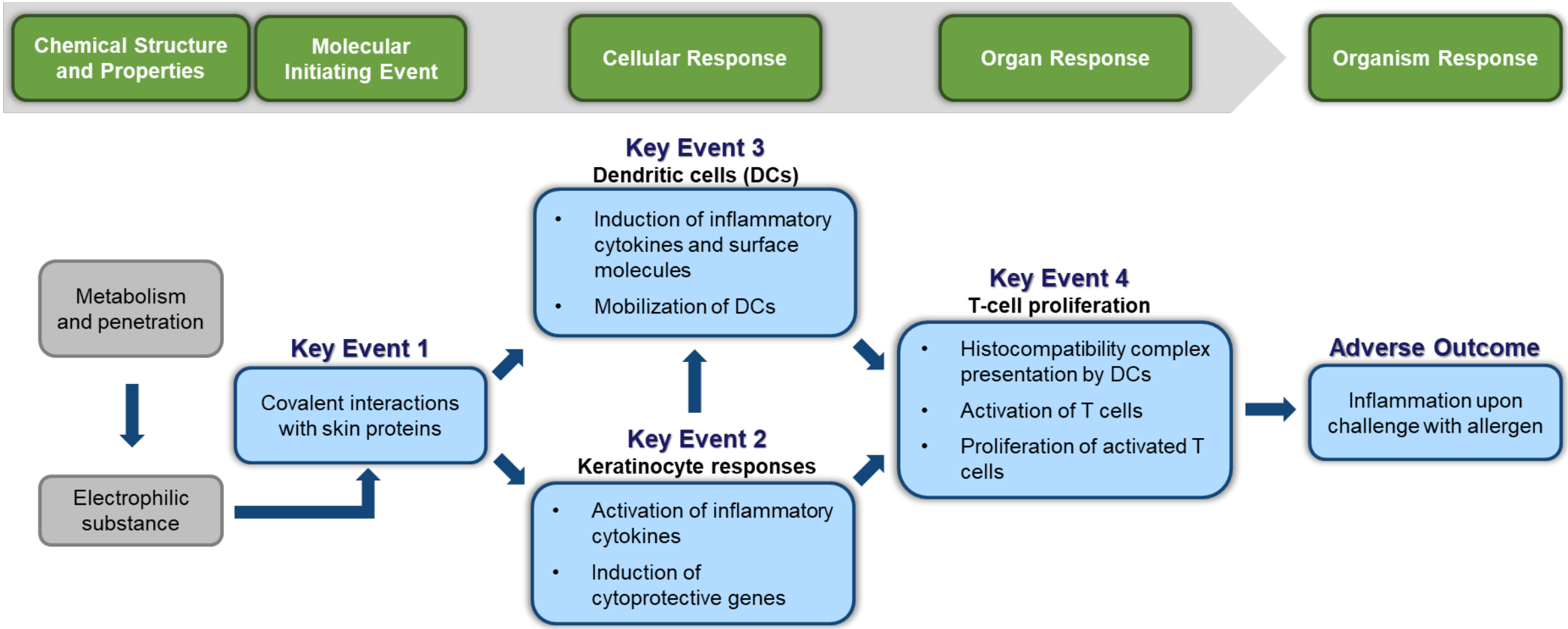
- Up to 20% of the population suffer from skin sensitization reactions[1].
- Historically, skin sensitization has been tested using in vivo methods such as the local lymph node assay (LLNA) or the guinea pig maximization test (gPMT).
- Regulatory frameworks, e.g., REACH, ask for information on predicting skin sensitization potential in humans.



[1]*Adler & DeLeo, JAMA Dermatol. 2021*

Adverse Outcome Pathway for Skin Sensitization

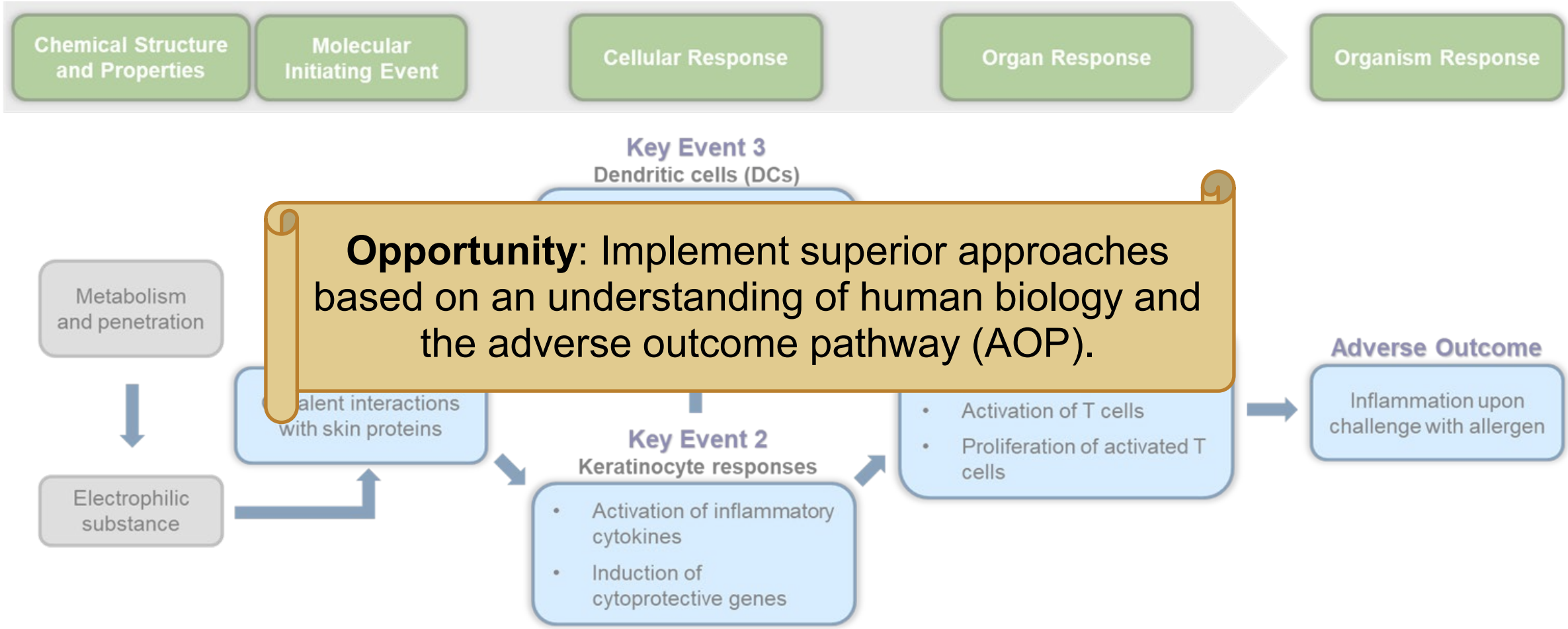
For sensitization initiated by covalent binding to proteins



OECD 2012. Guidance Document No. 168

Adverse Outcome Pathway for Skin Sensitization

For sensitization initiated by covalent binding to proteins

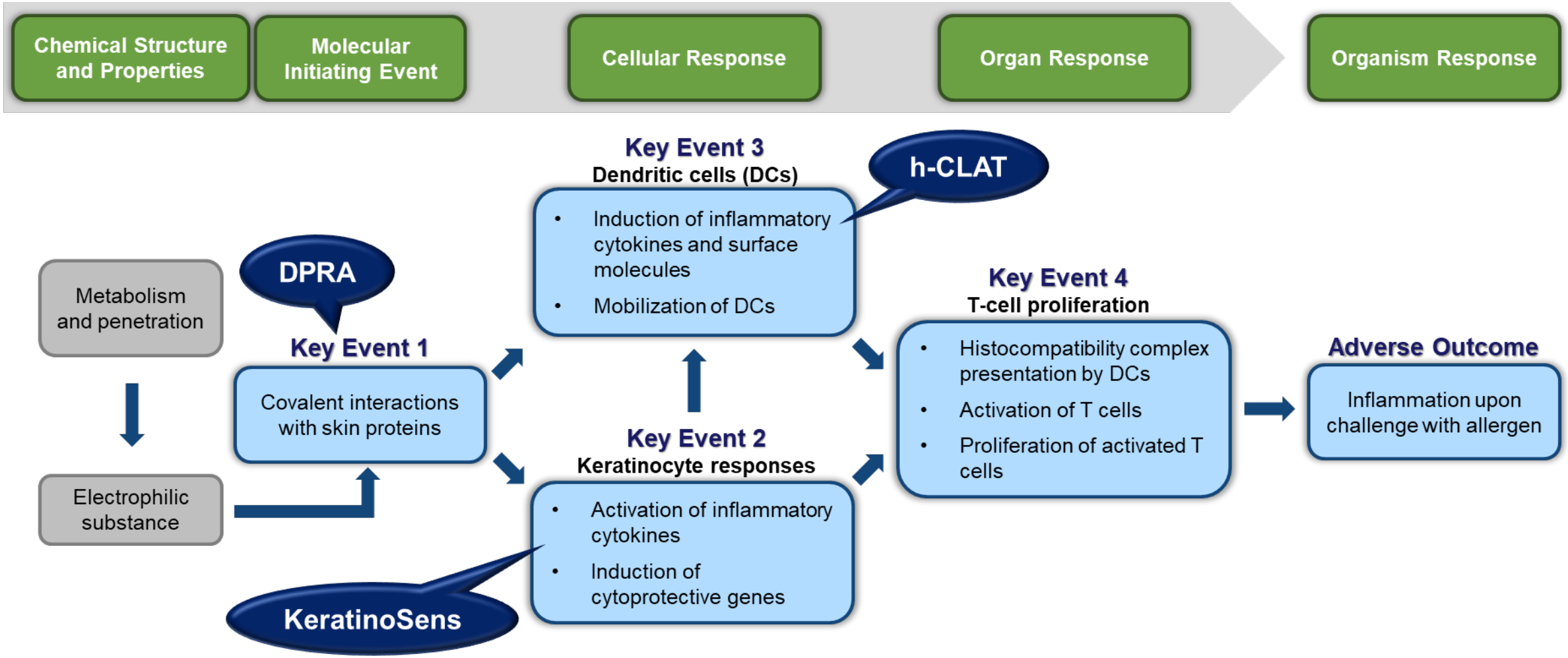


OECD 2012. Guidance Document No. 168

Non-animal methods for evaluating skin sensitization

- Mechanistically based methods that address key events in the skin sensitization AOP
  - Direct peptide reactivity assay (DPRA)
  - KeratinoSens™ (KS)
  - Human cell line activation test (h-CLAT)

Non-animal methods for evaluating skin sensitization



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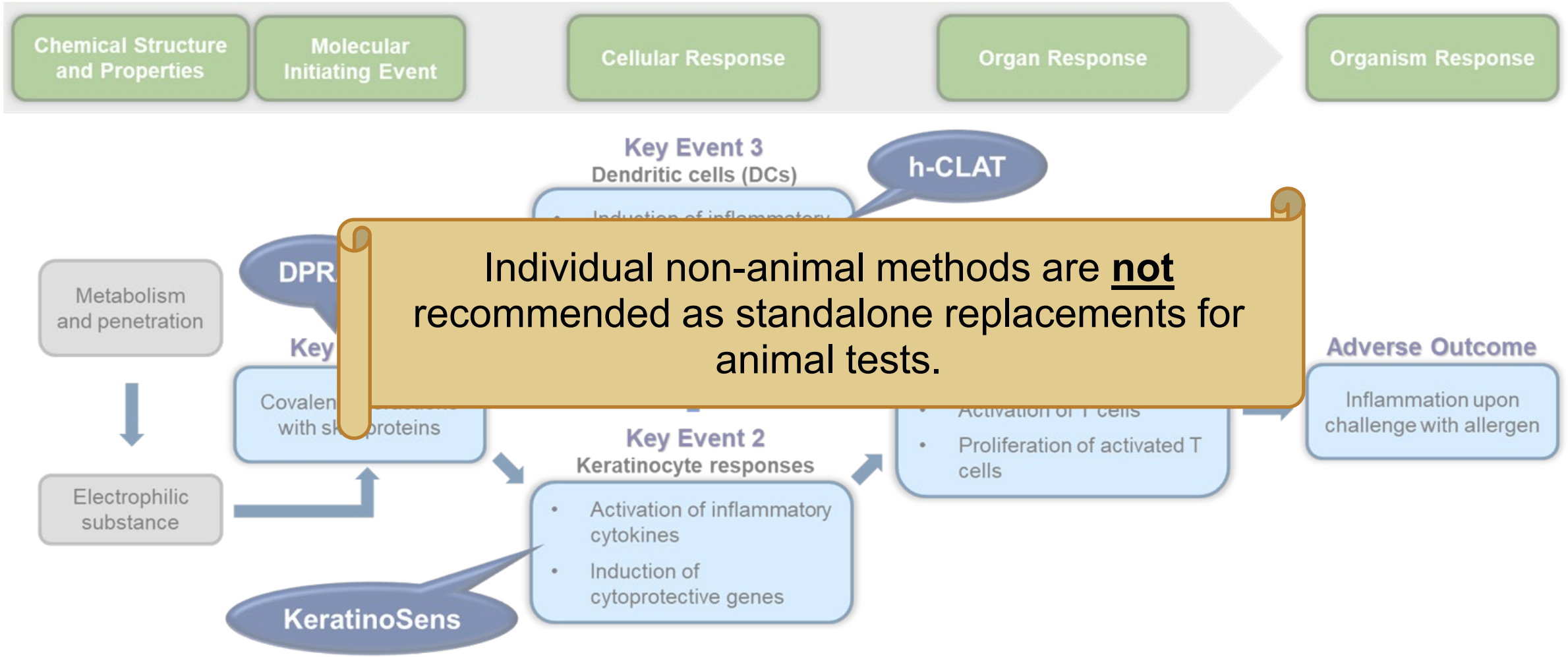
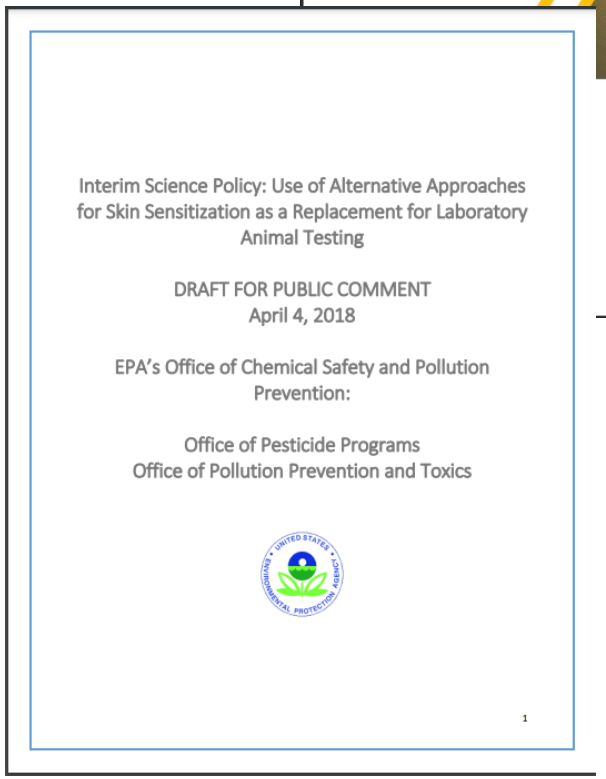
Non-animal methods for evaluating skin sensitization



OECD 2012. Guidance Document No. 168

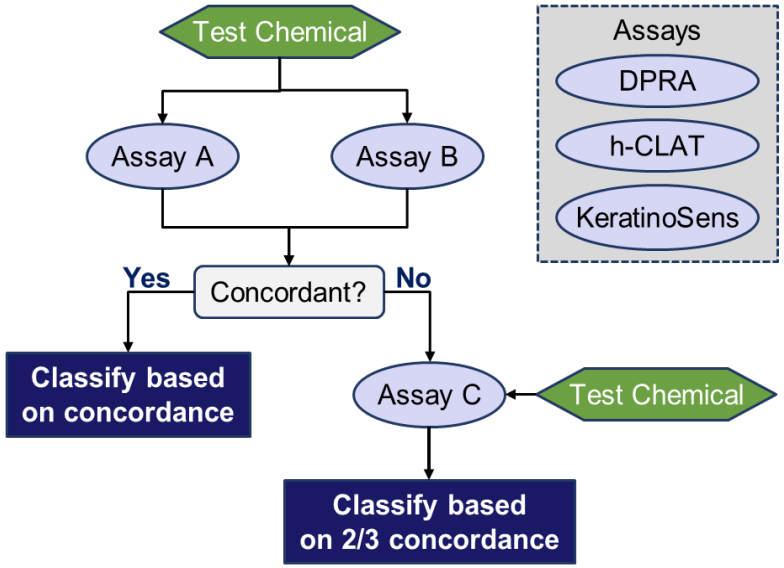
Defined Approaches

- Results from multiple assays can be combined to predict skin sensitization hazard and potency using **defined approaches (DAs)**.
- DAs combine data from a pre-determined set of information sources via fixed data interpretation procedures to derive toxicity predictions.
- **Defined approaches for skin sensitization (DASS)** have been developed and accepted by the OECD for hazard and potency predictions and by the U.S. EPA for hazard predictions.

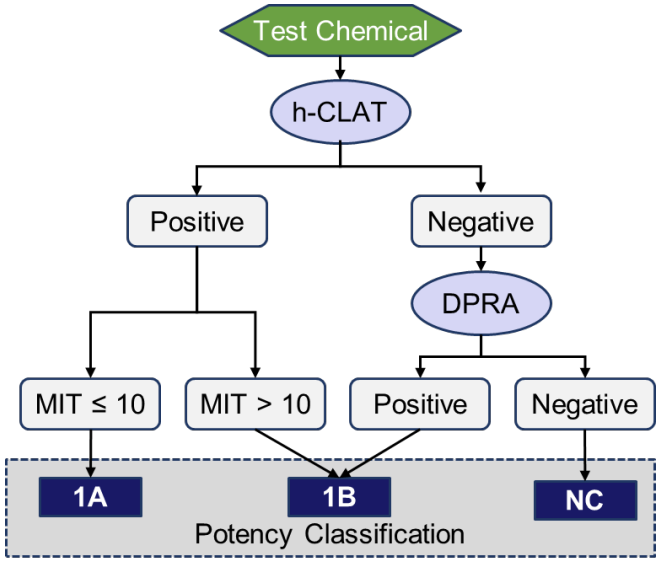


Defined Approaches for Skin Sensitization (DASS)

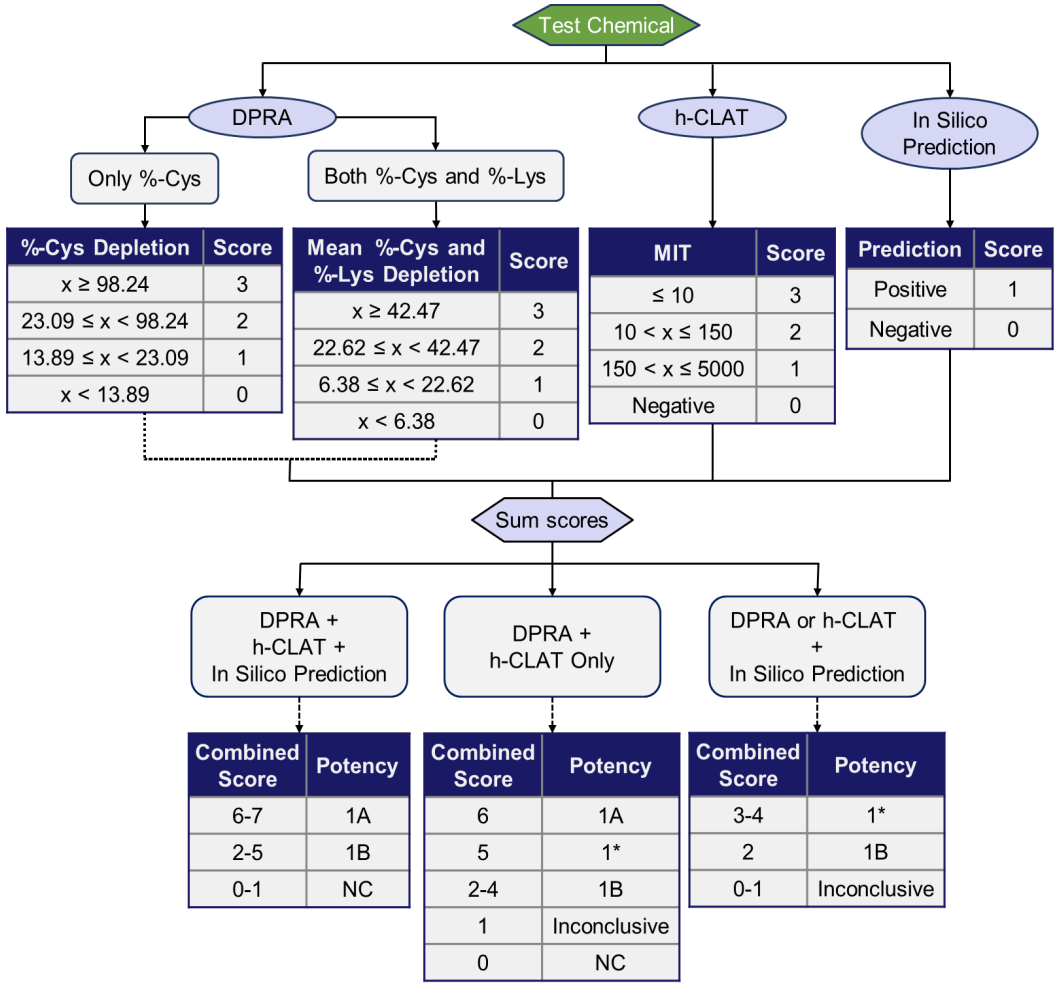
2 out of 3 (2o3)



Key Event 3/1 Sequential Testing Strategy (KE 3/1 STS)



Integrated Testing Strategy (ITS)



%-Cys Depletion	Score
x ≥ 98.24	3
23.09 ≤ x < 98.24	2
13.89 ≤ x < 23.09	1
x < 13.89	0

Mean %-Cys and %-Lys Depletion	Score
x ≥ 42.47	3
22.62 ≤ x < 42.47	2
6.38 ≤ x < 22.62	1
x < 6.38	0

MIT	Score
≤ 10	3
10 < x ≤ 150	2
150 < x ≤ 5000	1
Negative	0

Prediction	Score
Positive	1
Negative	0

Combined Score	Potency
6-7	1A
2-5	1B
0-1	NC

Combined Score	Potency
6	1A
5	1*
2-4	1B
1	Inconclusive
0	NC

Combined Score	Potency
3-4	1*
2	1B
0-1	Inconclusive

Accuracy of Methods Against Human Reference Data

- The DAs show higher or equivalent accuracy than the LLNA when compared to human reference data.

Hazard Identification

	Accuracy
LLNA	74.20%
KS	75.80%
h-CLAT	78%
DPRA	73.40%
2o3 (KS + h-CLAT + DPRA)	77.20%
ITSv1 (h-CLAT + DPRA + DEREK)	85%
KE 3/1 STS (h-CLAT + DPRA)	80.20%

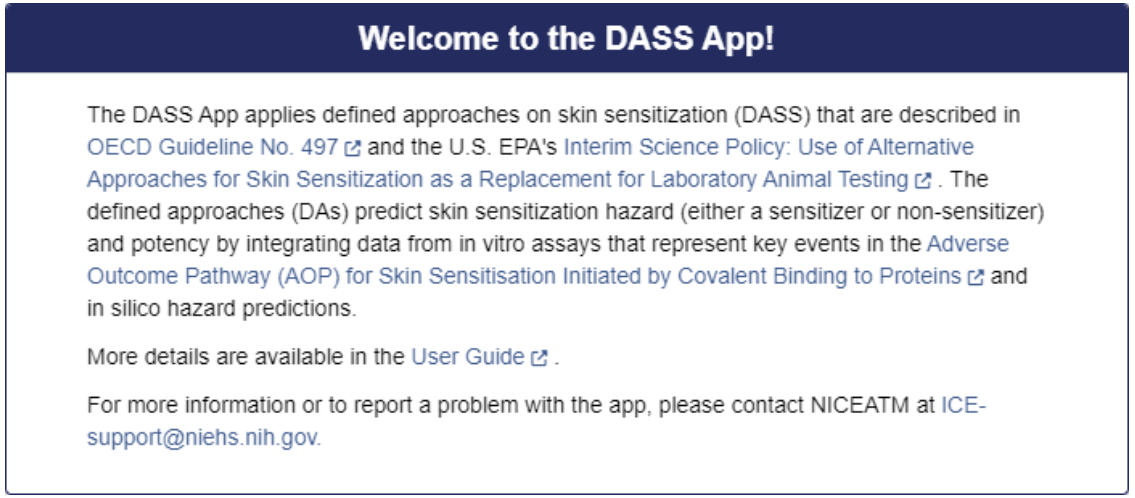
Potency

	Accuracy
LLNA	59.4%
ITSv1 (h-CLAT + DPRA + DEREK)	69.2%
KE 3/1 STS (h-CLAT + DPRA)	63.5%

Kleinstreuer et al. 2018 Crit Rev Tox
Hoffmann et al. 2018 Crit Rev Tox

The DASS App

- DASS logic can be easily implemented in a coding environment (e.g., R, Python)
- **The DASS App is an open-source web application that enables users to apply these validated non-animal approaches to their own data**
- No account is required, and no data are retained by the application



Access the DASS App
https://ntp.niehs.nih.gov/go/952311

https://github.com/NIEHS/DASS
To et.al 2023. Cambridge Open Engage. Preprint.

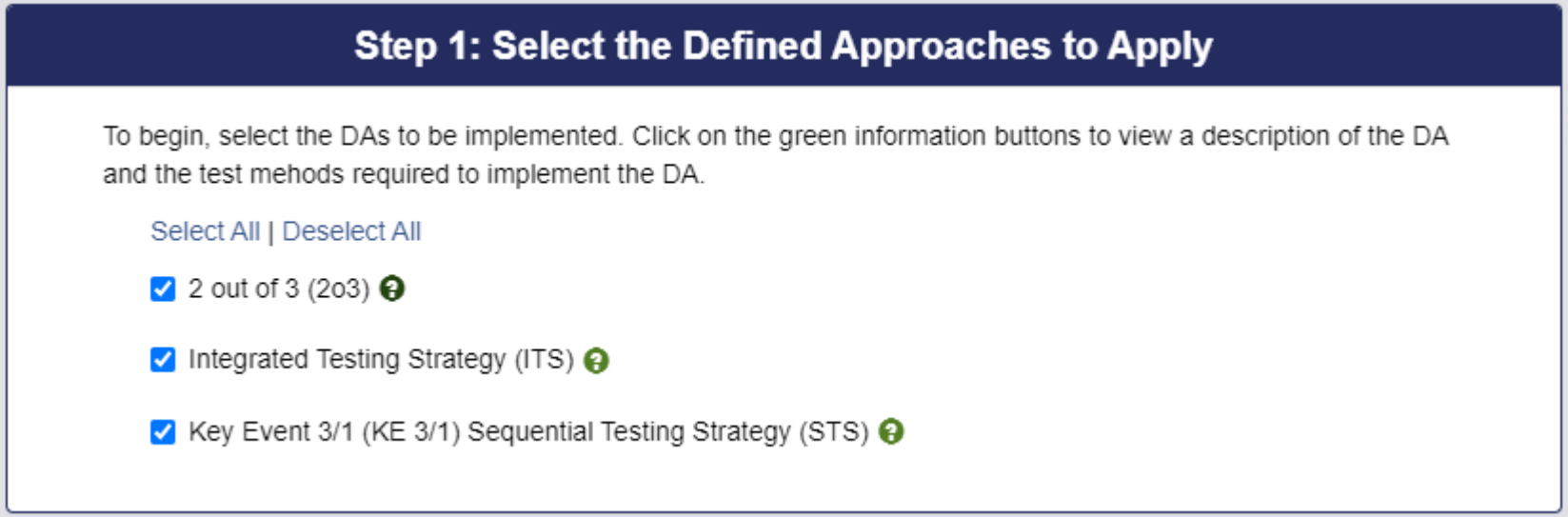
Demo

Evaluating data from OECD GL497

https://ntp.niehs.nih.gov/go/952311

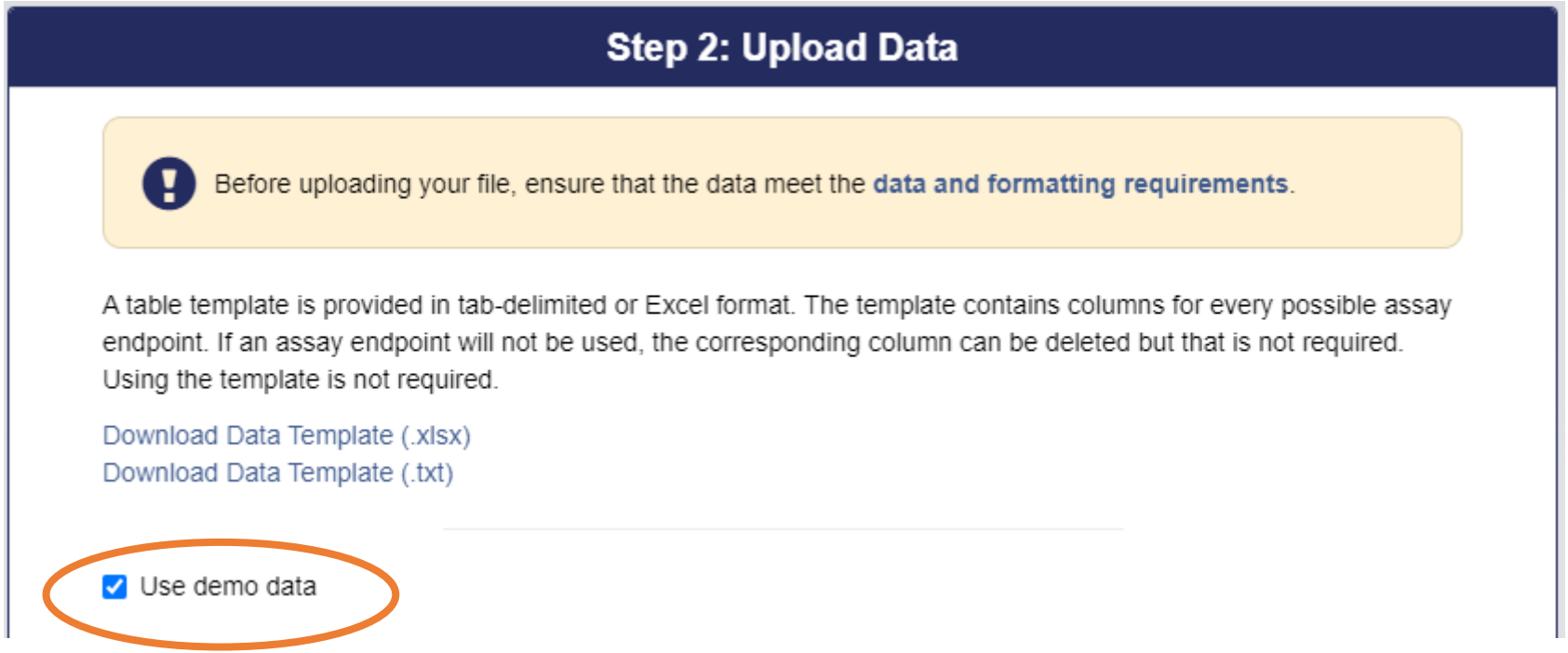
DASS App Demo

1. Navigate to the DASS App: https://ntp.niehs.nih.gov/go/952311
2. Select the DAs you would like to apply. Additional information about the DAs can be found by clicking on the green information circles.



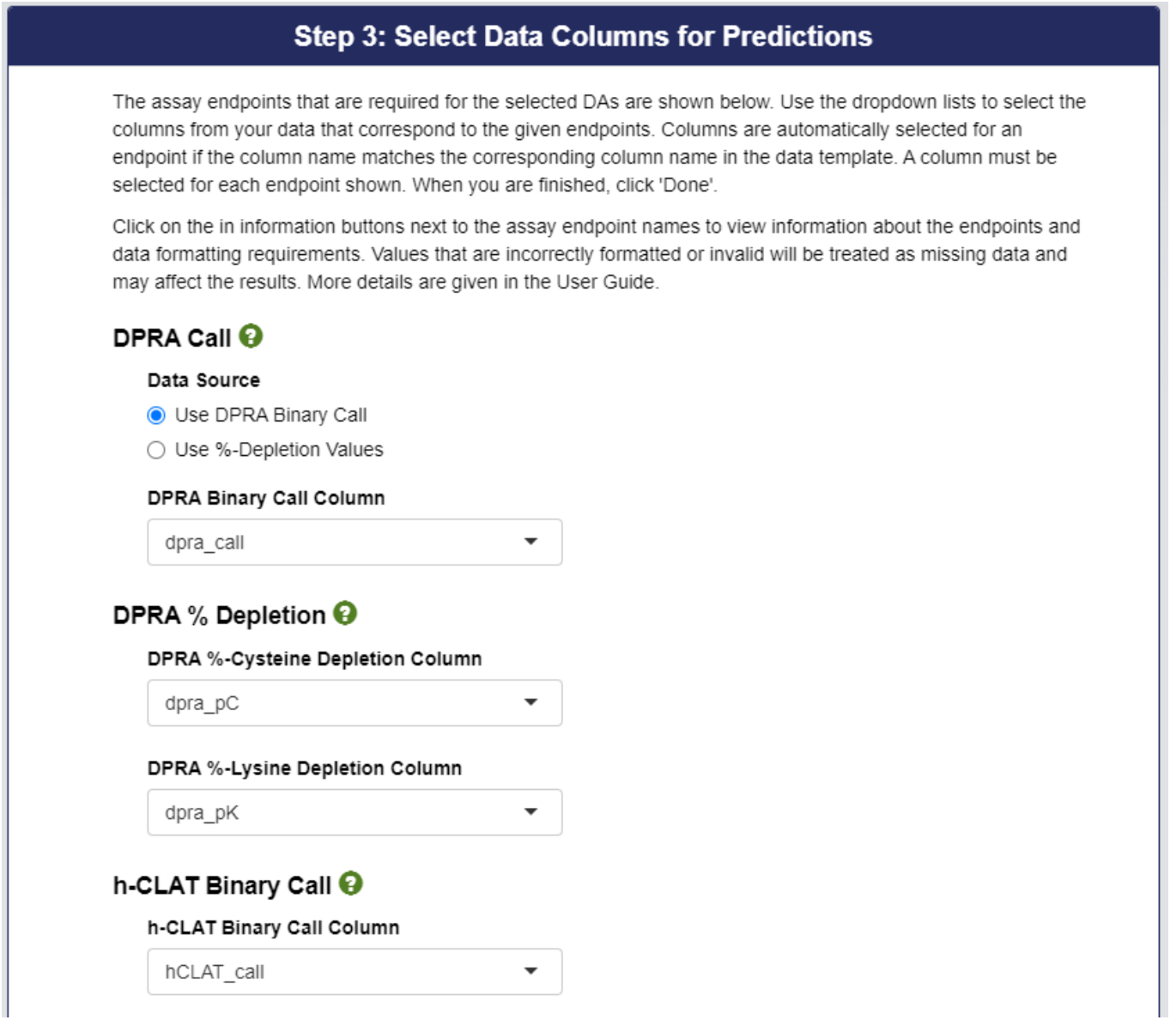
DASS App Demo

3. The app accepts .csv, .txt, and .xlsx file extensions. Check the box for “Use demo data” to load a demo data set sourced from OECD GL 497.



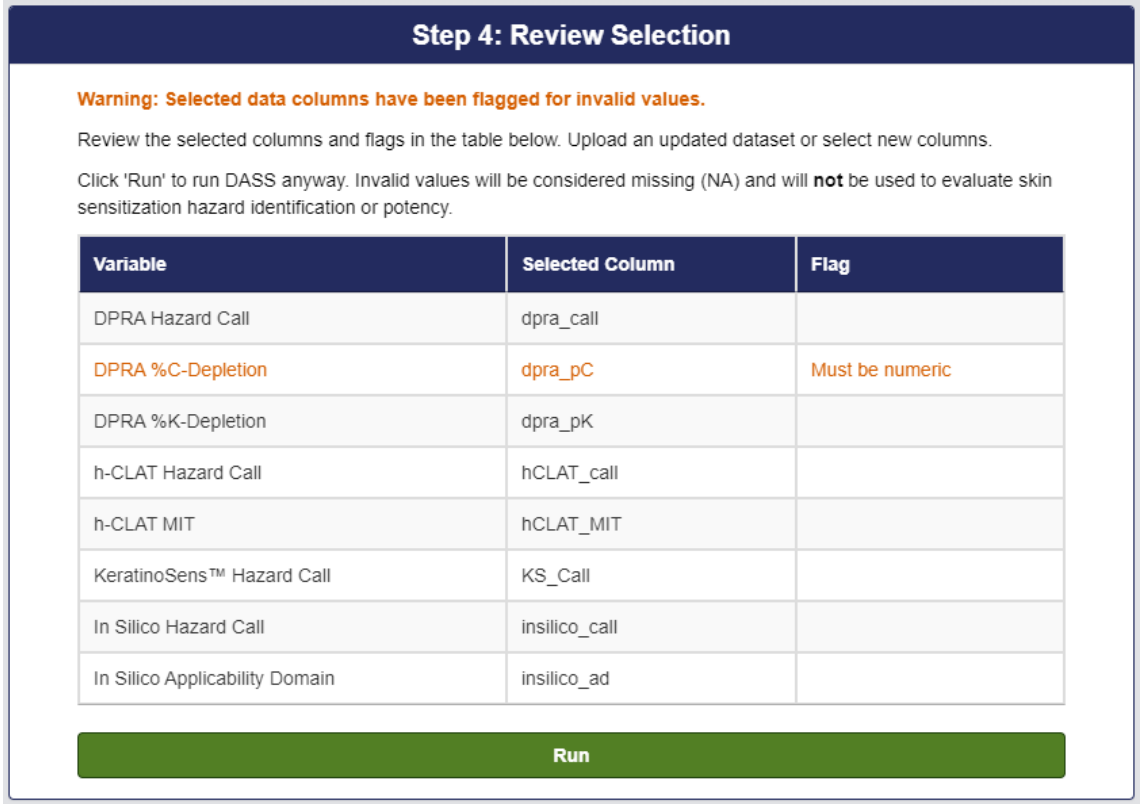
DASS App Demo

5. Select the columns corresponding to a given assay endpoint.
   - Using the demo data will pre-populate the selection boxes with the appropriate column name.
6. Click “Done” at the bottom of the Step 3 module.



DASS App Demo

7. Review the selected columns.
   - The column “dpra_pC” is flagged due to non-numeric data.
8. Click “Run” to apply the DAs using the selected data.
9. A pop-up window will appear to confirm that the DAs will be applied to flagged data. Click “Run”.



Step 4: Review Selection

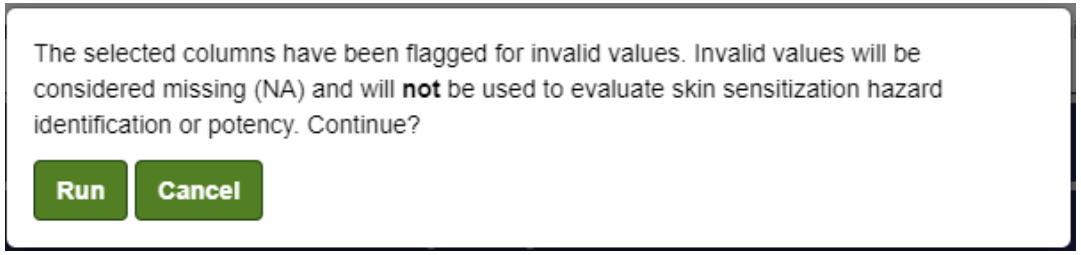
Warning: Selected data columns have been flagged for invalid values.

Review the selected columns and flags in the table below. Upload an updated dataset or select new columns.

Click 'Run' to run DASS anyway. Invalid values will be considered missing (NA) and will **not** be used to evaluate skin sensitization hazard identification or potency.

Variable	Selected Column	Flag
DPRA Hazard Call	dpra_call	
DPRA %C-Depletion	dpra_pC	Must be numeric
DPRA %K-Depletion	dpra_pK	
h-CLAT Hazard Call	hCLAT_call	
h-CLAT MIT	hCLAT_MIT	
KeratinoSens™ Hazard Call	KS_Call	
In Silico Hazard Call	insilico_call	
In Silico Applicability Domain	insilico_ad	

Run



The selected columns have been flagged for invalid values. Invalid values will be considered missing (NA) and will **not** be used to evaluate skin sensitization hazard identification or potency. Continue?

Run Cancel

DASS App Demo

10. DA predictions are appended to the original data.

- Use the “Column visibility” menu to toggle the columns shown
- Results can be downloaded as a .txt or .xlsx file.

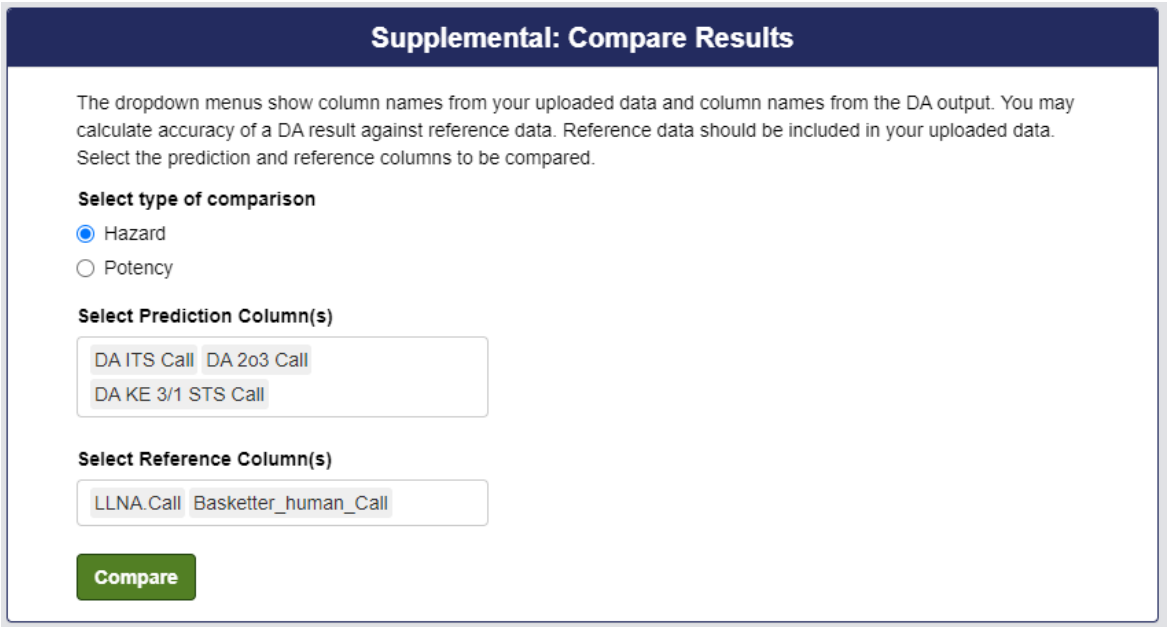
Download Results

Column visibility

CASRN	SMILES	DA ITS Call	DA ITS Potency	DA 2o3 Call	DA KE 3/1 STS Call	DA KE 3/1 STS Potency
514-10-3	CC(C)C1CC[C@H]2C(=CC[C@@H]3[C@]2(C)CCC[C@@]3(C)C(O)=O)C=1	1	1B	1	1	1B
100-06-1	COc1ccc(cc1)C(C)=O	0	NC	0	0	NC
874-23-7	CC(=O)C1CCCCC1=O	1	1B	1	1	1B
140-67-0	COc1ccc(CC=C)cc1	1	1B	1	1	1B
7493-74-5	C=CCOC(=O)COc1ccccc1	0	NC	0	0	NC
150-13-0	Nc1ccc(cc1)C(O)=O	0	NC	0	0	NC
2835-99-6	Cc1cc(O)ccc1N	1	1A	1	1	1B
2835-95-2	Cc1ccc(N)cc1O	1	1A	1	1	1B
95-55-6	Nc1ccccc1O	1	1A	1	1	1A
591-27-5	Nc1cccc(O)c1	1	1B	0	1	1B

DASS App Demo

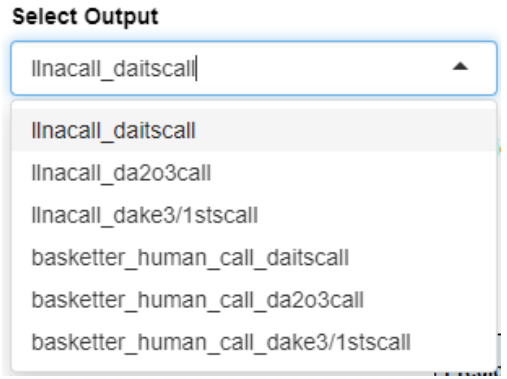
11. Users may supply reference data to evaluate the DA results. The demo data include LLNA and Human reference data. In the Performance Metrics module, select:
    - Type of comparison: Hazard
    - Prediction columns: DA ITS Call, DA 2o3 Call, DA KE 3/1 STS Call
    - Reference columns: LLNA.Call, Basketter_human_Call
12. Click the “Compare” button.



DASS App Demo

13. Confusion matrices and performance metrics will be shown for every comparison. Use the drop-down menu to view specific comparisons.

14. Click the “Download” button to open a pop-up and download a PDF of the tables.

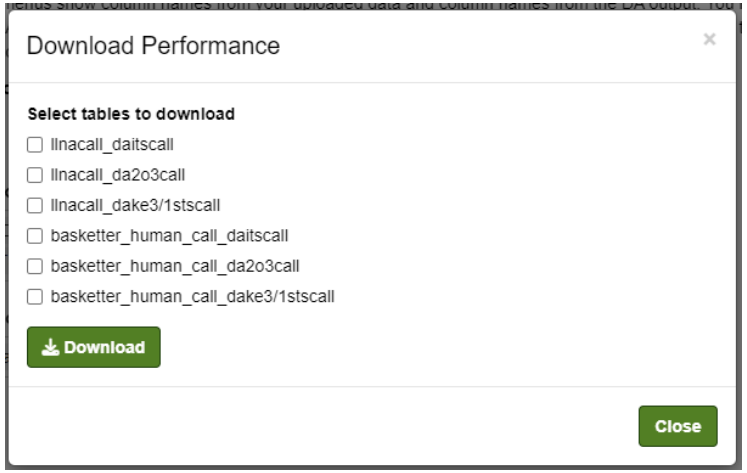


Confusion Matrix and Performance Metrics

Reference Column: LLNA.Call

Prediction Column: DA ITS Call

		Reference	
		0	1
Predicted	0	23	15
	1	10	117



Metric	Value
N	165
Accuracy	85%
Balanced Accuracy	79%
F1 Score	90%
True Positive Rate	89%
False Positive Rate	30%
True Negative Rate	70%
False Negative Rate	11%

Summary

- The DASS App provides access to validated non-animal testing strategies from international OECD guidelines and U.S. federal policies.
- Additional assays are being evaluated for inclusion in the DASS data interpretation procedures.
  - The DASS App will be updated to include these alternate assays.

Conclusion

- NICEATM provides open-source data-driven computational tools to support chemical safety assessment.
- **ICE** provides curated toxicologically relevant data and contains tools for data interpretation and exploration.
- **OPERA** features models for predicting physicochemical properties and environmental fate endpoints.
- **ChemMaps.com** enables exploration of the environmental chemical space and integrates data from OPERA models and ICE.
- **The DASS App** supports implementation of validated non-animal approaches.

National Institute of Environmental Health Sciences
Division of Translational Toxicology

Acknowledgments

The NICEATM Group

NIEHS/DTT Contributors

UNITED STATES ICCVAM *Advancing Alternatives to Animal Testing*

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Sciome

CEBS Chemical Effects in Biological Systems

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Integrated Chemical Environment
https://ice.ntp.niehs.nih.gov/

OPERA OPEn (q)saR App
https://github.com/NIEHS/OPERA

ChemMaps.com
https://sandbox.ntp.niehs.nih.gov/chemmaps/

The DASS App
https://ntp.niehs.nih.gov/go/952311