National Institute of Environmental Health Sciences
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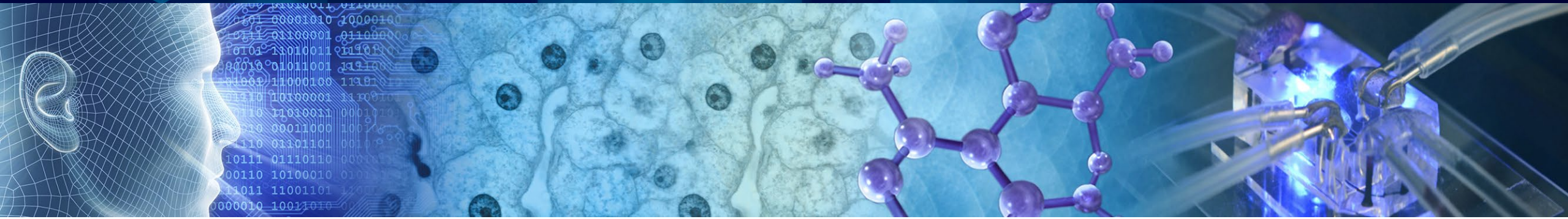

Training Session on the Integrated Chemical Environment (ICE)

ICCVAM Public Forum: 22nd May 2024

Aswani Unnikrishnan, Victoria Hull, and Kim To

Inotiv, Inc., Contractors 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, DTT, or the official positions of any federal agency.

Objectives:

- Gain an understanding of the data within ICE and how to use ICE tools for data interpretation and exploration.
- Help the audience become acquainted with the website to the extent that they feel confident exploring it independently.

Integrated
Chemical
Environment

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

Agenda

☐	**Session 1: 1:00 pm – 1:50 pm**
☐	**Break: 1:50 pm – 2:00 pm**
☐	**Session 2: 2:00 pm – 2:50 pm**
☐	**Break: 2:50 pm – 3:00 pm**
☐	**Session 3: 3:00 pm – 3:50 pm**

- Introduction to ICE
- Data Sets and Curated Chemical Lists in ICE
- Search Tool
- Session Q & A

- Chemical Quest Tool
- Chemical Characterization Tool
- Curve Surfer Tool
- Session Q & A

- PBPK Tool
- IVIVE Tool
- Final Q & A

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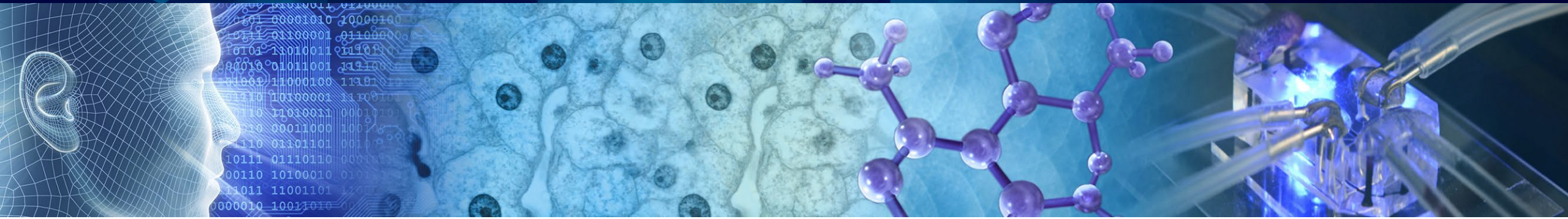

Training Session on the Integrated Chemical Environment (ICE)
Session 1 - ICE Overview and Search Tool

ICCVAM Public Forum: 22nd May 2024
1:00 pm – 1:50 pm

Aswani Unnikrishnan

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

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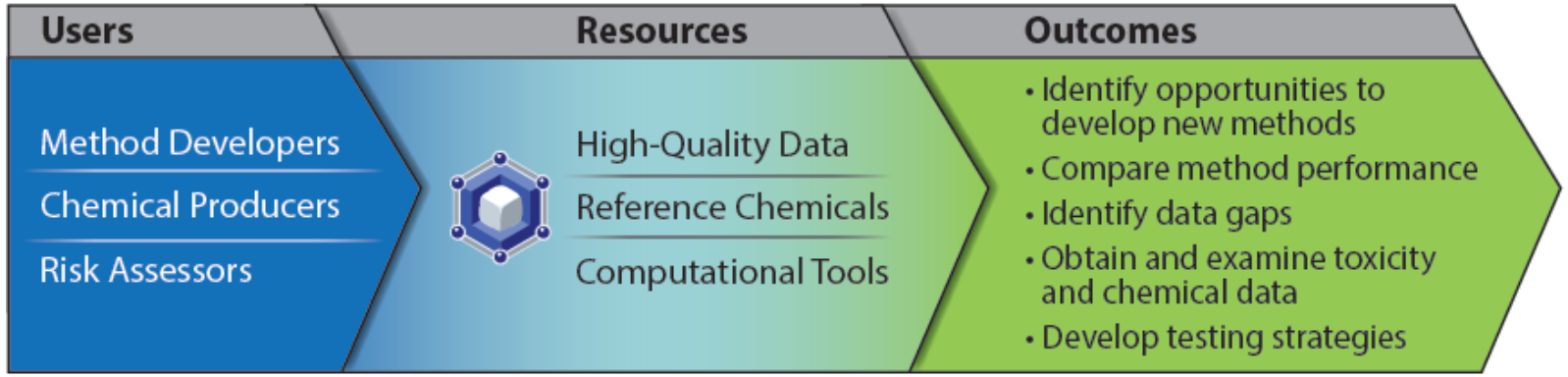
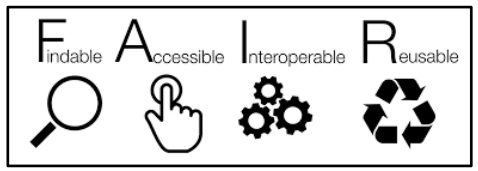
ICE: Integrated Chemical Environment

Releases in 2023:
ICE v4.0 (March)
ICE v4.0.1 (August)

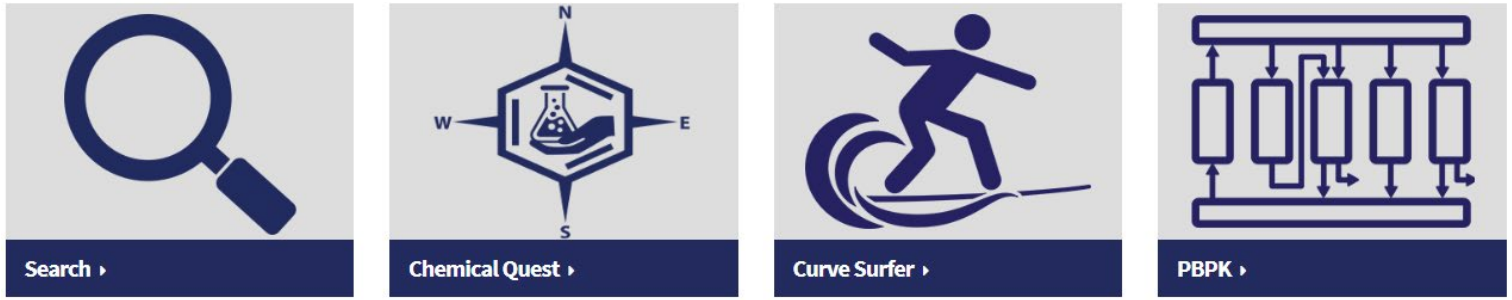
Releases in 2024:
ICE v4.0.2 (March)

Upcoming - ICE v4.1 (August)





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

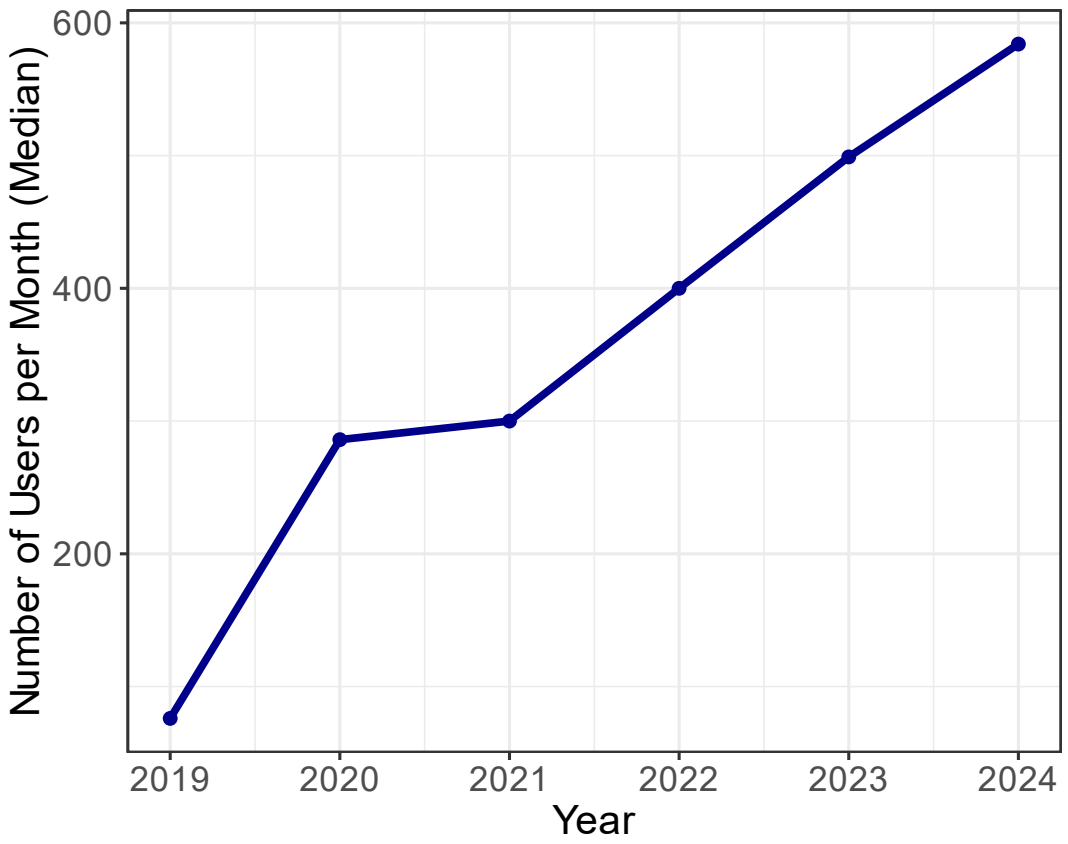


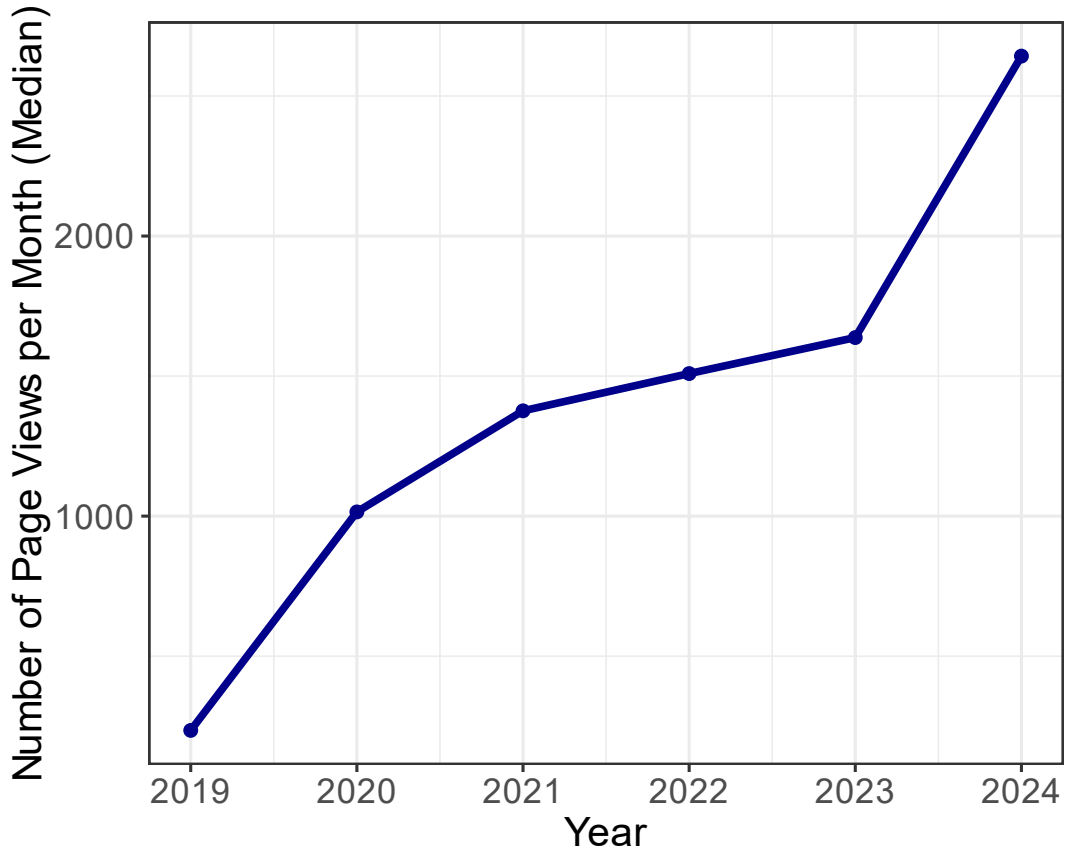
Integrated Chemical Environment

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

ICE Usage Statistics

- ICE was launched in 2017 and has been consistently updated with new data, tools, and features.

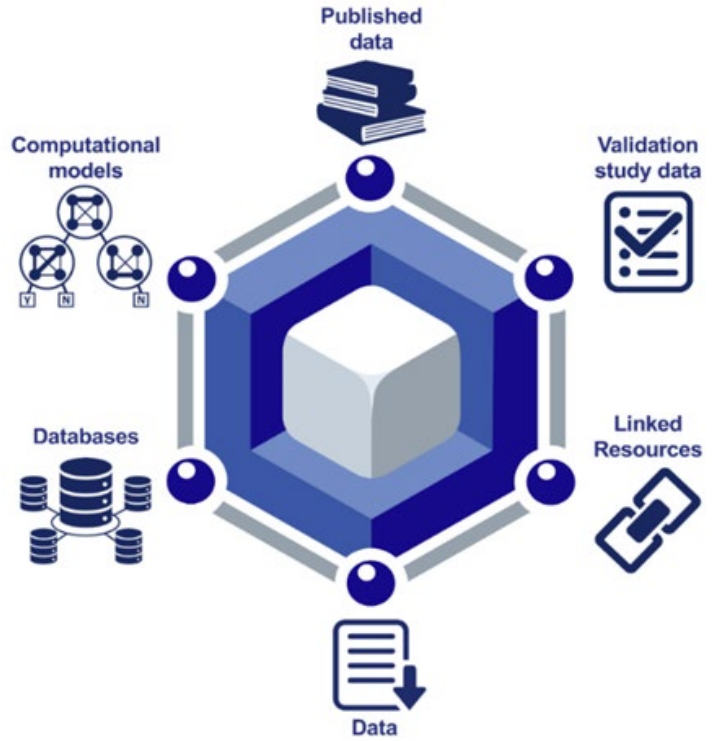




ICE Data

Data Sets
Acute Toxicity
ADME Parameters
Cancer
Chemical Parameters
cHTS*
DART

Data Sets
Endocrine
Exposure Predictions
Eye Irritation
Functional Use Categories
Product Use Categories
Skin Irritation
Skin Sensitization



Daniel et al. 2022 Front Toxicol
https://doi.org/10.3389/ftox.2022.987848

ICE Data (In Vivo and In Vitro)

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

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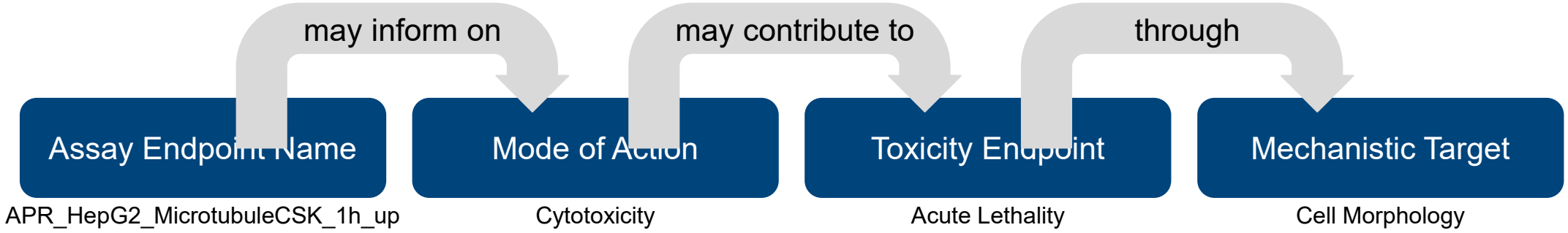
ICE Data (Curated High-Throughput Screening Data)

- ICE's curated high-throughput screening (cHTS) data set contains data from the U.S. federal Tox21 collaboration and EPA's ToxCast program for ~10000 chemicals.
- The data curation pipeline includes steps to flag results based on chemical QC, curve fit, or technological interference.

ICE cHTS Pipeline

- Assays are annotated to mechanistic targets that facilitate linkage to modes of action and subsequently to toxicological outcomes of regulatory interest.

Knowledge Organization Structure



ICE Data (In Silico Models/Integrated Approaches)

Endpoint	Model	# of Chemicals
Acute Oral Toxicity	**CATMoS**: Collaborative Acute Toxicity Modeling Suite – 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
	CERAPP: Collaborative Estrogen Receptor Activity Prediction Project *(Mansouri et al. EHP 2016)*	>1M
	COMPARA: Collaborative Modeling Project for Androgen Receptor Activity *(Mansouri et al. EHP 2020)*	>1M
Physicochemical Properties	**OPERA**: Open Structure-Activity/Property Relationship App *(Mansouri et al. J Cheminform 2018)*	>1M
Structural Properties	**OPERA**: Open Structure-Activity/Property Relationship App *(Mansouri et al. J Cheminform 2018)*	>1M
Predicted ADME Properties	**OPERA**: Open Structure-Activity/Property Relationship App *(Mansouri et al. J Cheminform 2018)*	>1M
Environmental Fate Properties	**OPERA**: Open Structure-Activity/Property Relationship App *(Mansouri et al. J Cheminform 2018)*	>1M
Exposure Predictions	**SEEM3**: U.S. EPA's Systematic Empirical Evaluation of Models *(Ring et al. Environ Sci Technol 2019)*	>475000

ICE Data (Exposure-Relevant Data)

- Population-level exposure predictions for chemicals in ICE are obtained from outputs of U.S. EPA's Systematic Empirical Evaluation of Models (SEEM3).
- Chemical use categories are derived from the EPA's Chemicals and Products Database (CPDat, Dionisio 2018).

Endpoint	# of Chemicals
Exposure Predictions *(Ring et al. Environ Sci Technol 2019)*	~475000
Curated Product Use Categories *(Isaacs et al. J Expo Sci Environ Epidemiol 2020)*	4896
Reported Functional Use Categories	9395
Predicted Functional Use Categories *(Phillips et al. Green Chem 2017)*	~200000

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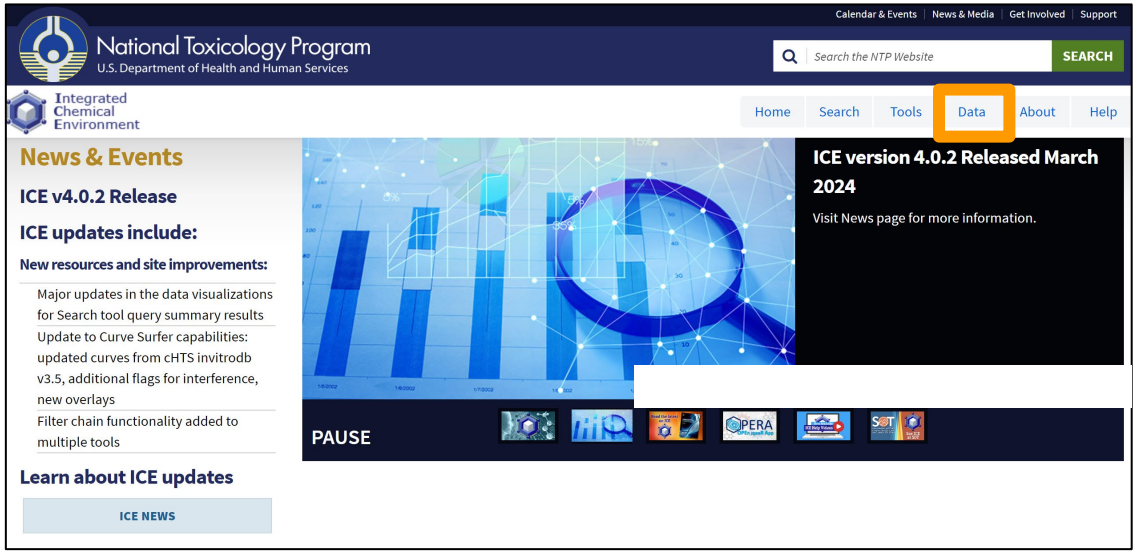
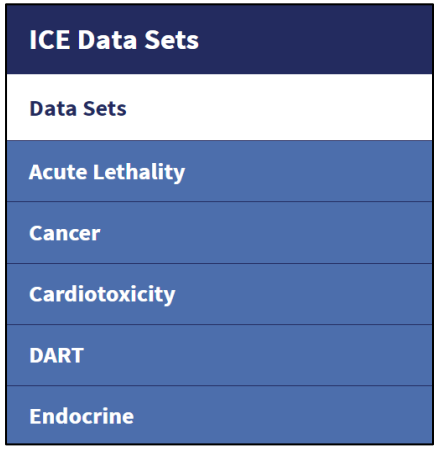
Accessing ICE Data

ICE Home Page and ICE Tools



Data Sets Page



All data in ICE are publicly available with no restrictions on use.

[ICE Data Inclusion Guidelines]

[Processing of ICE Data]

[Single Chemicals and Mixtures]

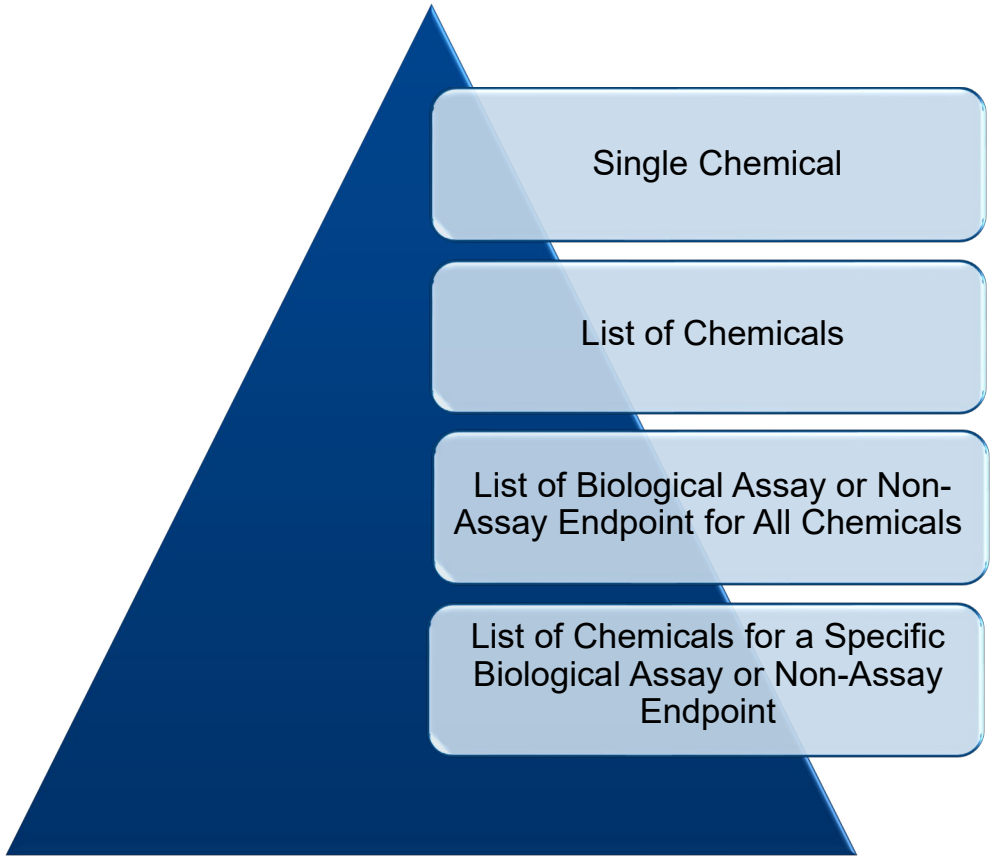
[Knowledge Organization of ICE Data]

Download Data Sets

Toxicity Endpoint	Description	Data Retrieval
Acute Oral Toxicity • 8638 Chemicals • 3 Endpoints • 12,796 Records	In vivo and in silico data compiled by NICEATM that describe toxic effects occurring within a few hours of one or more oral doses of a test substance within a 24-hr period. Includes data on mixtures and active ingredients. Learn more	• Download • Query (Search, REST API) • Overlay (IVIVE)
Acute Dermal Toxicity • 276 Chemicals • 3 Endpoints • 916 Records	In vivo data that describe toxic effects occurring within a few hours of a single dose of a test substance applied to the skin. Includes data on mixtures and active ingredients. Learn more	• Download • Query (Search, REST API)

ICE Data Access via REST API

ICE Queries



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

Output: Array of Assay-Endpoint Objects per Chemical

ICE Chemical Quick Lists

- NICEATM provides chemical lists to support the development and evaluation of new test methods.
  - These reference and non-reference chemical lists are included in ICE as “chemical quick lists” that can be used to populate queries across ICE tools.

Reference Chemical Lists
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

Reference Chemical Lists - Chemicals that cause a specified, well-characterized biological effect

Ongoing ICE Project
Add new PFAS quick list

Ongoing ICE Project
Update ROC chemical list with the 15th Report on Carcinogens

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

Non-reference Chemical Lists - Less restrictive inclusion criteria

ICE Tools

Search	Query ICE data and visualize results
Chemical Quest	Identify similar chemicals
Chemical Characterization	Explore chemical properties and use categories
Curve Surfer	Explore concentration-response curves
PBPK	Predict tissue-specific chemical concentrations
IVIVE	Predict equivalent administered dose from in vitro data

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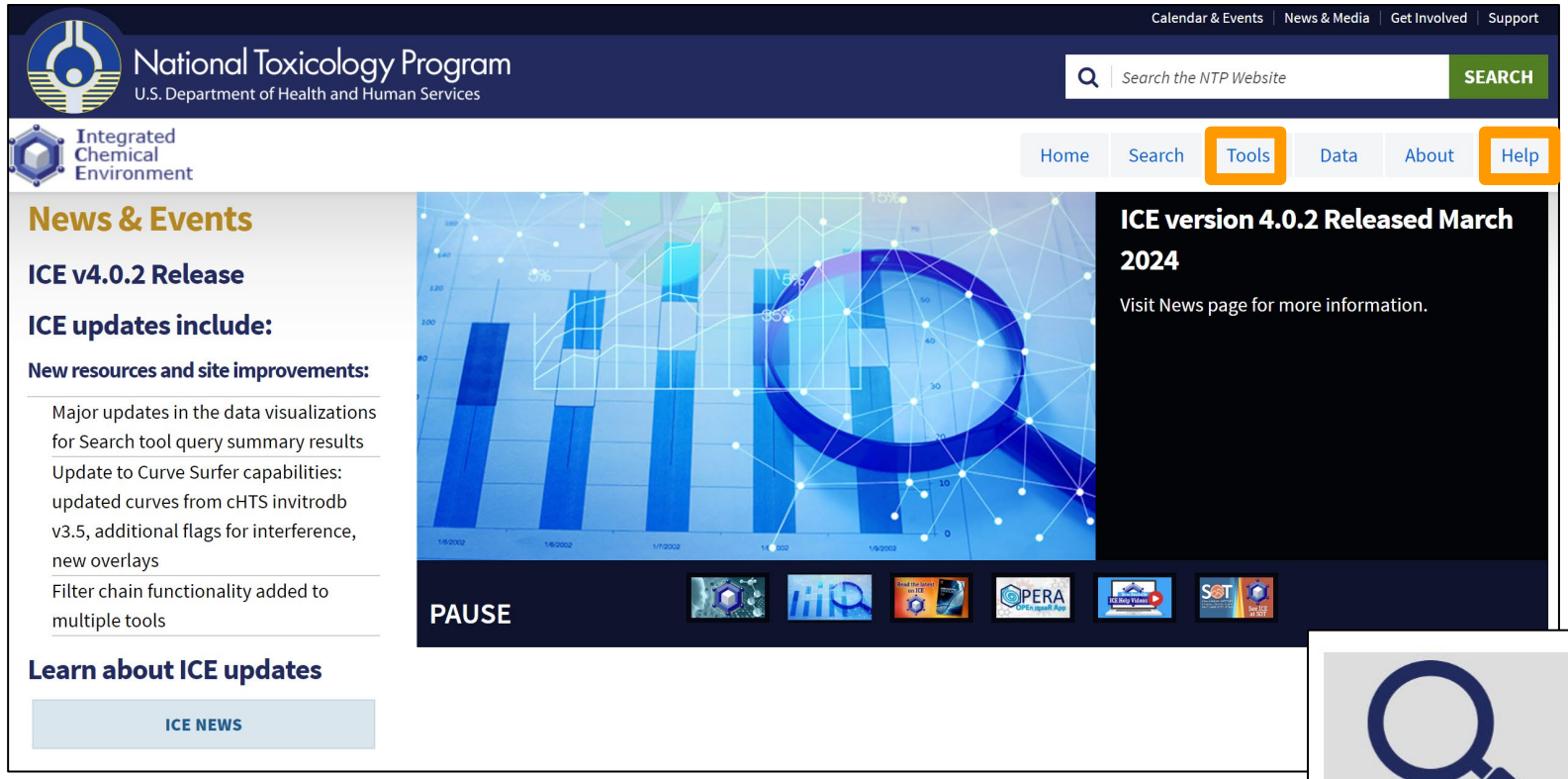
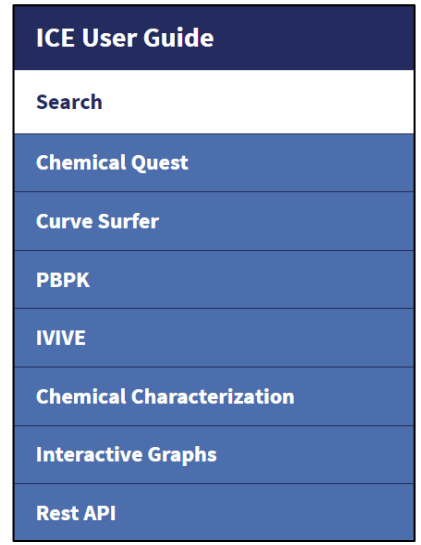
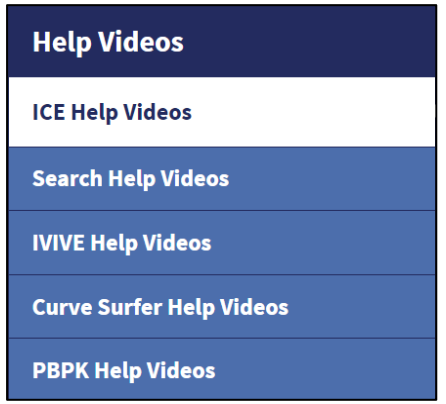
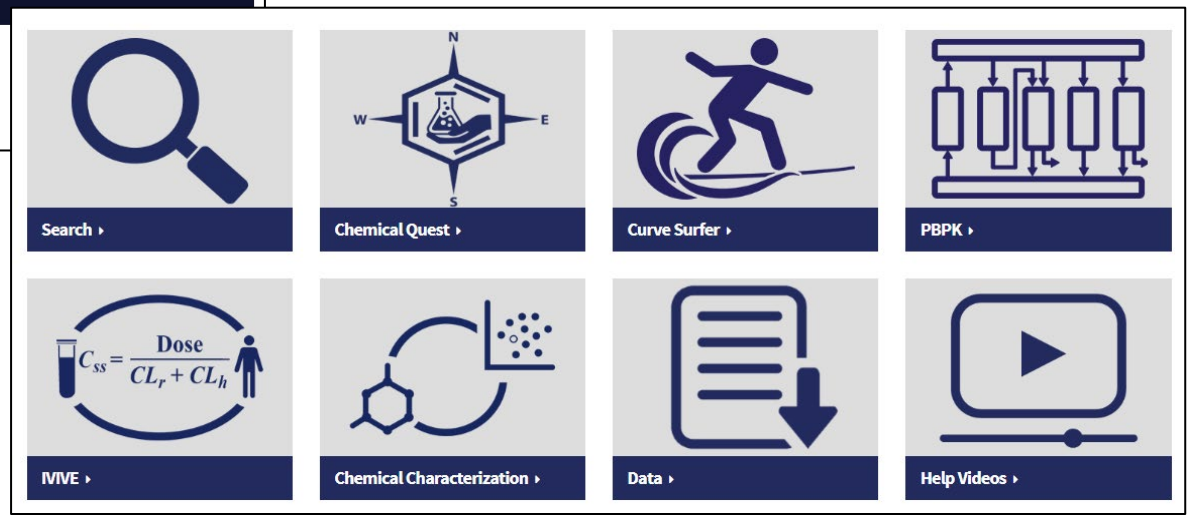
Accessing ICE Tools









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

Demo

Exploring ICE

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

ICE Tools

Search	Query ICE data and visualize results
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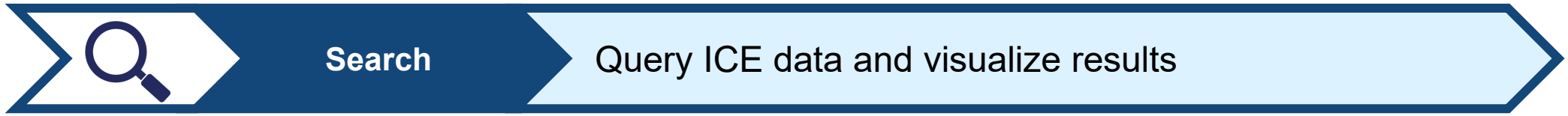

- The ICE Search tool enables interactive exploration of ICE data for chemicals of interest.
- Interpret in vitro high-throughput screening data using biologically relevant assay annotations.
- Leverage dynamic data filtering to refine chemical lists for further exploration using ICE tools.

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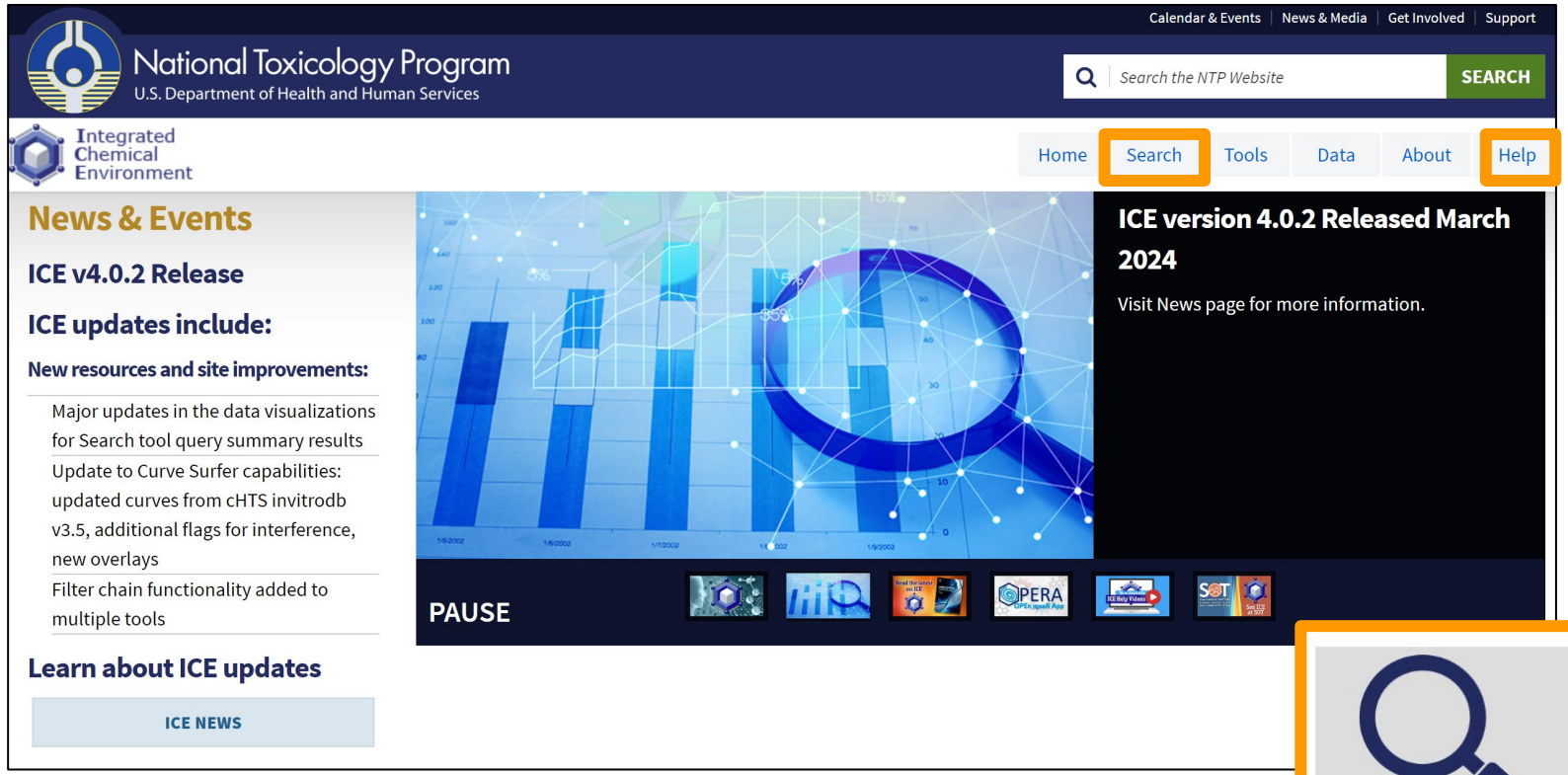
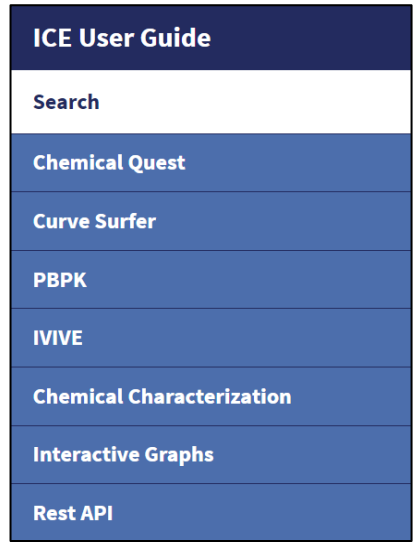
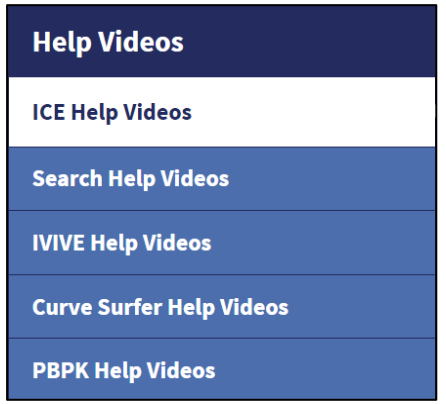
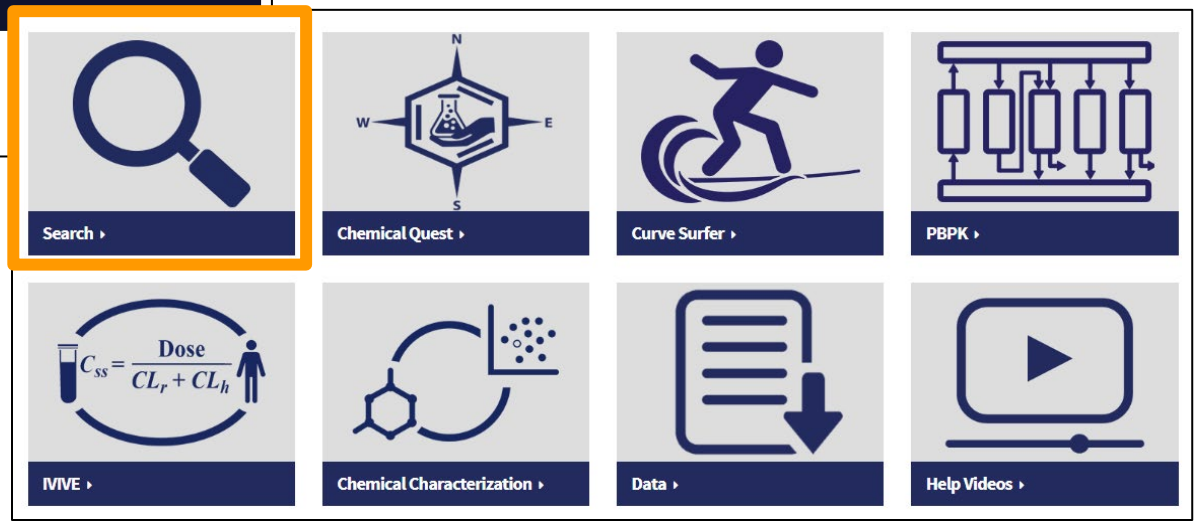
Accessing Search









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

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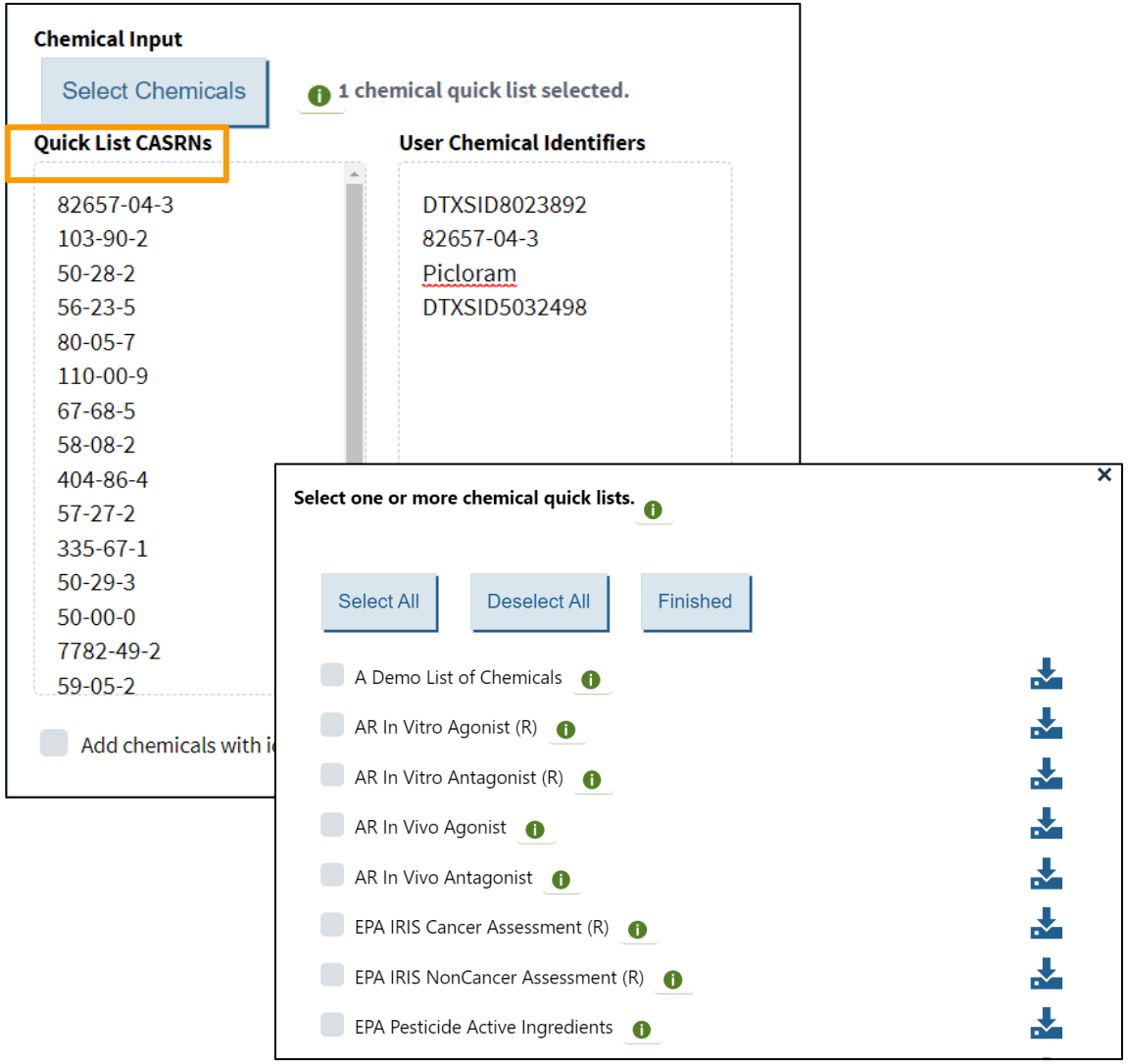
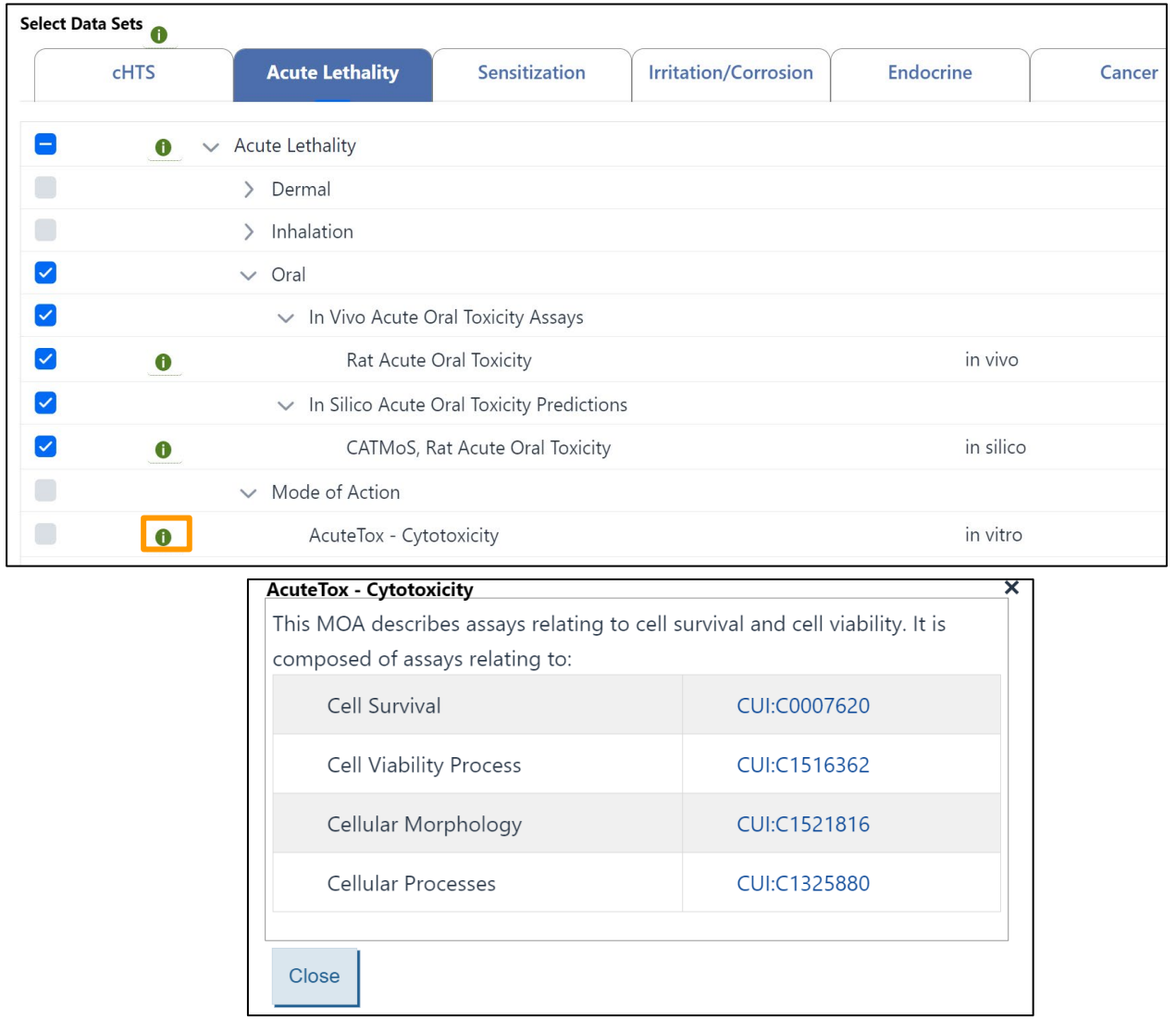
Search Input

Chemical Input



Data Set Input



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Search

New Search Results Interface

Input

Results

Search Results

- Selected Chemical Quick Lists (1)
- Selected Assays (0)
- Chemical Identifiers Not Returned By Query (0)

View Data Tables

Data Table | Data Summary | Download

Help

Help Video

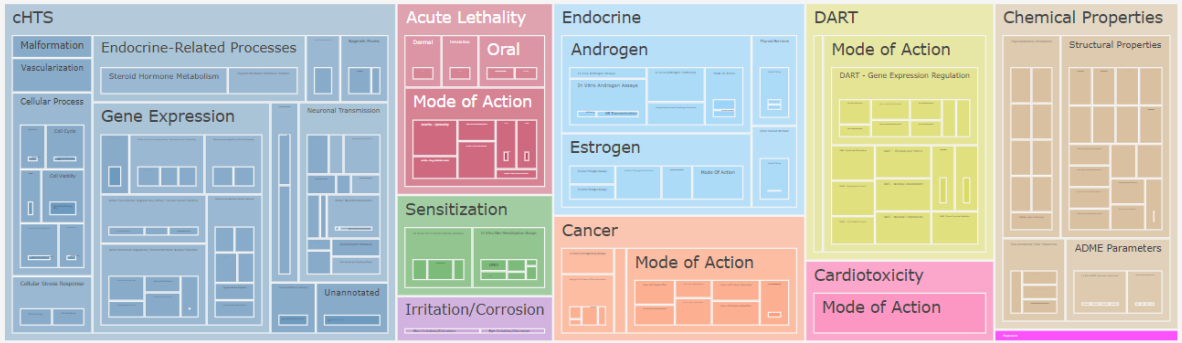
Report an Issue

Interact with Results

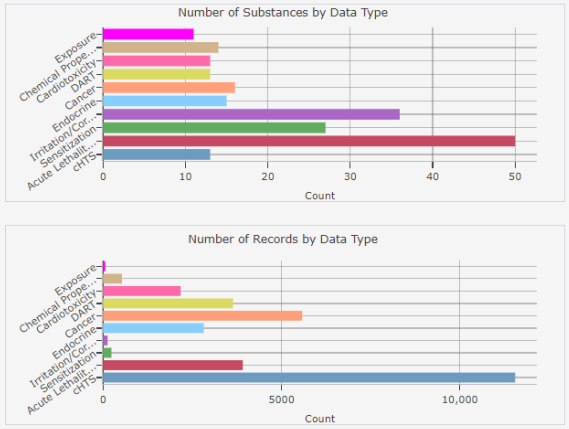
To zoom in to a specific data type, click on the box within the navigation map. Banners at the top of the map will indicate your position in the navigation map. To zoom out, click on the banner. As you navigate through the map, the information in the data tables and graphics on the right side will update to reflect data specific to your position in the map.

Select filter to add to chain: | Send filtered results to: Select tool... | Clear Filters

Search Results Navigation by Selected Data Sets



Substance and Record View



Results Distribution by Chemical Reference List (16 substances queried)

Chemical List	Queried	Not Ret...	Distribution of Records	Records
A Demo List of Chemicals	16	0		30618

Search Results by DTXSID, CASRN (13446 records for 54 substances)

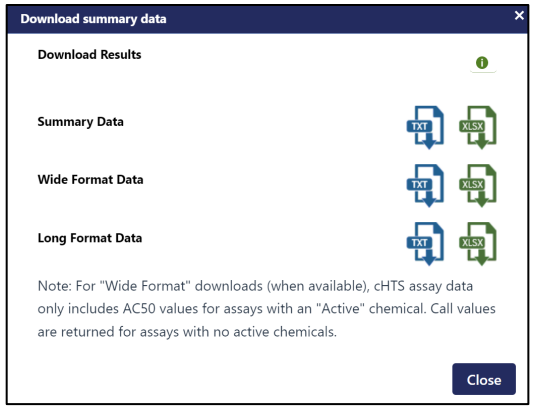
Name	Type	CASRN (CEBS I	DTXSID (Das	Distribution of Records	Rec...
Cisplatin	Chemical	15663-27-1	DTXSID4024983		576
The Andersons 0.058% Bifenthri	Mixture	138261-41-3: 0.11 82657-04-3: 0.058	DTXSID5032442: DTXSID9020160:		9

Search

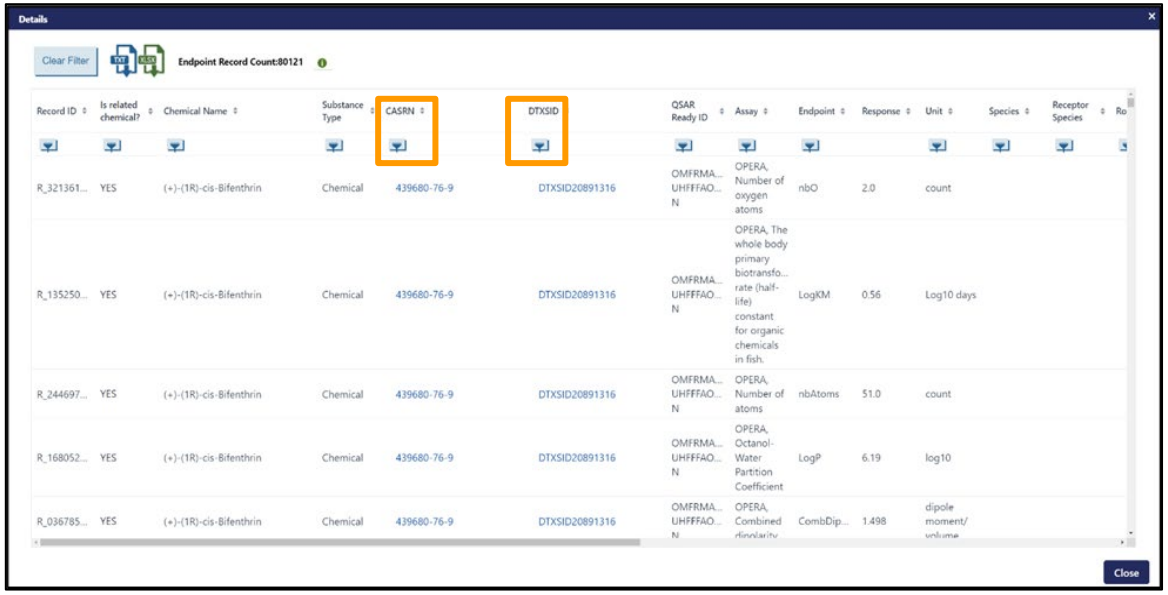
Search Results

View Data Tables

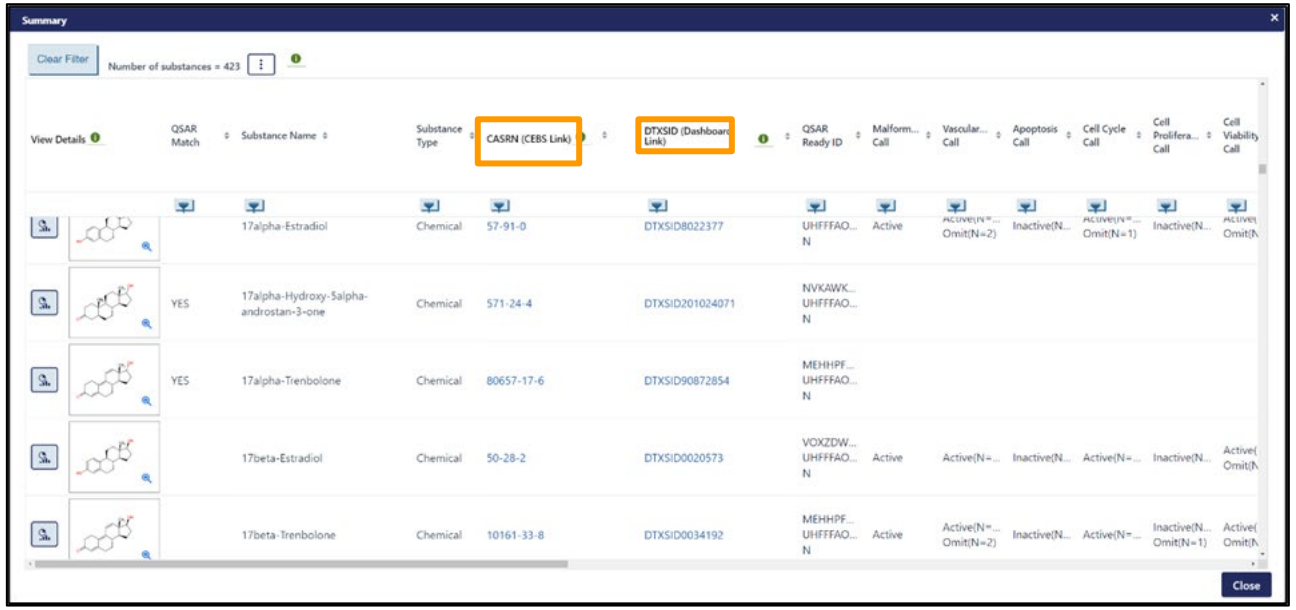
Data Table | Data Summary | Download



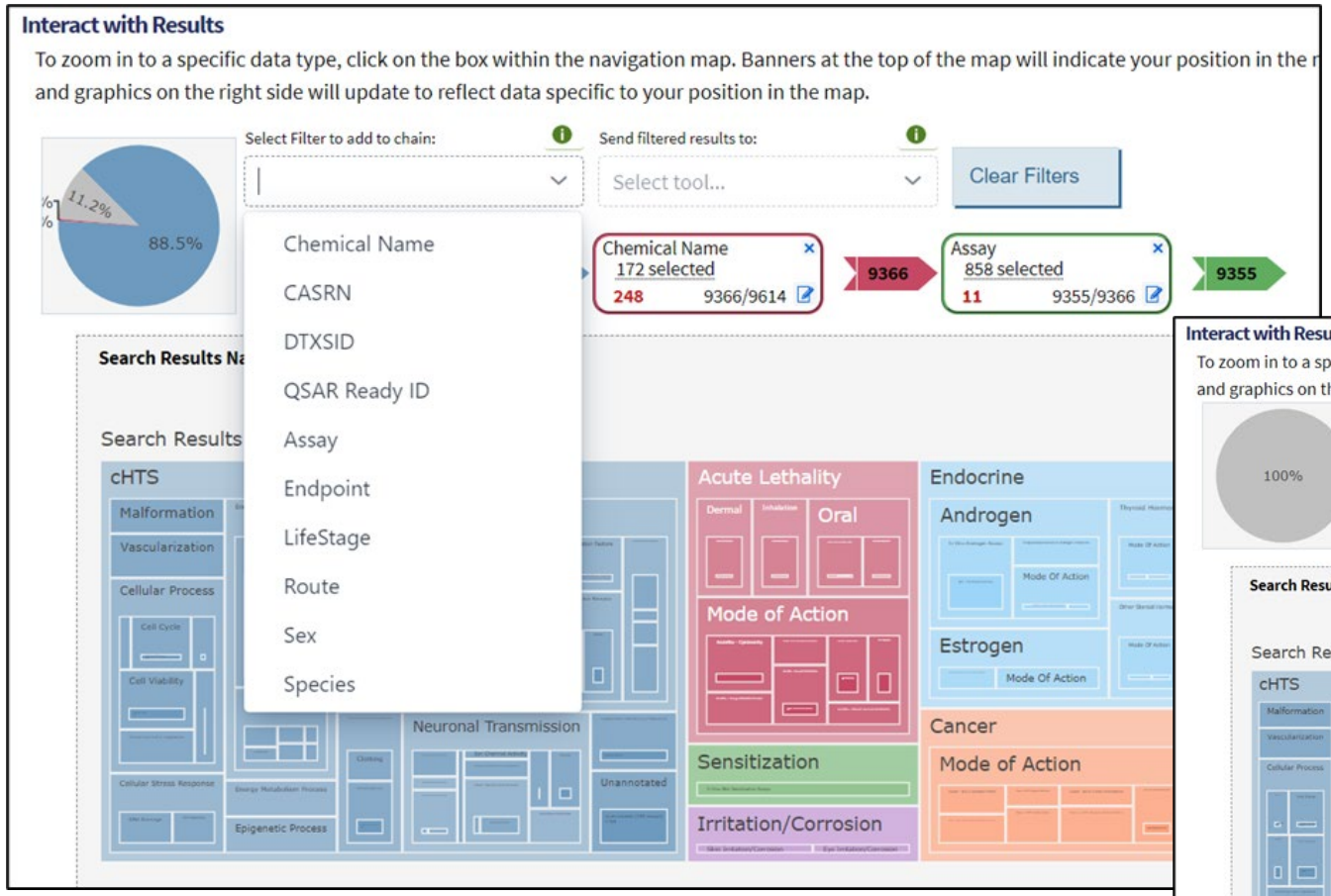
The long format data table displays data for each substance-endpoint record.



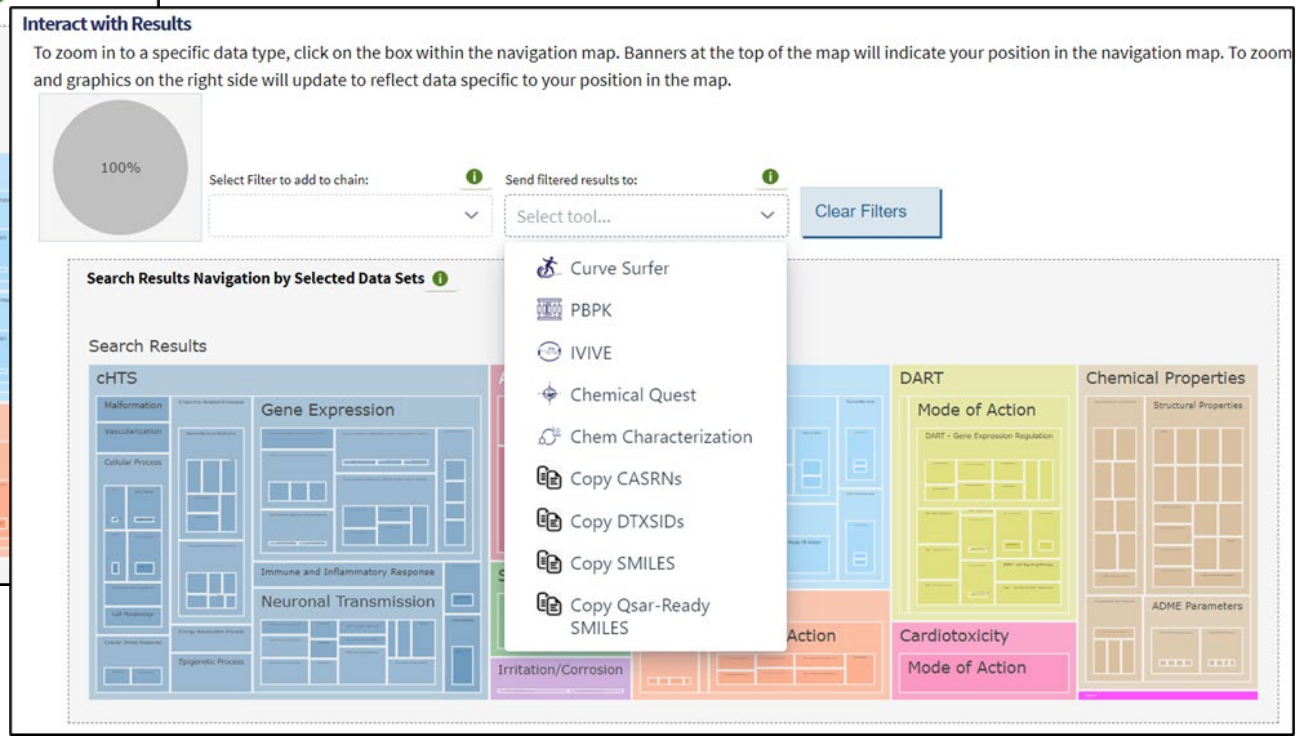
The wide format data table displays summarized results for substance-endpoint pairs.



Filter Search Results



Send Search Results to Other ICE Tools



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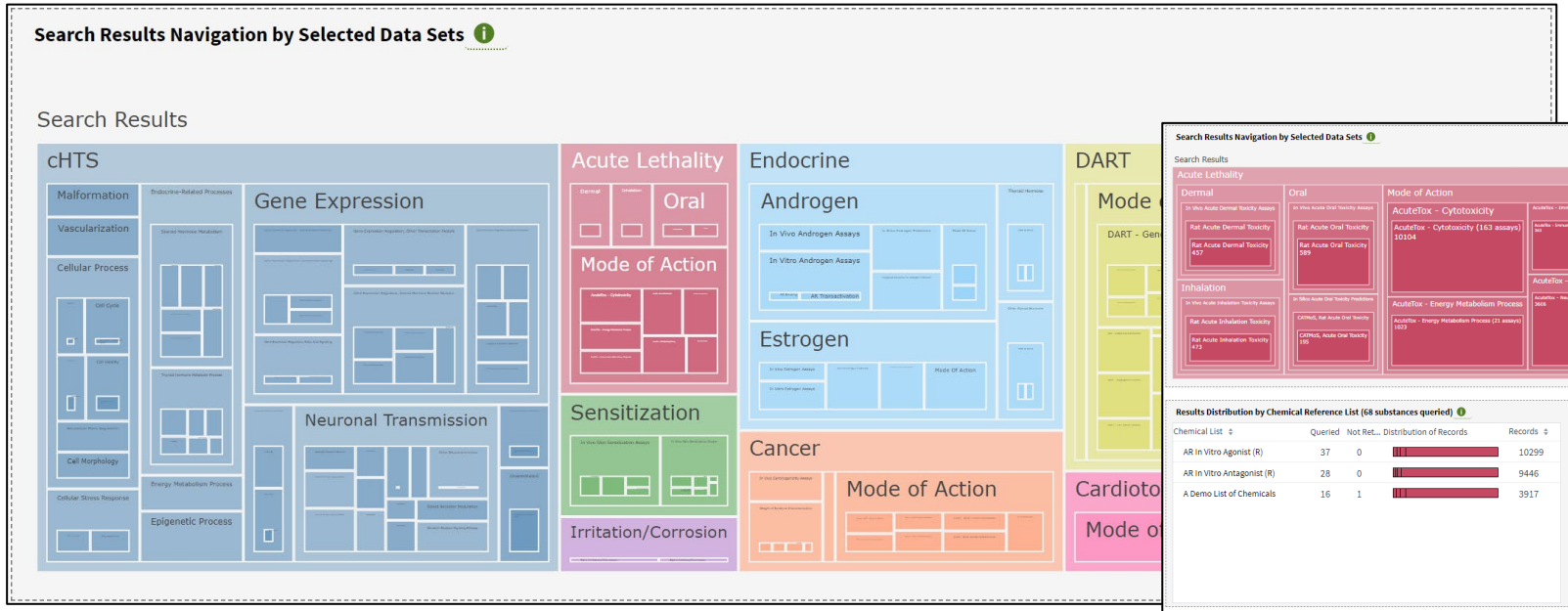
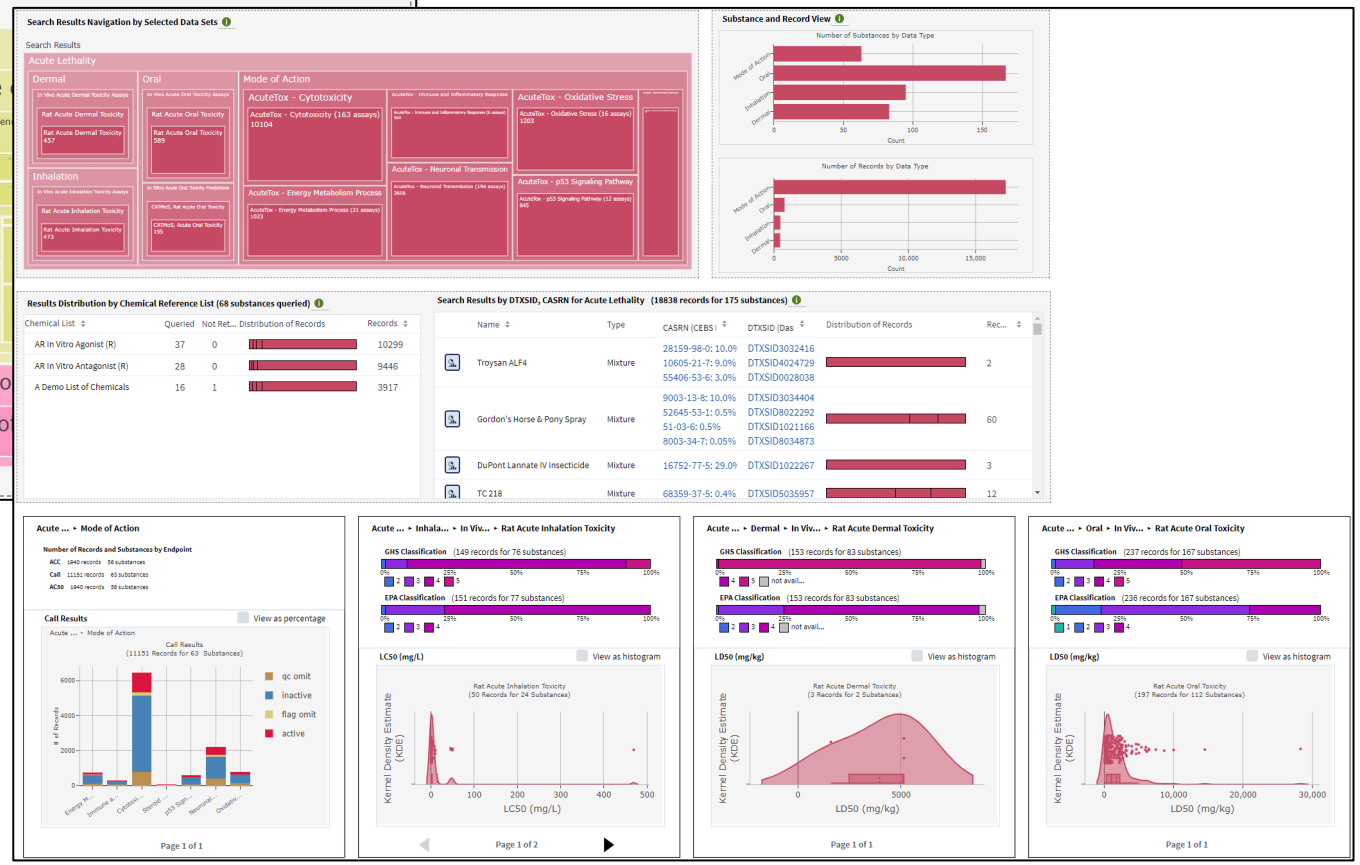
Search

Search Results

Results can be explored using the navigation map that organizes results based on data set.

Data visualizations aggregate results by data set/subset based on the user's position in the navigation map.

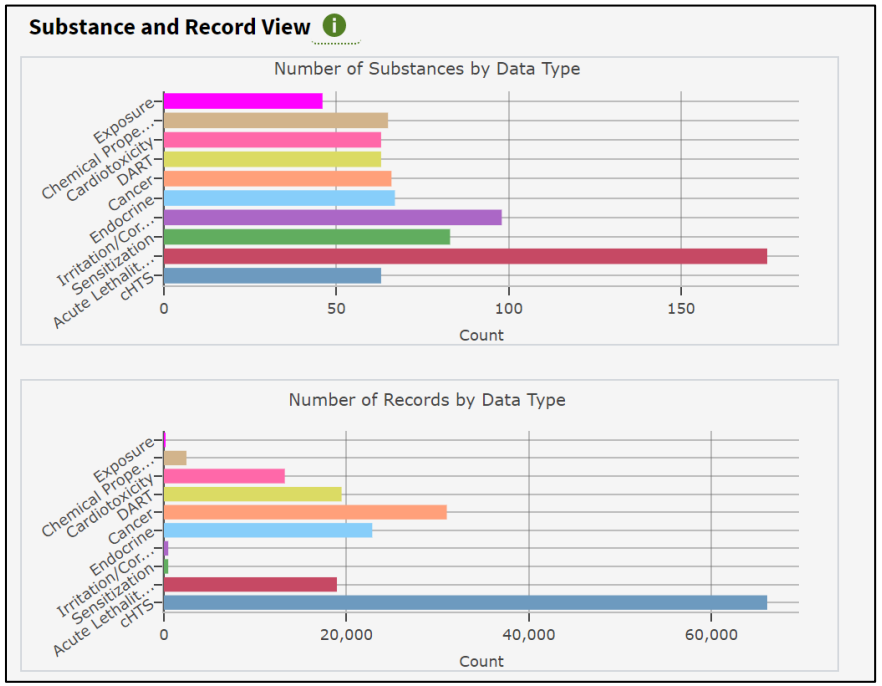


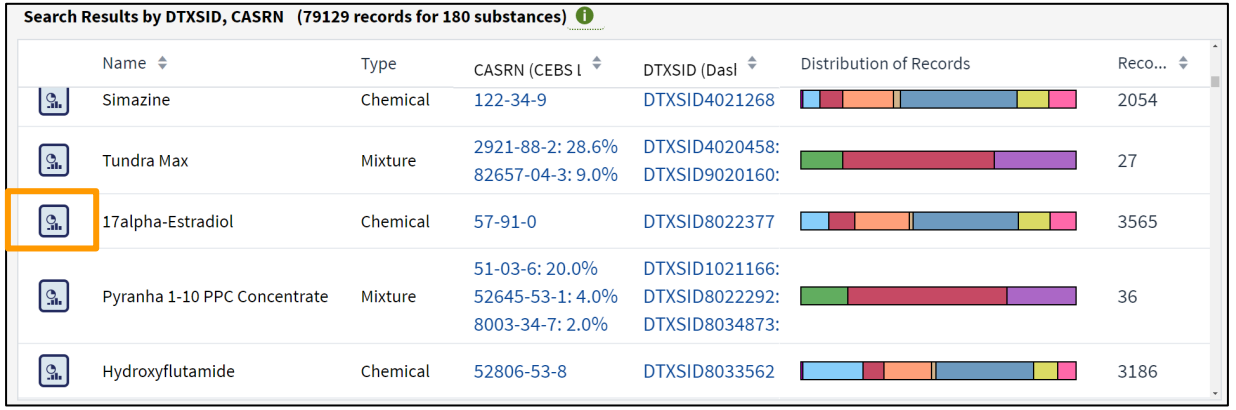


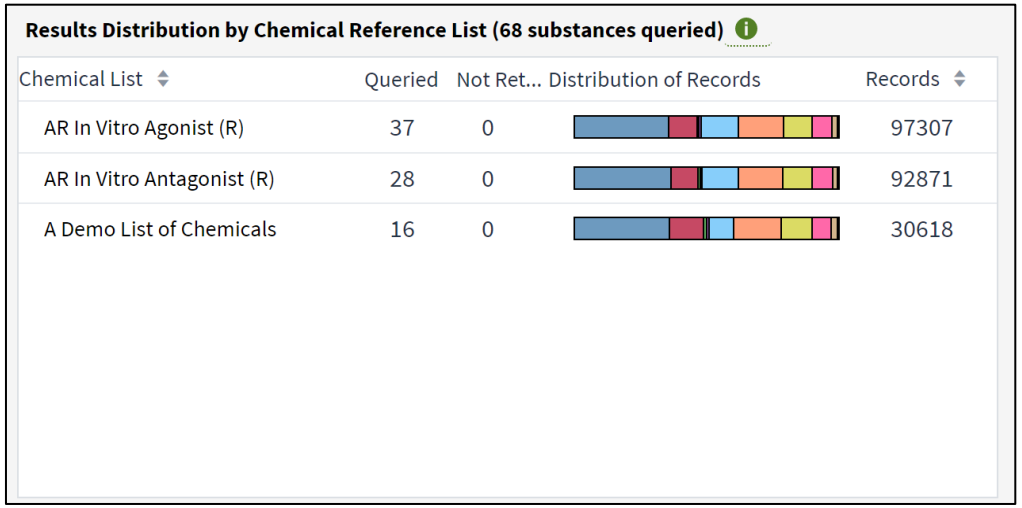
Search Results

Bar graphs display the number of substances and records in the query results.

Interactive tables display the amount of data available for individual substances.



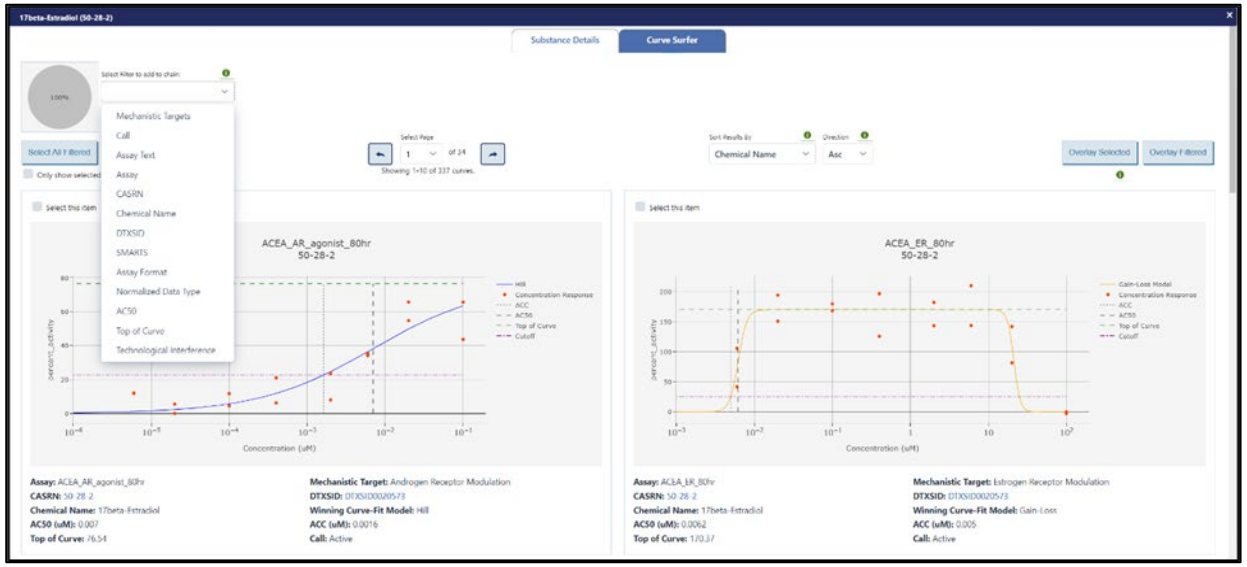




Search Results

Search

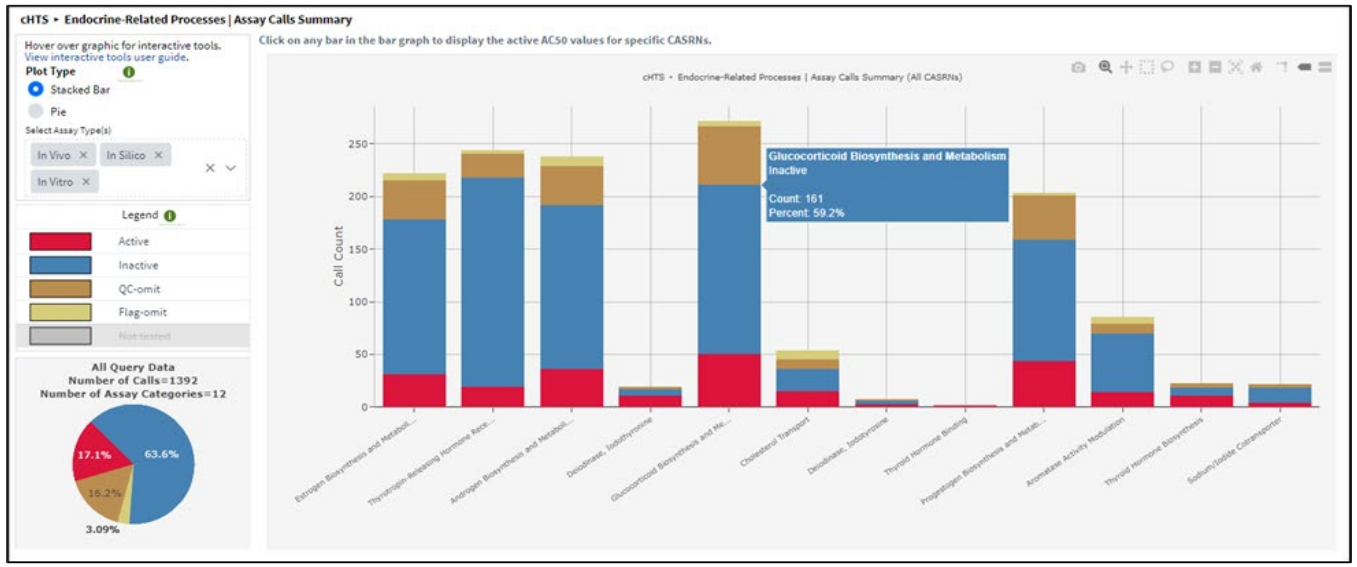
Curve Surfer View

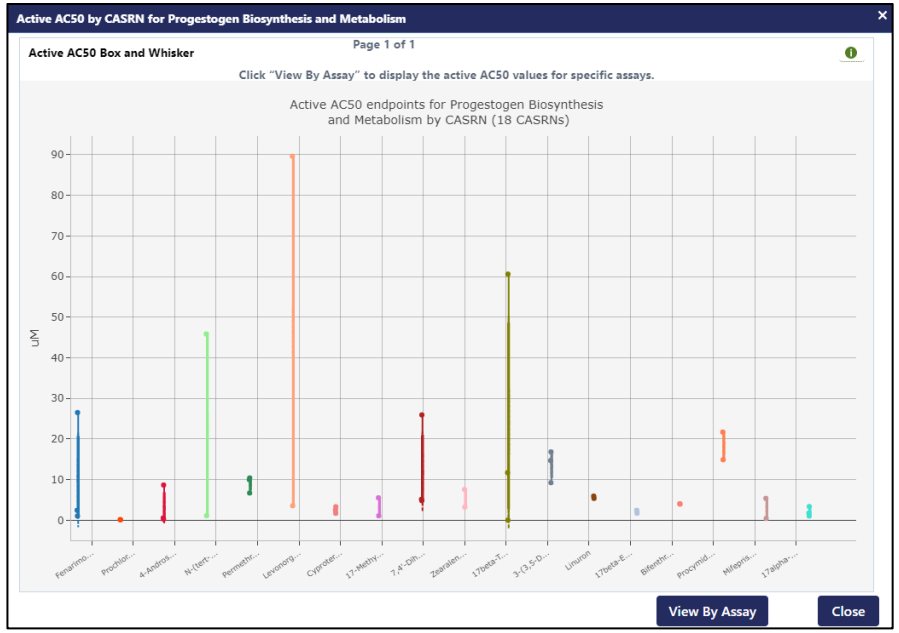


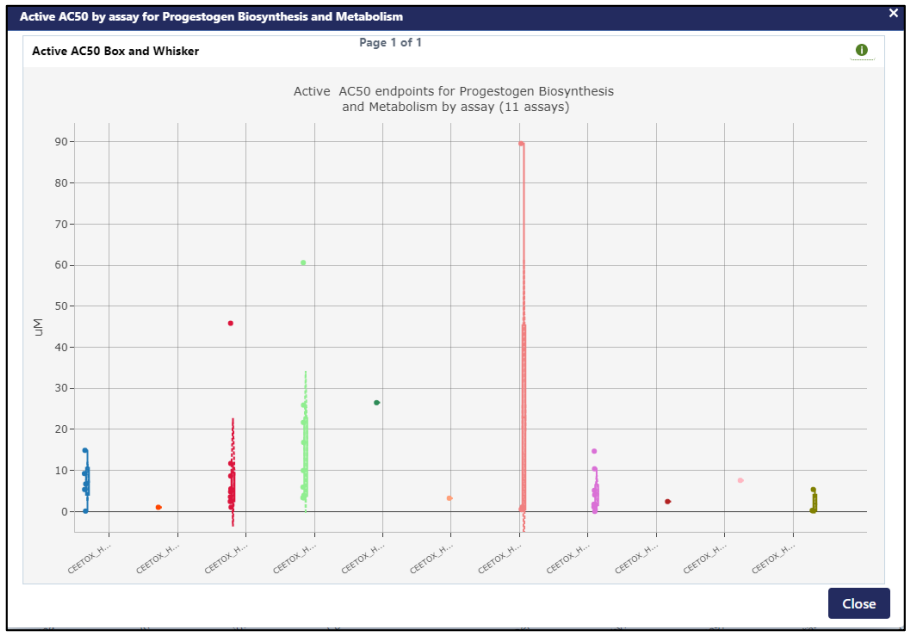
Substance Detail View for Single Chemical

Substance Detail View for Mixture

Bioactivity Summary







Demo

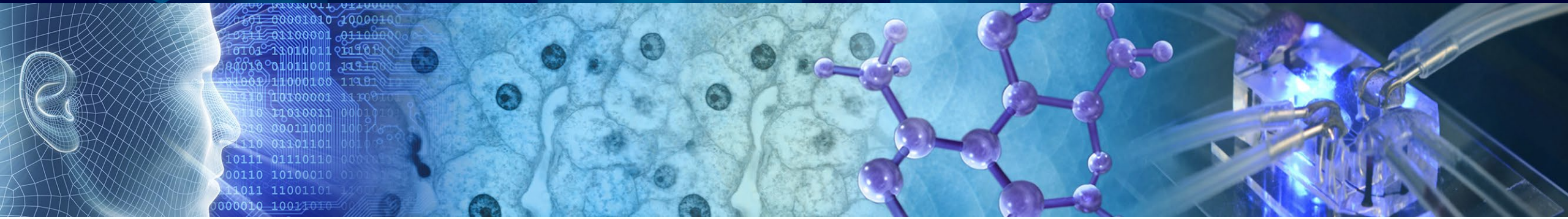
Exploring ICE Search Tool Using
“A Demo List of Chemicals”

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

Session Questions

Contact: ICE-support@niehs.nih.gov

National Institute of Environmental Health Sciences
Division of Translational Toxicology



Training Session on the Integrated Chemical Environment (ICE) Session 2 - Chemical Quest, Chemical Characterization, and Curve Surfer Tools

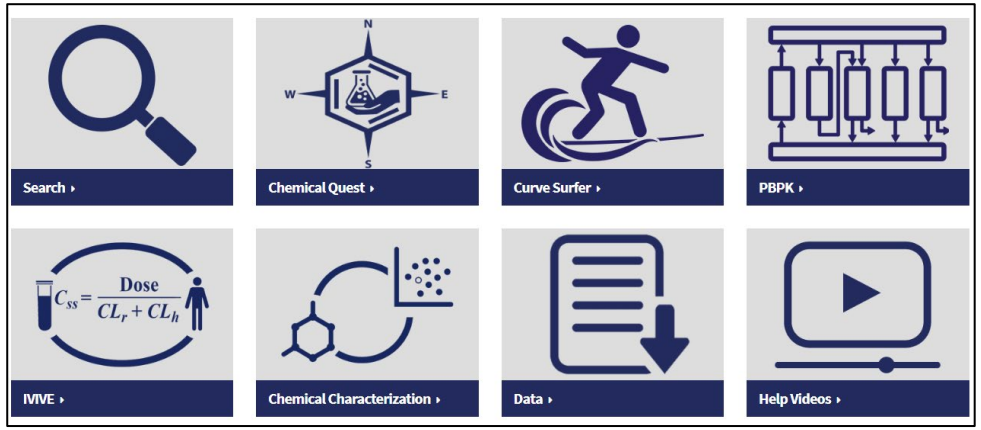
ICCVAM Public Forum: 22nd May 2024
2:00 pm – 2:50 pm

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.

Integrated Chemical Environment



Session 1 Summary

- Introduction to ICE interface
  - ICE is an open-access computational tool that allows users to explore toxicologically-relevant endpoints and models
- ICE data sets and reference lists
  - Access data sets using ICE interface or API
  - ICE documentation details the different sources of each data set and the data curation process
- Search tool summarizes toxicity endpoint, chemical property, and exposure data for a set of queried chemicals

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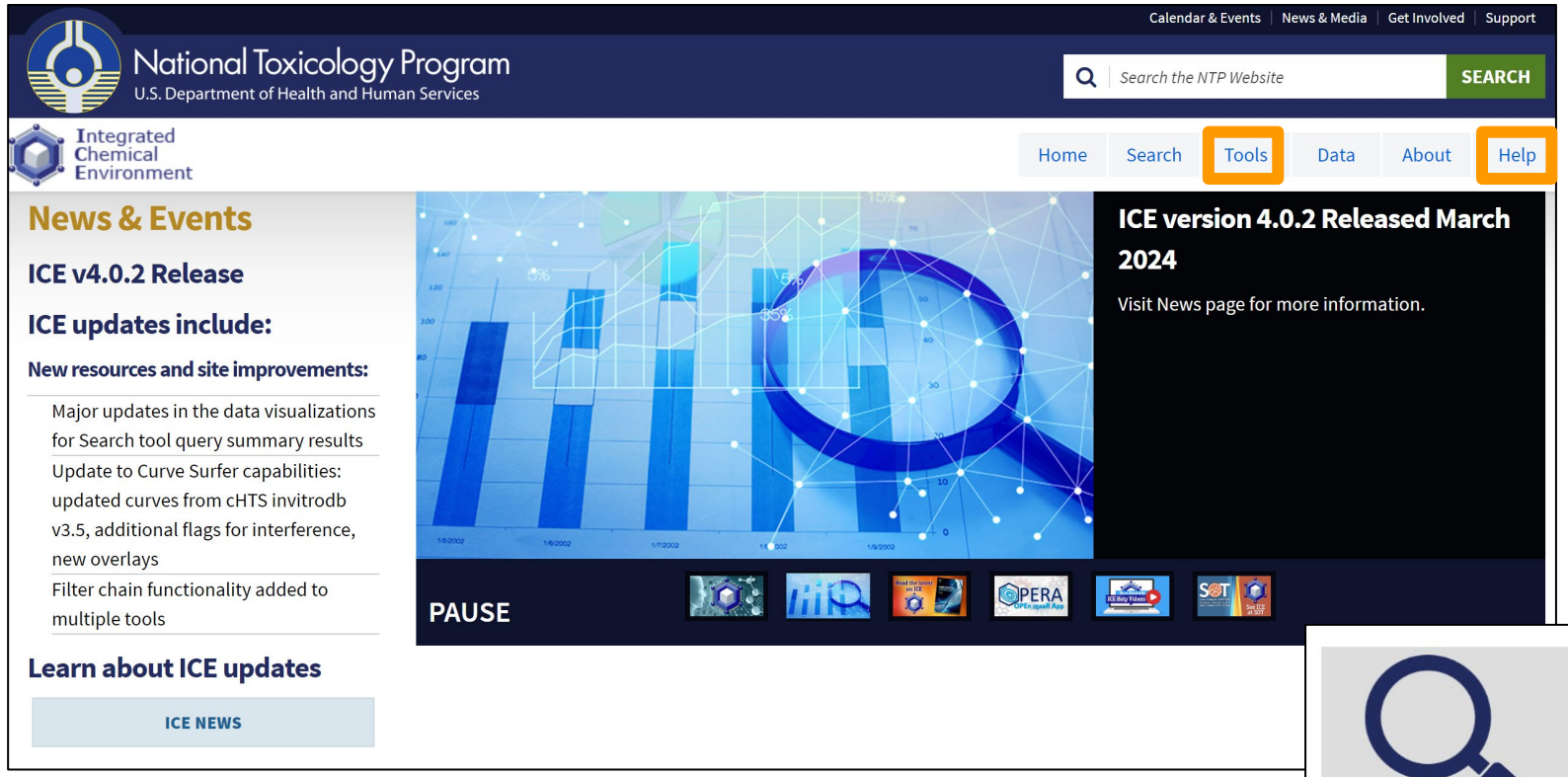
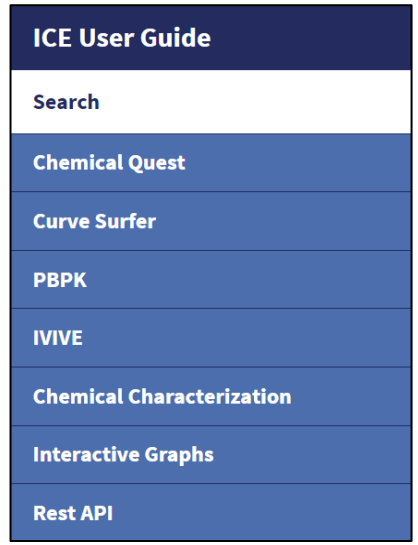
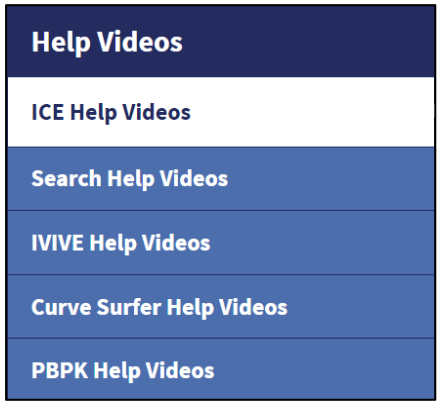
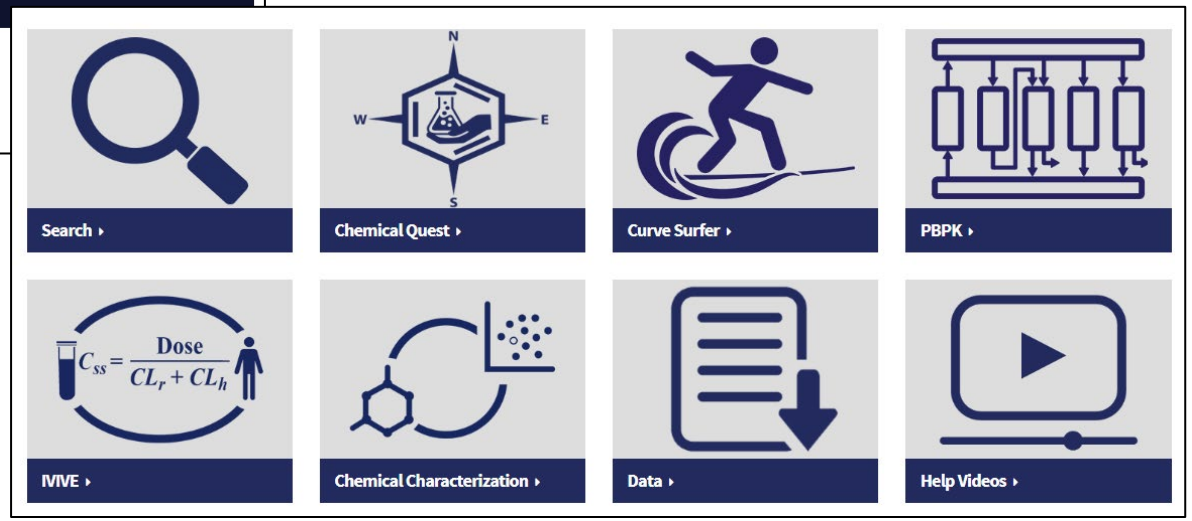
Division of Translational Toxicology

Accessing ICE Tools









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

Chemical Quest

Search	Query ICE data and visualize results
Chemical Quest	Identify similar chemicals
Chemical Characterization	Explore chemical properties and use categories
Curve Surfer	Explore concentration-response curves
PBPK	Predict tissue-specific chemical concentrations
IVIVE	Predict equivalent administered dose from in vitro data

Chemical Quest — Identify similar chemicals

- The Chemical Quest tool enables the identification of structurally similar chemicals.
- Leverage dynamic filtering to identify similar chemicals with bioactivity data available in ICE.
- Expand lists of data-poor chemicals for further exploration in ICE tools.

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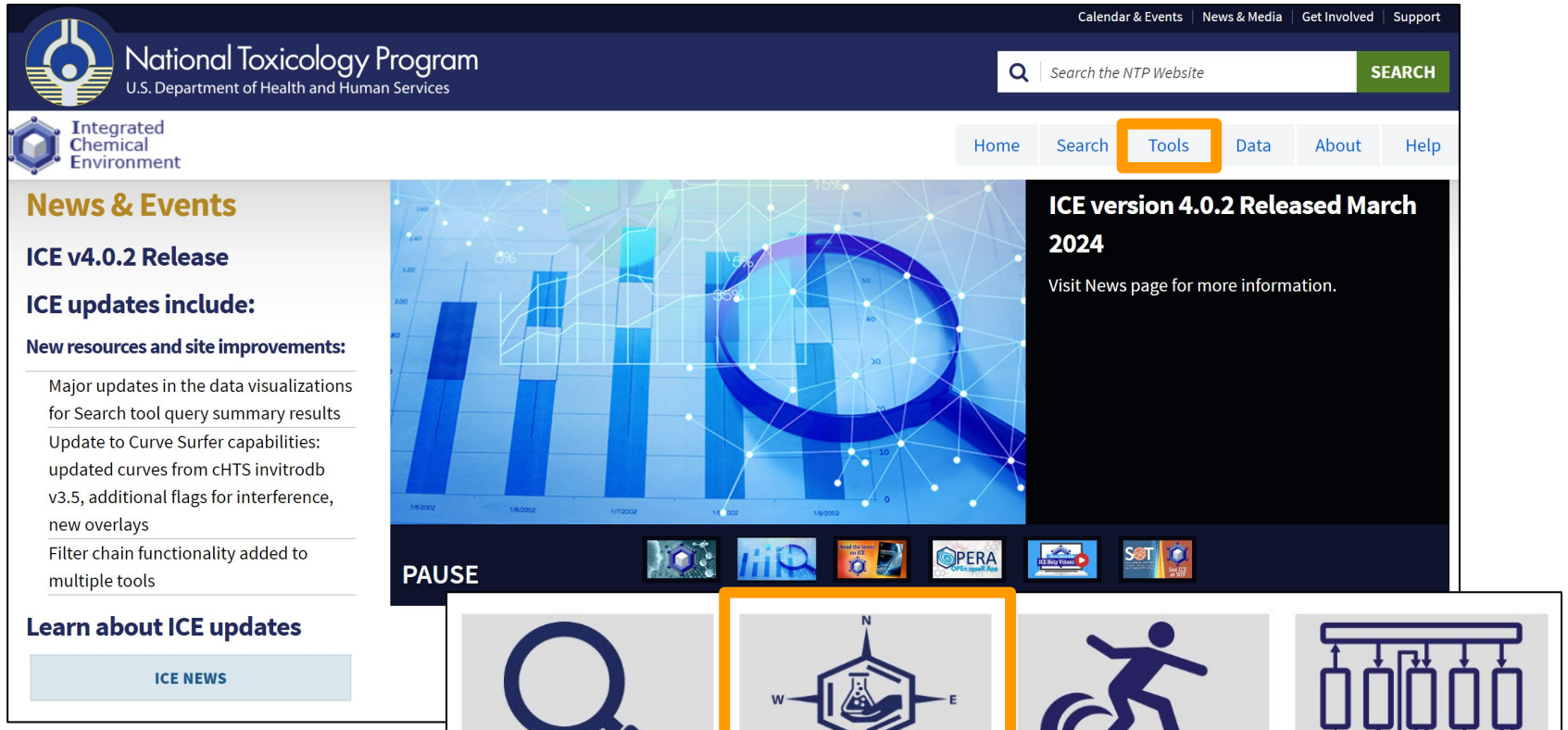
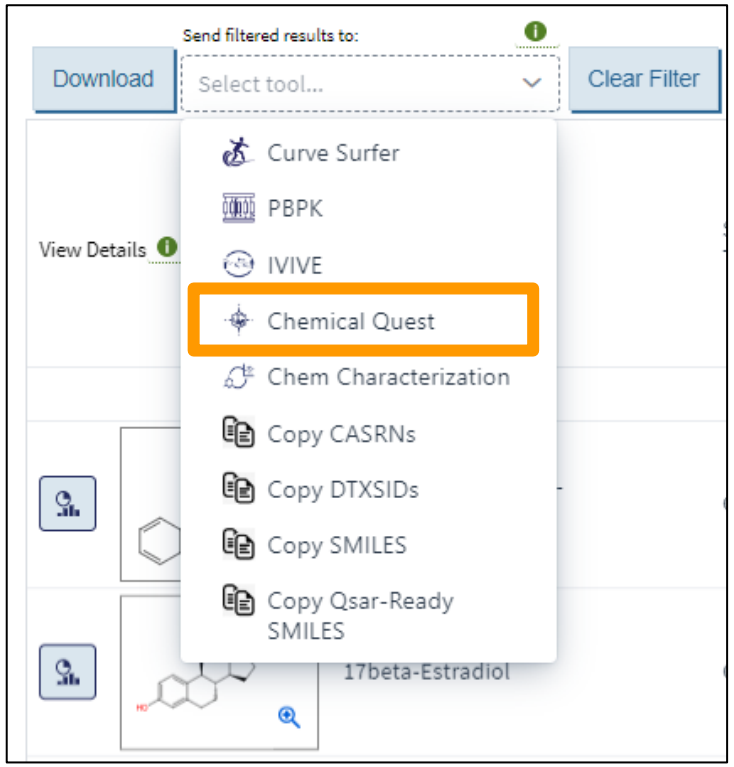
Accessing Chemical Quest



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



Chemical Quest Input

Chemical Identifier

Chemical ID input (one per line).

133-06-2
63-25-2
82657-04-3
103-90-2
50-28-2
56-23-5
80-05-7
110-00-9
67-68-5
58-08-2
404-86-4
57-27-2
335-67-1
50-29-3
50-00-0
7782-49-2
59-05-2

SMILES String

Smiles Structures for similarity search

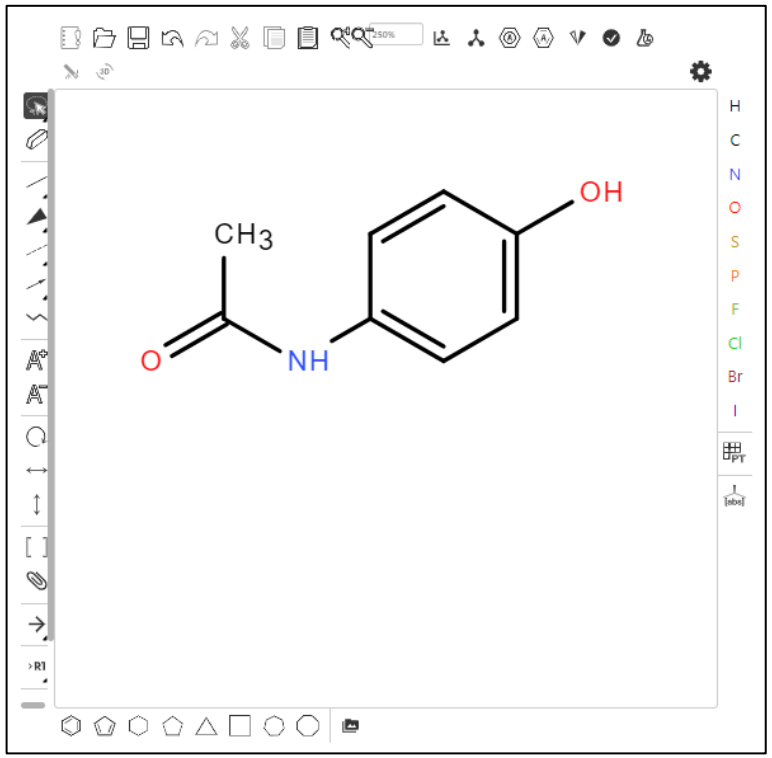
Draw | Enter

Chemical Structure
NC(=N)NC#N
C=O
CC(=O)NC1C=CC(O)=CC=1
CC(C)(C1C=CC(O)=CC=1)C1C=CC(O)=CC=1

Enter SMILES String:

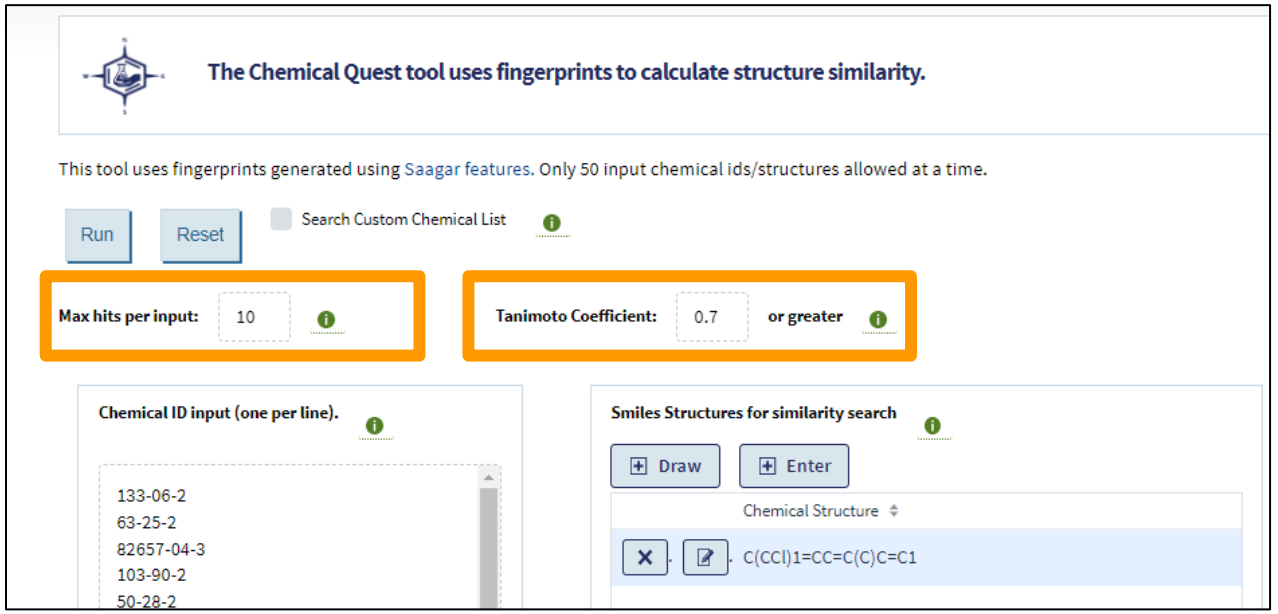
C(C)1=CC(C)=CC(O)=C1

Close

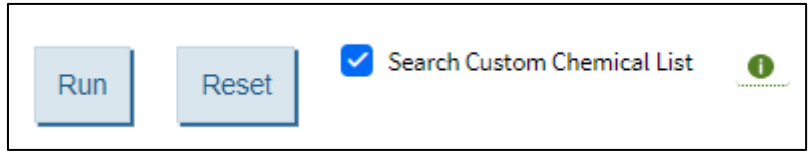


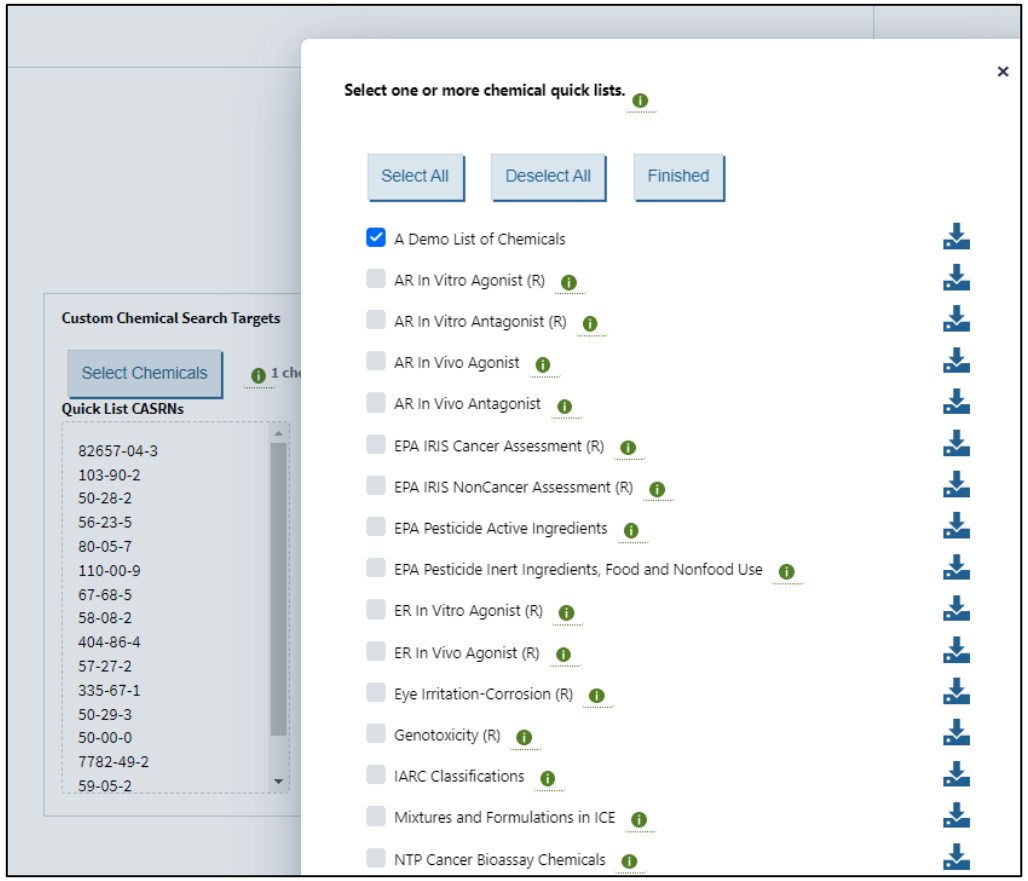
Chemical Quest Input

Specify Number of Hits and Similarity Threshold



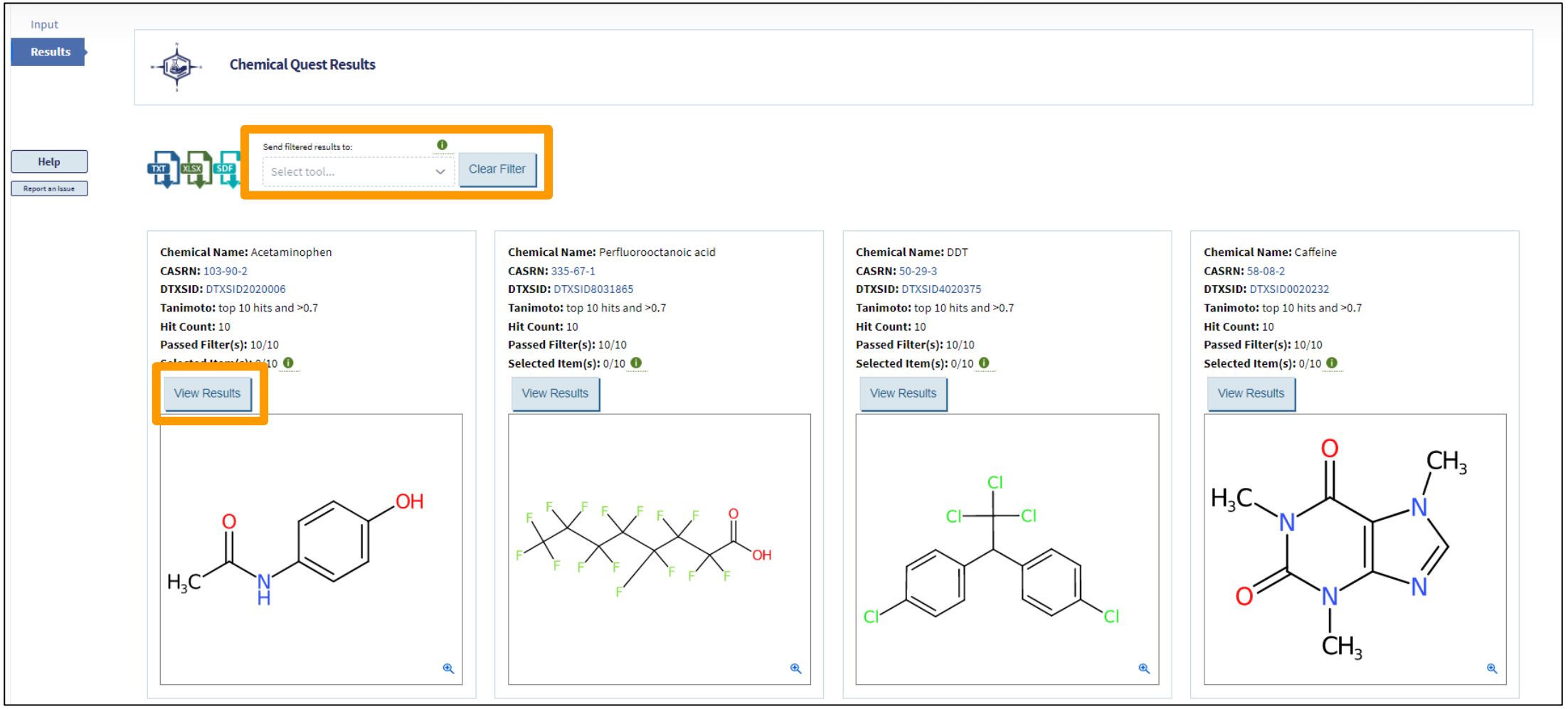
Query Against All Chemicals in ICE or a Custom Chemical List





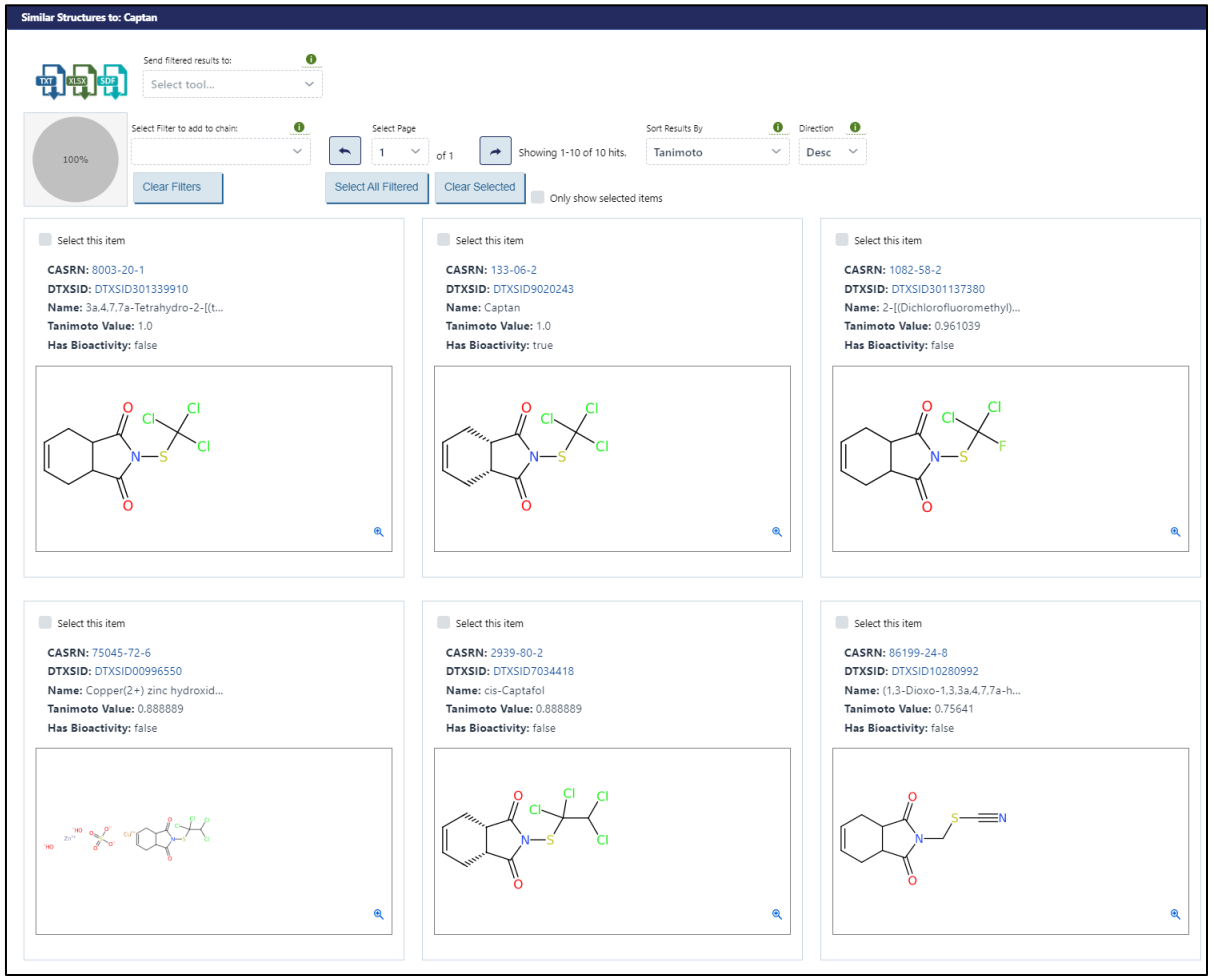
Chemical Quest Results

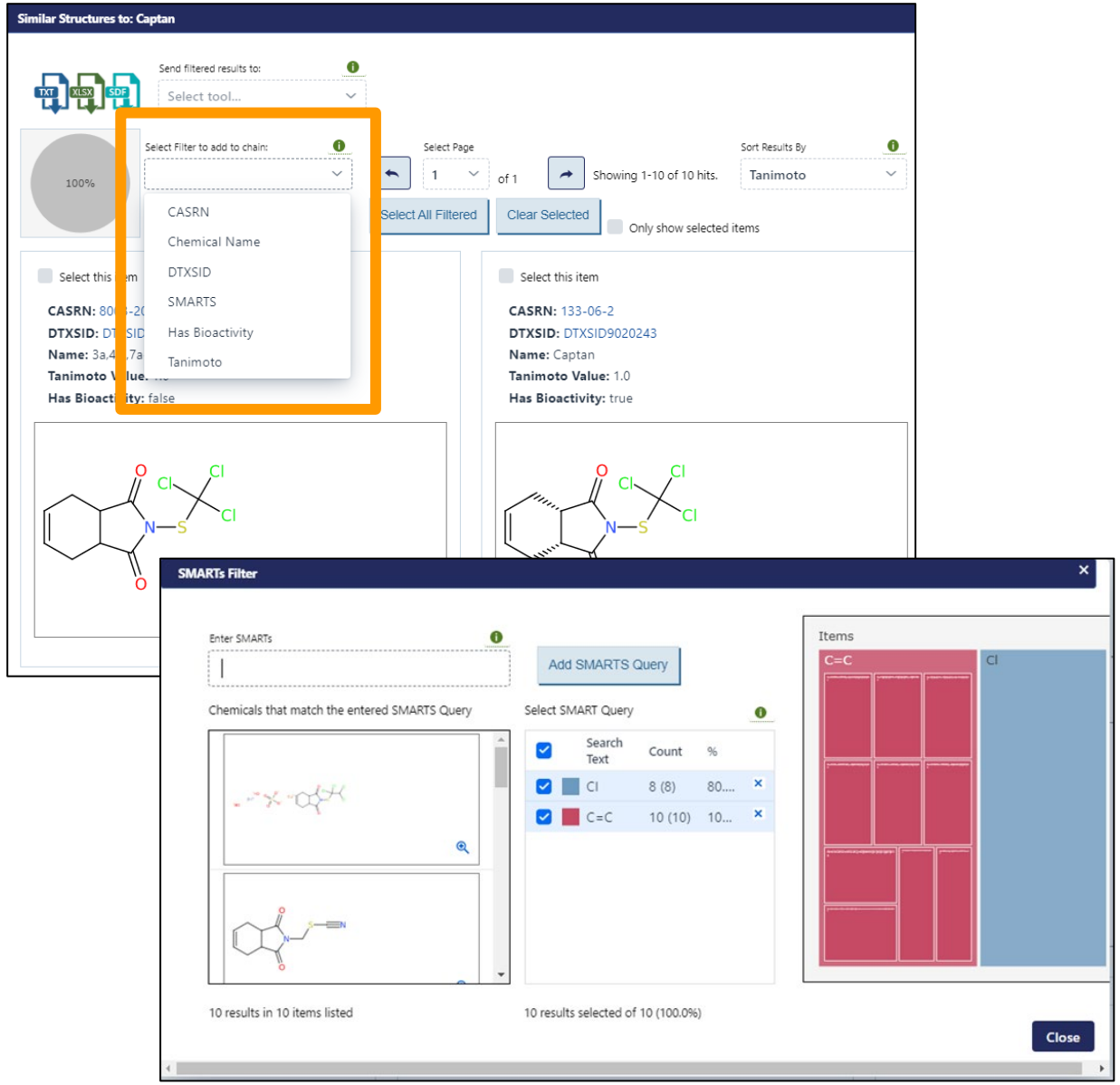
Identified chemicals can be filtered and sent to other ICE tools or downloaded for use in external workflows.



Chemical Quest Results

Refine results for individual chemicals using interactive filters.





Demo

Exploring ICE Chemical Quest Tool

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

Chemical Characterization

Search	Query ICE data and visualize results
Chemical Quest	Identify similar chemicals
Chemical Characterization	Explore chemical properties and use categories
Curve Surfer	Explore concentration-response curves
PBPK	Predict tissue-specific chemical concentrations
IVIVE	Predict equivalent administered dose from in vitro data

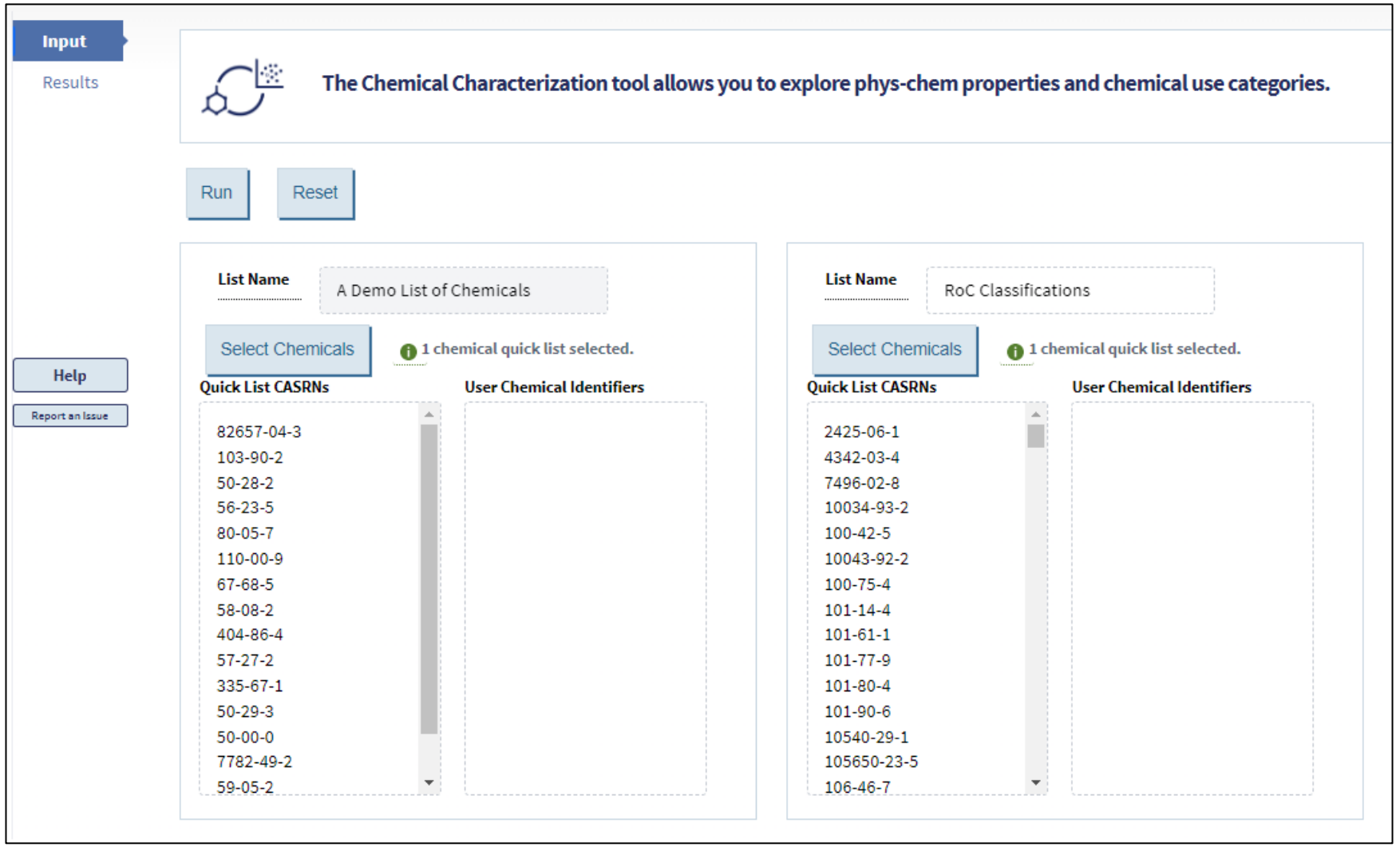
Chemical Characterization

Chemical Characterization Explore chemical properties and use categories

- The Chemical Characterization tool allows for the comparison of physicochemical properties from OPERA and chemical use categories from US EPA's Chemical and Products Database (CPDat).
- Evaluate the range of chemical property coverage of a chemical list in preparation for testing.
- Explore known or potential use and exposure scenarios for chemicals of interest.

Chemical Characterization Input

Explore properties for one chemical list or compare properties between two chemical lists.



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Chemical Characterization

Chemical Characterization Results

View or download chemical property data tables.

Chemical Properties Summary

Values displayed are Open Structure-Activity/Property Relationship App (OPERA) predictions:

Lists Both Chemical Lists

OPERA
OPEn (q)saR App

OPERA v2.8
(*Mansouri et al. J Cheminform 2018*)

Send filtered results to: Select tool...

Chemical List (OPERA) Predictions by Input List, CASRN

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	Capsaicin	404-86-4	DTXSID0020241	305.199	419.0	-8.0	65.0	10.06	9.21	3.35	3.35	-9.27	-4.47

Chemical List Statistical Summary of (OPERA) Predictions

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

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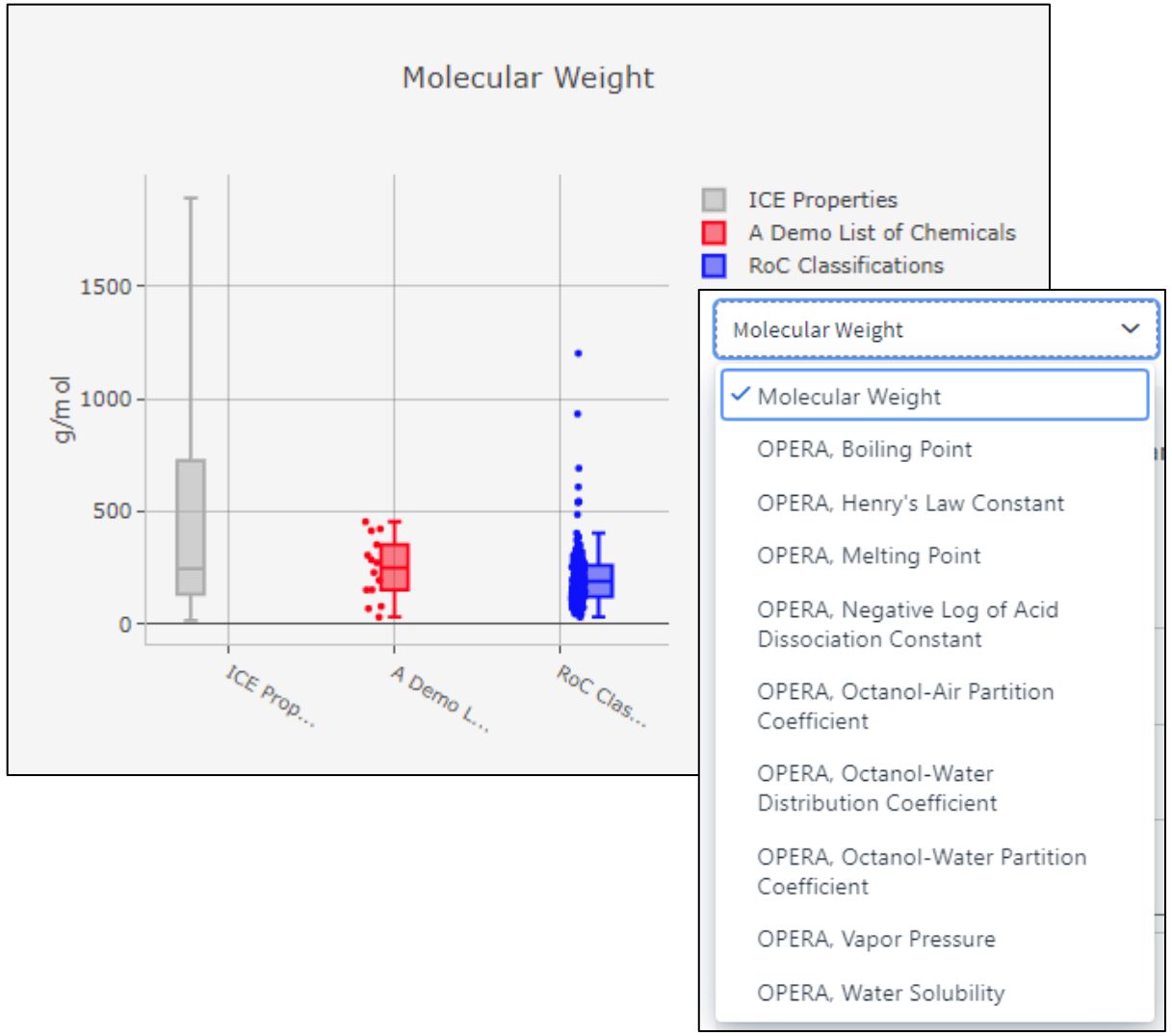
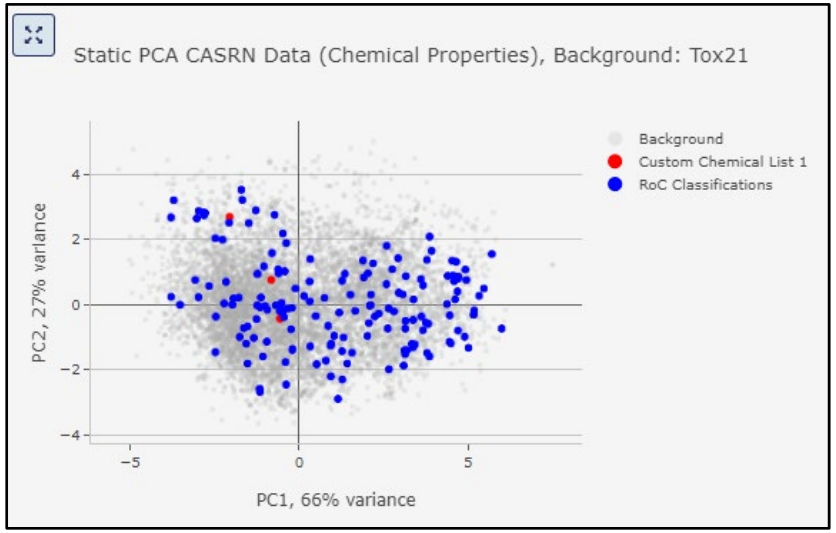
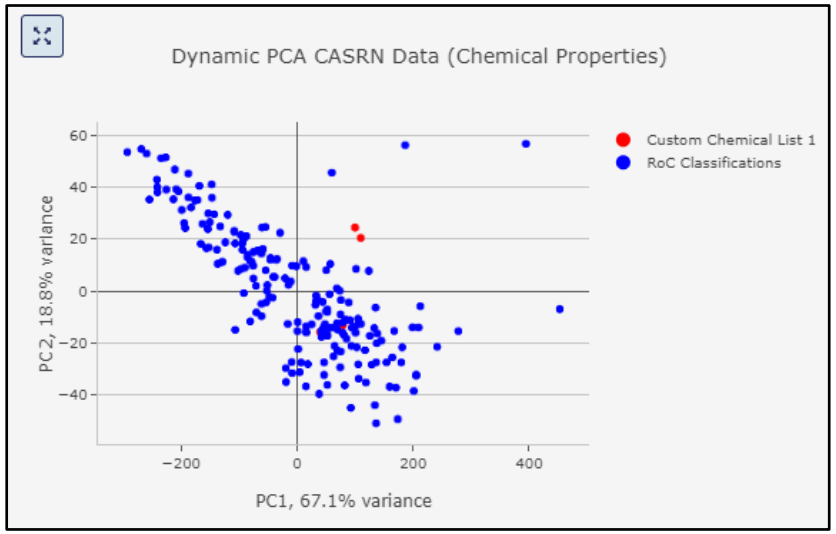
Chemical Characterization

Chemical Characterization Results

Visualize and compare chemical properties with interactive boxplots and Principal Component Analysis (PCA) plots.

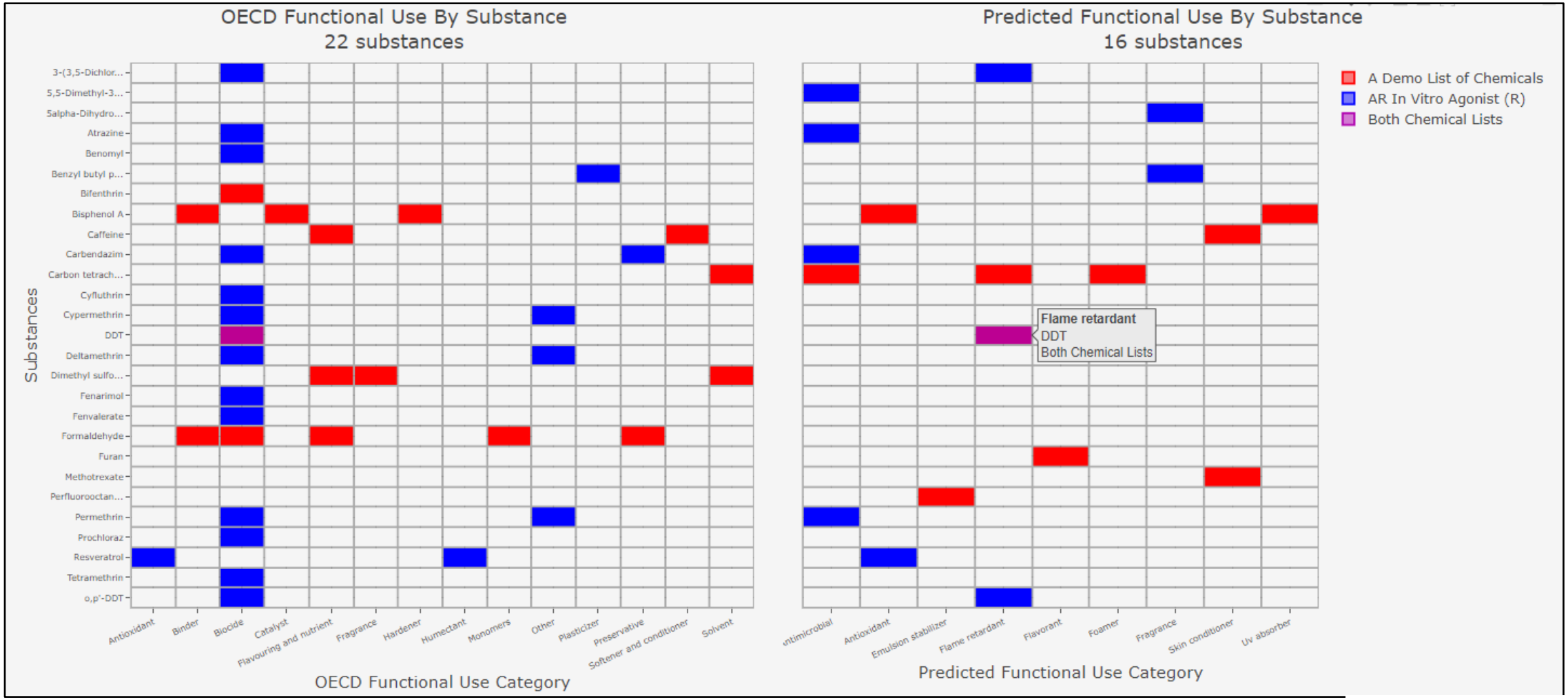






Chemical Characterization Results

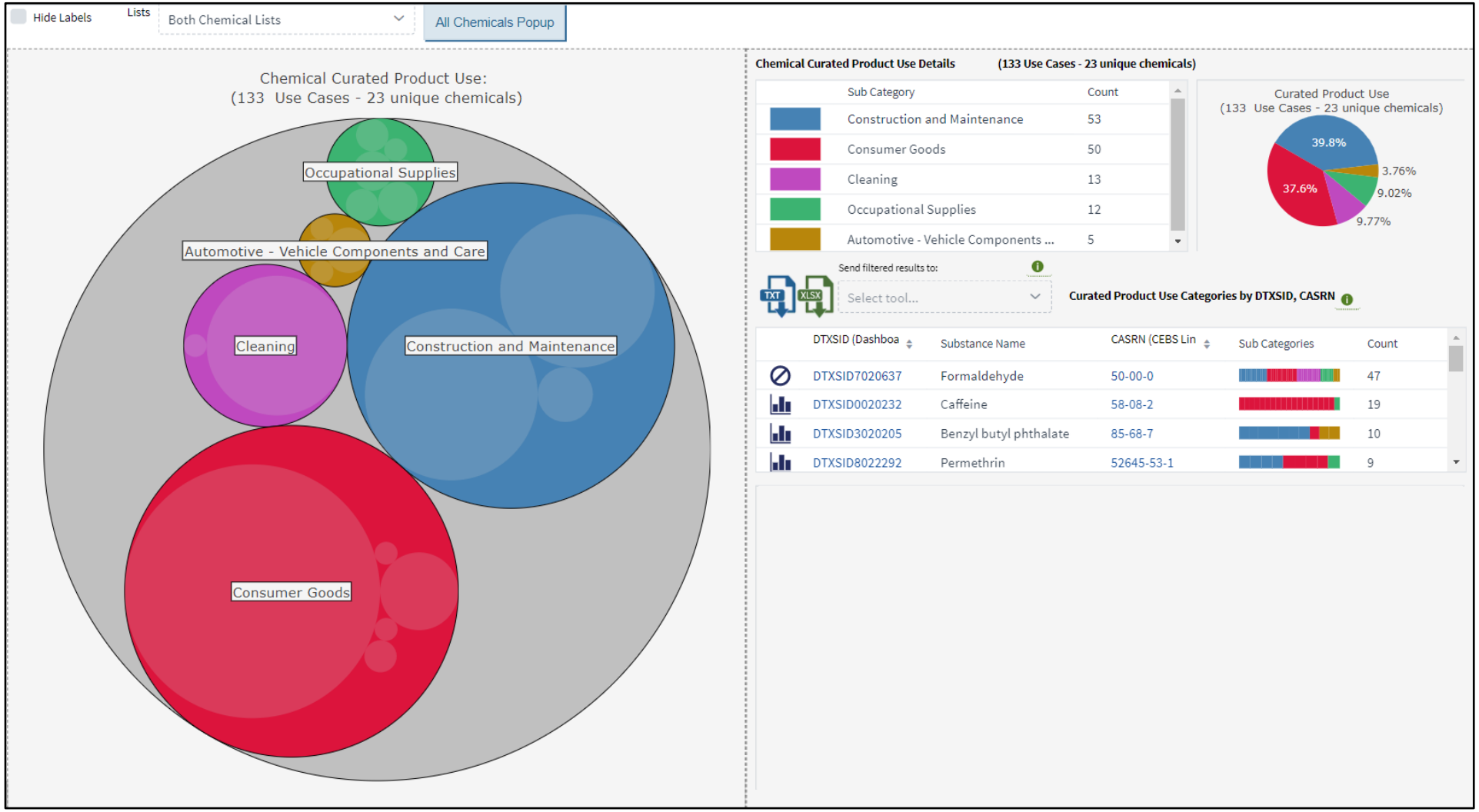
Compare reported and predicted functional use categories within and between chemical lists to understand the roles chemicals may play within products.



CPDat v3 (*Williams 2017*)

Chemical Characterization Results

Explore potential exposure scenarios with the Curated Product Use Explorer.



CPDat v3 (*Williams 2017*)

Demo

Chemical Characterization

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

Curve Surfer

Search	Query ICE data and visualize results
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PBPK	Predict tissue-specific chemical concentrations
IVIVE	Predict equivalent administered dose from in vitro data

- The Curve Surfer tool visualizes concentration-response curves for curated high-throughput screening (cHTS) data and provides detailed information on EPA's ToxCast and Tox21 assays.
- Use assay annotations to contextualize bioactivity data based on biological processes and facilitate interpretation of data from related assays.

ICE Data Sets – Curated High Throughput Screening Data

- ICE's curated high-throughout screening (cHTS) data set contains data from the U.S. federal Tox21 collaboration and EPA's ToxCast program for ~10000 chemicals.

ICE cHTS Pipeline

Retrieve Data	Flag: Chemical QC	Flag: Curve Fit	Flag: Technological Interference	Annotate
Retrieve data from the U.S. EPA's invitrodb v3.5 (Feshuk 2022).	Integrate chemical QC information released via the Tox21 Tripod site.	Review curve fits. Integrate flags and custom rules for flagging less robust fits.	Review assay technology and chemical structures to identify potential false signals.	Leverage EPA's technological assay annotations and create annotations for biological interpretation.

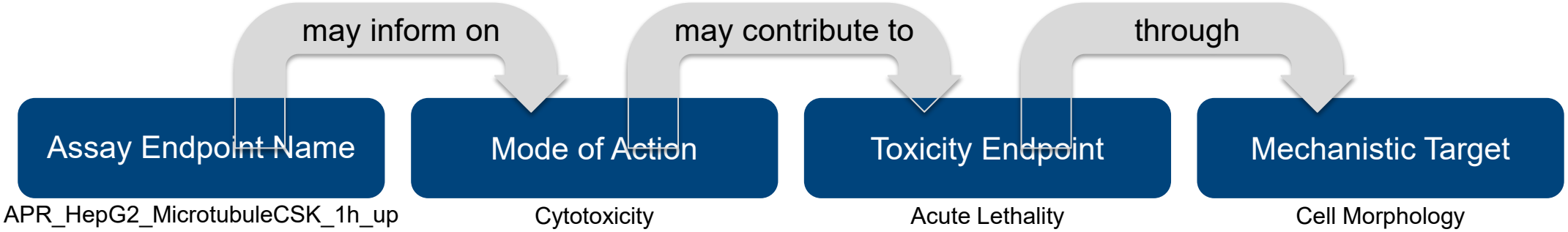
Ongoing Project: Update Pipeline with Invitrodb v4.1

The U.S. EPA released invitrodb v4.1 (*Feshuk et al. Front Toxicol 2023*), introducing new curve-fitting models and updating data formatting within their database. The ICE team is currently updating the cHTS pipeline to integrate changes between v3.5 and v4.1.

ICE Data Sets – cHTS Assay Annotations

- Assays are annotated to mechanistic targets that facilitate linkage to modes of action and subsequently to toxicological outcomes of regulatory interest.
- ICE annotations are based on controlled vocabulary terminology from the National Cancer Institute's (NCI) Metathesaurus (https://ncim.nci.nih.gov) which encompasses a wide range of biomedical space.

Knowledge Organization Structure



Ongoing Project: OBO Foundry Update

Update annotations using the Open Biological and Biomedical Ontology (OBO) Foundry (http://obofoundry.org/) to encompass a broader range of biologic and toxicologic processes.

Read more about cHTS on the ICE Data Sets page.

ICE Data Sets
Data Sets
Acute Lethality
Cancer
Cardiotoxicity
DART
Endocrine
Irritation-Corrosion
Sensitization
cHTS
Chemical Properties
Exposure Predictions
Chemical Use

Curated High-throughput Screening Data

Curated high-throughput screening (cHTS) data in ICE were derived from the federal Tox21 collaboration which include EPA's ToxCast program. For inclusion in ICE, NICEATM applies additional curation to these data. Details of the ICE curation process are provided below.

Data sources:

- ICE cHTS data includes:
  - ToxCast: data generated by the EPA's ToxCast program.
  - Tox21: quantitative-HTS data generated by NCATS as part of the Tox21 program. These data are, identified with a "Tox21" prefix in the assay name.
- All data were retrieved from the EPA invitrodb v3.5 (September 2022), as analyzed using the ToxCast Pipeline (tcpl, version 2.1.0) processing algorithm .
- cHTS data in ICE are derived from the representative curves for each chemical-assay combination, which were identified using the tcpl function "tcplsubsetchid".

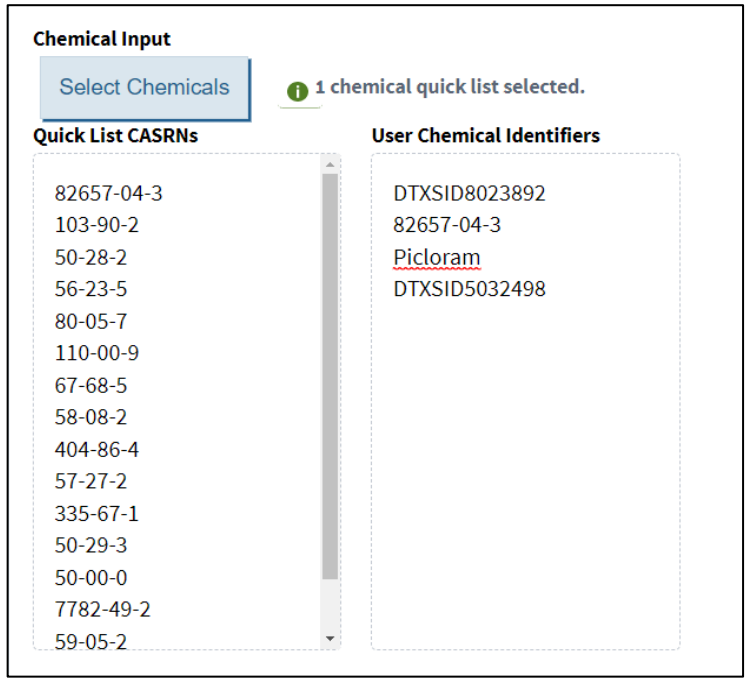
Endpoints:

- Call (active or inactive)
- AC50 (uM)
- ACC (uM)
- Top of curve

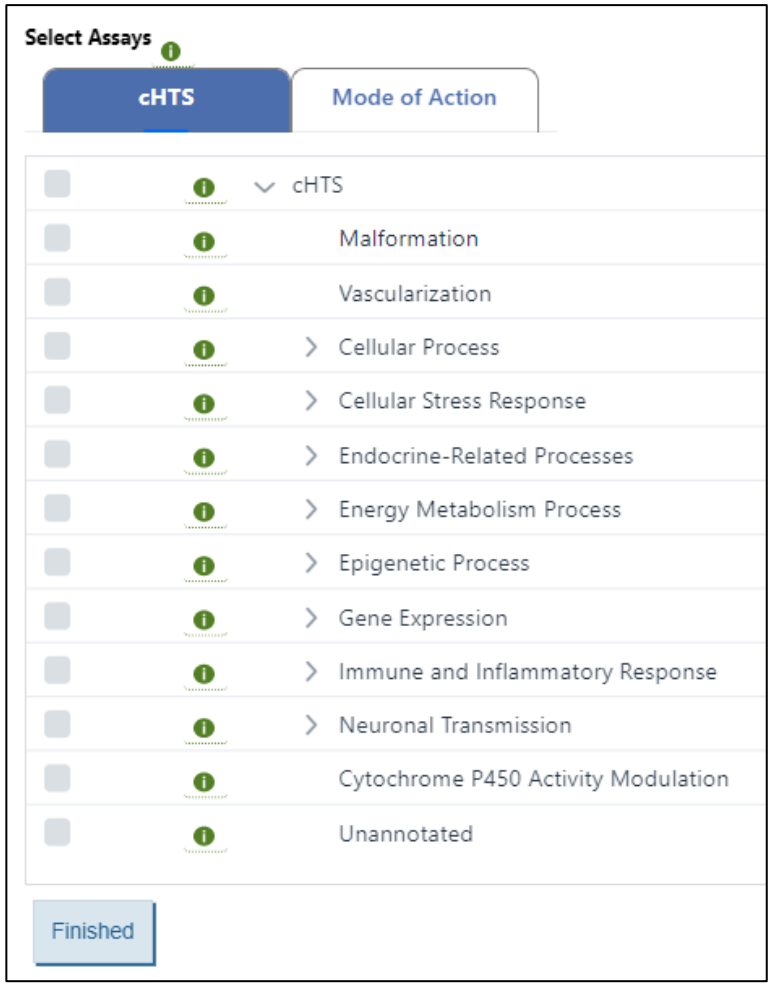
For ToxCast BioSeek (BSK) assays, the tcpl processing algorithm returns LOEC values in place of AC50 and ACC values during the curve-fitting process. This is due to BSK assays having relatively few data points, leading to uncertainty in curve fitting. Please note that the LOEC is provided in the AC50 and ACC field for all data from these assays. This allows the BSK assays to be used with the other cHTS assays as input for IVIVE analysis in ICE.

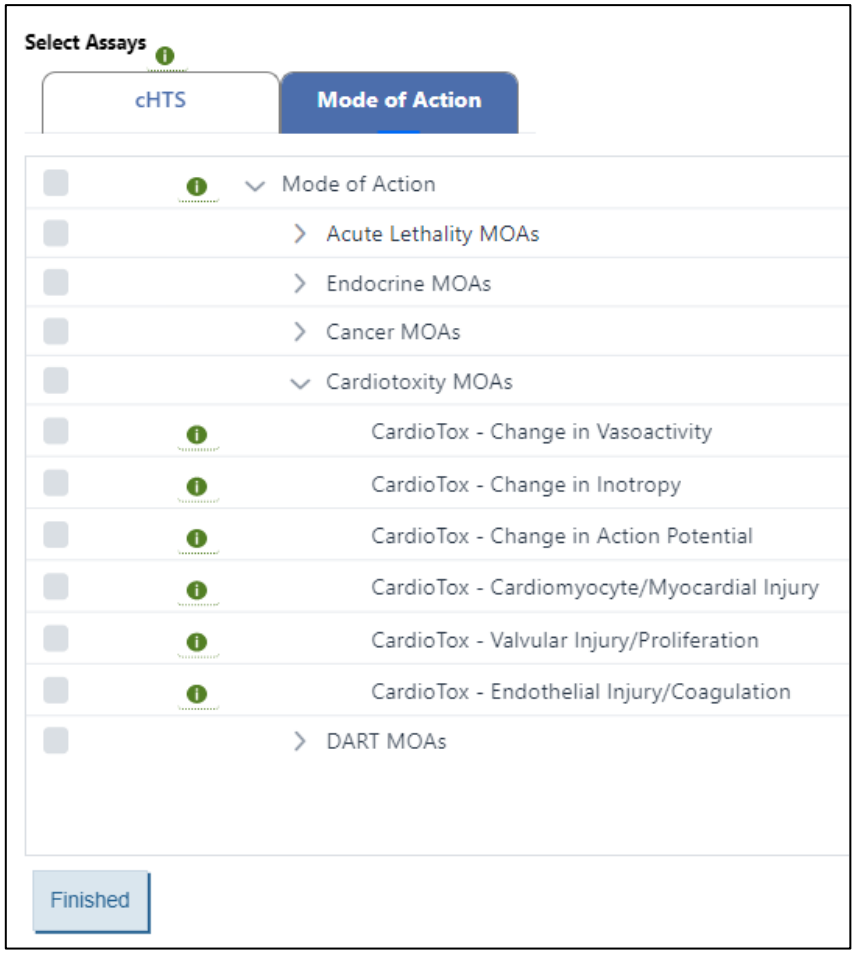
Curve Surfer Input

Chemical Input



Assay Input





The cHTS annotations facilitate selection and retrieval of sets of related assays using biologically interpretable terminology.

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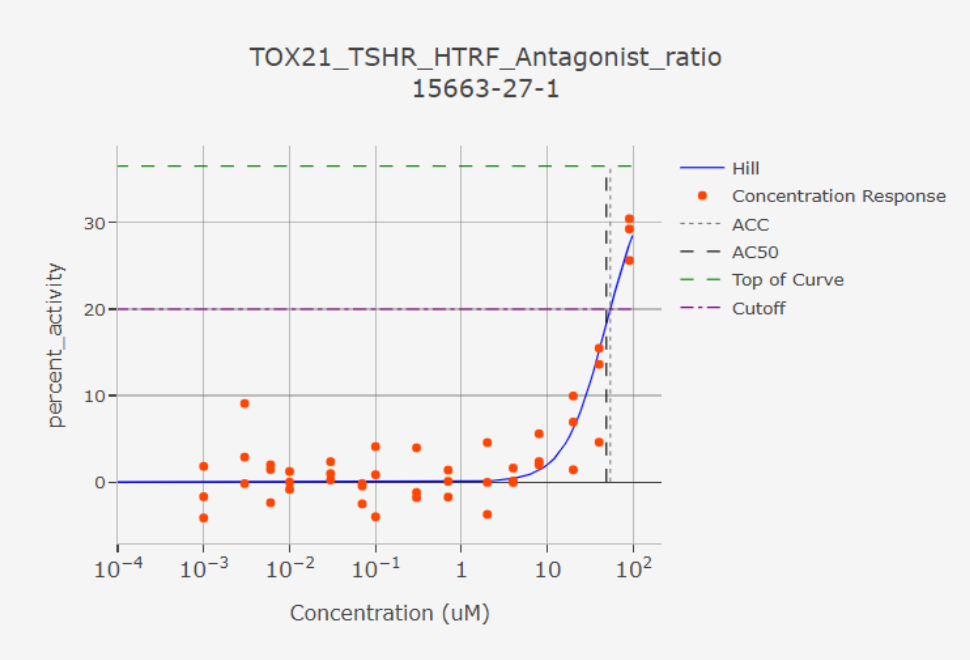
Curve Surfer

Curve Surfer Results

Interactive concentration-response curves are displayed for each chemical-endpoint pair along with chemical and assay information.

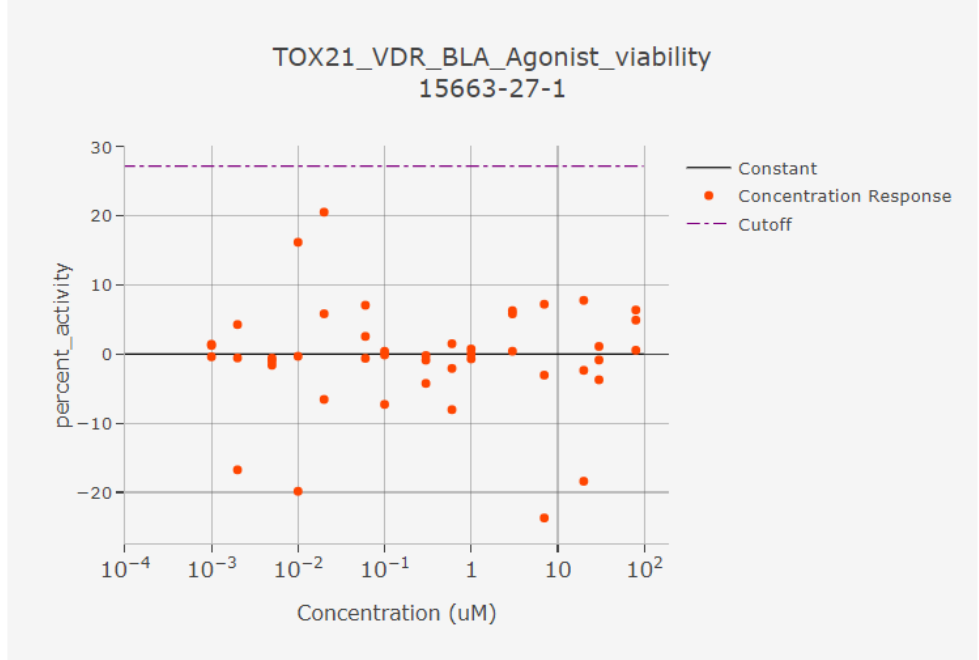
Select this item



Assay: TOX21_TSHR_HTRF_Antagonist_ratio
CASRN: 15663-27-1
Chemical Name: Cisplatin
AC50 (uM): 48.58
Top of Curve: 36.55

Mechanistic Target: Thyrotropin-Releasing Hormone Receptor Modulation
DTXSID: DTXSID4024983
Winning Curve-Fit Model: Hill
ACC (uM): 53.97
Call: Active

Select this item

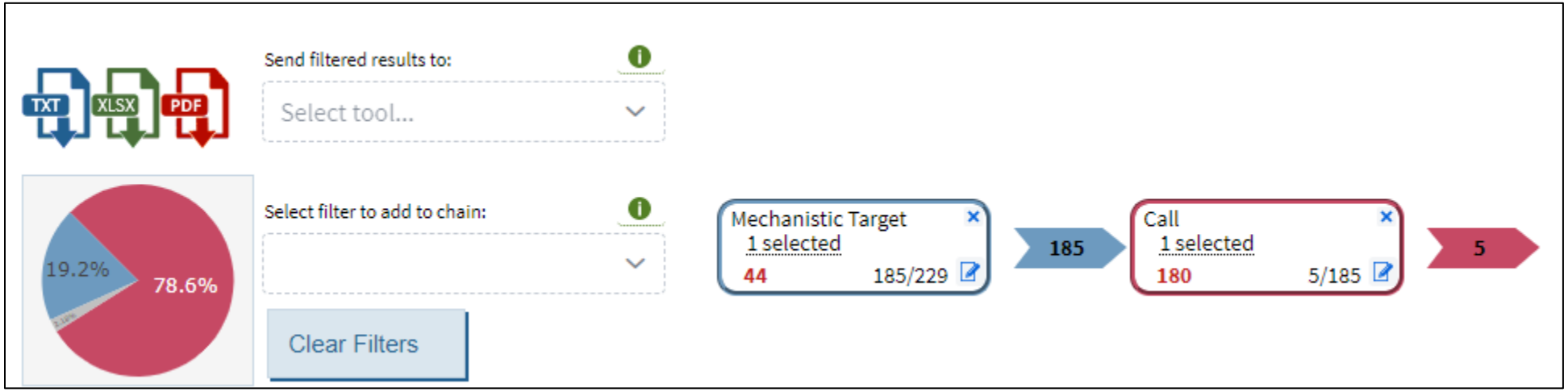


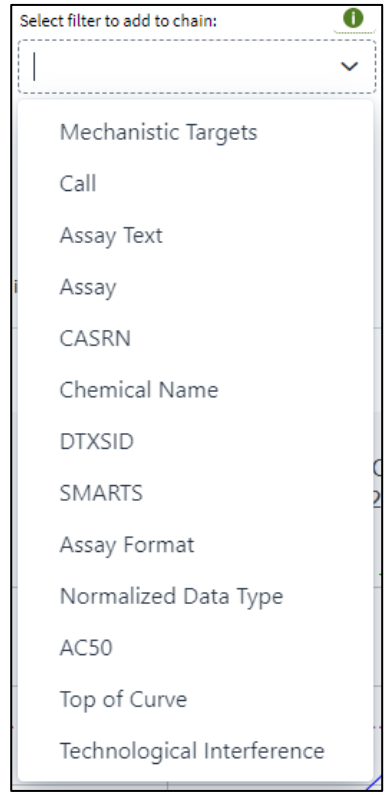
Assay: TOX21_VDR_BLA_Agonist_viability
CASRN: 15663-27-1
Chemical Name: Cisplatin
AC50 (uM): NA
Top of Curve: NA

Mechanistic Target: Cell Viability
DTXSID: DTXSID4024983
Winning Curve-Fit Model: Cnst
ACC (uM): NA
Call: Inactive

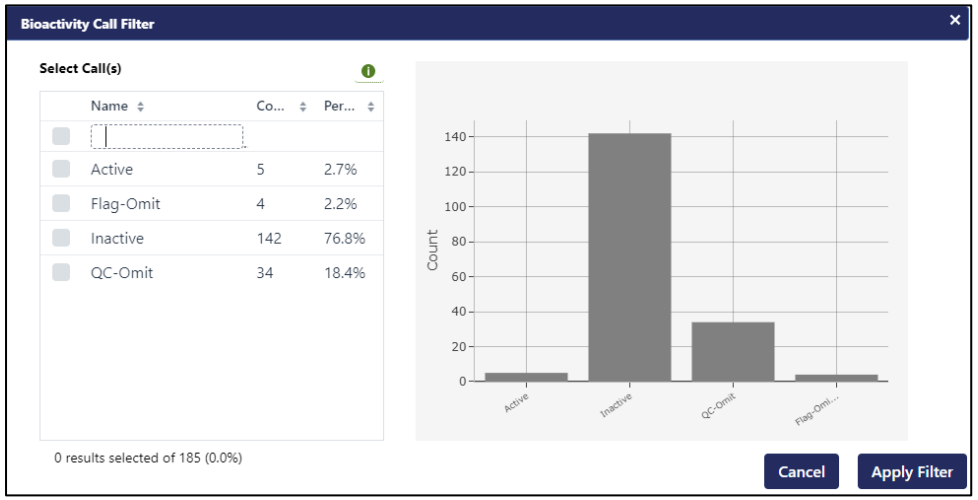
Curve Surfer Results

Results can be refined by applying filters for parameters such as “Mechanistic Target” or “Call”.





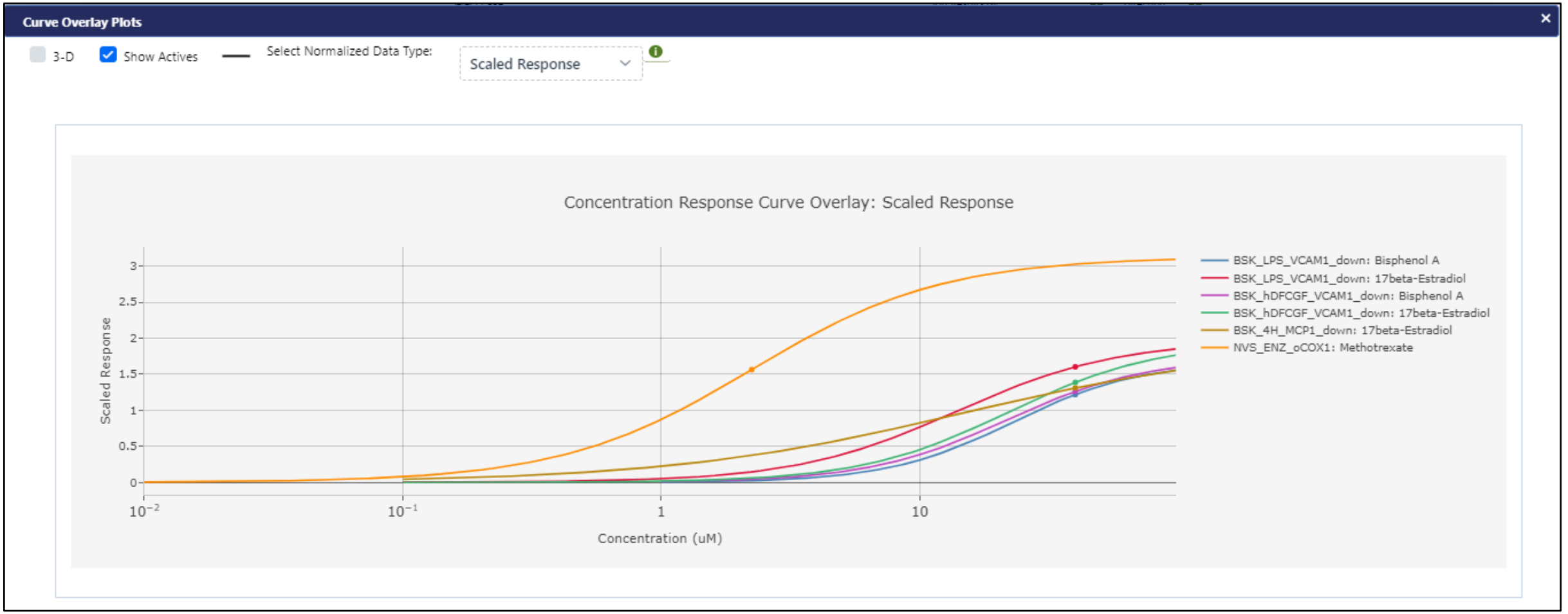
Filtering menu displays breakdown of selected parameter.



Curve Surfer

Curve Surfer Results

Filtering facilitates selection of complementary assay results that can be overlaid for direct comparison.



Demo

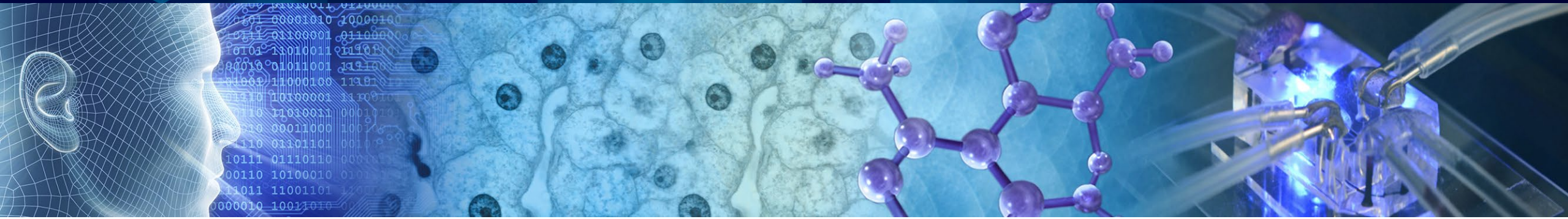
Exploring ICE Curve Surfer Tool Using
“A Demo List of Chemicals”

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

Session Questions

Contact: ICE-support@niehs.nih.gov

National Institute of Environmental Health Sciences
Division of Translational Toxicology



Training Session on the Integrated Chemical Environment (ICE)
Session 3 - PBPK and IVIVE Tools

ICCVAM Public Forum: 22nd May 2024
3:00 pm – 3:50 pm

Aswani Unnikrishnan and Victoria Hull

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

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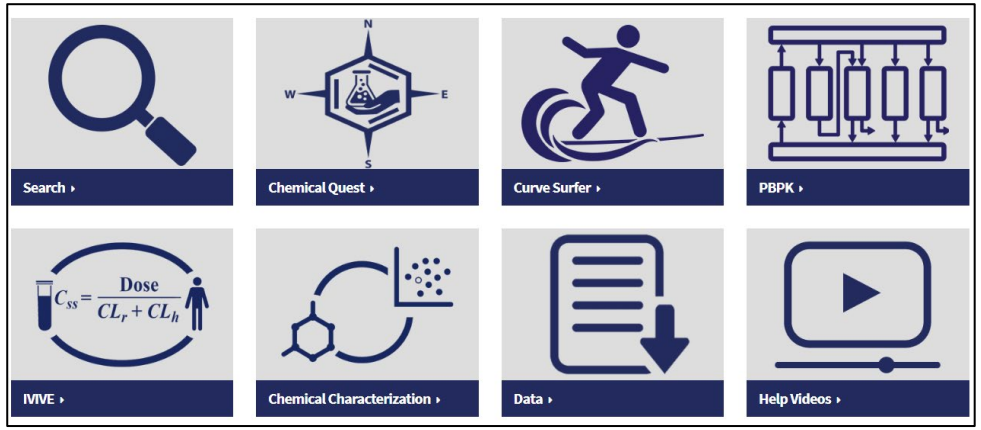
Integrated Chemical Environment



Session 1 Summary

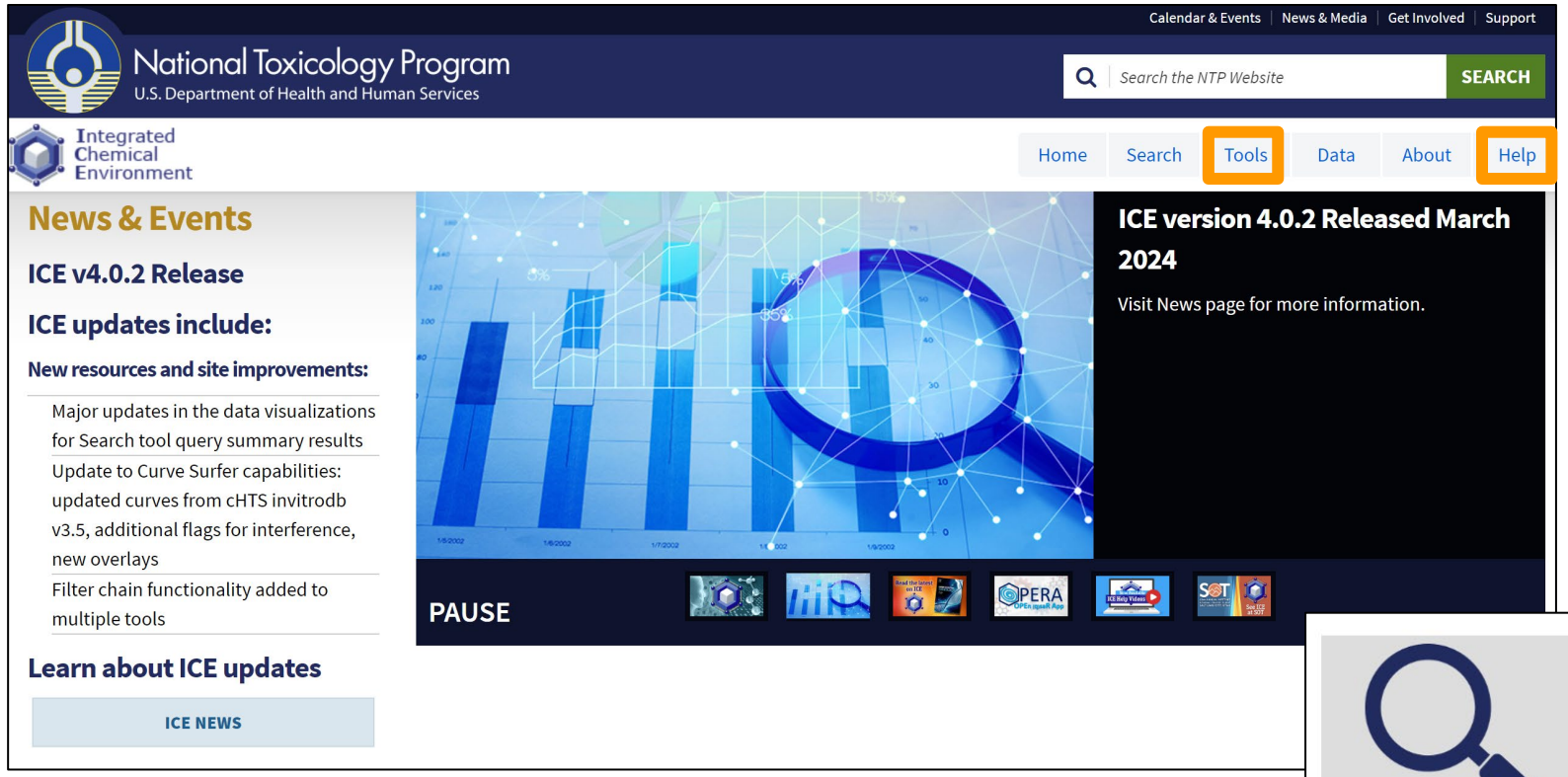
- Introduction to ICE interface
- ICE data sets and reference lists
- Search tool summarizes toxicity endpoint, chemical property, and exposure data for a set of queried chemicals

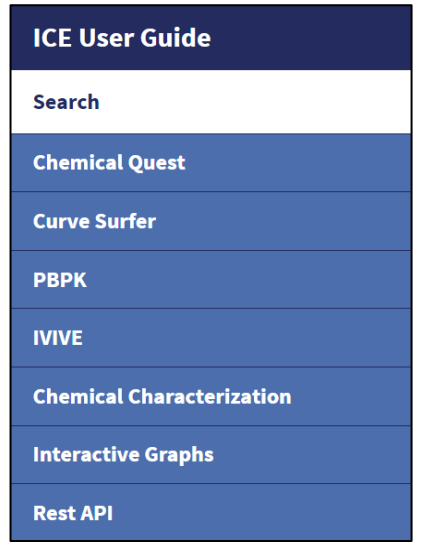
Session 2 Summary

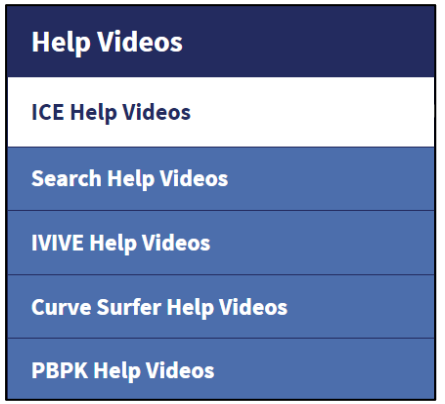
- Chemical Quest tool to find structurally similar chemicals that can help fill data gaps
- Chemical Characterization tool to look at property distribution and chemical use cases between one or two lists of chemicals
- Curve Surfer tool to visualize concentration response-curves for curated high-throughput screening (cHTS) data

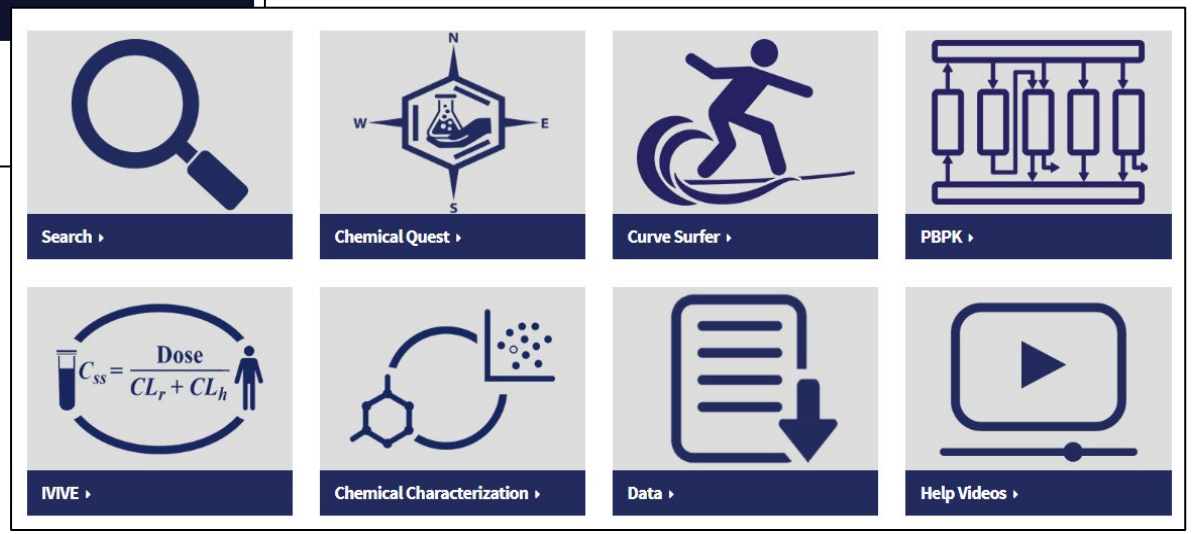
National Institute of Environmental Health Sciences
Division of Translational Toxicology

Accessing ICE Tools





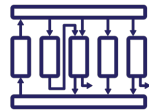




https://ice.ntp.niehs.nih.gov/

PBPK

Search	Query ICE data and visualize results
Chemical Quest	Identify similar chemicals
Chemical Characterization	Explore chemical properties and use categories
Curve Surfer	Explore concentration-response curves
PBPK	Predict tissue-specific chemical concentrations
IVIVE	Predict equivalent administered dose from in vitro data



PBPK

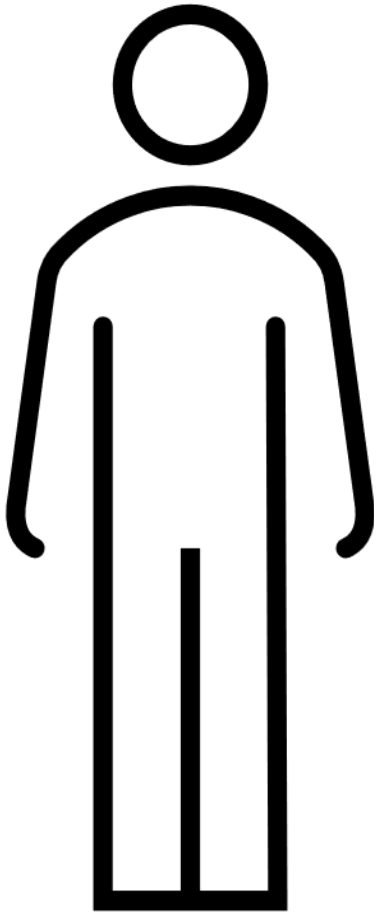
Predict tissue-specific chemical concentrations

- The Physiologically Based Pharmacokinetic (PBPK) tool provides predictions of tissue-specific chemical concentration profiles following a dosing event.
- Apply models from the EPA's httk R package (Pearce et al., 2017) with user-selected model parameters to predict chemical disposition over time.

What is PBPK modeling?

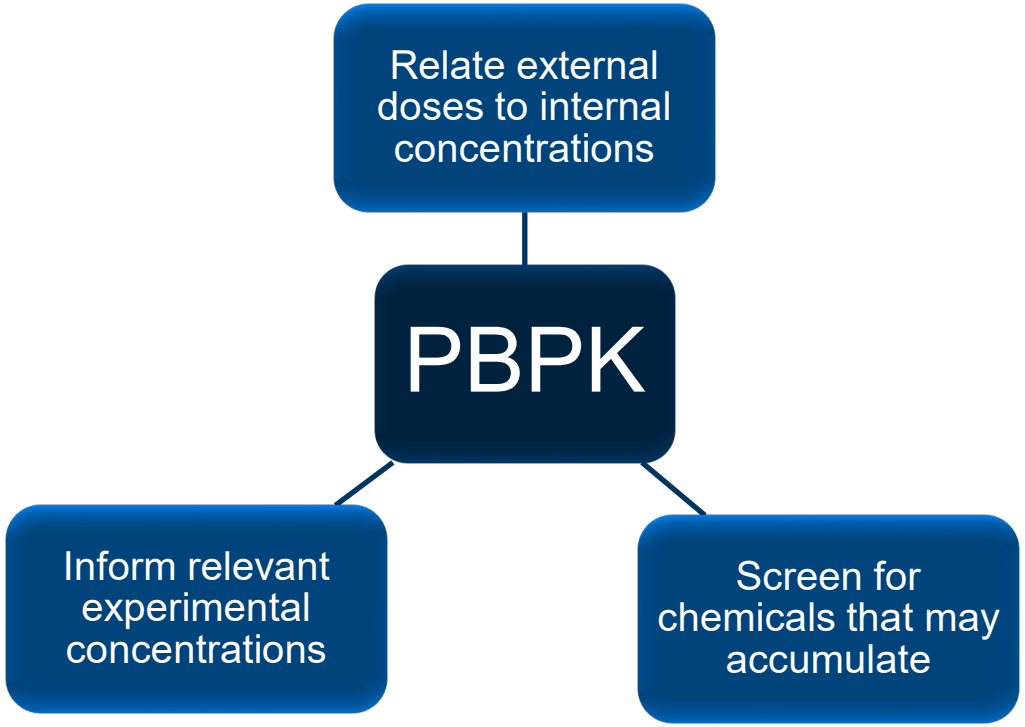
Absorption
How much chemical makes into body?

Distribution
Does chemical accumulate in tissues?



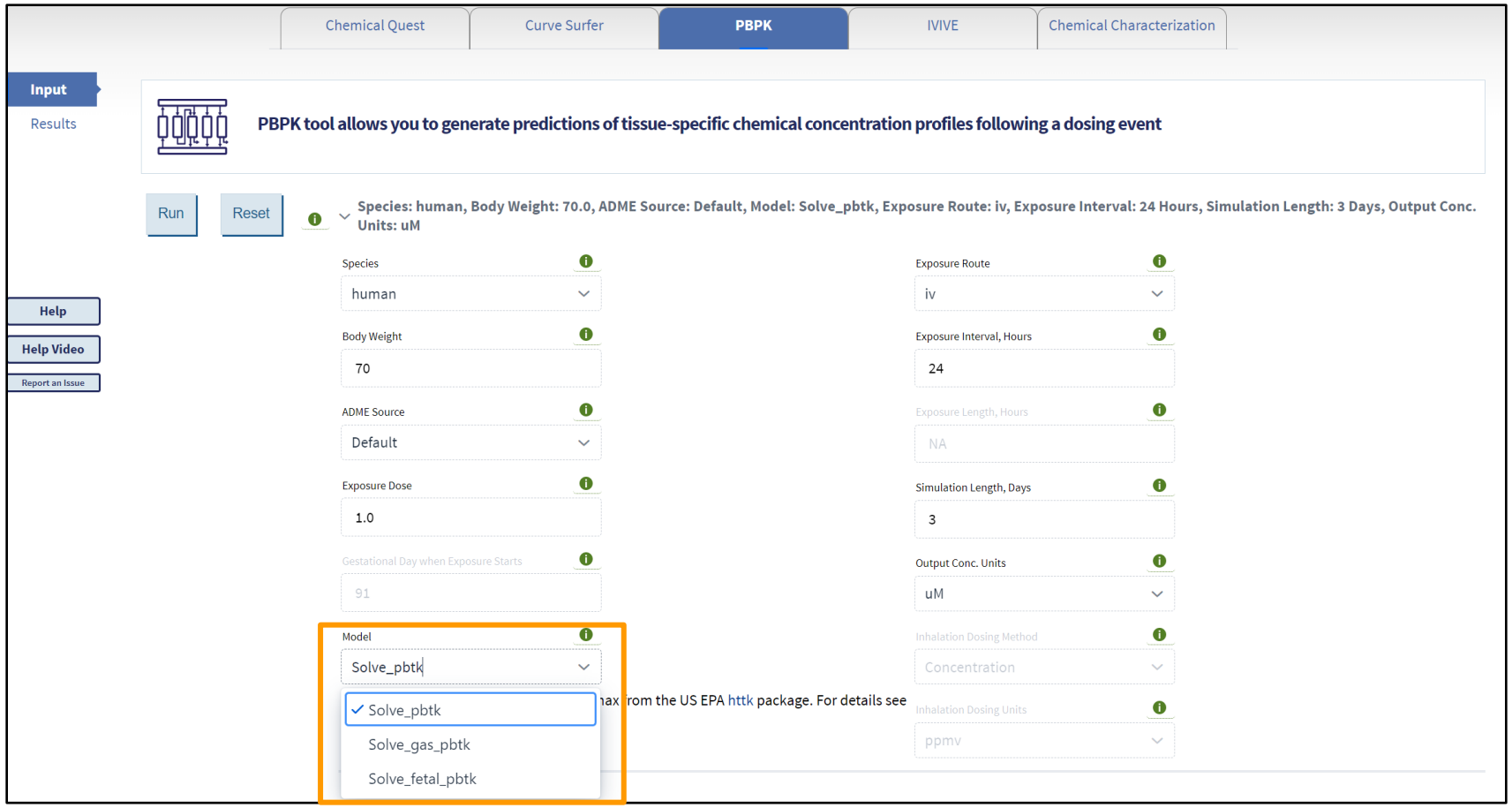
Metabolism
How quickly do body enzymes clear the chemical?

Excretion
How much of chemical is removed through excretion?

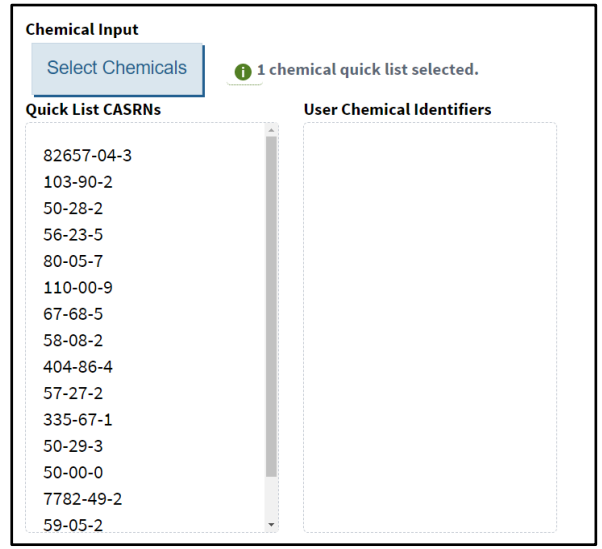


PBPK Input

Customizable Model Parameters



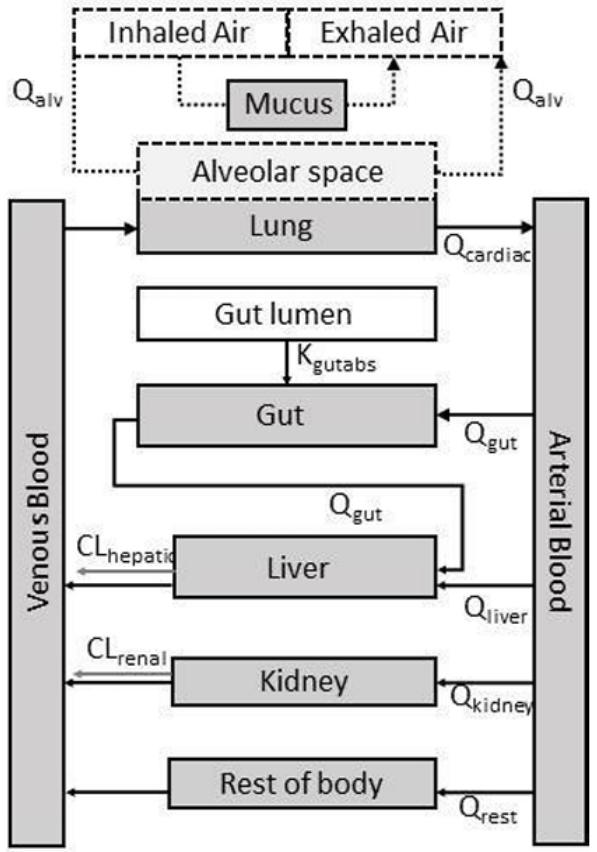
Chemical Input



httk v2.2.2
(Pearce et al. J Stat Softw 2017)

- Three PK models are available for calculating plasma concentrations in tissues
  - Solve_pbtk*: Multi-compartment model that estimates plasma C_{max} following oral or IV exposure
  - Solve_gas_pbtk*: Multi-compartment model that estimates plasma C_{max} following inhalation (gas) exposure
  - Solve_fetal_pbtk*: Multi-compartment model that estimates maternal and fetal plasma C_{max} following oral or IV exposure

Structure of the solve_gas_pbtk model



*httk v2.2.2
(Pearce et al. J Stat Softw 2017)

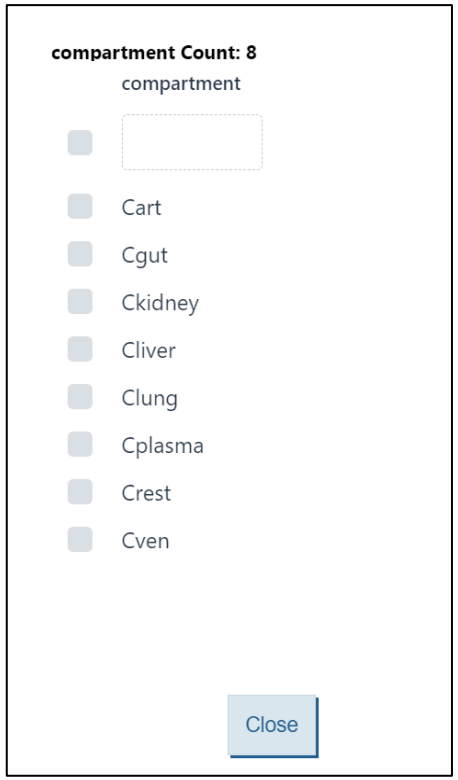
PBPK

PBPK Results

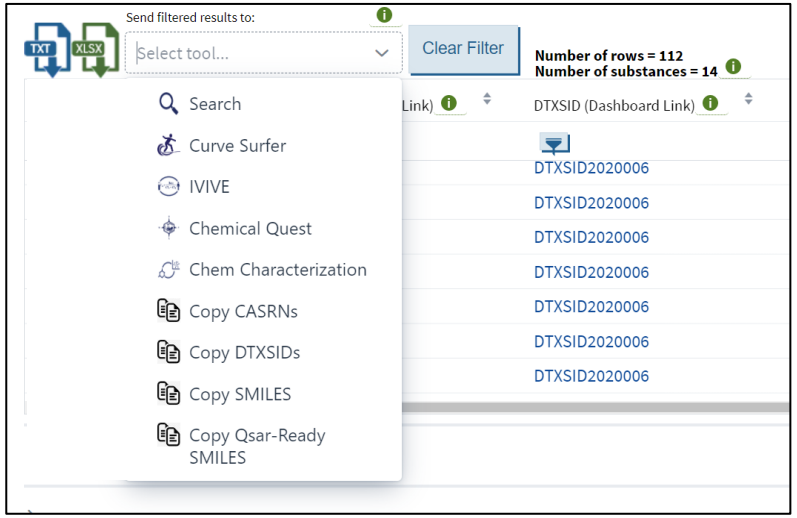
Interactive Table

Chemical	CASRN (CEBS Link)	DTXSID (Dashboard Link)	Compartment	CSS	Cmax
Acetaminophen	103-90-2	DTXSID2020006	Ckidney	1.695	123.0
Acetaminophen	103-90-2	DTXSID2020006	Cliver	1.695	28.27
Acetaminophen	103-90-2	DTXSID2020006	Clung	1.695	24.34
Acetaminophen	103-90-2	DTXSID2020006	Cplasma	1.695	16.87
Acetaminophen	103-90-2	DTXSID2020006	Crest	1.695	6.285
Acetaminophen	103-90-2	DTXSID2020006	Cven	1.695	16.87
Bifenthrin	82657-04-3	DTXSID9020160	Cart	9213.0	12.11

Filtering Options



Export Results



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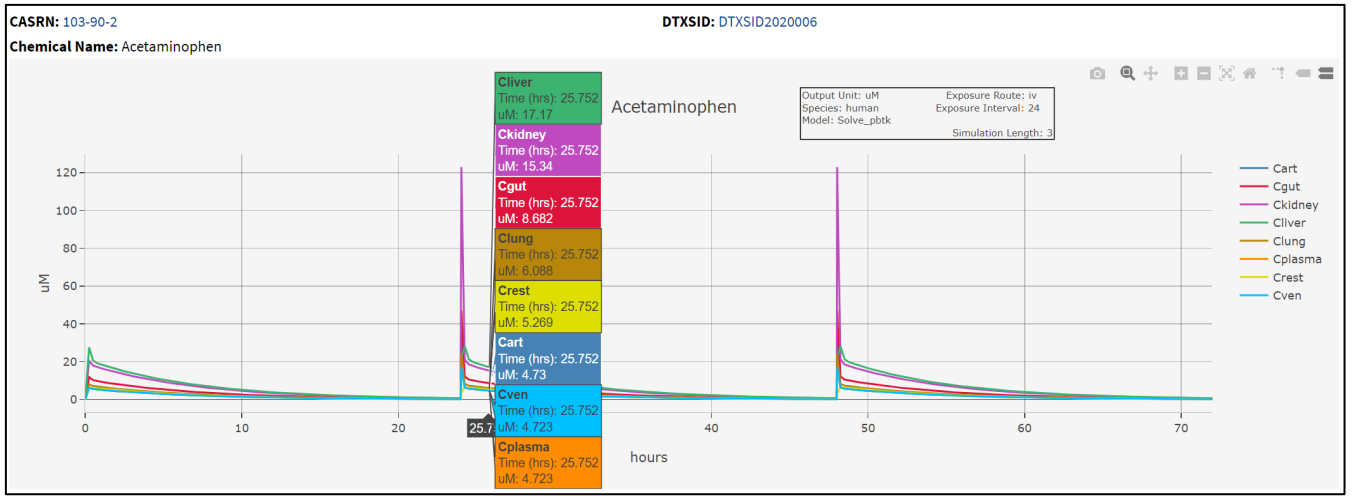
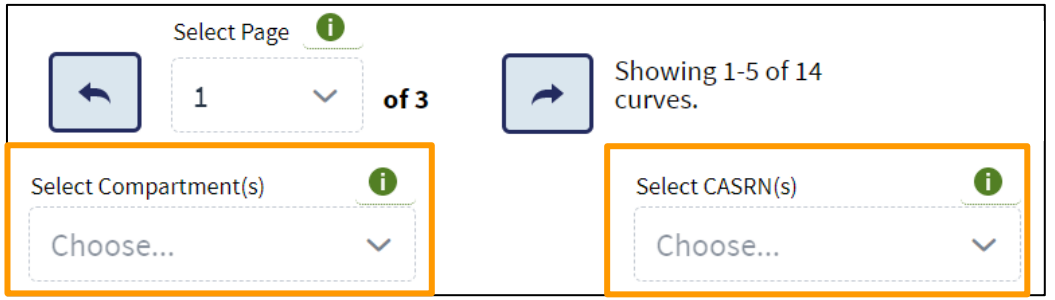
PBPK

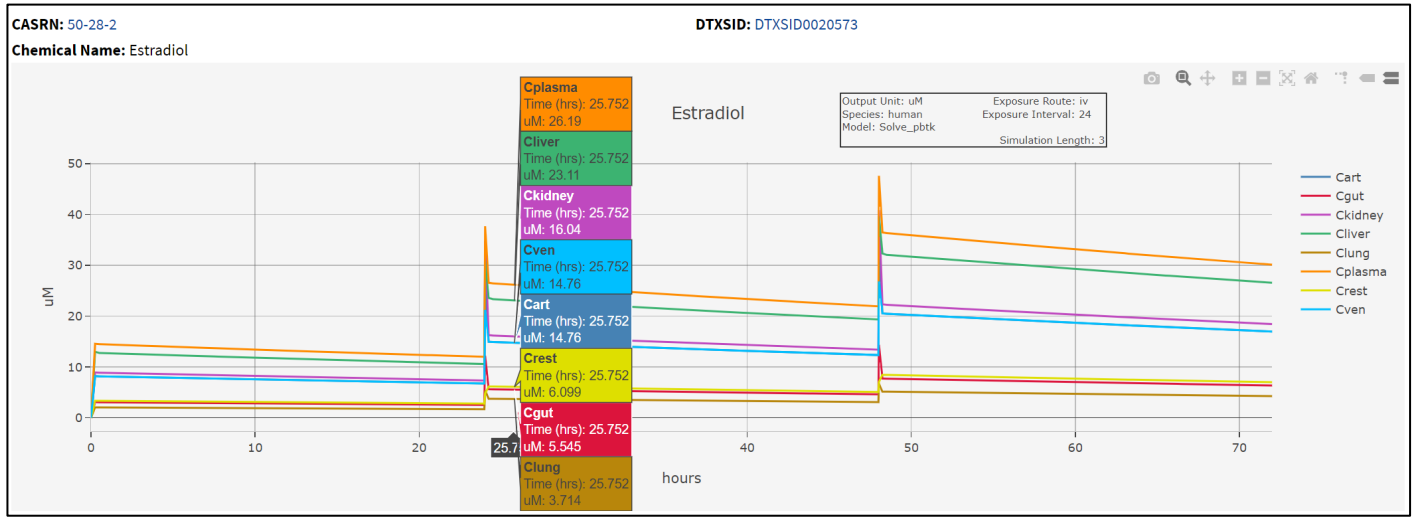
PBPK Result Visualizations

Concentration Time Series Plots



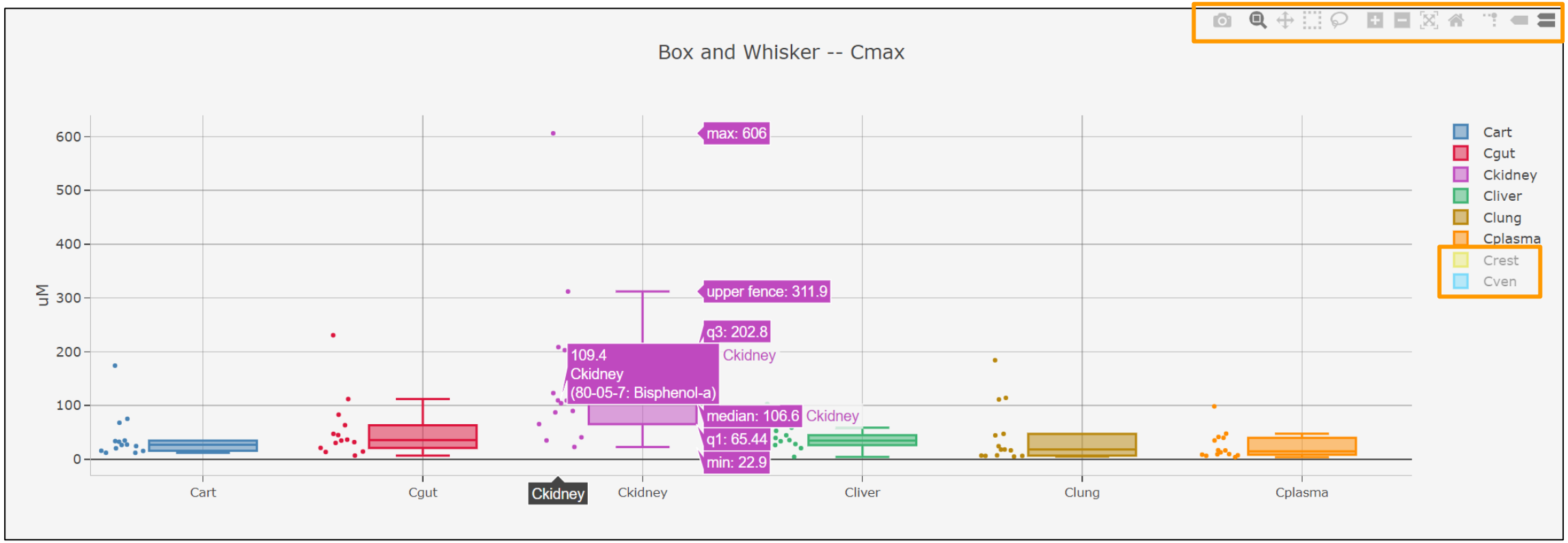
Filtering Options





PBPK Result Visualizations

Visualize Cmax Distribution



Demo

Exploring ICE PBPK Tool

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

IVIVE

Search	Query ICE data and visualize results
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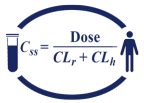


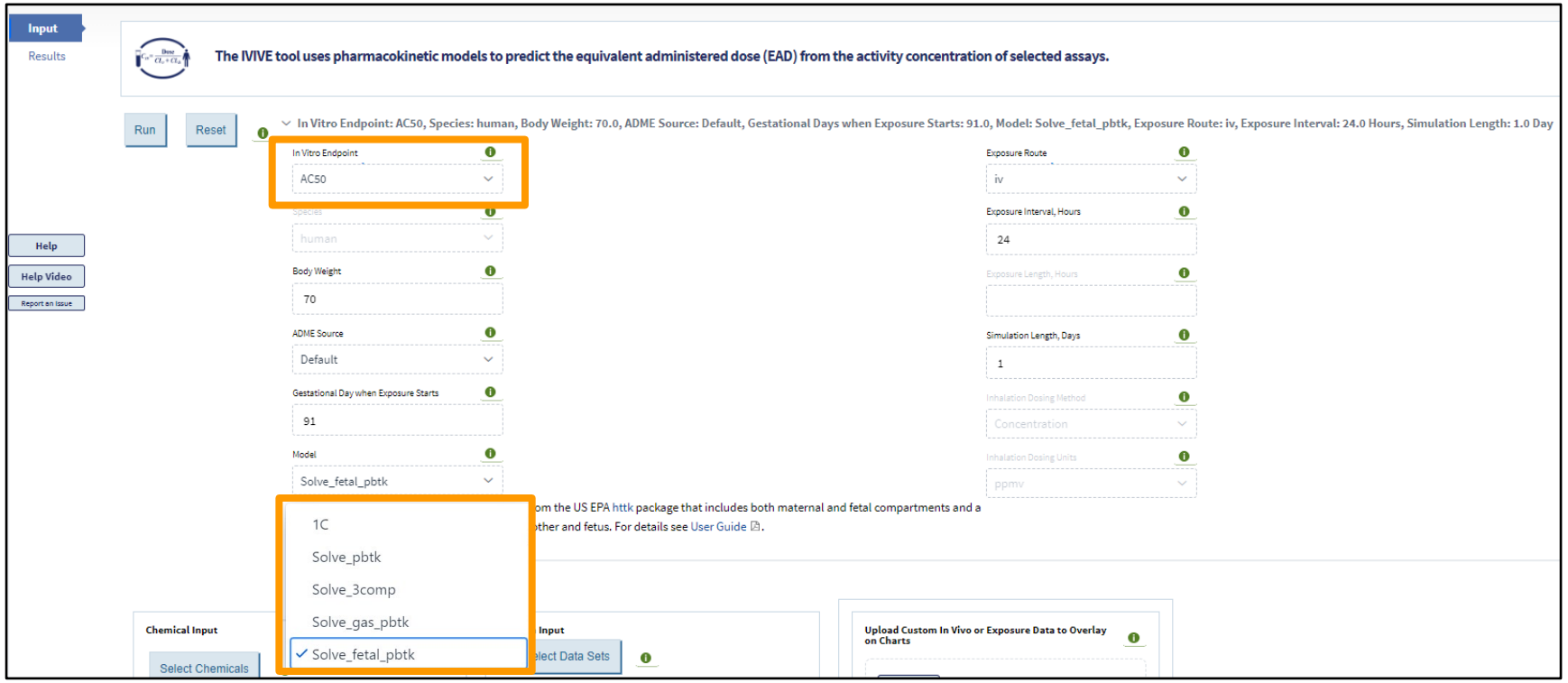
IVIVE

Predict equivalent administered dose from in vitro data

- The IVIVE tool allows the estimation of the 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.
- Predict human-relevant external exposure doses using ICE cHTS data or user-uploaded in vitro assay data.
- Contextualize EAD predictions against in vivo assay data and exposure predictions.

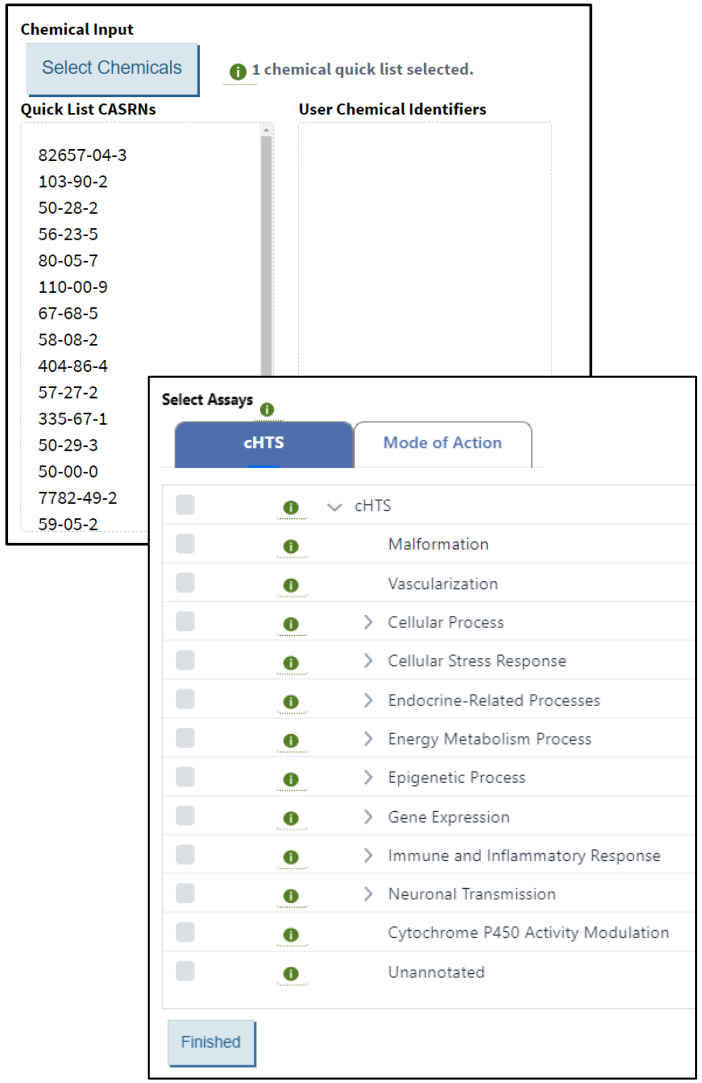
IVIVE Input

Customizable Model Parameters and Selection Criteria



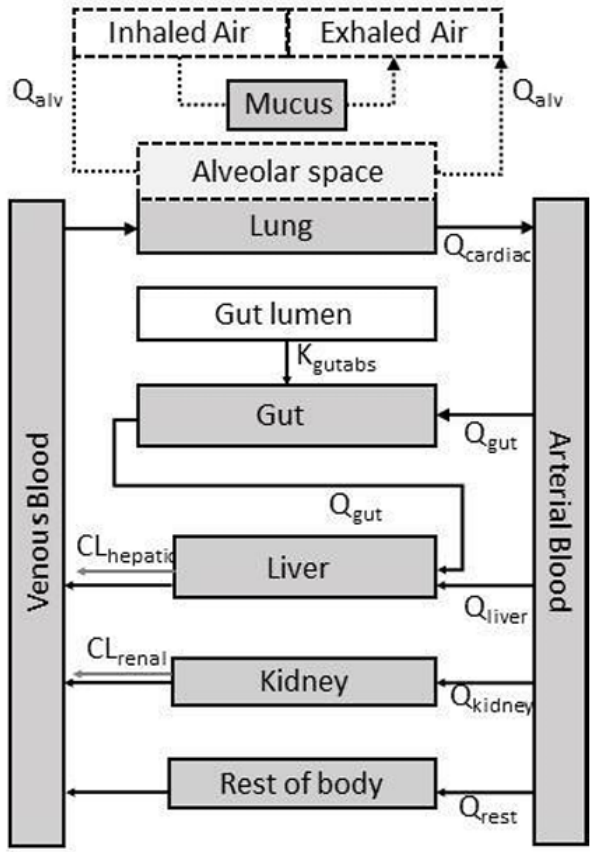
httk v2.2.2
(*Pearce et al. J Stat Softw 2017*)

Chemical and Assay Input



- Five PK models are available to estimate the plasma concentration used to calculate EAD.
  - 1C: Single compartment, population-based model that estimates C_{SS} from a single bolus dose without differentiation between exposure route (Wetmore 2012)
  - Solve_3comp*: Three-compartment model that estimates plasma C_{max} following oral or IV exposure
  - Solve_pbtk*: Multi-compartment model that estimates plasma C_{max} following oral or IV exposure
  - Solve_gas_pbtk*: Multi-compartment model that estimates plasma C_{max} following inhalation (gas) exposure
  - Solve_fetal_pbtk*: Multi-compartment model that estimates maternal and fetal plasma C_{max} following oral or IV exposure

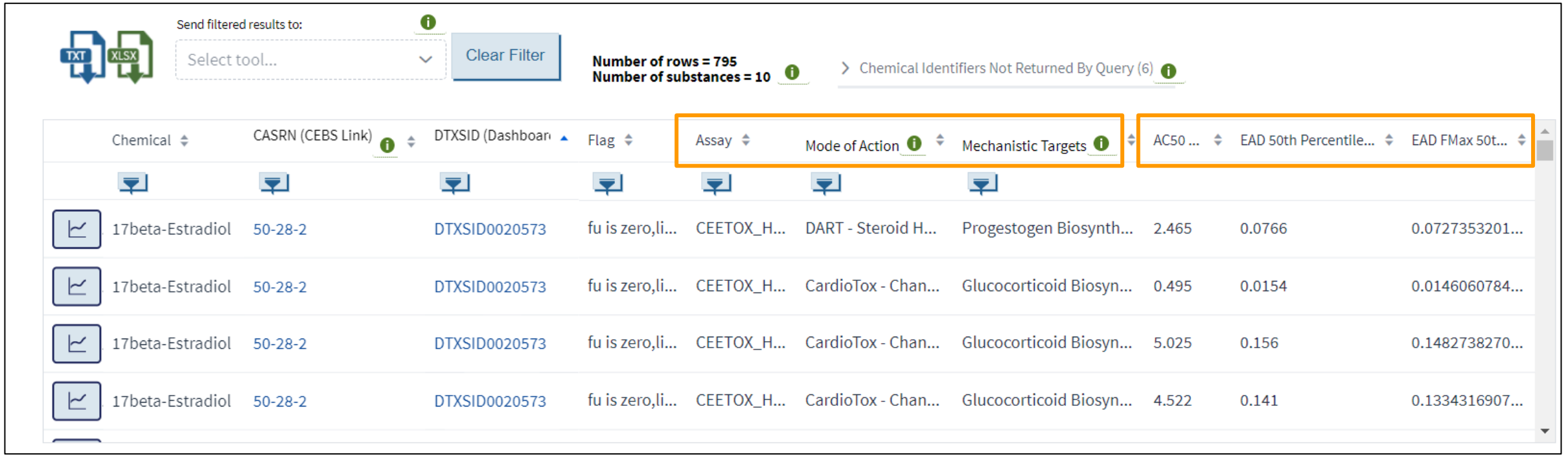
Structure of the solve_gas_pbtk model



*httk v2.2.2
(Pearce et al. J Stat Softw 2017)

IVIVE Results

View summary results, including AC50 and Equivalent Administered Dose (EAD) for each assay and chemical.

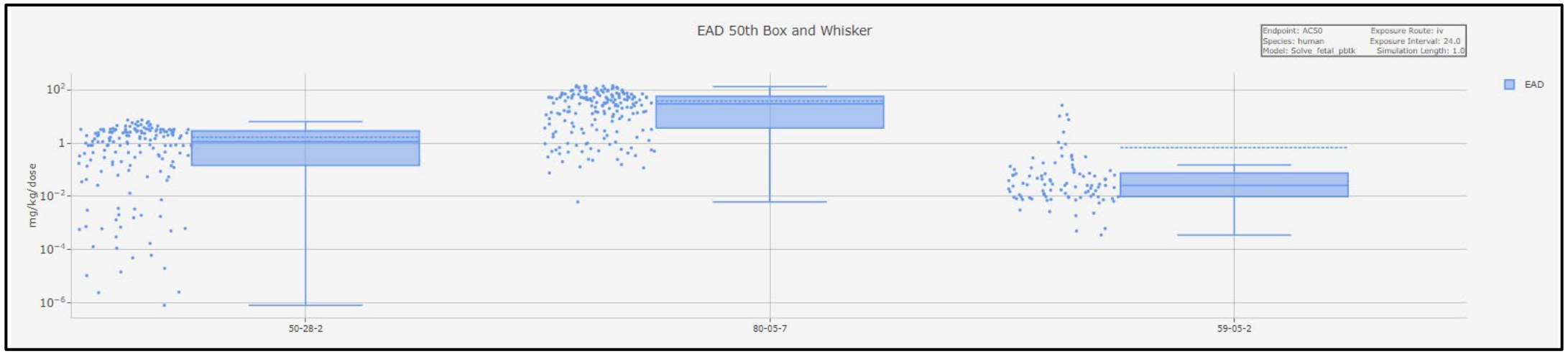


Chemical	CASRN (CEBS Link)	DTXSID (Dashboar	Flag	Assay	Mode of Action	Mechanistic Targets	AC50 ...	EAD 50th Percentile...	EAD FMax 50t...
17beta-Estradiol	50-28-2	DTXSID0020573	fu is zero,li...	CEETOX_H...	DART - Steroid H...	Progestogen Biosynth...	2.465	0.0766	0.0727353201...
17beta-Estradiol	50-28-2	DTXSID0020573	fu is zero,li...	CEETOX_H...	CardioTox - Chan...	Glucocorticoid Biosyn...	0.495	0.0154	0.0146060784...
17beta-Estradiol	50-28-2	DTXSID0020573	fu is zero,li...	CEETOX_H...	CardioTox - Chan...	Glucocorticoid Biosyn...	5.025	0.156	0.1482738270...
17beta-Estradiol	50-28-2	DTXSID0020573	fu is zero,li...	CEETOX_H...	CardioTox - Chan...	Glucocorticoid Biosyn...	4.522	0.141	0.1334316907...

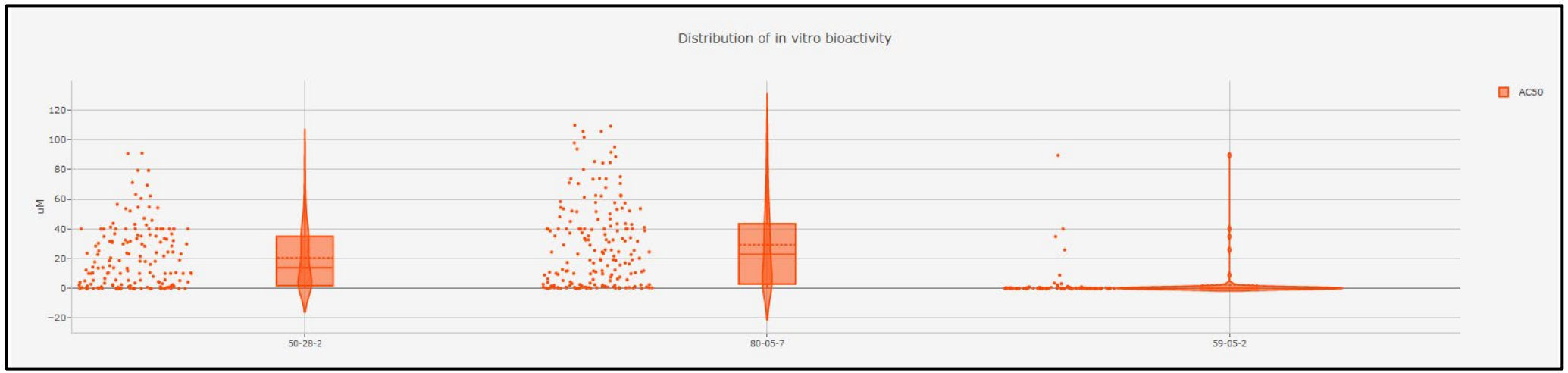
Filter by assay, mode of action, or mechanistic target

IVIVE Results

Visualize EAD for input chemicals using boxplots.

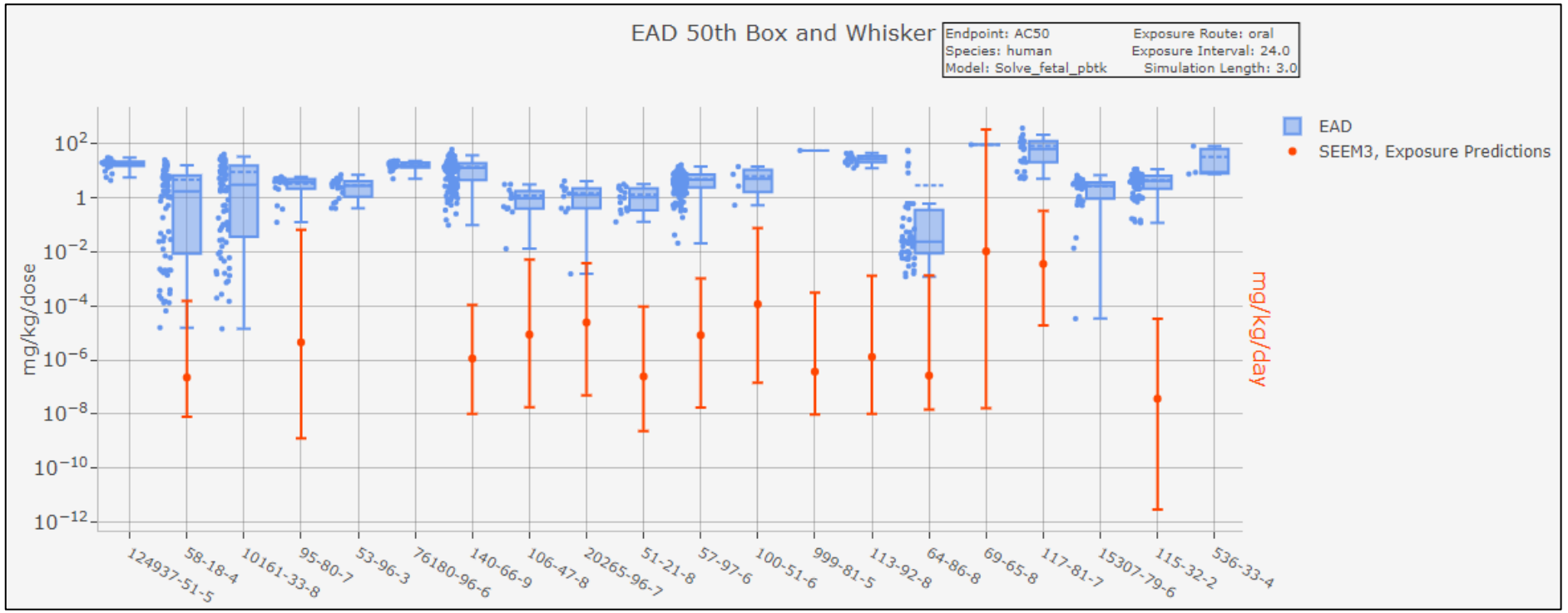


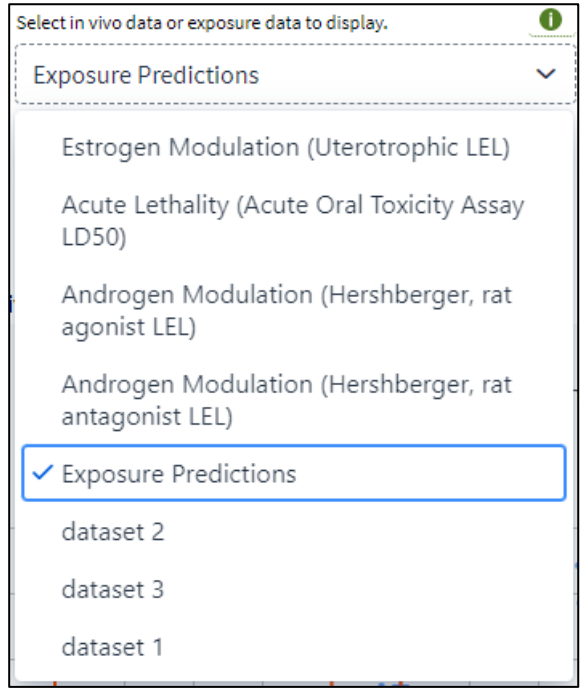
Violin plots show distribution of in invitro bioactivity.



IVIVE Results

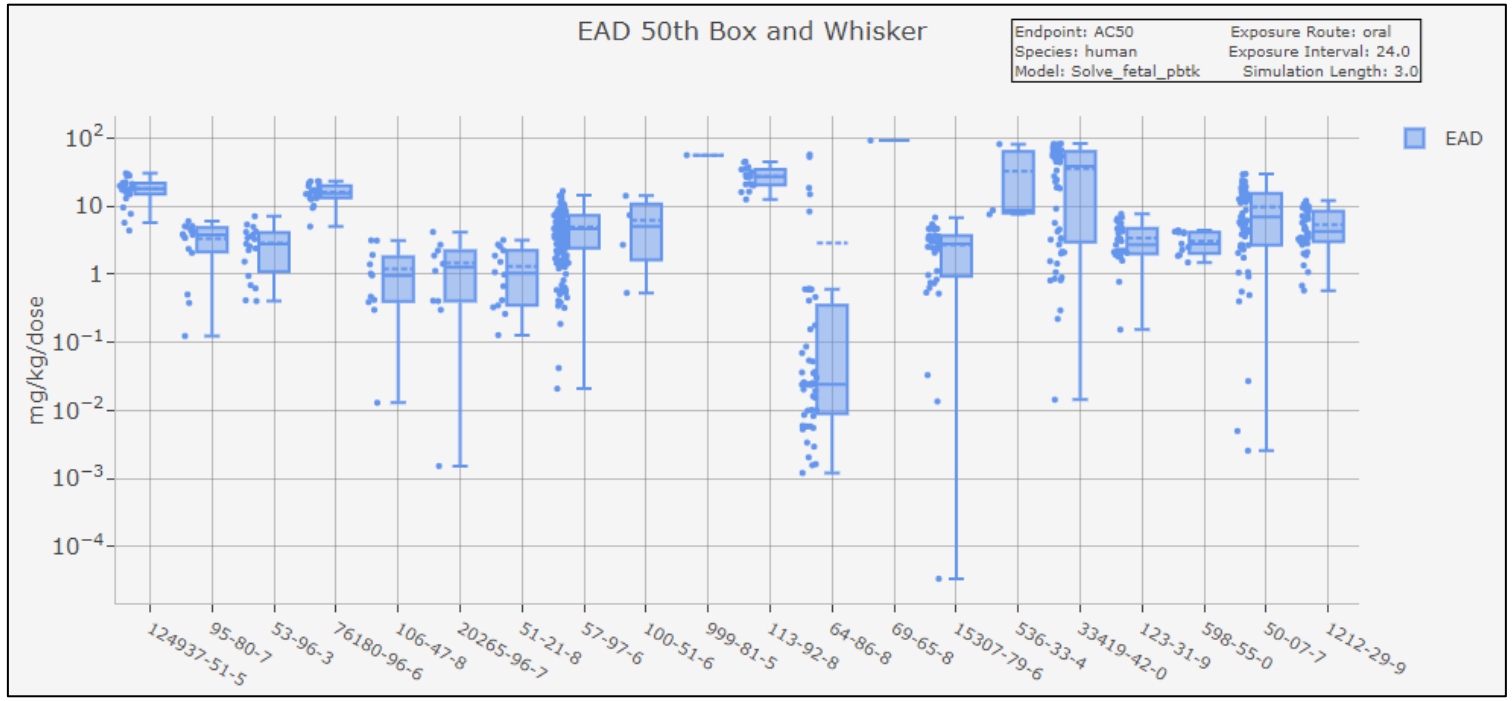
The EADs can be visualized next to in vivo data or SEEM3 exposure predictions.





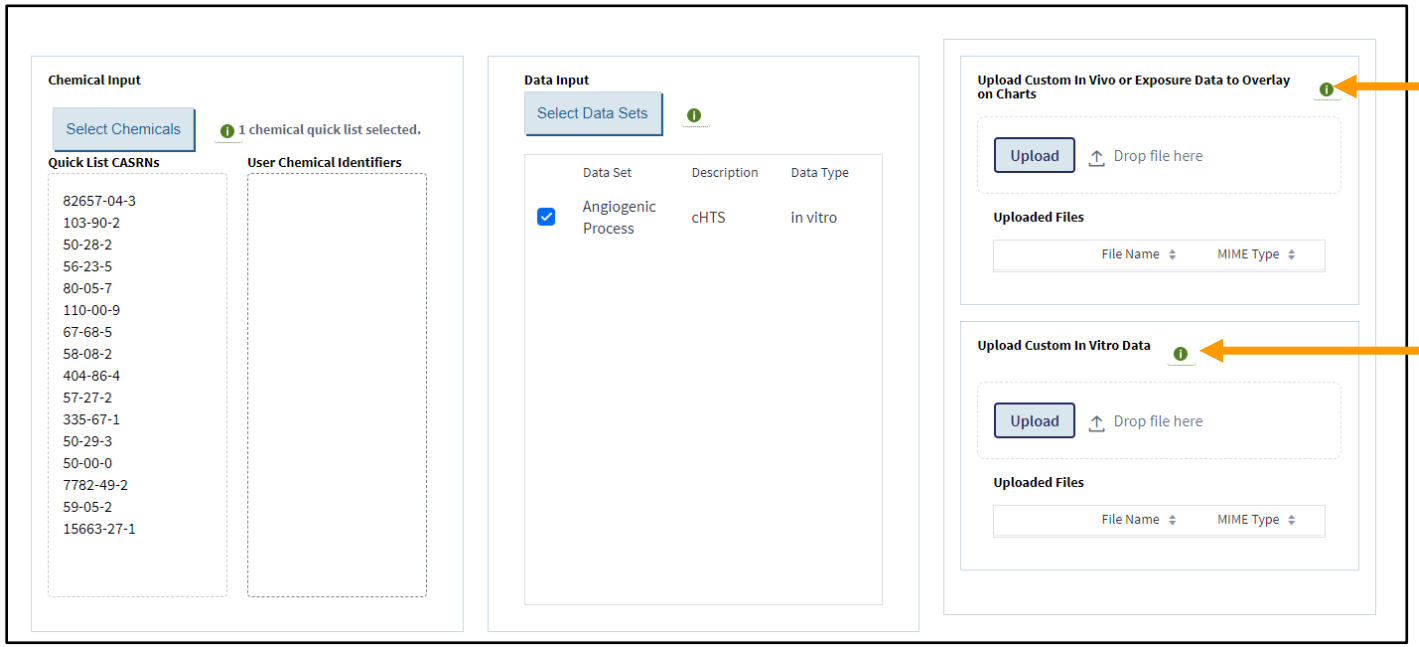
IVIVE Results

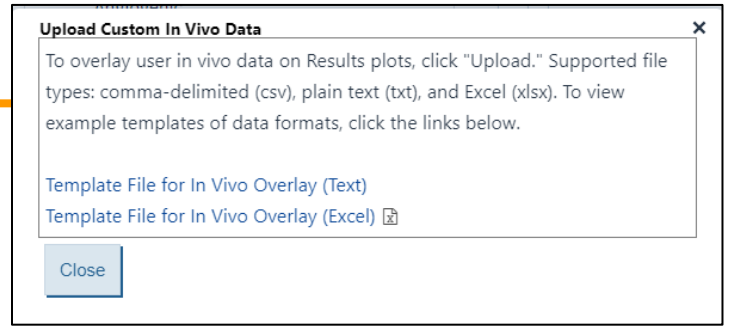
Clicking individual points will display the corresponding chemical-assay concentration-response curve.

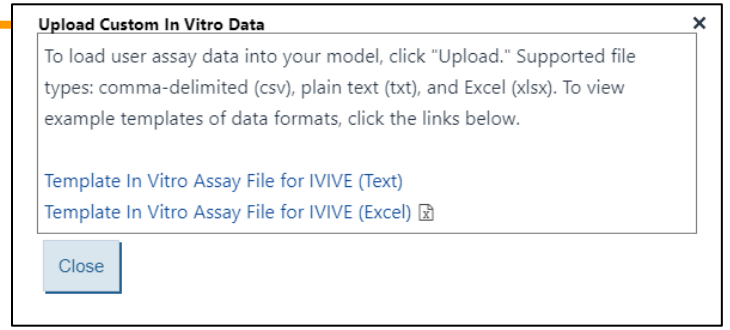


IVIVE Results

Run IVIVE Using Custom Data







In Vivo Data Template

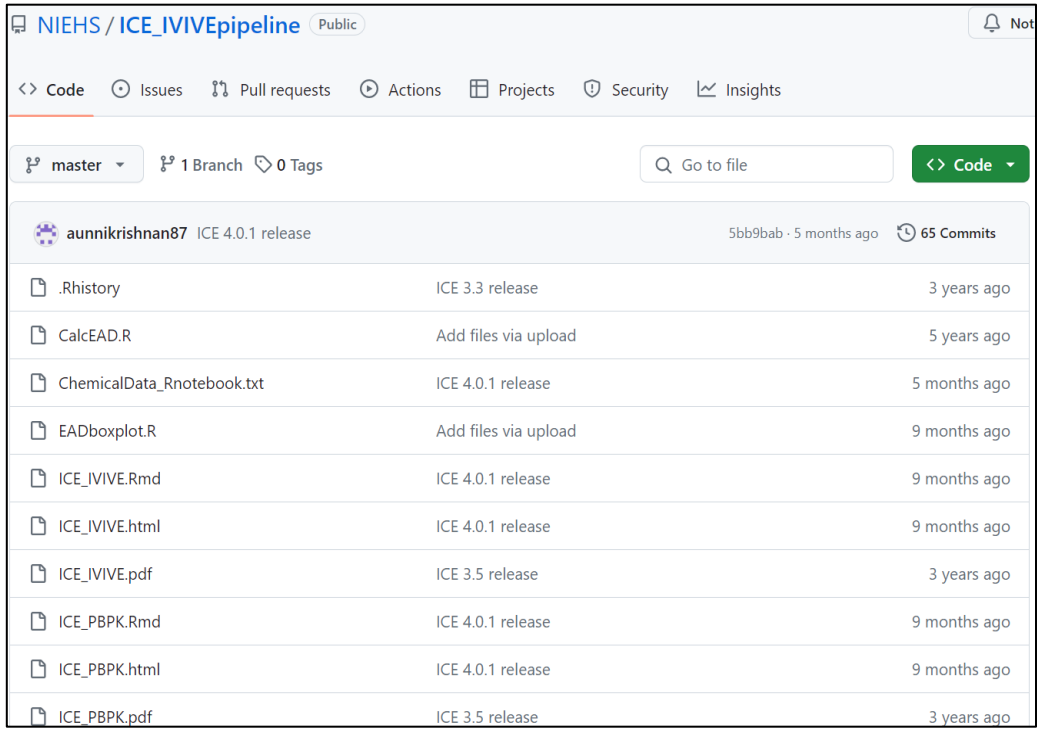
casn	dxsid	chem name	dataset	assay1	assay2	assay3	assay4	assay5	assay6	assay7	assay8	assa9	assay10
115-32-2	dtxsid1	17-Methylte	dataset 1	1	23	4	213	8	9		98	9	
117-81-7	dtxsid2	Testosterone	dataset 1	55	65	55	4	3	466		66	88	
120-47-8	dtxsid2	17beta-Trenl	dataset 1	788	887	997	778	997	997	56	7	76	67
13311-84-7	dtxsid2	Testosterone	dataset 1	9876	7687	877	679	547	123	234	45	456	6
140-66-9	dtxsid1	17-Methylte	dataset 2	987	76	987	4	54	54	556	456	567	77
57-85-2	dtxsid2	Testosterone	dataset 2	98		9	98				98		9
10161-33-8	dtxsid2	17beta-Trenl	dataset 2	123		2345	567	567			45		56
58-22-0	dtxsid2	Testosterone	dataset 2	876			87		6443	345		678	
58-18-4	dtxsid1	17-Methylte	dataset 3	987	234	23	567	775	445	7878	123	456	

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

PBPK and IVIVE Pipeline

- R Notebooks for running the ICE PBPK and IVIVE workflows are available on GitHub:
  - https://github.com/NIEHS/ICE_IVIVEpipeline
- The R Notebooks can be used to run the workflows using custom chemical property and in vitro assay data.



Demo

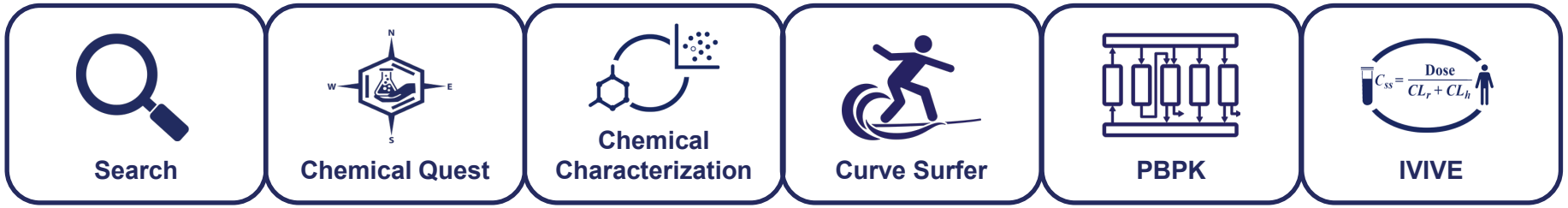
Exploring ICE IVIVE Tool

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

ICE Summary

- Curated in vivo, in vitro, and in silico toxicity data
- Measured and predicted chemical properties
- Predicted exposure
- Reported and predicted chemical use categories

The data are used across ICE tools.



- Explore ICE data through interactive visualizations
- Identify structurally similar chemicals
- Leverage computational models without coding

Inter-connected tools → Send chemical and assay selections between tools

ICE Summary

ICE Data	
Chemical Quick Lists	Identify data relevant to endpoints or activities of interest
Search	Query ICE data and visualize results
Chemical Quest	Identify similar chemicals
Chemical Characterization	Explore chemical properties and use categories
Curve Surfer	Explore concentration-response curves
PBPK	Predict tissue-specific chemical concentrations
IVIVE	Predict equivalent administered dose from in vitro data

Ongoing ICE Projects

- Update cHTS annotations with OBO Foundry controlled vocabulary
- Add PFAS chemical quick list
- Update ROC chemical quick list with 15th Report on Carcinogens
- Continuous development of data visualizations in Search tool
- Enable custom ADME parameter inputs in PBPK and IVIVE tools
- Add Curve Surfer concentration-response data to REST API
- Update cHTS pipeline with invitrodb v4.1 (Feshuk 2023)

Let us know what you would like to see next!

National Institute of Environmental Health Sciences
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Acknowledgments

The NICEATM Group

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

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

NIEHS/DTT Contributors

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