

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:

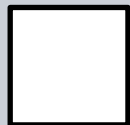
- Gain an understanding of the data within ICE and how to use ICE tools for data interpretation and exploration.
- Help the audience become acquainted with the website to the extent that they feel confident exploring it independently.



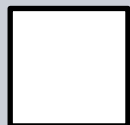
**Integrated
Chemical
Environment**



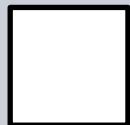
<https://ice.ntp.niehs.nih.gov/>



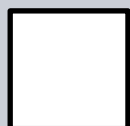
Session 1: 1:00 pm – 1:50 pm



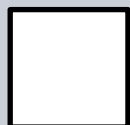
Break: 1:50 pm – 2:00 pm



Session 2: 2:00 pm – 2:50 pm



Break: 2:50 pm – 3:00 pm



Session 3: 3:00 pm – 3:50 pm

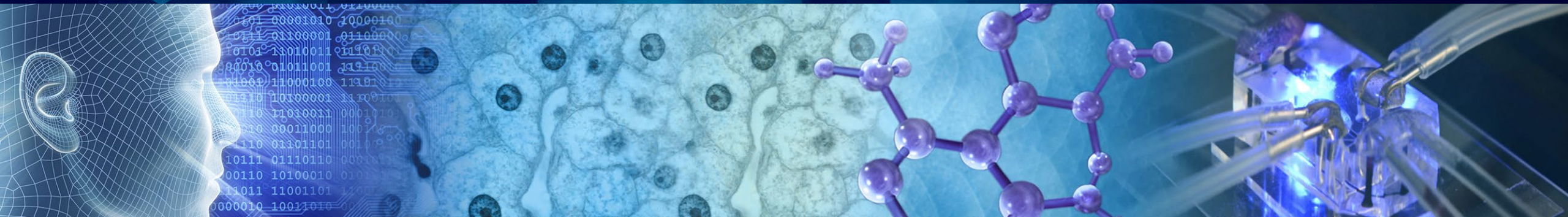
- Introduction to ICE
- Data Sets and Curated Chemical Lists in ICE
- Search Tool
- Session Q & A

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

- PBPK Tool
- IVIVE Tool
- Final Q & A



National Institute of
Environmental Health Sciences
Division of Translational Toxicology



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

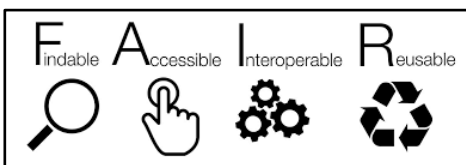
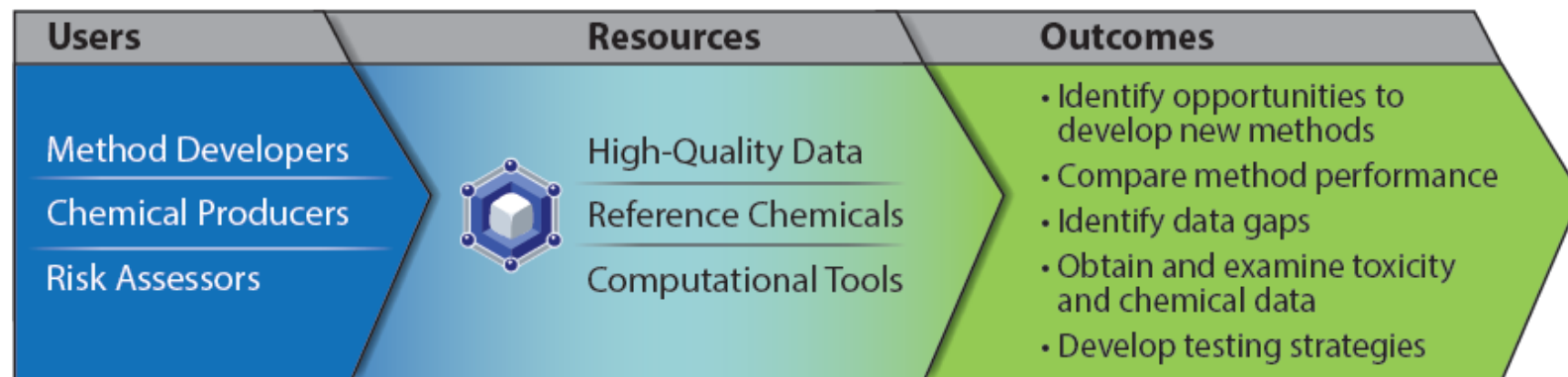
**Inotiv, Inc., Contractor Supporting the NTP Interagency Center for the Evaluation
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Releases in 2023:
ICE v4.0 (March)
ICE v4.0.1 (August)

Releases in 2024:
ICE v4.0.2 (March)

Upcoming - ICE v4.1 (August)



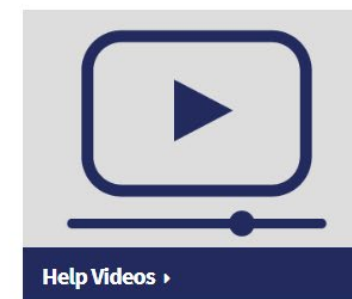
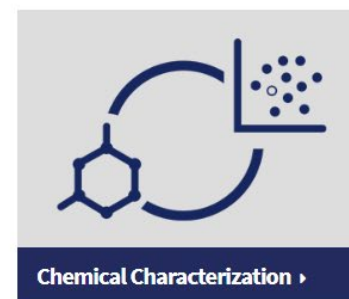
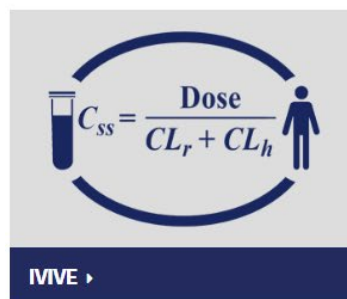
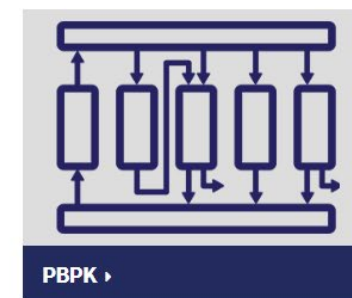
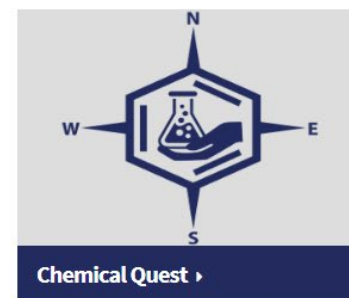
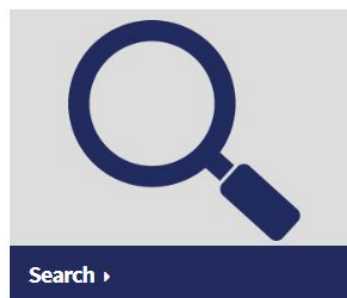
Bell et al. EHP 2017
Bell et al. Tox In Vitro 2020
Abedini et al. Comp Tox 2021
Daniel et al. Front Toxicol 2022



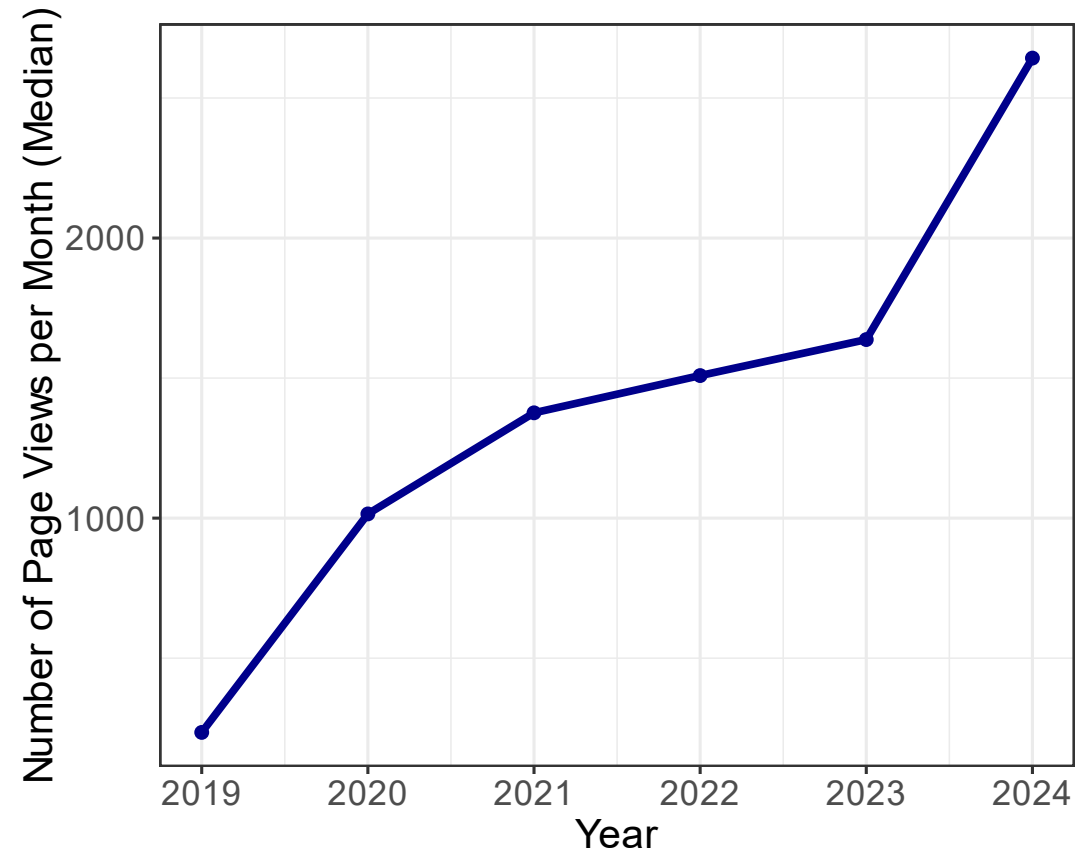
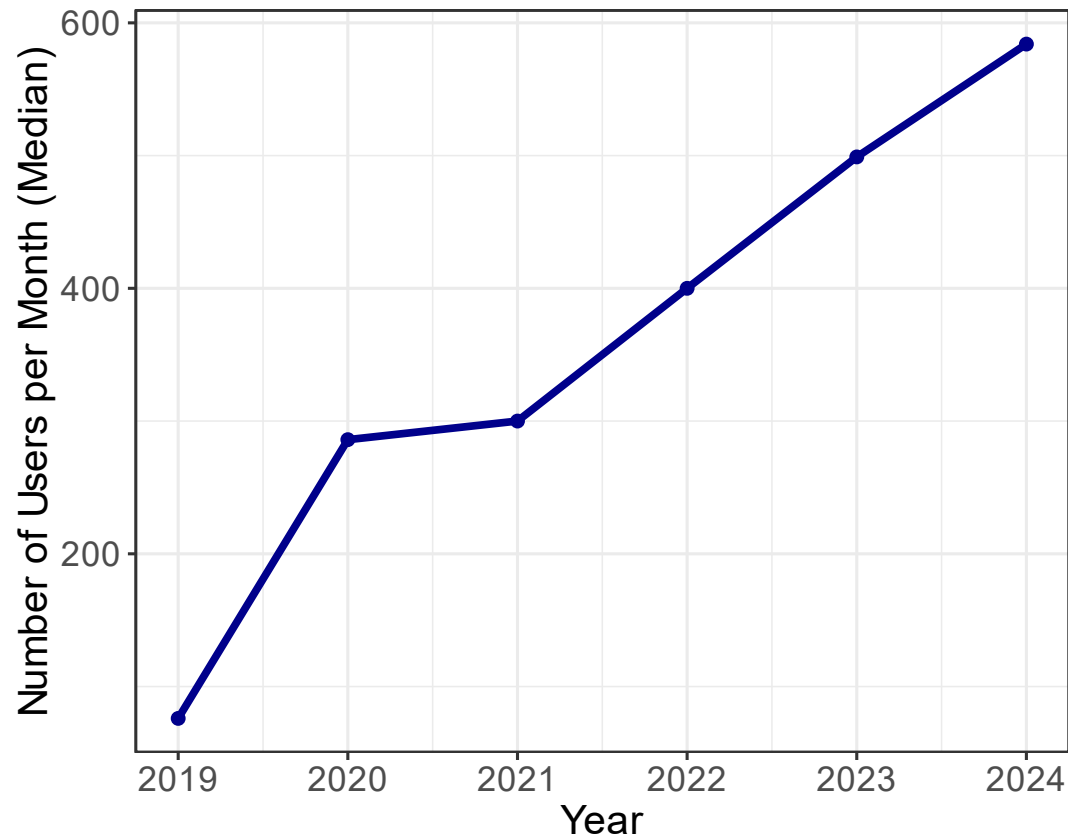
**Integrated
Chemical
Environment**



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

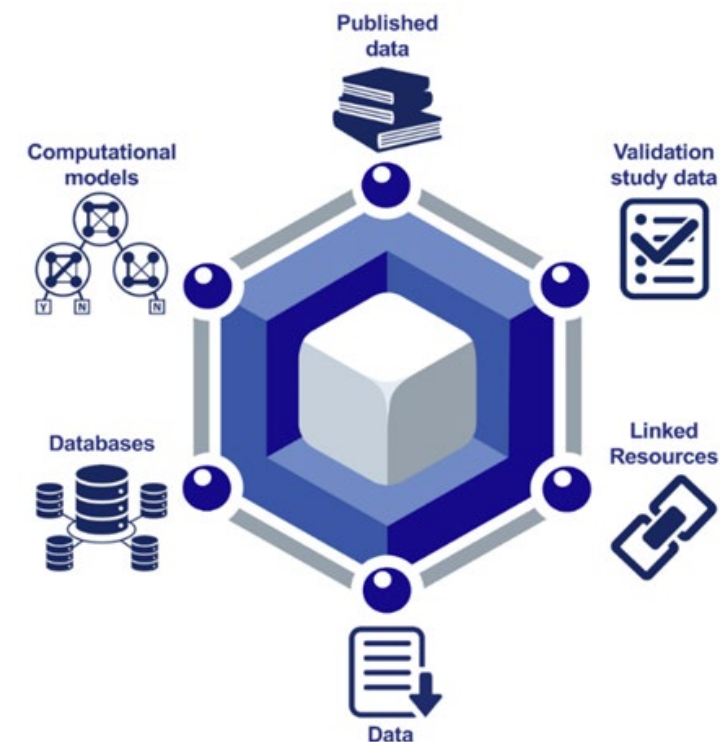


- ICE was launched in 2017 and has been consistently updated with new data, tools, and features.



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>



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



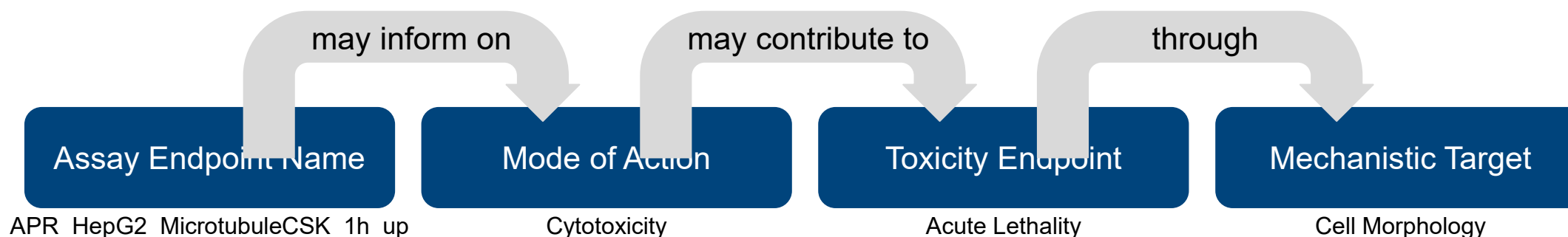
- ICE's curated high-throughput screening (cHTS) data set contains data from the U.S. federal Tox21 collaboration and EPA's ToxCast program for ~10000 chemicals.
- The data curation pipeline includes steps to flag results based on chemical QC, curve fit, or technological interference.

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





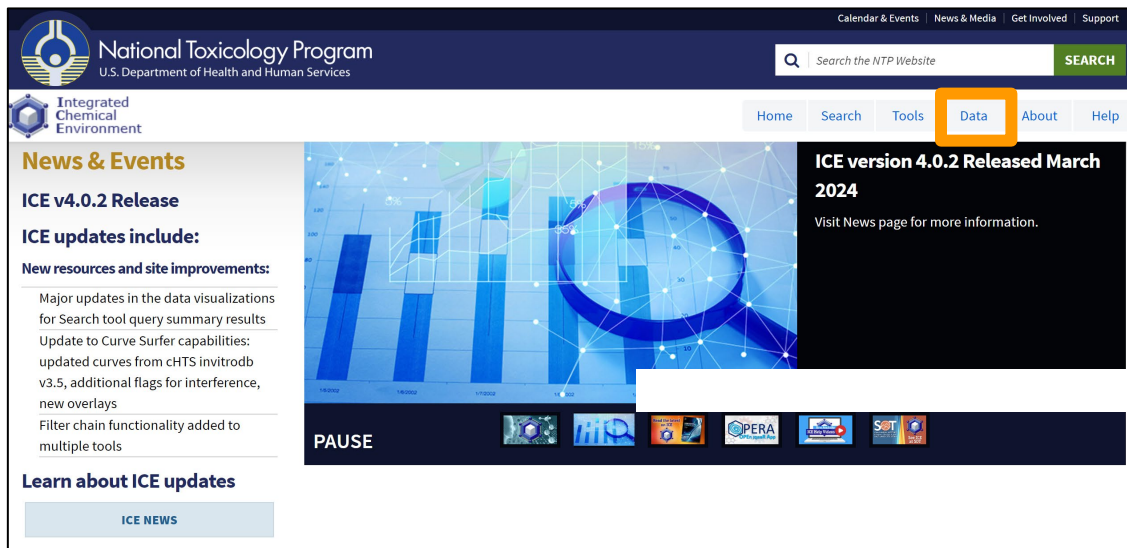
Endpoint	Model	# of Chemicals
Acute Oral Toxicity	CATMoS : Collaborative Acute Toxicity Modeling Suite – Rat Acute Oral Toxicity (Mansouri et al. EHP 2021)	>1M
Endocrine	Estrogen Receptor Pathway Model (Browne et al. ES&T 2015)	1812
	Androgen Receptor Pathway Model (Kleinstreuer et al. Chem Res Tox 2017)	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



- 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 <i>(Ring et al. Environ Sci Technol 2019)</i>	~475000
Curated Product Use Categories <i>(Isaacs et al. J Expo Sci Environ Epidemiol 2020)</i>	4896
Reported Functional Use Categories	9395
Predicted Functional Use Categories <i>(Phillips et al. Green Chem 2017)</i>	~200000

ICE Home Page and ICE Tools





Data Sets Page

ICE Data Sets
Data Sets
Acute Lethality
Cancer
Cardiotoxicity
DART
Endocrine

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 <ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Download  Query (Search , REST API) Overlay (IVIVE)
Acute Dermal Toxicity <ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Download  Query (Search , REST API)





ICE Queries

Single Chemical

List of Chemicals

List of Biological Assay or Non-Assay Endpoint for All Chemicals

List of Chemicals for a Specific Biological Assay or Non-Assay Endpoint

Output: Array of Assay-Endpoint Objects per Chemical

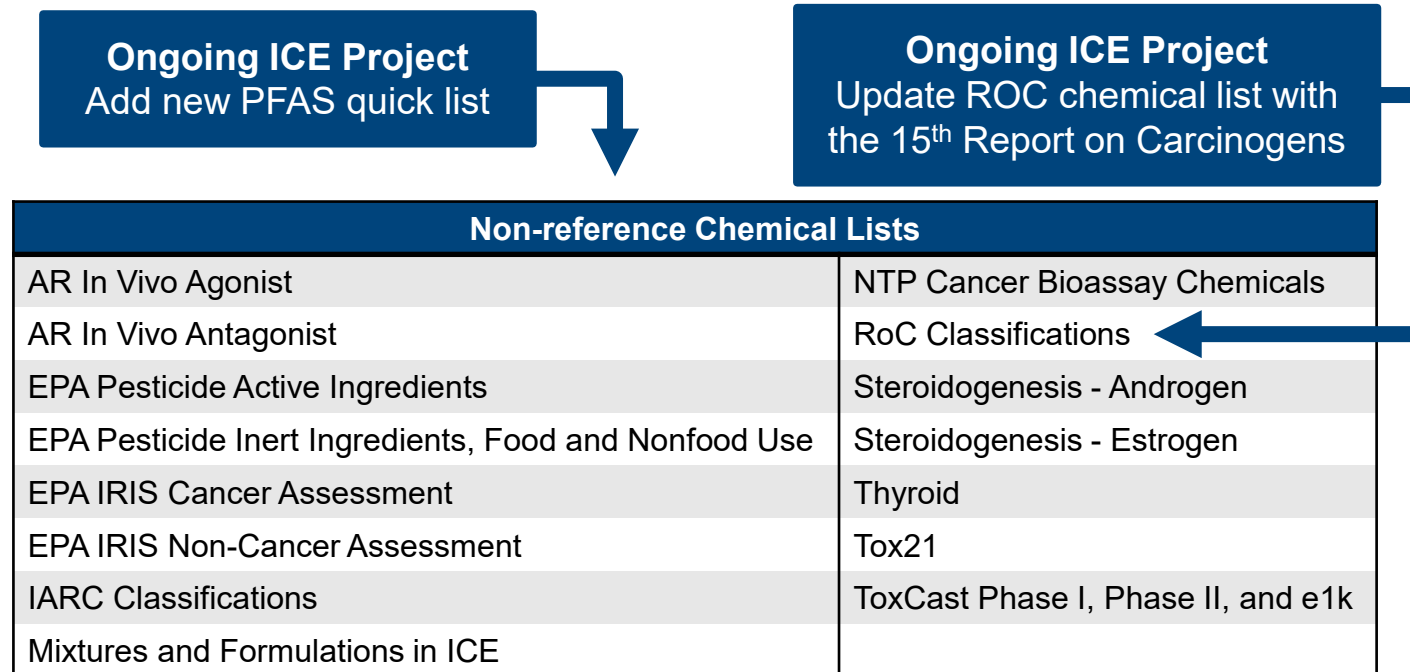
```
← → ↻ https://ice.ntp.niehs.nih.gov/api/v1/search?chemid=DTXSID7032004
JSON Raw Data Headers
Save Copy Collapse All Expand All (slow) Filter JSON
▶ 1568: {}
▶ 1569: {}
▶ 1570: {}
▶ 1571: {}
▶ 1572: {}
▶ 1573: {}
▼ 1574:
  assay: "Rat Acute Oral Toxicity"
  endpoint: "LD50"
  substanceType: "Chemical"
  casrn: "13311-84-7"
  qsarReadyId: "MKKKFYHWDHIYRV-UHFFFAOYSA-N"
  value: "787.0"
  unit: "mg/kg"
  species: "Rat"
  receptorSpecies: ""
  route: "NA"
  sex: ""
  strain: ""
  lifeStage: ""
  tissue: ""
  lesion: ""
  location: ""
  assaySource: ""
  inVitroAssayFormat: ""
  reference: "NLM ChemIDplus TEST (undated)"
  referenceUrl: "https://chem.nlm.nih.gov/chemidplus/"
  dtxsid: "DTXSID7032004"
  substanceName: "Flutamide"
  pubMedId: "NA"
▶ 1575: {}
▶ 1576: {}
▶ 1577: {}
▶ 1578: {}
▶ 1579: {}
▼ 1580:
  assay: "NVS_MP_rPBR"
  endpoint: "Top of curve"
  substanceType: "Chemical"
```

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

- 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



Non-reference Chemical Lists - Less restrictive inclusion criteria

**Search**

Query ICE data and visualize results

**Chemical Quest**

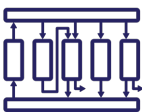
Identify similar chemicals

**Chemical
Characterization**

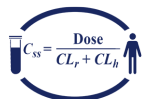
Explore chemical properties and use categories

**Curve Surfer**

Explore concentration-response curves

**PBPK**

Predict tissue-specific chemical concentrations

**IVIVE**

Predict equivalent administered dose from in vitro data

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

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

Integrated Chemical Environment

Home Search **Tools** Data About **Help**

News & Events

ICE v4.0.2 Release

ICE updates include:

New resources and site improvements:

- Major updates in the data visualizations for Search tool query summary results
- Update to Curve Surfer capabilities: updated curves from cHTS invitrodb v3.5, additional flags for interference, new overlays
- Filter chain functionality added to multiple tools

ICE version 4.0.2 Released March 2024

Visit News page for more information.

PAUSE

Learn about ICE updates

ICE NEWS

- ### ICE User Guide
- Search
 - Chemical Quest
 - Curve Surfer
 - PBPK
 - IVIVE
 - Chemical Characterization
 - Interactive Graphs
 - Rest API

- ### Help Videos
- ICE Help Videos
 - Search Help Videos
 - IVIVE Help Videos
 - Curve Surfer Help Videos
 - PBPK Help Videos



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

- Search
- Chemical Quest
- Curve Surfer
- PBPK
- IVIVE
- Chemical Characterization
- Data
- Help Videos



National Institute of
Environmental Health Sciences
Division of Translational Toxicology

Demo

Exploring ICE



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

**Search**

Query ICE data and visualize results

**Chemical Quest**

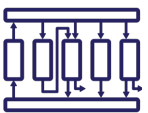
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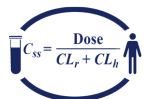
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Predict equivalent administered dose from in vitro data



Search

Query ICE data and visualize results

- 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.

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

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

Integrated Chemical Environment

Home **Search** Tools Data About **Help**

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 - Rest API

- Help Videos**
- ICE Help Videos
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 - Curve Surfer Help Videos
 - PBPK Help Videos



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

- Search
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Chemical Input

Chemical Input

Select Chemicals

1 chemical quick list selected.

Quick List CASRNs

- 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

Add chemicals with i

User Chemical Identifiers

- DTXSID8023892
- 82657-04-3
- Picloram
- DTXSID5032498

Select one or more chemical quick lists.

Select All Deselect All Finished

- A Demo List of Chemicals
- AR In Vitro Agonist (R)
- AR In Vitro Antagonist (R)
- AR In Vivo Agonist
- AR In Vivo Antagonist
- EPA IRIS Cancer Assessment (R)
- EPA IRIS NonCancer Assessment (R)
- EPA Pesticide Active Ingredients

Data Set Input

Select Data Sets

cHTS Acute Lethality Sensitization Irritation/Corrosion Endocrine Cancer

- Acute Lethality
 - Dermal
 - Inhalation
 - Oral
 - In Vivo Acute Oral Toxicity Assays
 - Rat Acute Oral Toxicity in vivo
 - In Silico Acute Oral Toxicity Predictions
 - CATMoS, Rat Acute Oral Toxicity in silico
 - Mode of Action
 - AcuteTox - Cytotoxicity in vitro

AcuteTox - Cytotoxicity

This MOA describes assays relating to cell survival and cell viability. It is composed of assays relating to:

Cell Survival	CUI:C0007620
Cell Viability Process	CUI:C1516362
Cellular Morphology	CUI:C1521816
Cellular Processes	CUI:C1325880

Close



Input

Results

Search Results

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

View Data Tables

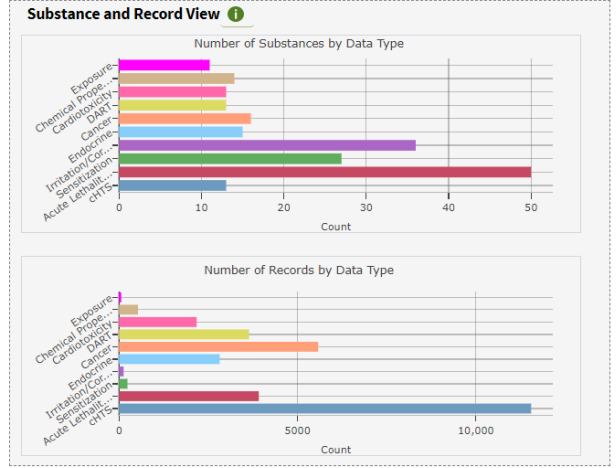
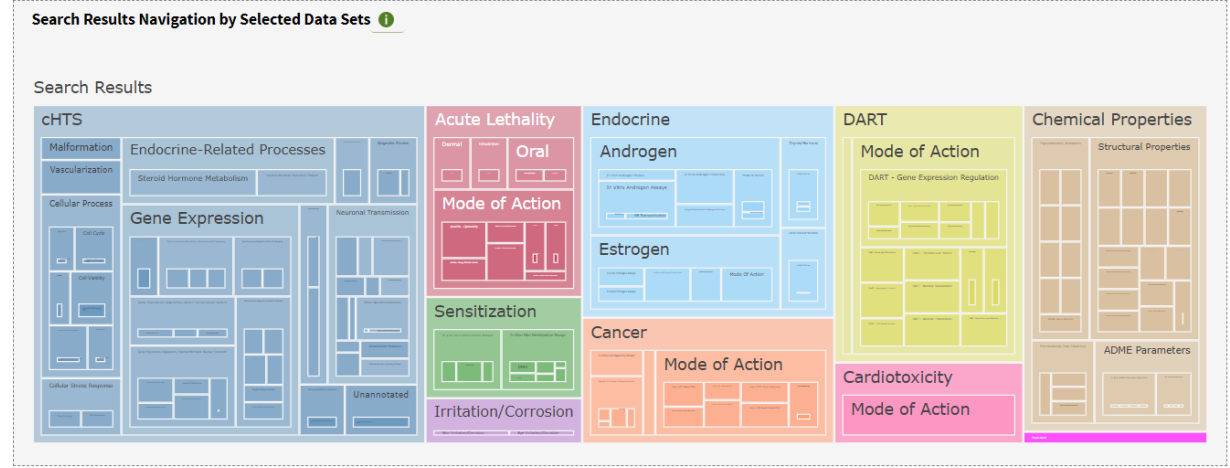
Data Table | Data Summary | Download

- 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: Clear Filters



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 (DasI)	Distribution of Records	Rec...
Cisplatin	Chemical	15663-27-1	DTXSID4024983		576
The Andersons 0.058% Bifenthrin	Mixture	138261-41-3: 0.11 82657-04-3: 0.058	DTXSID5032442: DTXSID9020160:		9

View Data Tables

Data Table

Data Summary

Download

Download summary data

Download Results

Summary Data

Wide Format Data

Long Format Data

Note: For "Wide Format" downloads (when available), cHTS assay data only includes AC50 values for assays with an "Active" chemical. Call values are returned for assays with no active chemicals.

Close

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

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

Details

Endpoint Record Count: 80121

Record ID	Is related chemical	Chemical Name	Substance Type	CASRN	DTXSID	QSAR Ready ID	Assay	Endpoint	Response	Unit	Species	Receptor Species
R_321361...	YES	(+)-(1R)-cis-Bifenthrin	Chemical	439680-76-9	DTXSID20891316	OMFRMA_UHFFFAO...N	OPERA, Number of oxygen atoms	nbO	2.0	count		
R_135250...	YES	(+)-(1R)-cis-Bifenthrin	Chemical	439680-76-9	DTXSID20891316	OMFRMA_UHFFFAO...N	OPERA, The whole body primary biotransformation rate (half-life) constant for organic chemicals in fish	LogKM	0.56	Log10 days		
R_244697...	YES	(+)-(1R)-cis-Bifenthrin	Chemical	439680-76-9	DTXSID20891316	OMFRMA_UHFFFAO...N	OPERA, Number of atoms	nbAtoms	51.0	count		
R_168052...	YES	(+)-(1R)-cis-Bifenthrin	Chemical	439680-76-9	DTXSID20891316	OMFRMA_UHFFFAO...N	OPERA, Octanol-Water Partition Coefficient	LogP	6.19	log10		
R_036785...	YES	(+)-(1R)-cis-Bifenthrin	Chemical	439680-76-9	DTXSID20891316	OMFRMA_UHFFFAO...N	OPERA, Combined	CombDip...	1.498	dipole moment/volume		

Close

Summary

Number of substances = 423

View Details

QSAR Match

Substance Name

Substance Type

CASRN (CEBS Link)

DTXSID (Dashboard Link)

QSAR Ready ID

Malform... Call

Vascular... Call

Apoptosis... Call

Cell Cycle... Call

Cell Prolifera... Call

Cell Viability... Call

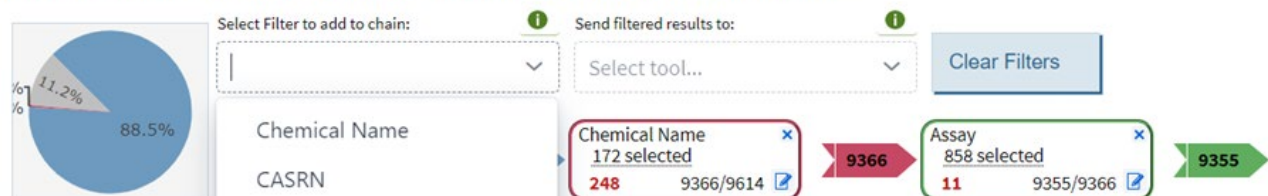
		17alpha-Estradiol	Chemical	57-91-0	DTXSID8022377	UHFFFAO...N	Active	ACOVERL... Omit(N=2)	Inactive(N...)	ACTIVE(N... Omit(N=1)	Inactive(N...)	ACTIVE(Omit(N...)
	YES	17alpha-Hydroxy-5alpha-androstan-3-one	Chemical	571-24-4	DTXSID201024071	NVKAWK...UHFFFAO...N						
	YES	17alpha-Trenbolone	Chemical	80657-17-6	DTXSID90872854	MEHHPF...UHFFFAO...N						
		17beta-Estradiol	Chemical	50-28-2	DTXSID0020573	VOXZDW...UHFFFAO...N	Active	Active(N...)	Inactive(N...)	Active(N...)	Inactive(N...)	Active(Omit(N...)
		17beta-Trenbolone	Chemical	10161-33-8	DTXSID0034192	MEHHPF...UHFFFAO...N	Active	Active(N... Omit(N=2)	Inactive(N...)	Active(N...)	Inactive(N... Omit(N=1)	Active(Omit(N...)

Close

Filter Search Results

Interact with Results

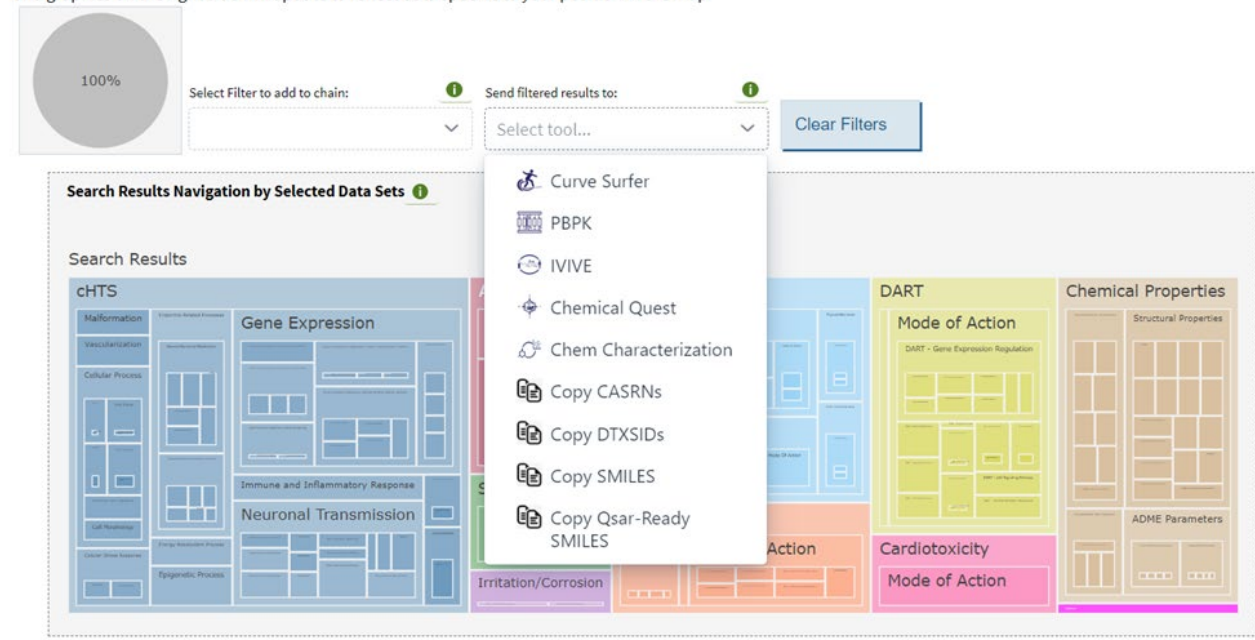
To zoom in to a specific data type, click on the box within the navigation map. Banners at the top of the map will indicate your position in the map and graphics on the right side will update to reflect data specific to your position in the map.



Send Search Results to Other ICE Tools

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 in and graphics on the right side will update to reflect data specific to your position in the map.

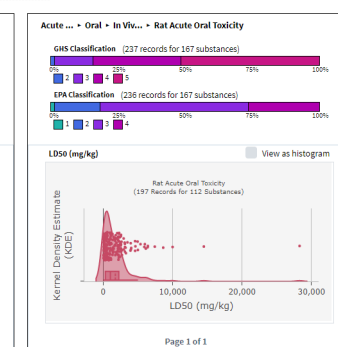
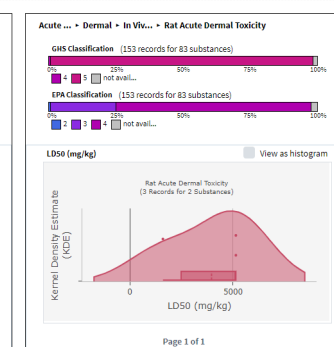
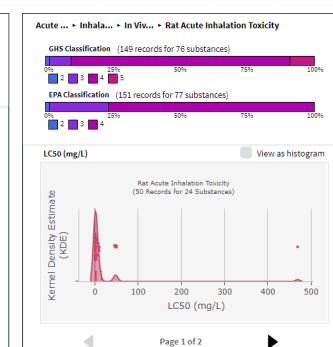
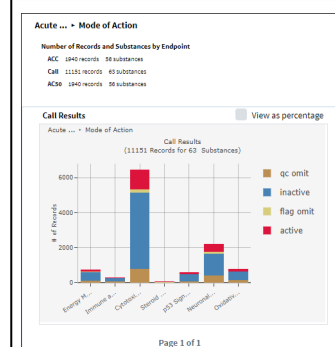
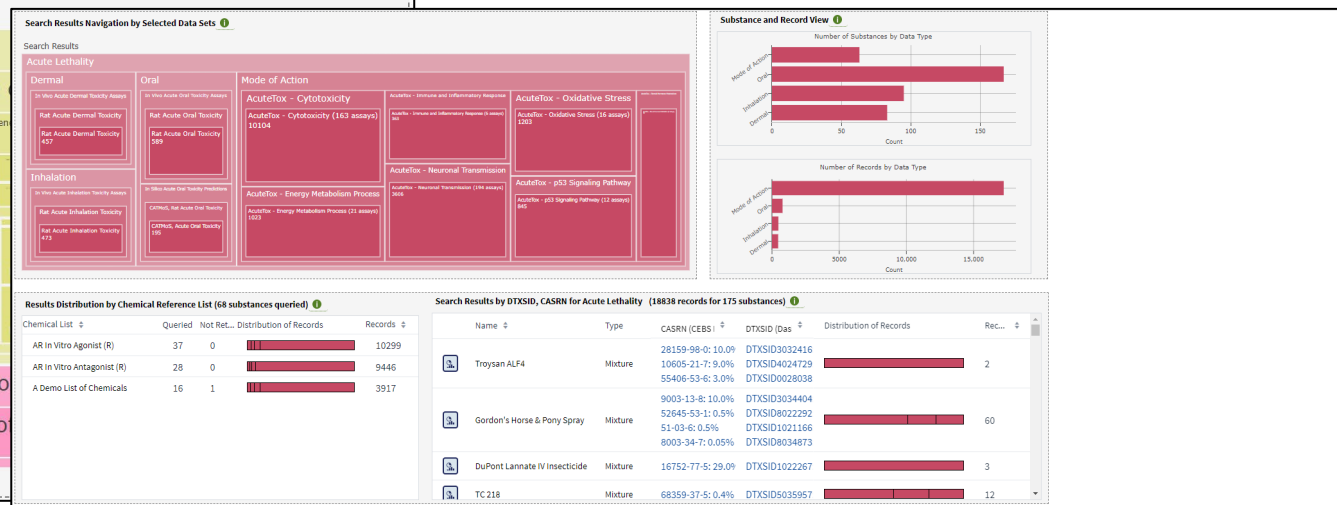
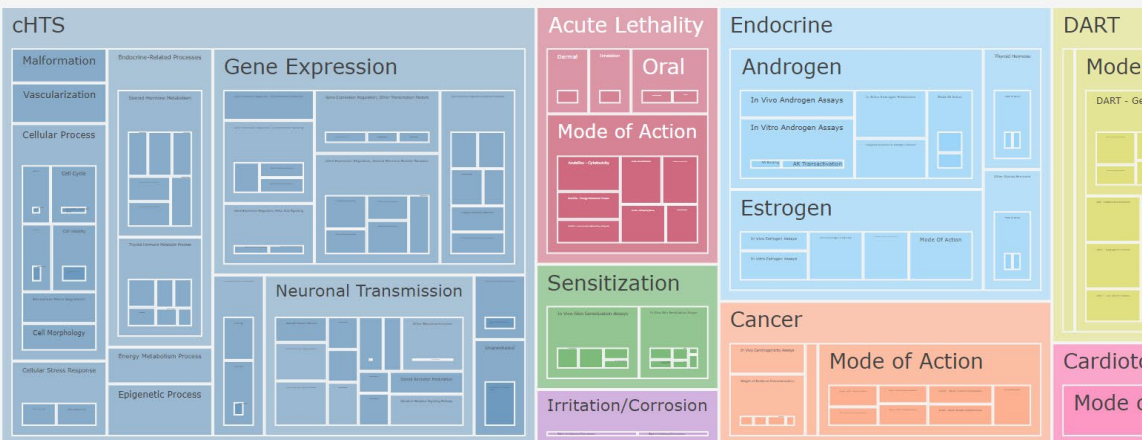


Results can be explored using the navigation map that organizes results based on data set.

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

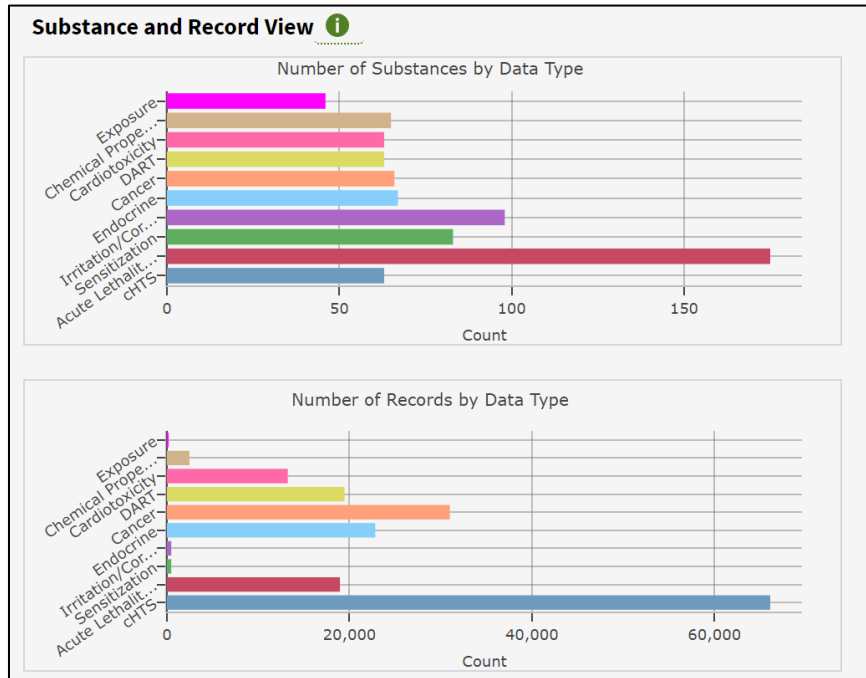
Search Results Navigation by Selected Data Sets ?

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 by DTXSID, CASRN (79129 records for 180 substances) i

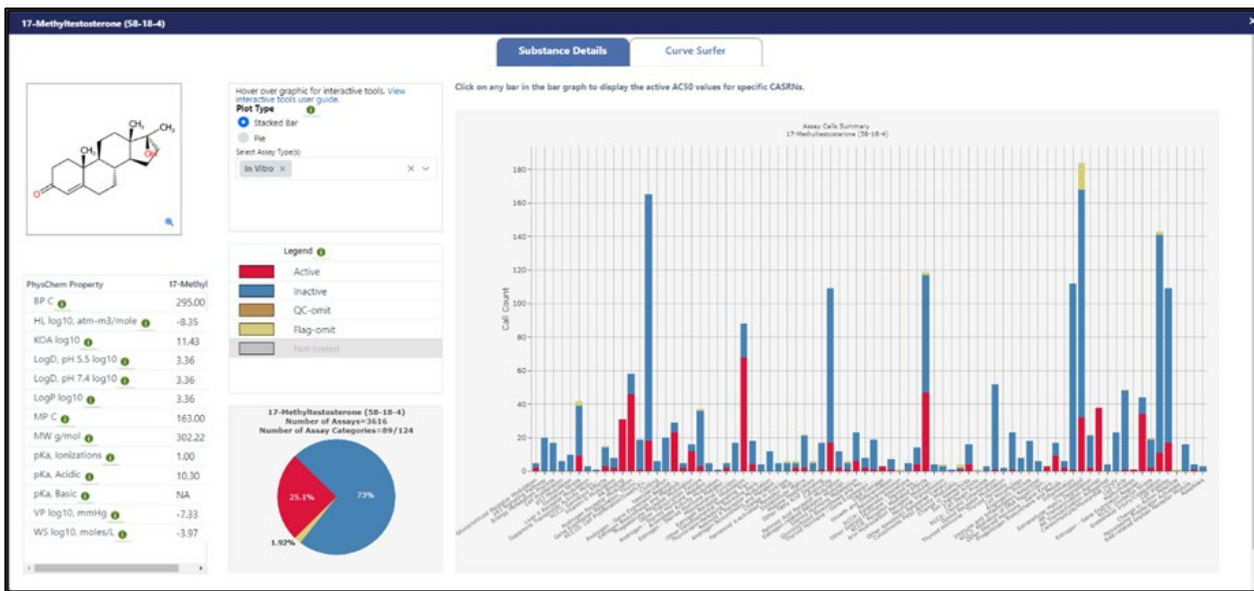
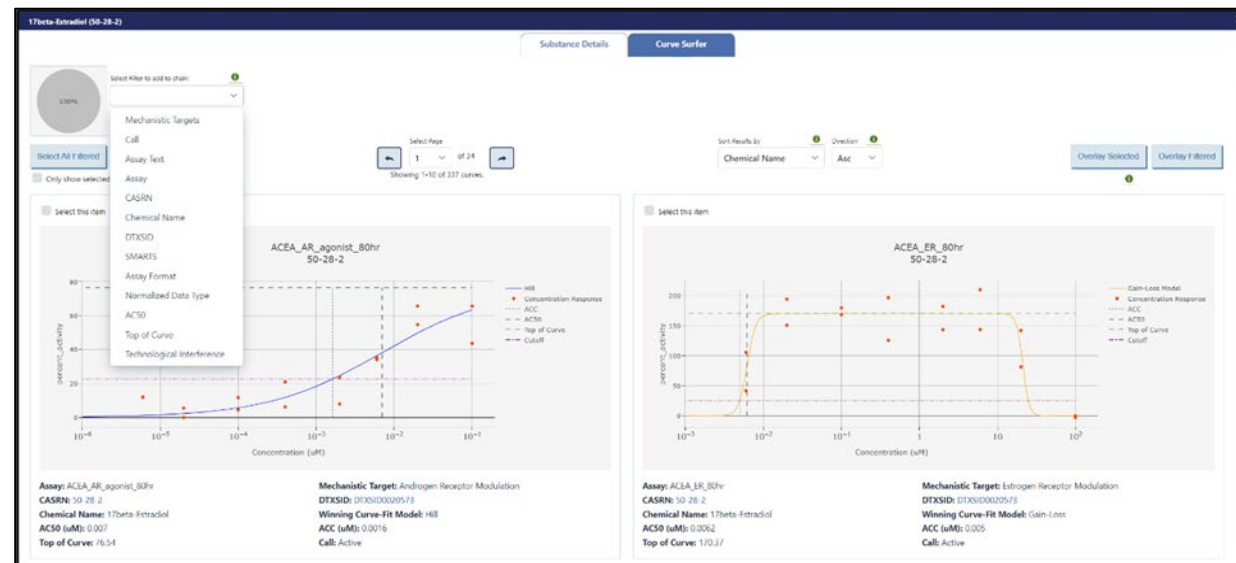
Name	Type	CASRN (CEBS I)	DTXSID (DasI)	Distribution of Records	Records
Simazine	Chemical	122-34-9	DTXSID4021268		2054
Tundra Max	Mixture	2921-88-2: 28.6% 82657-04-3: 9.0%	DTXSID4020458: DTXSID9020160:		27
17alpha-Estradiol	Chemical	57-91-0	DTXSID8022377		3565
Pyranha 1-10 PPC Concentrate	Mixture	51-03-6: 20.0% 52645-53-1: 4.0% 8003-34-7: 2.0%	DTXSID1021166: DTXSID8022292: DTXSID8034873:		36
Hydroxyflutamide	Chemical	52806-53-8	DTXSID8033562		3186

Results Distribution by Chemical Reference List (68 substances queried) i

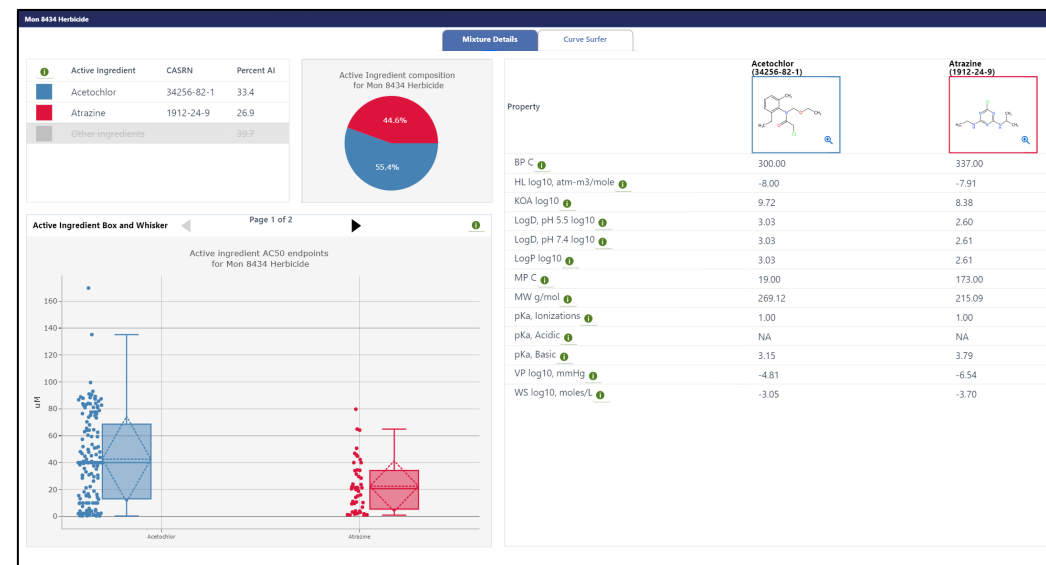
Chemical List	Queried	Not Ret...	Distribution of Records	Records
AR In Vitro Agonist (R)	37	0		97307
AR In Vitro Antagonist (R)	28	0		92871
A Demo List of Chemicals	16	0		30618

Curve Surfer View

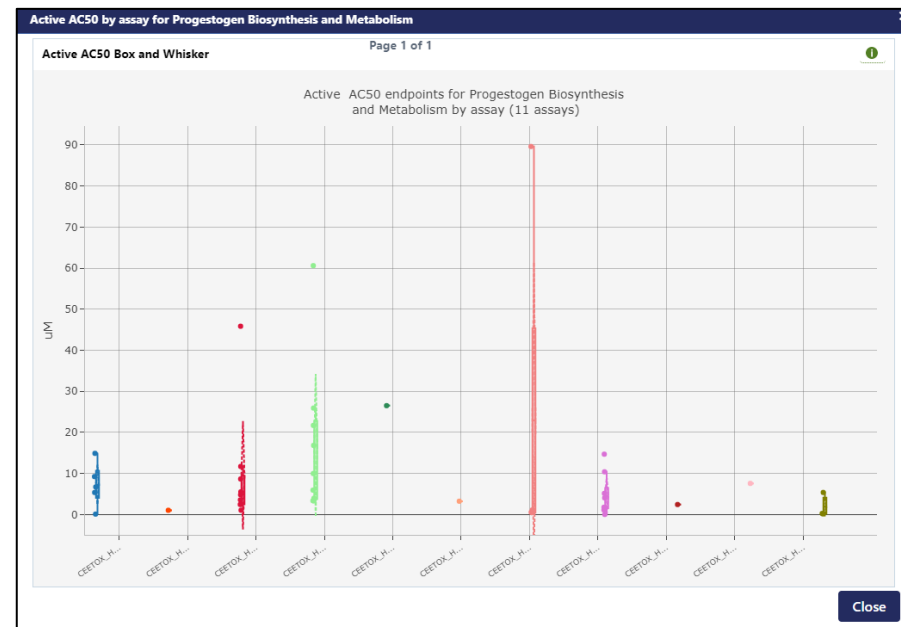
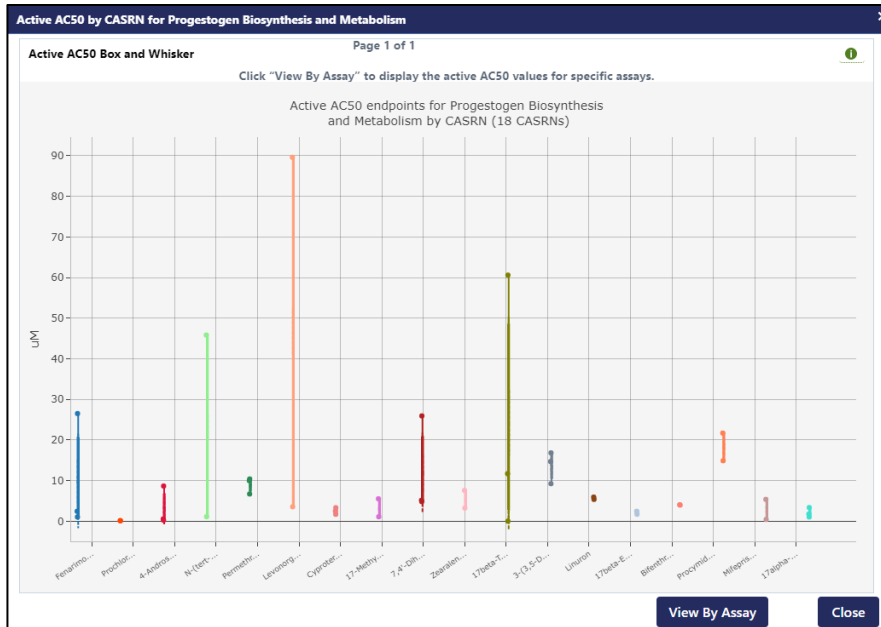
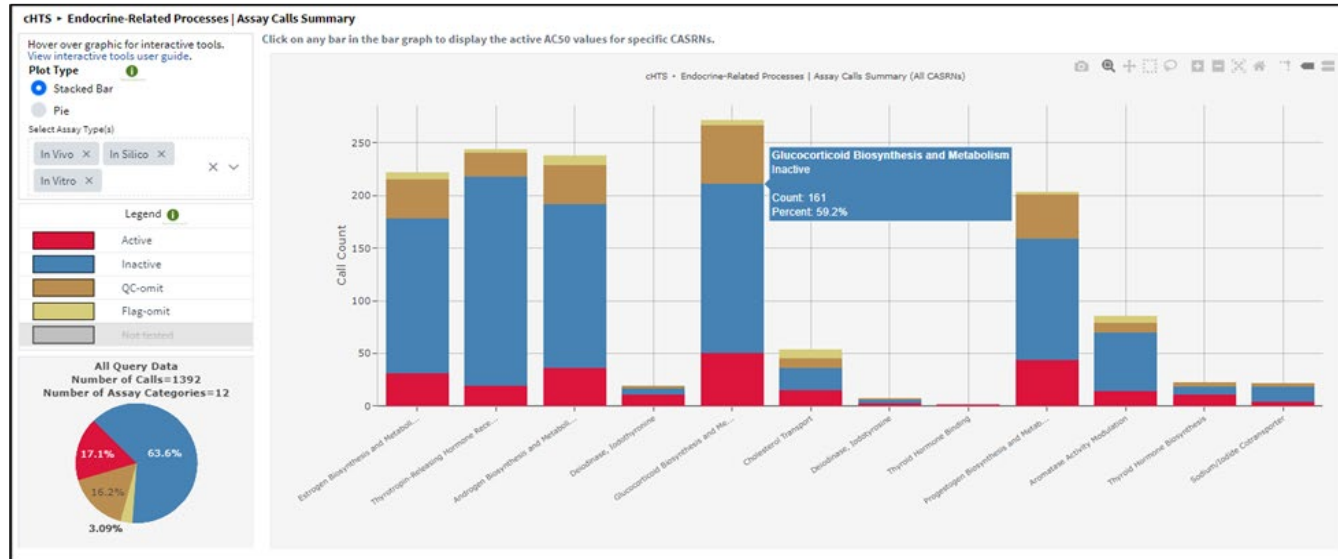
Substance Detail View for Single Chemical



Substance Detail View for Mixture



Bioactivity Summary



Demo

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



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



National Institute of
Environmental Health Sciences
Division of Translational Toxicology

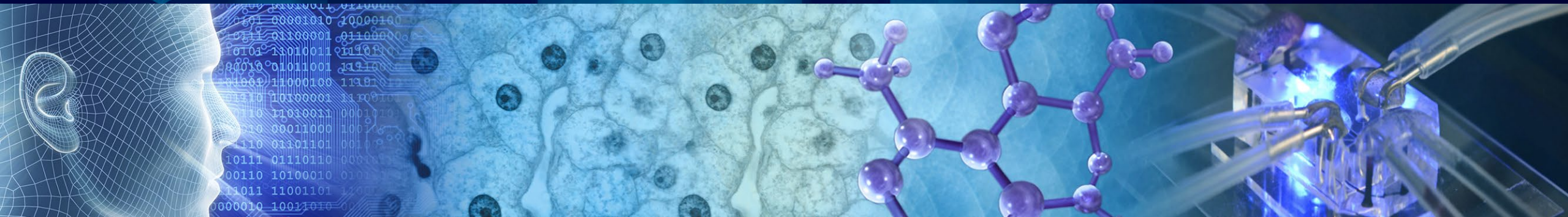


Session Questions

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

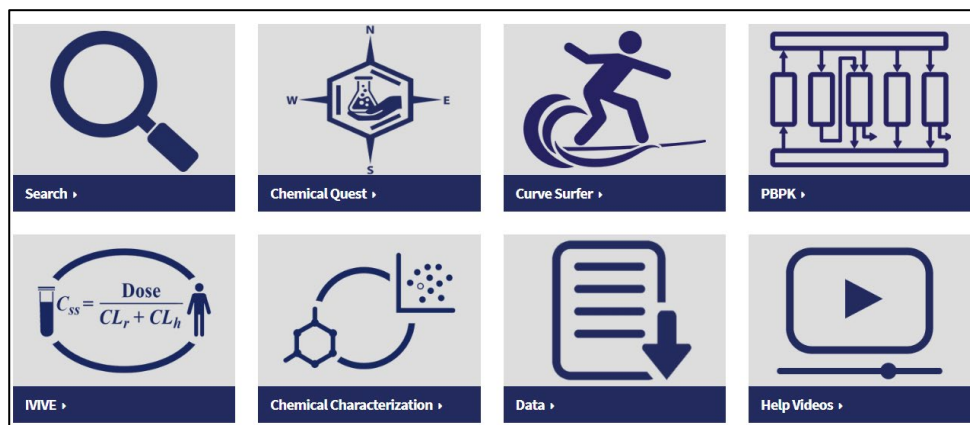
**Inotiv, Inc., Contractor Supporting the NTP Interagency Center for the Evaluation
of Alternative Toxicological Methods (NICEATM)**

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

National Institutes of Health • U.S. Department of Health and Human Services



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

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

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

Integrated Chemical Environment

Home Search **Tools** Data About **Help**

News & Events

ICE v4.0.2 Release

ICE updates include:

New resources and site improvements:

- Major updates in the data visualizations for Search tool query summary results
- Update to Curve Surfer capabilities: updated curves from cHTS invitrodb v3.5, additional flags for interference, new overlays
- Filter chain functionality added to multiple tools

ICE version 4.0.2 Released March 2024

Visit News page for more information.

PAUSE

Learn about ICE updates

ICE NEWS

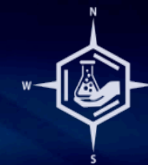
- ### ICE User Guide
- Search
 - Chemical Quest
 - Curve Surfer
 - PBPK
 - IVIVE
 - Chemical Characterization
 - Interactive Graphs
 - Rest API

- ### Help Videos
- ICE Help Videos
 - Search Help Videos
 - IVIVE Help Videos
 - Curve Surfer Help Videos
 - PBPK Help Videos



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

- Search
- Chemical Quest
- Curve Surfer
- PBPK
- IVIVE
- Chemical Characterization
- Data
- Help Videos

**Search**

Query ICE data and visualize results

**Chemical Quest**

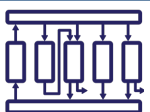
Identify similar chemicals

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

Search the NTP Website SEARCH

Home Search **Tools** Data About Help

News & Events

ICE v4.0.2 Release

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- Filter chain functionality added to multiple tools

ICE version 4.0.2 Released March 2024

Visit News page for more information.

PAUSE

PERA

SOT



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

Learn about ICE updates

ICE NEWS

Search >

Chemical Quest >

Curve Surfer >

PBPK >

IVIVE >

Chemical Characterization >

Data >

Help Videos >

Send filtered results to:

Download Select tool... Clear Filter

View Details

Chemical Quest

Chem Characterization

Copy CASRNs

Copy DTXSIDs


Copy SMILES

Copy Qsar-Ready SMILES

17beta-Estradiol





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

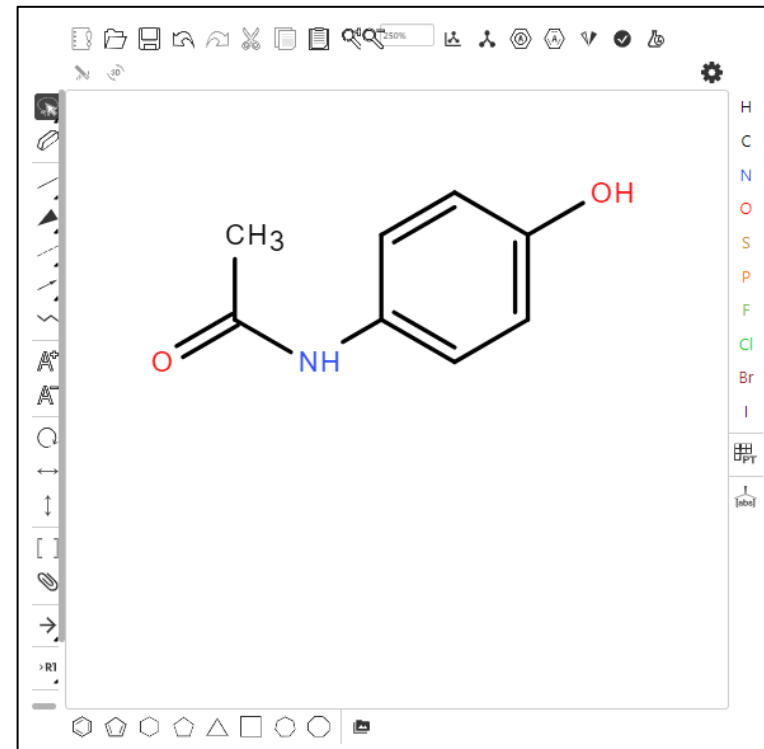
SMILES String

Smiles Structures for similarity search 

Chemical Structure 


<input type="button" value="X"/>	<input type="button" value="edit"/>	<chem>NC(=N)NC#N</chem>
<input type="button" value="X"/>	<input type="button" value="edit"/>	<chem>C=O</chem>
<input type="button" value="X"/>	<input type="button" value="edit"/>	<chem>CC(=O)NC1C=CC(O)=CC=1</chem>
<input type="button" value="X"/>	<input type="button" value="edit"/>	<chem>CC(C)(C1C=CC(O)=CC=1)C1C=CC(O)=CC=1</chem>

Enter SMILES String:








Specify Number of Hits and Similarity Threshold


 The Chemical Quest tool uses fingerprints to calculate structure similarity.

This tool uses fingerprints generated using *Saagar* features. Only 50 input chemical ids/structures allowed at a time.


Search Custom Chemical List 


Max hits per input: 

Tanimoto Coefficient: **or greater** 

Chemical ID input (one per line). 

133-06-2
63-25-2
82657-04-3
103-90-2
50-28-2


Smiles Structures for similarity search 


Chemical Structure 

Query Against All Chemicals in ICE or a Custom Chemical List


Run


Reset


Search Custom Chemical List 


Select one or more chemical quick lists. 


A Demo List of Chemicals


AR In Vitro Agonist (R) 


AR In Vitro Antagonist (R) 


AR In Vivo Agonist 


AR In Vivo Antagonist 


EPA IRIS Cancer Assessment (R) 


EPA IRIS NonCancer Assessment (R) 


EPA Pesticide Active Ingredients 


EPA Pesticide Inert Ingredients, Food and Nonfood Use 


ER In Vitro Agonist (R) 


ER In Vivo Agonist (R) 

Eye Irritation-Corrosion (R) 


Genotoxicity (R) 

IARC Classifications 

Mixtures and Formulations in ICE 

NTP Cancer Bioassay Chemicals 

Custom Chemical Search Targets

 1 ch

Quick List CASRNs

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



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

Input

Results

Chemical Quest Results

Send filtered results to:
Select tool...

TXT XLSX SDF

Help

Report an Issue

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

CC(=O)Nc1ccc(O)cc1

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

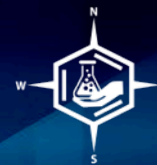
FC(F)(F)C(F)(F)C(F)(F)C(F)(F)C(F)(F)C(F)(F)C(F)(F)C(=O)O

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

ClC1=CC=C(Cl)C=C1C(Cl)(Cl)C2=CC=C(Cl)C=C2

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

CN1C=NC2=C1C(=O)N(C)C(=O)N2C



Refine results for individual chemicals using interactive filters.

Similar Structures to: Captan

Send filtered results to: Select tool...

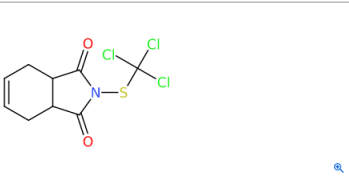
Select Filter to add to chain: [Dropdown]

Select Page: 1 of 1 Showing 1-10 of 10 hits. Sort Results By: Tanimoto Direction: Desc

Clear Filters Select All Filtered Clear Selected Only show selected items

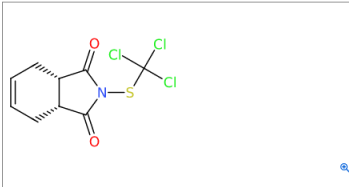
Select this item

CASRN: 8003-20-1
DTXSID: DTXSID301339910
Name: 3a,4,7,7a-Tetrahydro-2-[[t...
Tanimoto Value: 1.0
Has Bioactivity: false



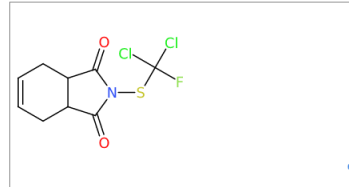
Select this item

CASRN: 133-06-2
DTXSID: DTXSID9020243
Name: Captan
Tanimoto Value: 1.0
Has Bioactivity: true



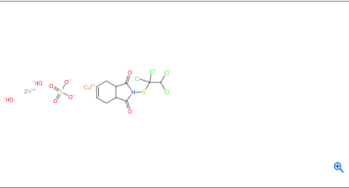
Select this item

CASRN: 1082-58-2
DTXSID: DTXSID301137380
Name: 2-[[Dichlorofluoromethyl)]...
Tanimoto Value: 0.961039
Has Bioactivity: false



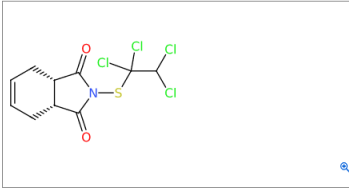
Select this item

CASRN: 75045-72-6
DTXSID: DTXSID00996550
Name: Copper(2+) zinc hydroxid...
Tanimoto Value: 0.888889
Has Bioactivity: false



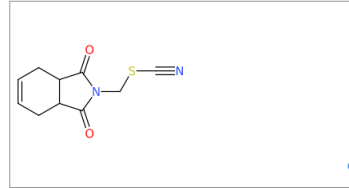
Select this item

CASRN: 2939-80-2
DTXSID: DTXSID7034418
Name: cis-Captafol
Tanimoto Value: 0.888889
Has Bioactivity: false



Select this item

CASRN: 86199-24-8
DTXSID: DTXSID10280992
Name: (1,3-Dioxo-1,3,3a,4,7,7a-h...
Tanimoto Value: 0.75641
Has Bioactivity: false



Similar Structures to: Captan

Send filtered results to: Select tool...

Select Filter to add to chain: [Dropdown]

Select Page: 1 of 1 Showing 1-10 of 10 hits. Sort Results By: Tanimoto

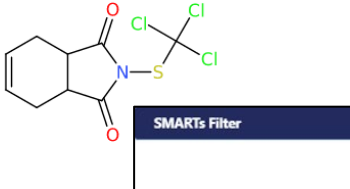
Select All Filtered Clear Selected Only show selected items

Select Filter to add to chain:

- CASRN
- Chemical Name
- DTXSID
- SMARTS
- Has Bioactivity
- Tanimoto

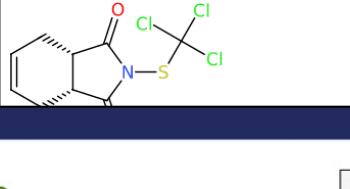
Select this item

CASRN: 8003-20-1
DTXSID: DTXSID301339910
Name: 3a,4,7,7a-Tetrahydro-2-[[t...
Tanimoto Value: 1.0
Has Bioactivity: false



Select this item

CASRN: 133-06-2
DTXSID: DTXSID9020243
Name: Captan
Tanimoto Value: 1.0
Has Bioactivity: true



SMARTS Filter

Enter SMARTS: [Input]

Add SMARTS Query

Chemicals that match the entered SMARTS Query

Search Text	Count	%
Cl	8 (8)	80...
C=C	10 (10)	10...

10 results in 10 items listed

10 results selected of 10 (100.0%)

Items: C=C Cl

Close



Demo

Exploring ICE Chemical Quest Tool



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

**Search**

Query ICE data and visualize results

**Chemical Quest**

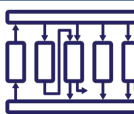
Identify similar chemicals

**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

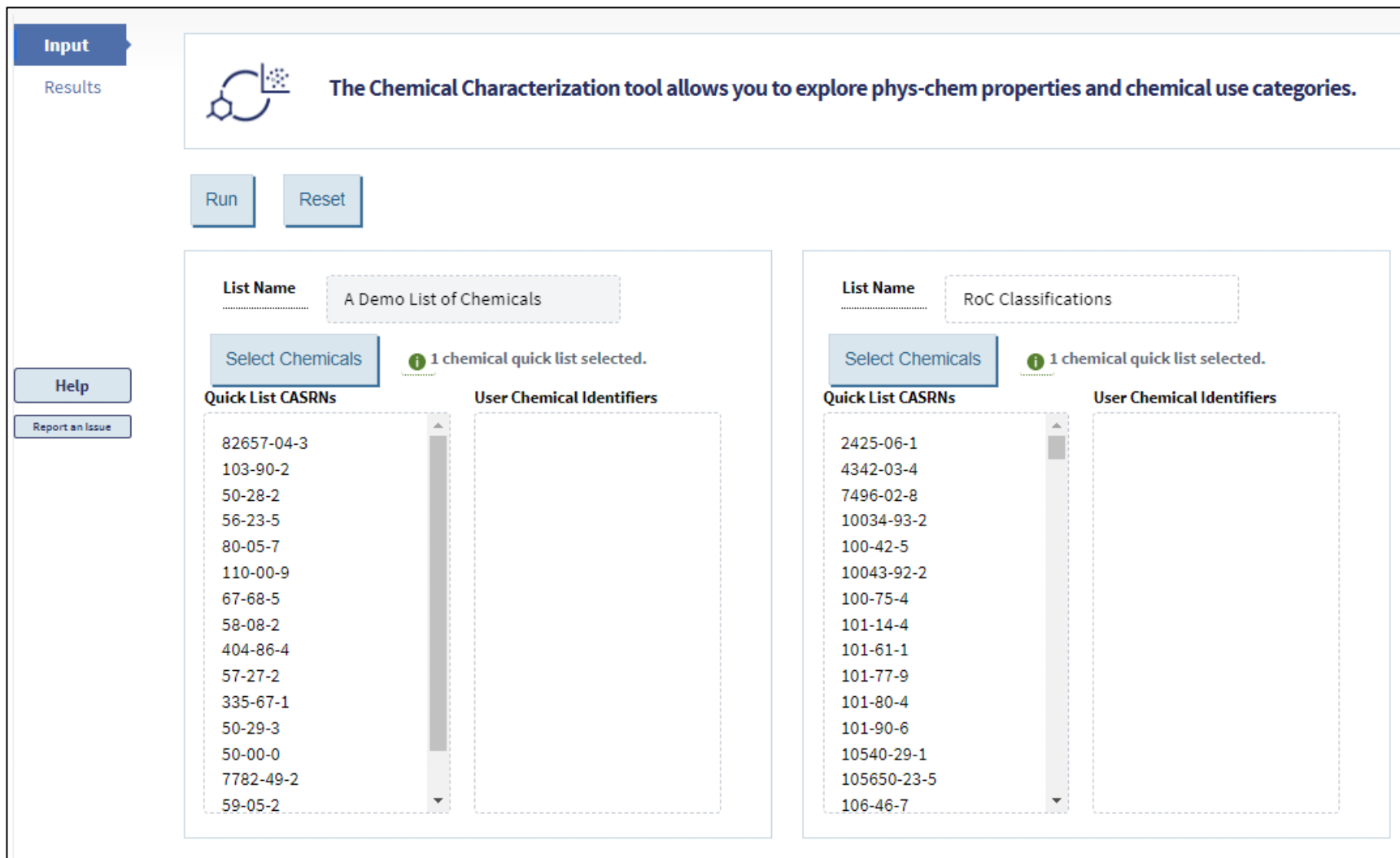


Chemical Characterization

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.

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



The screenshot shows the 'Input' section of the Chemical Characterization tool. It features a navigation menu on the left with 'Input' (selected) and 'Results'. A central banner reads: 'The Chemical Characterization tool allows you to explore phys-chem properties and chemical use categories.' Below this are 'Run' and 'Reset' buttons. The main area contains two panels for chemical lists. The left panel is titled 'A Demo List of Chemicals' and the right panel is titled 'RoC Classifications'. Both panels have a 'Select Chemicals' button and a status indicator '1 chemical quick list selected.'. Each panel has two columns: 'Quick List CASRNs' and 'User Chemical Identifiers'. The 'Quick List CASRNs' column in the left panel contains a list of 15 CASRN numbers, and the right panel contains a list of 15 RoC classification numbers. The 'User Chemical Identifiers' column in both panels is currently empty.

Input
Results

 The Chemical Characterization tool allows you to explore phys-chem properties and chemical use categories.

Run Reset

List Name A Demo List of Chemicals

Select Chemicals 1 chemical quick list selected.

Quick List CASRNs **User Chemical Identifiers**

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

List Name RoC Classifications

Select Chemicals 1 chemical quick list selected.

Quick List CASRNs **User Chemical Identifiers**

2425-06-1
4342-03-4
7496-02-8
10034-93-2
100-42-5
10043-92-2
100-75-4
101-14-4
101-61-1
101-77-9
101-80-4
101-90-6
10540-29-1
105650-23-5
106-46-7

Help
Report an Issue

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

Send filtered results to: Select tool...

Chemical List (OPERA) Predictions by Input List, CASRN



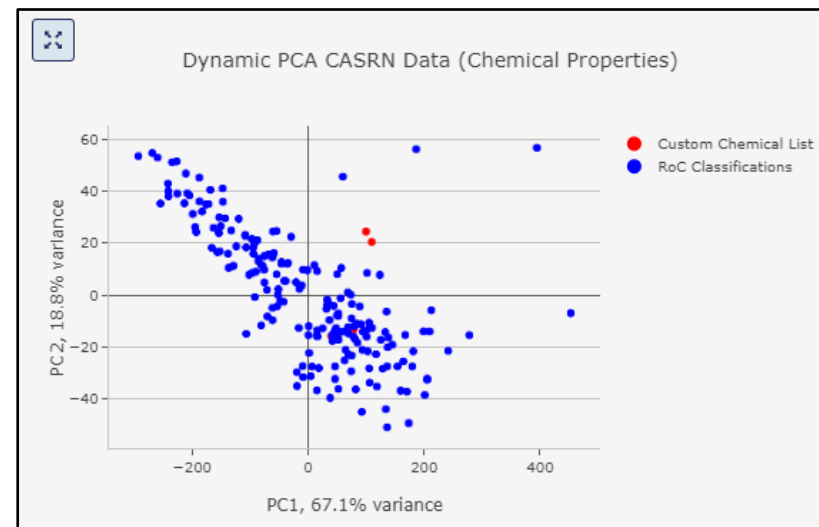
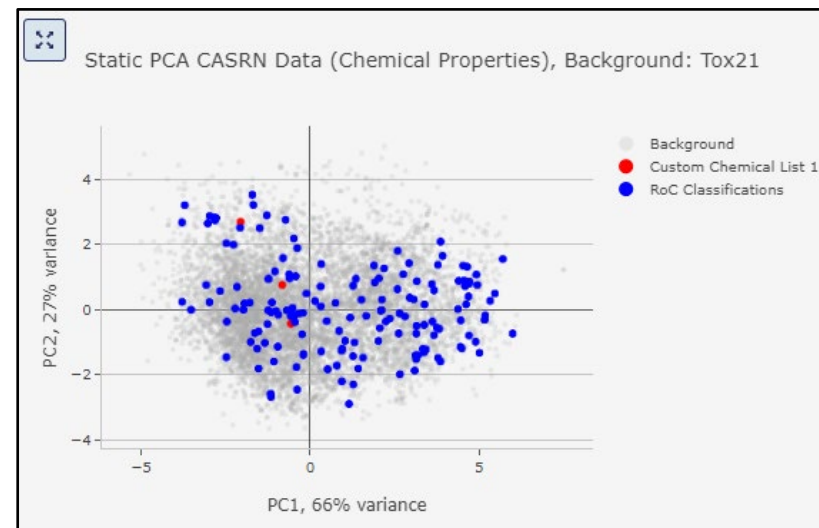
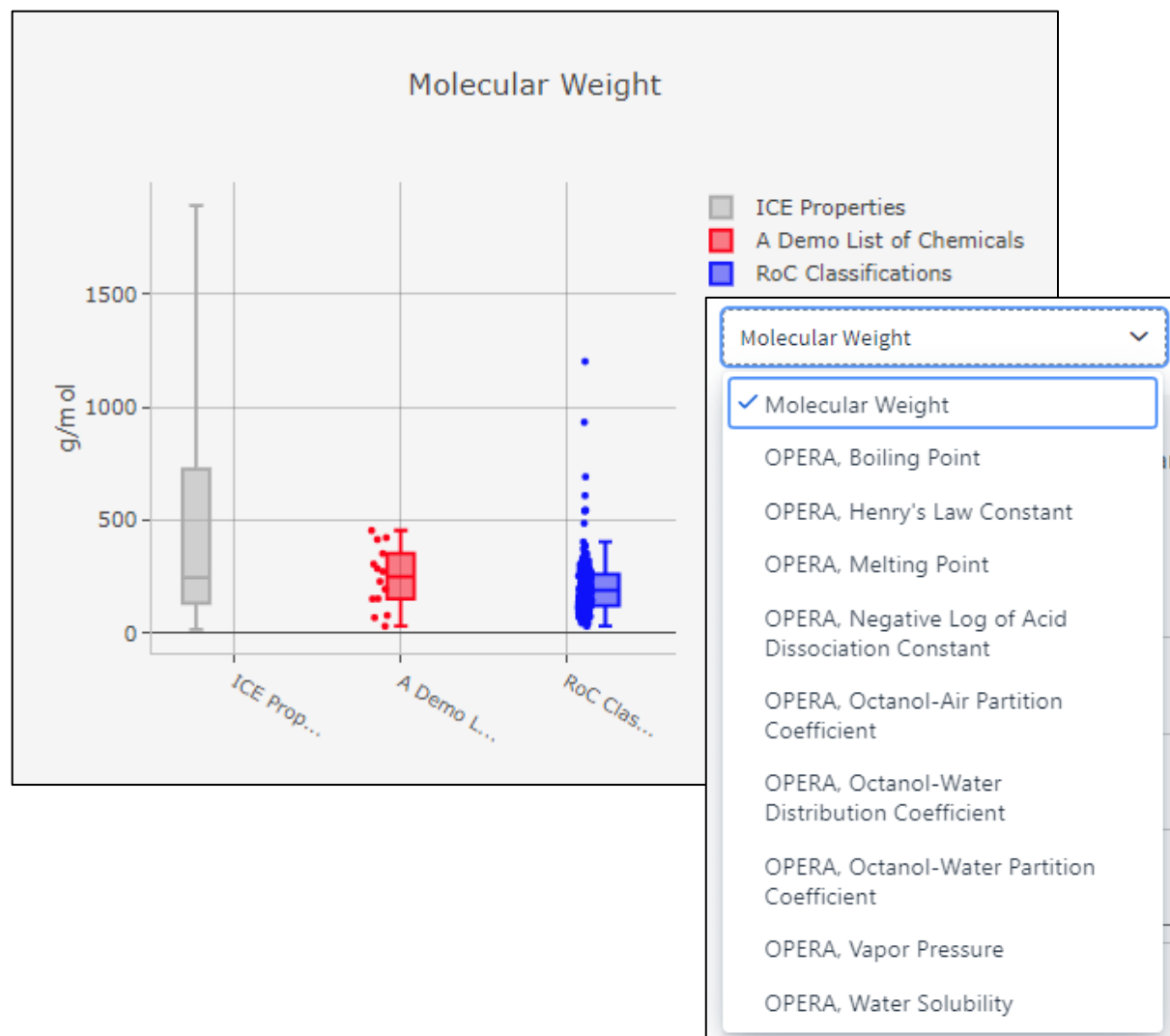
OPERA v2.8
(Mansouri et al. J Cheminform 2018)

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 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

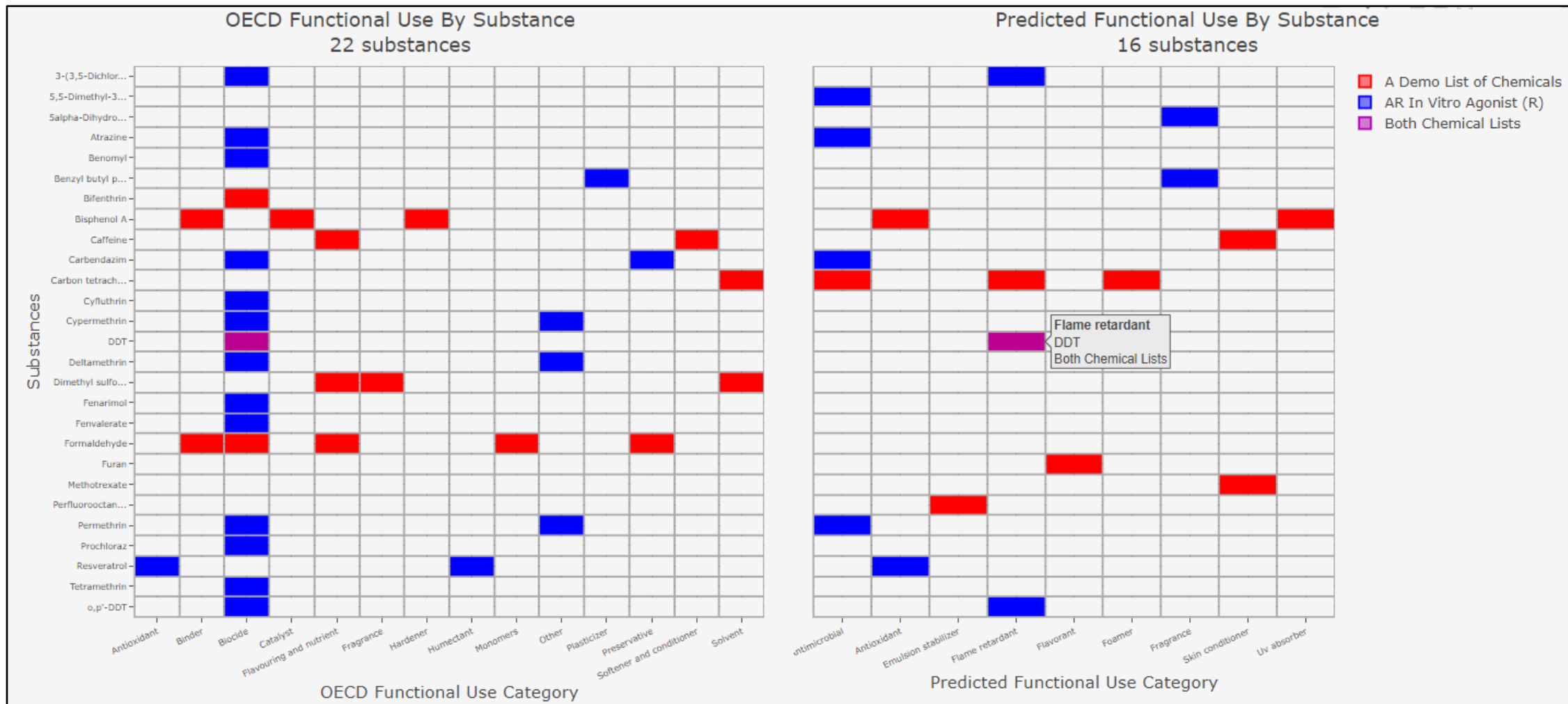
Chemical List Statistical Summary of (OPERA) Predictions

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

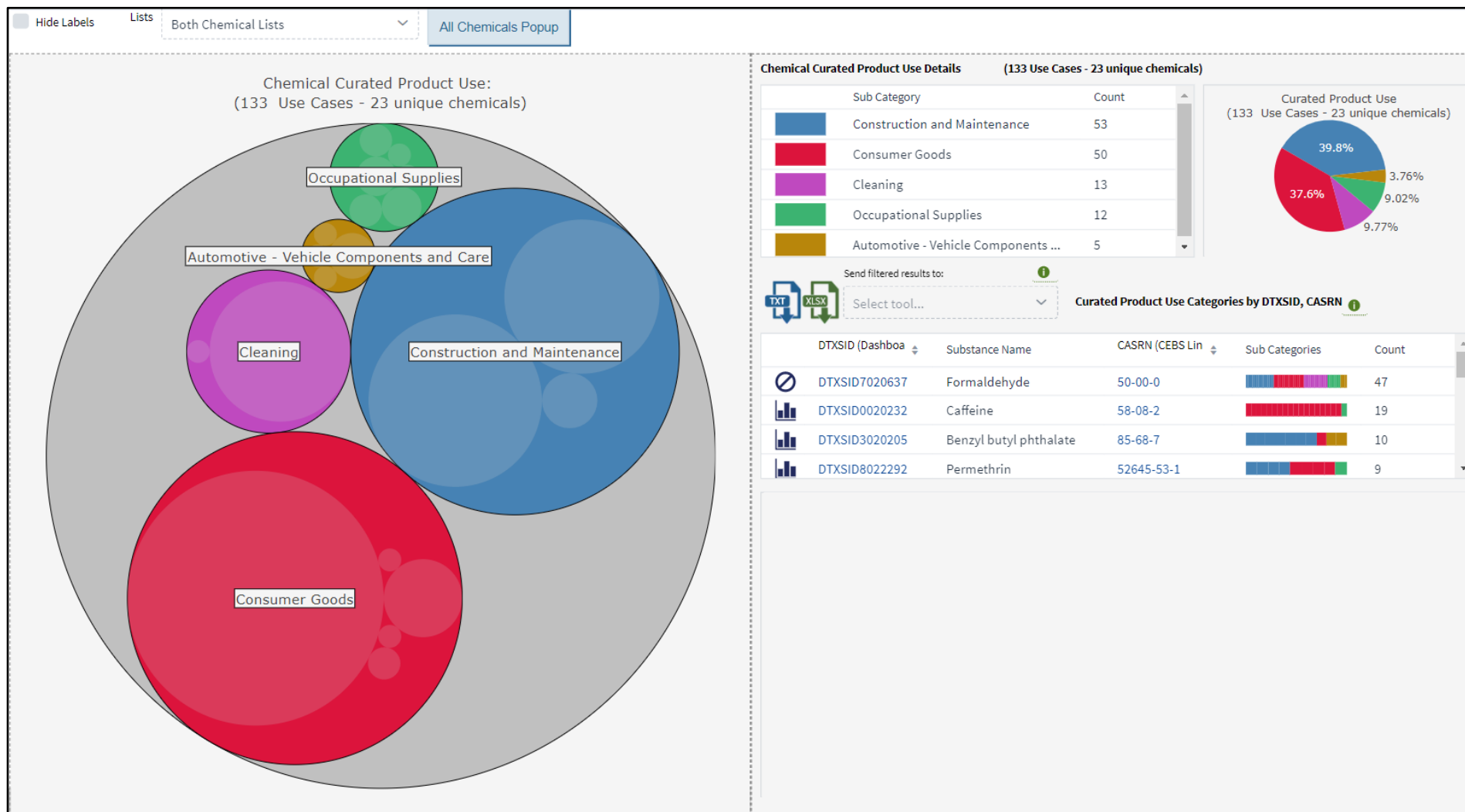
Visualize and compare chemical properties with interactive boxplots and Principal Component Analysis (PCA) plots.



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

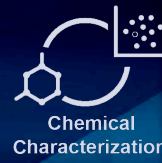


Explore potential exposure scenarios with the Curated Product Use Explorer.





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Chemical Characterization

Demo

Chemical Characterization



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

**Search**

Query ICE data and visualize results

**Chemical Quest**

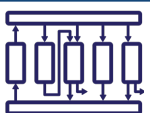
Identify similar chemicals

**Chemical
Characterization**

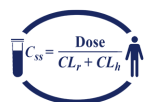
Explore chemical properties and use categories

**Curve Surfer**

Explore concentration-response curves

**PBPK**

Predict tissue-specific chemical concentrations

**IVIVE**

Predict equivalent administered dose from in vitro data



Curve Surfer

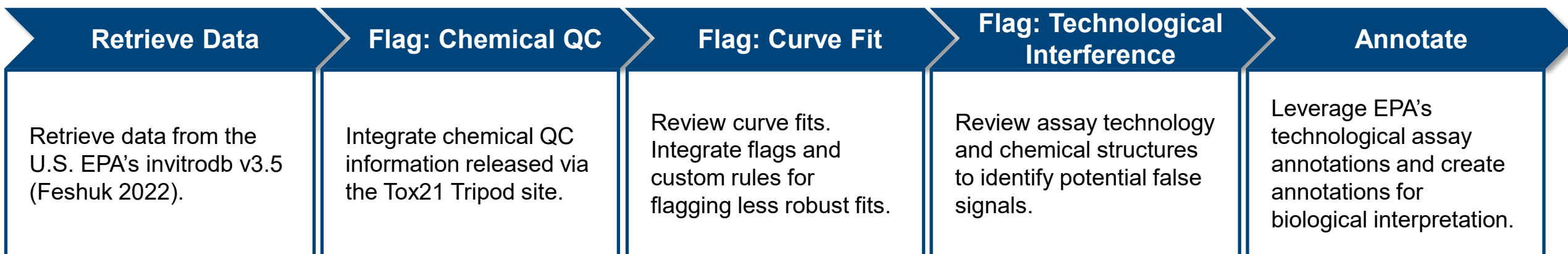
Explore concentration-response curves

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

ICE cHTS Pipeline



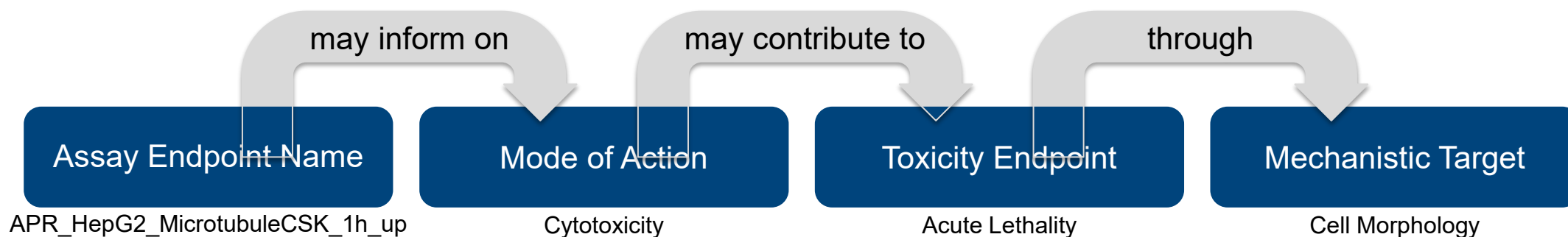
Ongoing Project: Update Pipeline with Invitrodb v4.1

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.

Chemical Input

Chemical Input

Select Chemicals 1 chemical quick list selected.

Quick List CASRNs	User Chemical Identifiers
82657-04-3	DTXSID8023892
103-90-2	82657-04-3
50-28-2	<u>Picloram</u>
56-23-5	DTXSID5032498
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	

Assay Input

Select Assays 1

cHTS | Mode of Action

<input type="checkbox"/>	1 cHTS
<input type="checkbox"/>	Malformation
<input type="checkbox"/>	Vascularization
<input type="checkbox"/>	> Cellular Process
<input type="checkbox"/>	> Cellular Stress Response
<input type="checkbox"/>	> Endocrine-Related Processes
<input type="checkbox"/>	> Energy Metabolism Process
<input type="checkbox"/>	> Epigenetic Process
<input type="checkbox"/>	> Gene Expression
<input type="checkbox"/>	> Immune and Inflammatory Response
<input type="checkbox"/>	> Neuronal Transmission
<input type="checkbox"/>	Cytochrome P450 Activity Modulation
<input type="checkbox"/>	Unannotated

Finished

Select Assays 1

cHTS | **Mode of Action**

<input type="checkbox"/>	1 Mode of Action
<input type="checkbox"/>	> Acute Lethality MOAs
<input type="checkbox"/>	> Endocrine MOAs
<input type="checkbox"/>	> Cancer MOAs
<input type="checkbox"/>	> Cardiotoxicity MOAs
<input type="checkbox"/>	CardioTox - Change in Vasoactivity
<input type="checkbox"/>	CardioTox - Change in Inotropy
<input type="checkbox"/>	CardioTox - Change in Action Potential
<input type="checkbox"/>	CardioTox - Cardiomyocyte/Myocardial Injury
<input type="checkbox"/>	CardioTox - Valvular Injury/Proliferation
<input type="checkbox"/>	CardioTox - Endothelial Injury/Coagulation
<input type="checkbox"/>	> DART MOAs

Finished

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

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

Select this item

TOX21_TSHR_HTRF_Antagonist_ratio
15663-27-1

<p>Assay: TOX21_TSHR_HTRF_Antagonist_ratio</p> <p>CASRN: 15663-27-1</p> <p>Chemical Name: Cisplatin</p> <p>AC50 (uM): 48.58</p> <p>Top of Curve: 36.55</p>	<p>Mechanistic Target: Thyrotropin-Releasing Hormone Receptor Modulation</p> <p>DTXSID: DTXSID4024983</p> <p>Winning Curve-Fit Model: Hill</p> <p>ACC (uM): 53.97</p> <p>Call: Active</p>
---	--

Select this item

TOX21_VDR_BLA_Agonist_viability
15663-27-1

<p>Assay: TOX21_VDR_BLA_Agonist_viability</p> <p>CASRN: 15663-27-1</p> <p>Chemical Name: Cisplatin</p> <p>AC50 (uM): NA</p> <p>Top of Curve: NA</p>	<p>Mechanistic Target: Cell Viability</p> <p>DTXSID: DTXSID4024983</p> <p>Winning Curve-Fit Model: Cnst</p> <p>ACC (uM): NA</p> <p>Call: Inactive</p>
--	--

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

The interface shows a 'Send filtered results to:' dropdown with options for TXT, XLSX, and PDF. Below it is a 'Select filter to add to chain:' dropdown. A pie chart displays the distribution of selected filters: 19.2% (blue) and 78.6% (red). A 'Clear Filters' button is present. A flow diagram shows the process: 'Mechanistic Target 1 selected' (44 items, 185/229 total) leads to 'Call 1 selected' (180 items, 5/185 total).

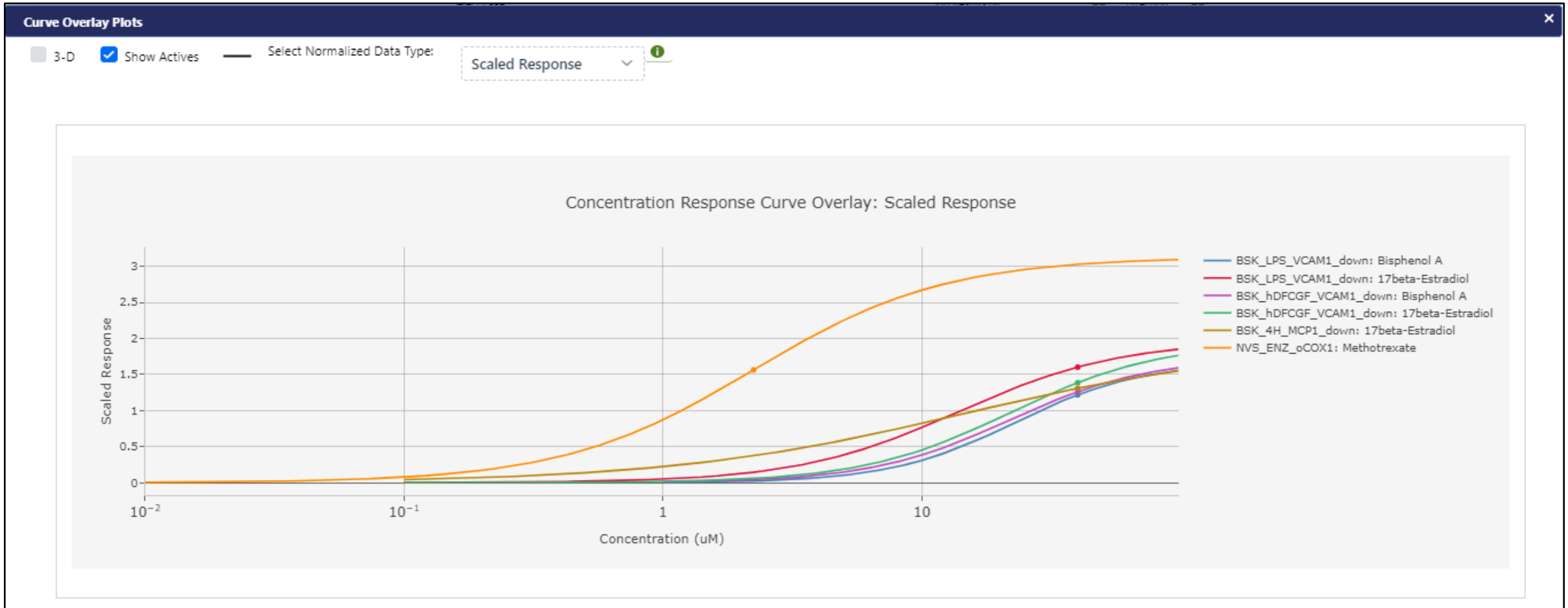
- Select filter to add to chain:
- Mechanistic Targets
 - Call
 - Assay Text
 - Assay
 - CASRN
 - Chemical Name
 - DTXSID
 - SMARTS
 - Assay Format
 - Normalized Data Type
 - AC50
 - Top of Curve
 - Technological Interference

Filtering menu displays breakdown of selected parameter.

The 'Bioactivity Call Filter' dialog box shows a table of call categories and a bar chart. The table lists: Active (5, 2.7%), Flag-Omit (4, 2.2%), Inactive (142, 76.8%), and QC-Omit (34, 18.4%). The bar chart shows the count for each category: Active (~5), Inactive (142), QC-Omit (34), and Flag-Omit (~4). The status at the bottom indicates '0 results selected of 185 (0.0%)'.

Name	Co...	Per...
Active	5	2.7%
Flag-Omit	4	2.2%
Inactive	142	76.8%
QC-Omit	34	18.4%

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/>

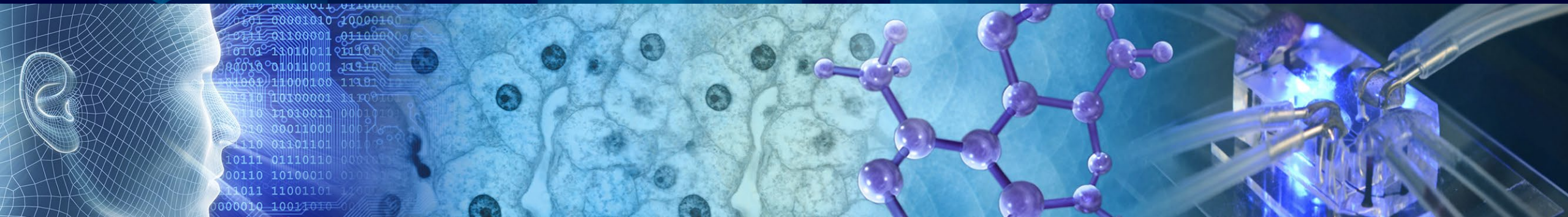


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Division of Translational Toxicology



Session Questions

Contact: ICE-support@niehs.nih.gov



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**

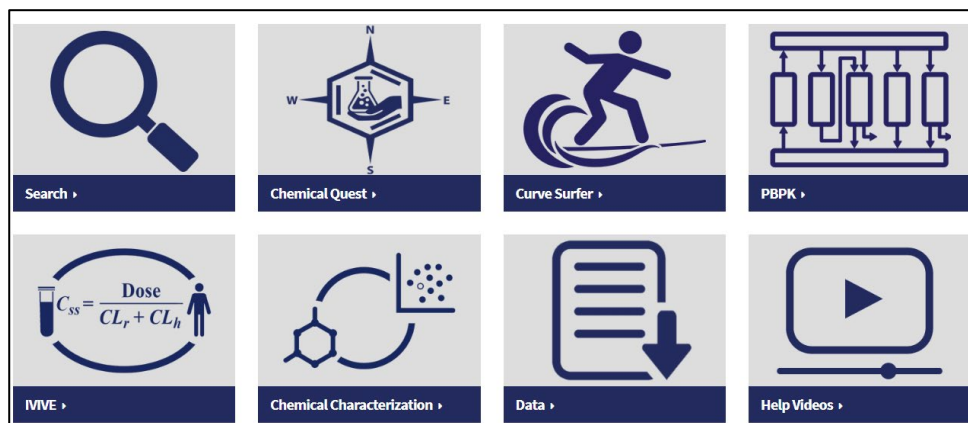
Aswani Unnikrishnan and Victoria Hull

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

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



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

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

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

Integrated Chemical Environment

Home Search **Tools** Data About **Help**

News & Events

ICE v4.0.2 Release

ICE updates include:

New resources and site improvements:

- Major updates in the data visualizations for Search tool query summary results
- Update to Curve Surfer capabilities: updated curves from cHTS invitrodb v3.5, additional flags for interference, new overlays
- Filter chain functionality added to multiple tools

Learn about ICE updates

ICE NEWS

ICE version 4.0.2 Released March 2024
Visit News page for more information.

PAUSE

ICE User Guide

- Search
- Chemical Quest
- Curve Surfer
- PBPK
- IVIVE
- Chemical Characterization
- Interactive Graphs
- Rest API

Help Videos

- ICE Help Videos
- Search Help Videos
- IVIVE Help Videos
- Curve Surfer Help Videos
- PBPK Help Videos



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

- Search
- Chemical Quest
- Curve Surfer
- PBPK
- IVIVE
- Chemical Characterization
- Data
- Help Videos

**Search**

Query ICE data and visualize results

**Chemical Quest**

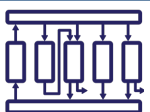
Identify similar chemicals

**Chemical
Characterization**

Explore chemical properties and use categories

**Curve Surfer**

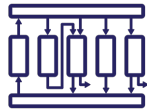
Explore concentration-response curves

**PBPK**

Predict tissue-specific chemical concentrations

**IVIVE**

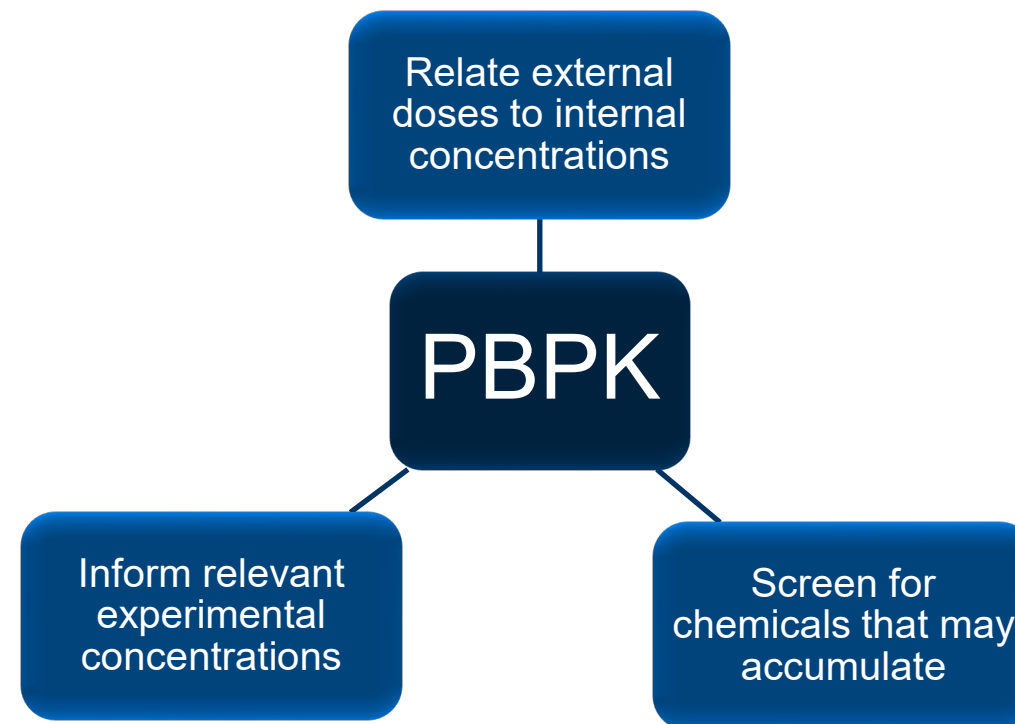
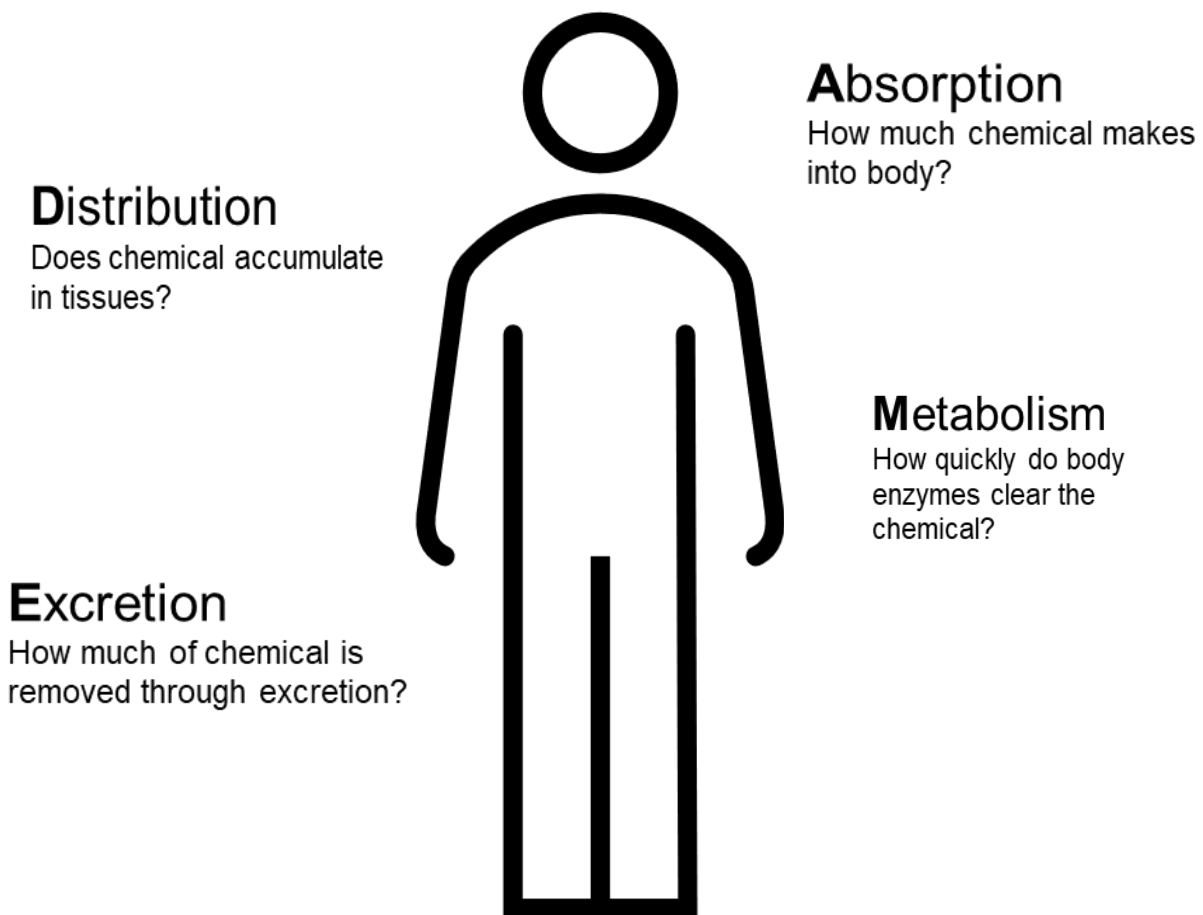
Predict equivalent administered dose from in vitro data

**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 htk R package (Pearce et al., 2017) with user-selected model parameters to predict chemical disposition over time.

What is PBPK modeling?




Customizable Model Parameters

Chemical Input

Chemical Quest | Curve Surfer | **PBPK** | IVIVE | Chemical Characterization

Input
 Results


PBPK tool allows you to generate predictions of tissue-specific chemical concentration profiles following a dosing event

Run | Reset | Species: human, Body Weight: 70.0, ADME Source: Default, Model: Solve_pbt~~k~~, Exposure Route: iv, Exposure Interval: 24 Hours, Simulation Length: 3 Days, Output Conc. Units: uM

Species i <input type="text" value="human"/>	Exposure Route i <input type="text" value="iv"/>
Body Weight i <input type="text" value="70"/>	Exposure Interval, Hours i <input type="text" value="24"/>
ADME Source i <input type="text" value="Default"/>	Exposure Length, Hours i <input type="text" value="NA"/>
Exposure Dose i <input type="text" value="1.0"/>	Simulation Length, Days i <input type="text" value="3"/>
Gestational Day when Exposure Starts i <input type="text" value="91"/>	Output Conc. Units i <input type="text" value="uM"/>
Model i <input type="text" value="Solve_pbtk"/> <ul style="list-style-type: none"> <input checked="" type="checkbox"/> Solve_pbtk <input type="checkbox"/> Solve_gas_pbtk <input type="checkbox"/> Solve_fetal_pbtk 	Inhalation Dosing Method i <input type="text" value="Concentration"/>
<small>max from the US EPA htk package. For details see</small>	Inhalation Dosing Units i <input type="text" value="ppmv"/>

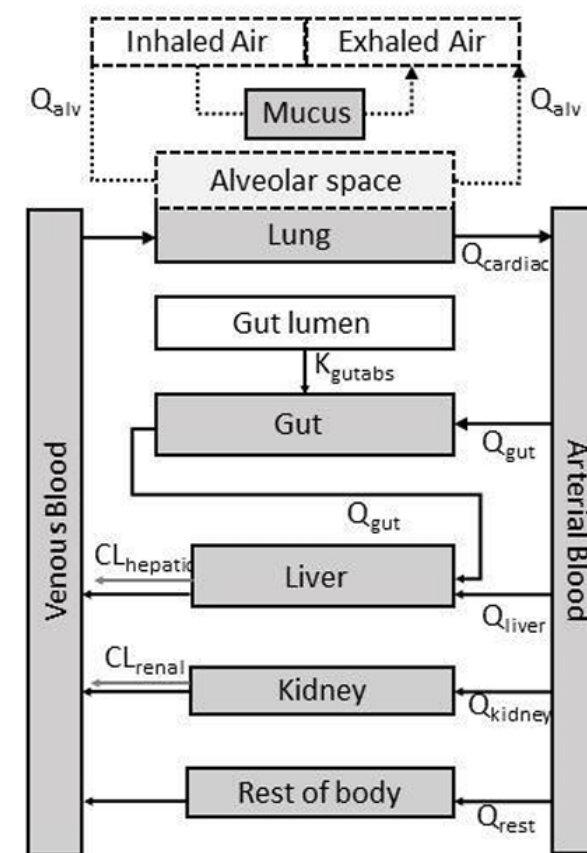
Chemical Input
 Select Chemicals i 1 chemical quick list selected.

Quick List CASRNs <input type="text" value="82657-04-3"/> <input type="text" value="103-90-2"/> <input type="text" value="50-28-2"/> <input type="text" value="56-23-5"/> <input type="text" value="80-05-7"/> <input type="text" value="110-00-9"/> <input type="text" value="67-68-5"/> <input type="text" value="58-08-2"/> <input type="text" value="404-86-4"/> <input type="text" value="57-27-2"/> <input type="text" value="335-67-1"/> <input type="text" value="50-29-3"/> <input type="text" value="50-00-0"/> <input type="text" value="7782-49-2"/> <input type="text" value="59-05-2"/>	User Chemical Identifiers <input type="text"/>
---	--



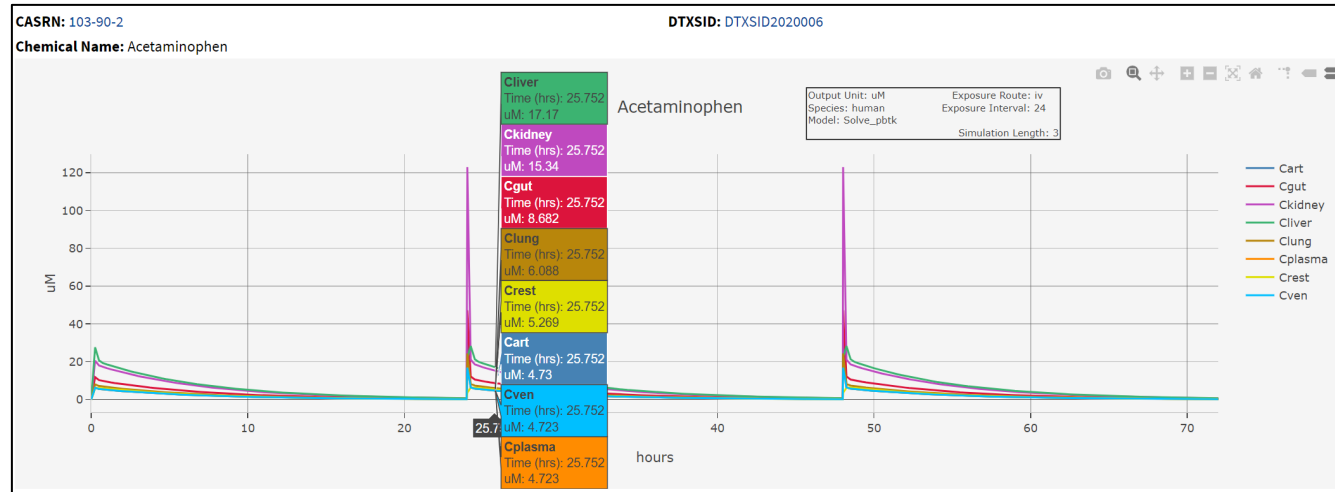
- Three PK models are available for calculating plasma concentrations in tissues
 - Solve_pbt^{*}: Multi-compartment model that estimates plasma C_{max} following oral or IV exposure
 - Solve_gas_pbt^{*}: Multi-compartment model that estimates plasma C_{max} following inhalation (gas) exposure
 - Solve_fetal_pbt^{*}: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

Structure of the solve_gas_pbt^{*} model



Concentration Time Series Plots

Filtering Options

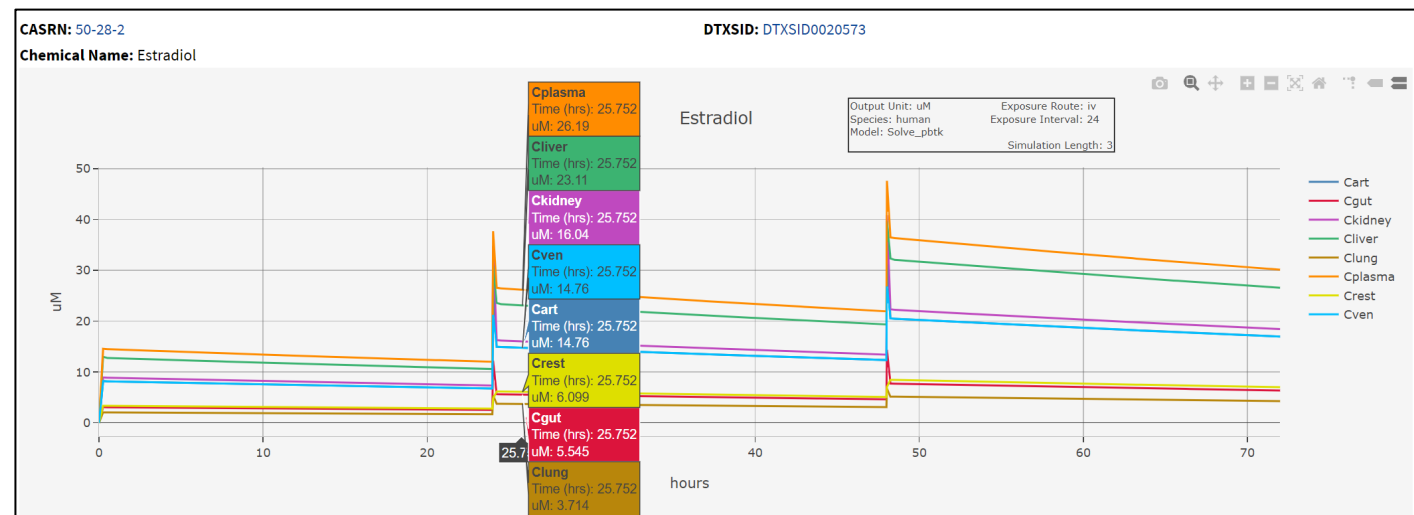


Select Page i

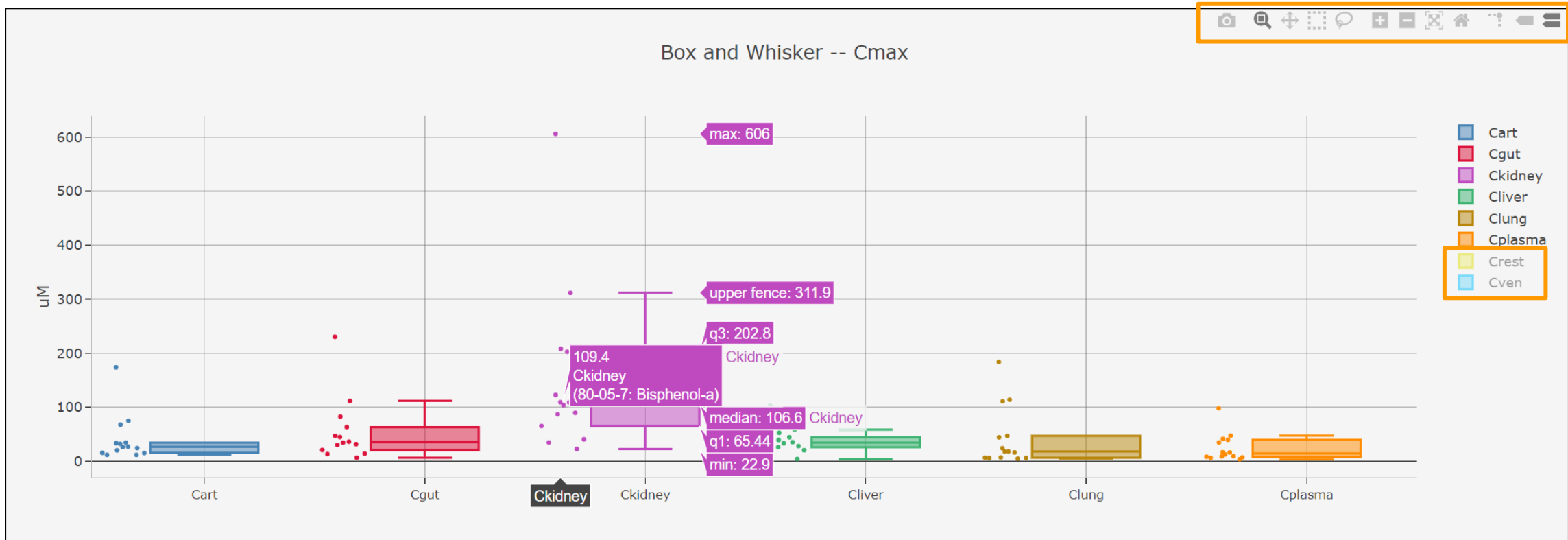
← 1 of 3 → Showing 1-5 of 14 curves.

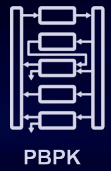
Select Compartment(s) i
Choose..

Select CASRN(s) i
Choose..



Visualize Cmax Distribution





Demo

Exploring ICE PBPK Tool



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

**Search**

Query ICE data and visualize results

**Chemical Quest**

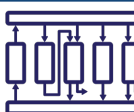
Identify similar chemicals

**Chemical
Characterization**

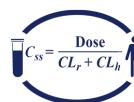
Explore chemical properties and use categories

**Curve Surfer**

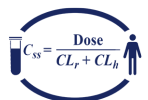
Explore concentration-response curves

**PBPK**

Predict tissue-specific chemical concentrations

**IVIVE**

Predict equivalent administered dose from in vitro data


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

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.

Customizable Model Parameters and Selection Criteria

Chemical and Assay Input

The IVIVE tool uses pharmacokinetic models to predict the equivalent administered dose (EAD) from the activity concentration of selected assays.

Run Reset

In Vitro Endpoint: ACS0, Species: human, Body Weight: 70.0, ADME Source: Default, Gestational Days when Exposure Starts: 91.0, Model: Solve_fetal_pbtck, Exposure Route: iv, Exposure Interval: 24.0 Hours, Simulation Length: 1.0 Day

In Vitro Endpoint: ACS0

Species: human

Body Weight: 70

ADME Source: Default

Gestational Day when Exposure Starts: 91

Model: Solve_fetal_pbtck

Exposure Route: iv

Exposure Interval, Hours: 24

Exposure Length, Hours:

Simulation Length, Days: 1

Inhalation Dosing Method: Concentration

Inhalation Dosing Units: ppmv

1C
Solve_pbtck
Solve_3comp
Solve_gas_pbtck
✓ Solve_fetal_pbtck

Upload Custom In Vivo or Exposure Data to Overlay on Charts

Chemical Input

Select Chemicals 1 chemical quick list selected.

Quick List CASRNs

- 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

User Chemical Identifiers

Select Assays 1

cHTS Mode of Action

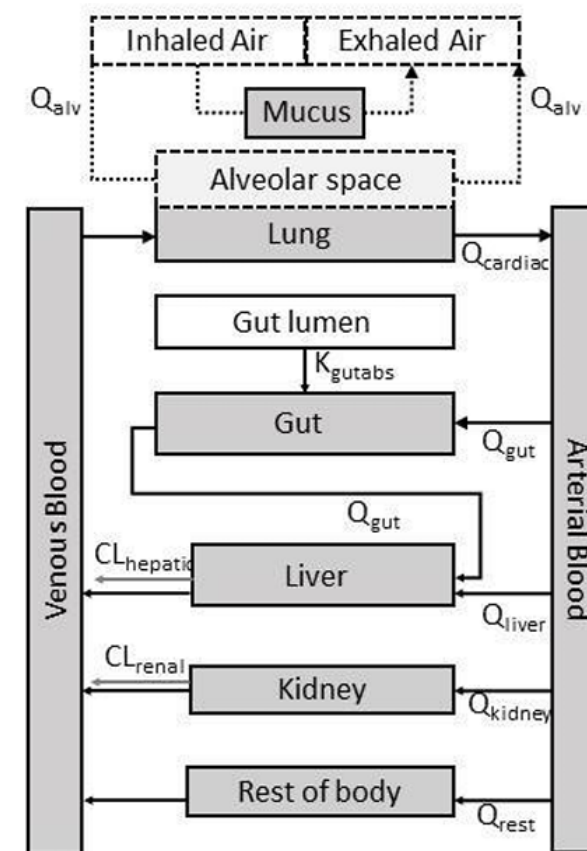
- cHTS
- Malformation
- Vascularization
- Cellular Process
- Cellular Stress Response
- Endocrine-Related Processes
- Energy Metabolism Process
- Epigenetic Process
- Gene Expression
- Immune and Inflammatory Response
- Neuronal Transmission
- Cytochrome P450 Activity Modulation
- Unannotated

Finished



- 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_pbtck*: Multi-compartment model that estimates plasma C_{max} following oral or IV exposure
 - Solve_gas_pbtck*: Multi-compartment model that estimates plasma C_{max} following inhalation (gas) exposure
 - Solve_fetal_pbtck*: Multi-compartment model that estimates maternal and fetal plasma C_{max} following oral or IV exposure

Structure of the solve_gas_pbtck model



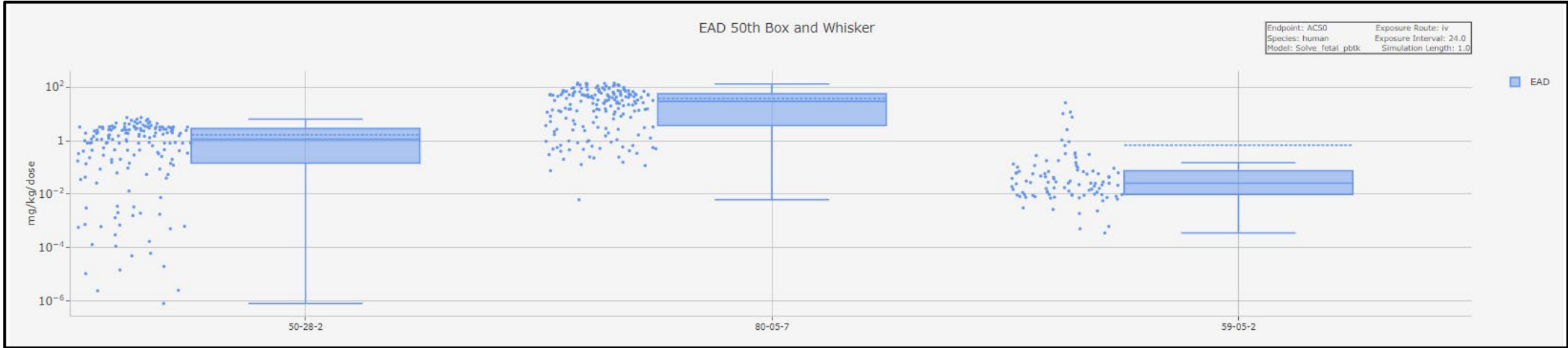
View summary results, including AC50 and Equivalent Administered Dose (EAD) for each assay and chemical.

Send filtered results to: TXT XLSX **Number of rows = 795** **Number of substances = 10** [Chemical Identifiers Not Returned By Query \(6\)](#)

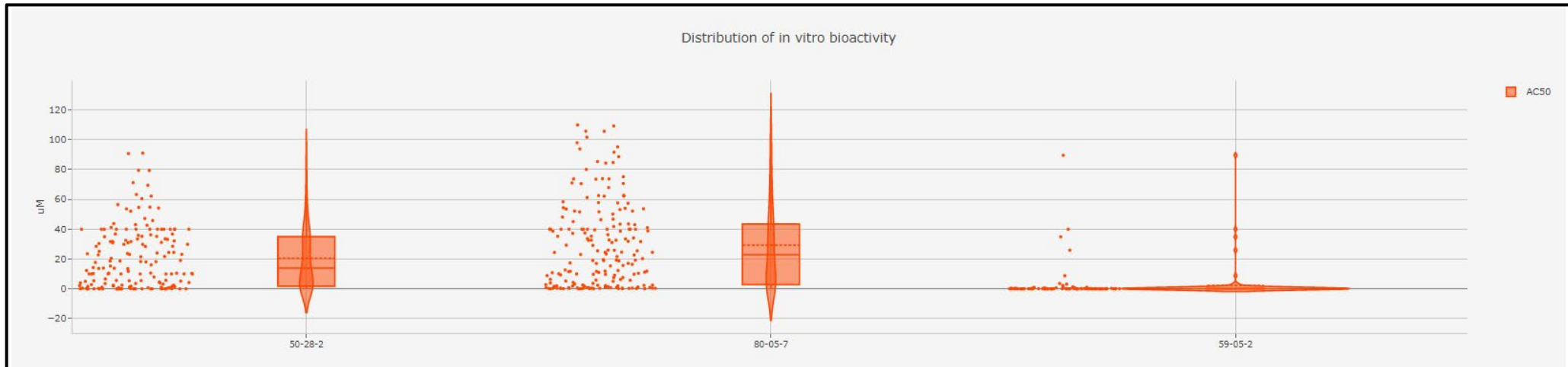
Chemical	CASRN (CEBS Link)	DTXSID (Dashboard)	Flag	Assay	Mode of Action	Mechanistic Targets	AC50 ...	EAD 50th Percentile...	EAD FMax 50t...
17beta-Estradiol	50-28-2	DTXSID0020573	fu is zero,li...	CEETOX_H...	DART - Steroid H...	Progestogen Biosynth...	2.465	0.0766	0.0727353201...
17beta-Estradiol	50-28-2	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

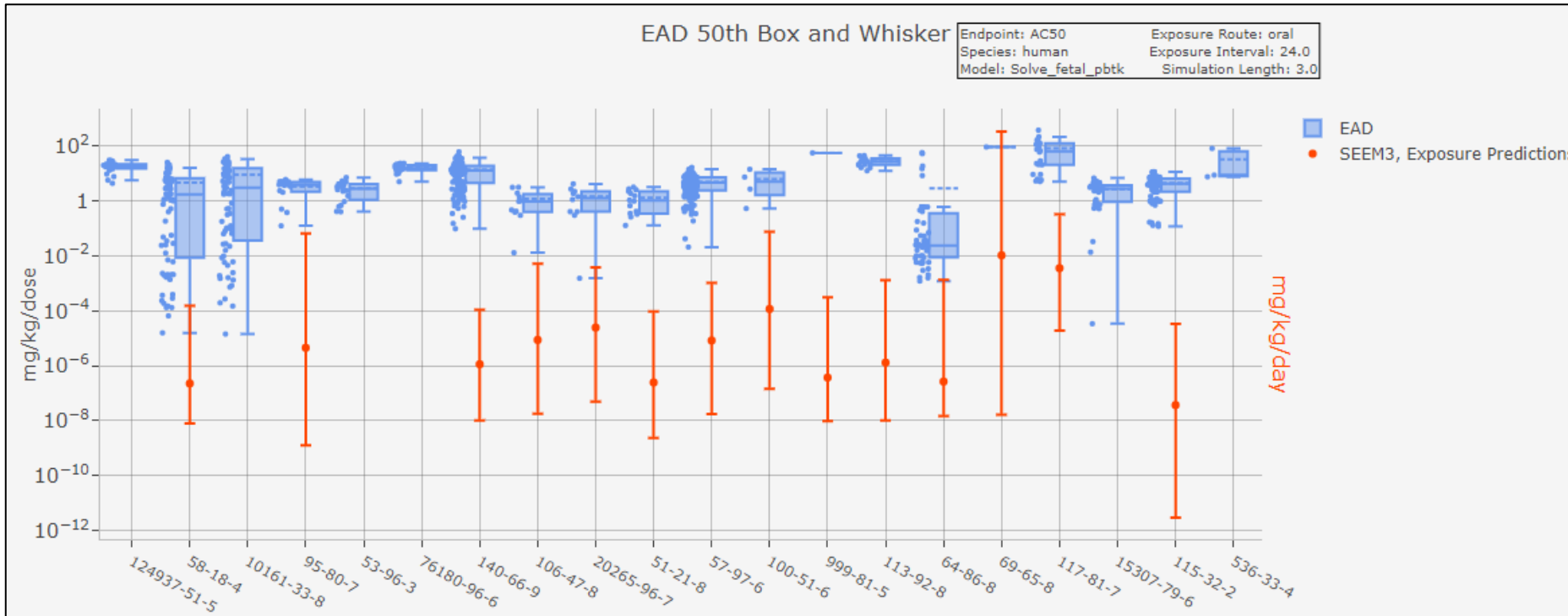
Visualize EAD for input chemicals using boxplots.



Violin plots show distribution of in vitro bioactivity.



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

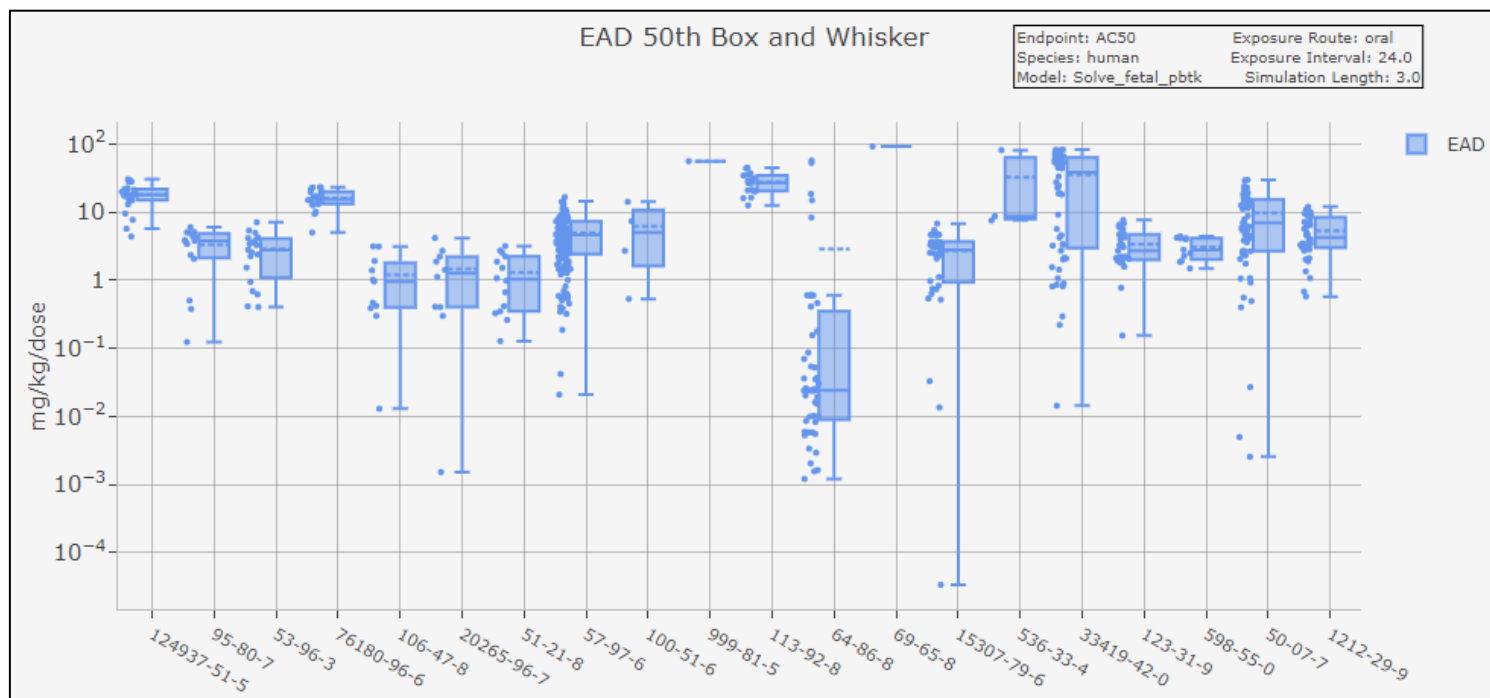


Select in vivo data or exposure data to display. ⓘ

Exposure Predictions ▾

- Estrogen Modulation (Uterotrophic LEL)
- Acute Lethality (Acute Oral Toxicity Assay LD50)
- Androgen Modulation (Hershberger, rat agonist LEL)
- Androgen Modulation (Hershberger, rat antagonist LEL)
- Exposure Predictions
- dataset 2
- dataset 3
- dataset 1

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



Run IVIVE Using Custom Data

Chemical Input

Select Chemicals 1 chemical quick list selected.

Quick List CASRNs

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
15663-27-1

User Chemical Identifiers

Data Input

Select Data Sets 1

Data Set	Description	Data Type
<input checked="" type="checkbox"/>	Angiogenic Process	cHTS in vitro

Upload Custom In Vivo or Exposure Data to Overlay on Charts 1

Upload Drop file here

Uploaded Files

File Name	MIME Type

Upload Custom In Vitro Data 1

Upload Drop file here

Uploaded Files

File Name	MIME Type

Upload Custom In Vivo Data ✕

To overlay user in vivo data on Results plots, click "Upload." Supported file types: comma-delimited (csv), plain text (txt), and Excel (xlsx). To view example templates of data formats, click the links below.

[Template File for In Vivo Overlay \(Text\)](#)
[Template File for In Vivo Overlay \(Excel\)](#)

Close

Upload Custom In Vitro Data ✕

To load user assay data into your model, click "Upload." Supported file types: comma-delimited (csv), plain text (txt), and Excel (xlsx). To view example templates of data formats, click the links below.

[Template In Vitro Assay File for IVIVE \(Text\)](#)
[Template In Vitro Assay File for IVIVE \(Excel\)](#)

Close

In Vivo Data Template

casn	dtxsid	chem name	dataset	assay1	assay2	assay3	assay4	assay5	assay6	assay7	assay8	assay9	assay10
115-32-2	dtxsid1	17-Methyltestosterone	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-Trenbolone	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-Methyltestosterone	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-Trenbolone	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-Methyltestosterone	dataset 3	987	234	23	567	775	445	7878	123	456	

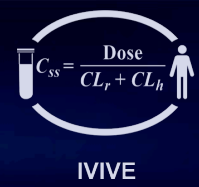
In Vitro Data Template

casn	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.

File Name	Commit Message	Time Ago
.Rhistory	ICE 3.3 release	3 years ago
CalcEAD.R	Add files via upload	5 years ago
ChemicalData_Rnotebook.txt	ICE 4.0.1 release	5 months ago
EADboxplot.R	Add files via upload	9 months ago
ICE_IVIVE.Rmd	ICE 4.0.1 release	9 months ago
ICE_IVIVE.html	ICE 4.0.1 release	9 months ago
ICE_IVIVE.pdf	ICE 3.5 release	3 years ago
ICE_PBPK.Rmd	ICE 4.0.1 release	9 months ago
ICE_PBPK.html	ICE 4.0.1 release	9 months ago
ICE_PBPK.pdf	ICE 3.5 release	3 years ago



Demo

Exploring ICE IVIVE Tool



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

ICE Summary



ICE Data

- 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.



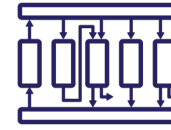
Search



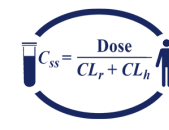
Chemical Quest

Chemical
Characterization

Curve Surfer



PBPK

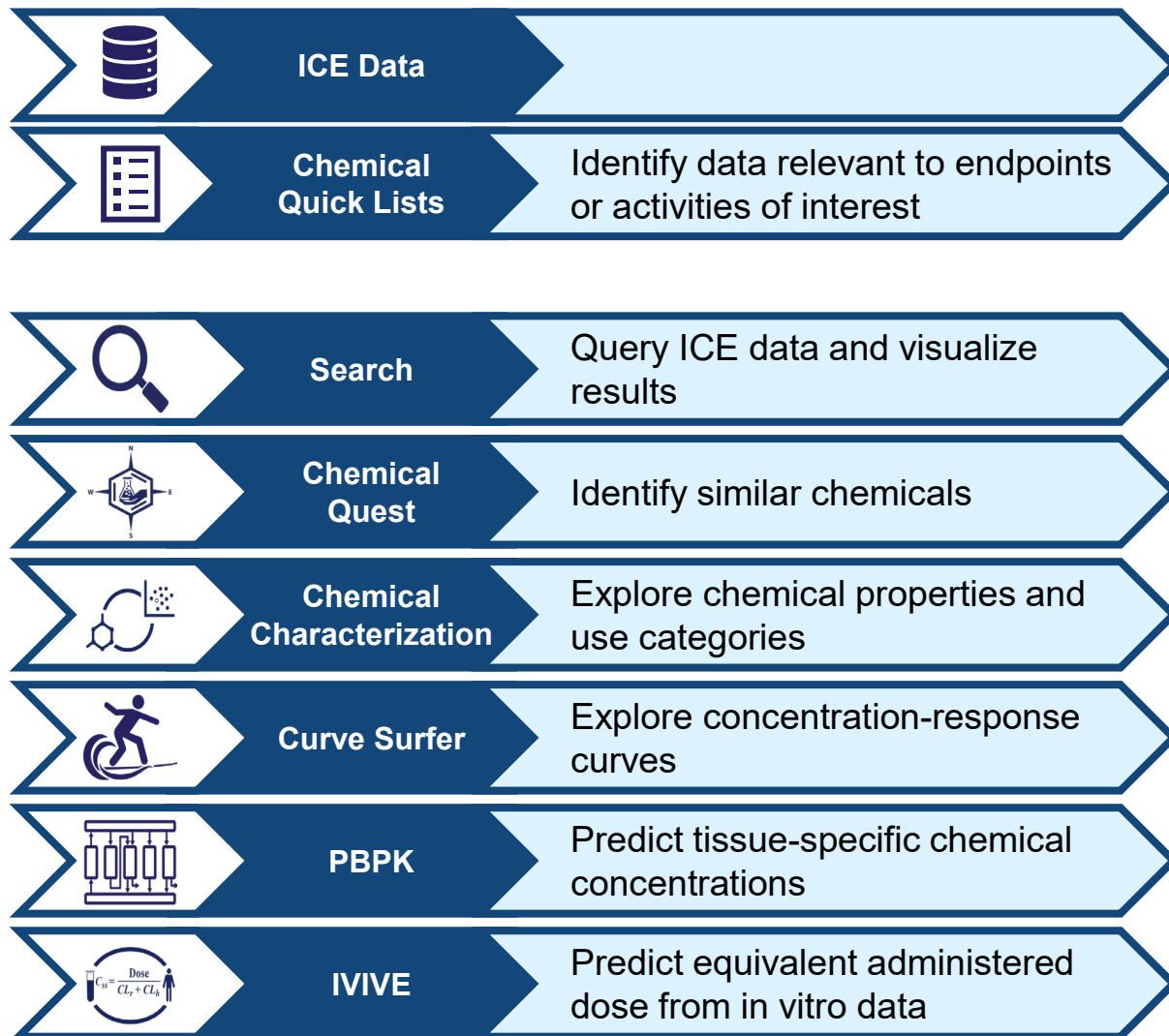


IVIVE

- 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



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!

The NICEATM Group



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Questions & Feedback

Contact: ICE-support@niehs.nih.gov