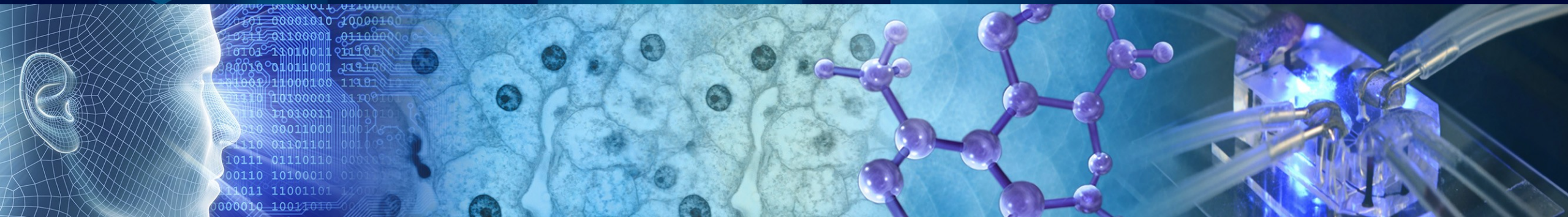




National Institute of
Environmental Health Sciences
Division of Translational Toxicology



Updates to the Integrated Chemical Environment (ICE)

Kamel Mansouri, PhD

NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)

SACATM 2025



ice.ntp.niehs.nih.gov

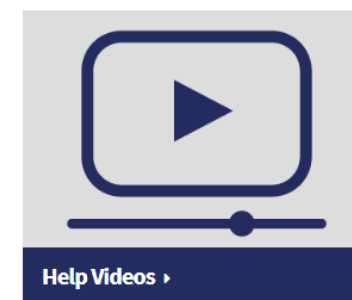
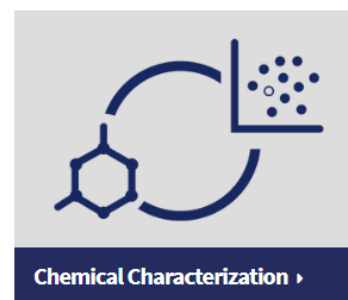
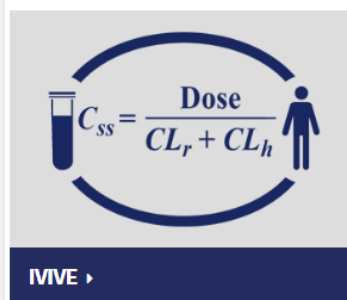
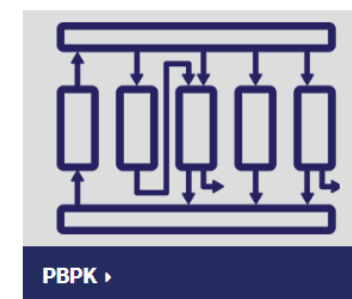
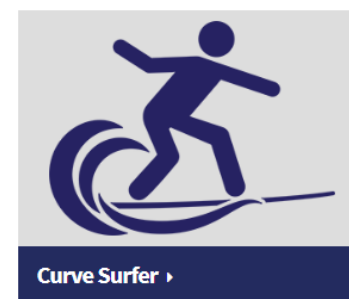
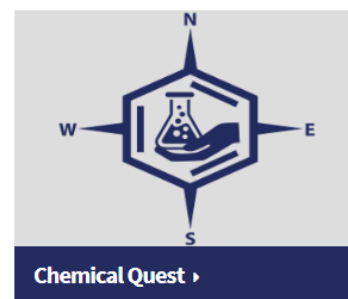
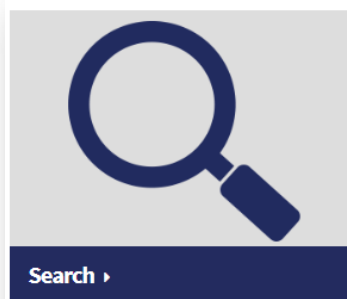
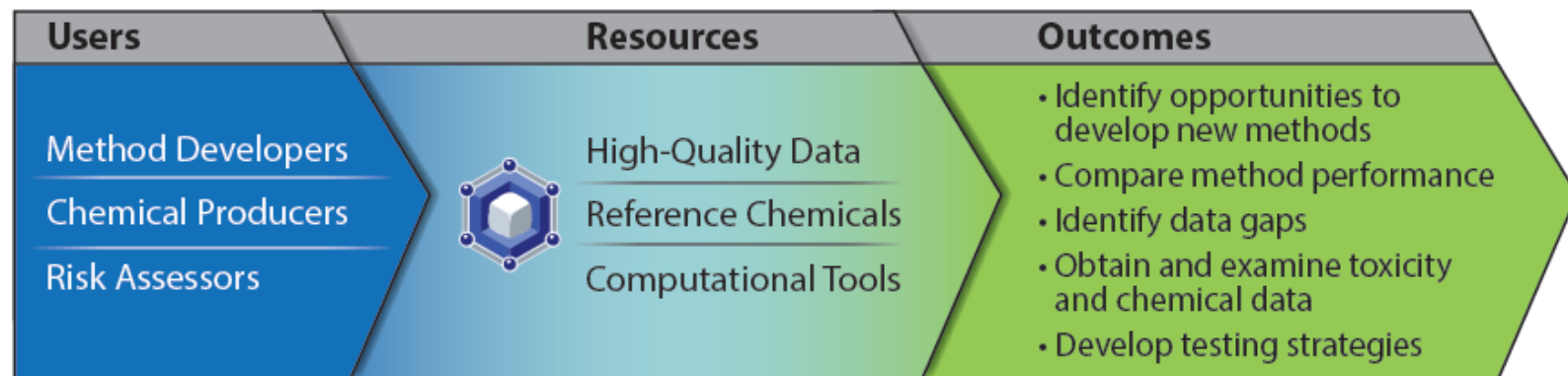
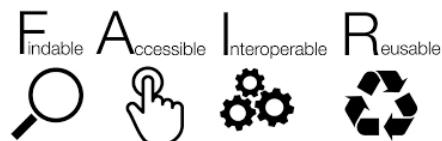
- Overview of the Integrated Chemical Environment (ICE)
- Data and updates
- Tools and updates
- Ongoing work and future enhancements



Integrated Chemical Environment

- Curated *in vivo* and *in vitro* test data
- *In silico* toxicity predictions and chemical property data
- Reference and non-reference chemical lists
- Computational tools for chemical characterization and predicting toxicity

Releases in 2025:
ICE v4.1.1 (February)
ICE v4.2 (July)



In Vivo and In Vitro Data

- ICE includes in vivo and in vitro assay data curated from literature, validation studies, and databases for toxicity endpoints of regulatory concern.

Toxicity Endpoint	In Vivo	In Vitro	# of Chemicals
Acute Lethality (Oral, Dermal, Inhalation)	x		11168
Cancer ¹	x	x	3038
DART	x		628
Eye Irritation and Corrosion	x	x	455
Endocrine	x	x	1940
Skin Irritation and Corrosion	x	x	564
Skin Sensitization	x	x	1818

¹Cancer data also include weight of evidence data from various agencies

Curated High-Throughput Screening Data

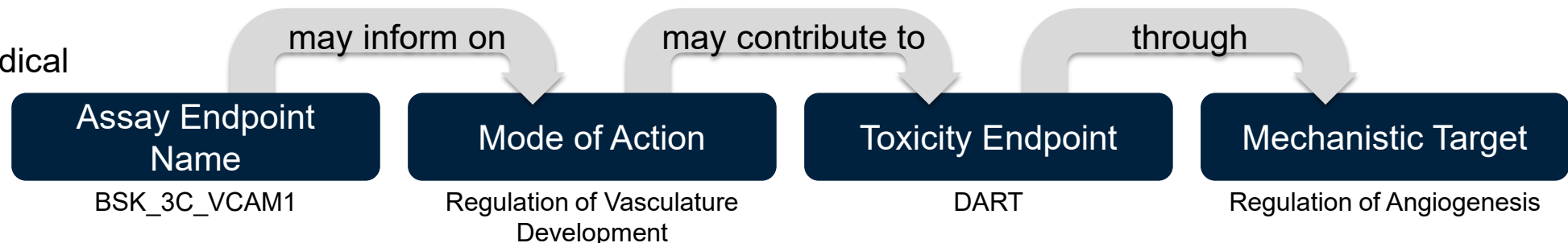
- ICE's curated high-throughput screening (cHTS) data set contains data from the U.S. federal Tox21 collaboration and EPA's ToxCast program for ~10000 chemicals.
- ICE cHTS data align with the EPA's invitrodb.

Updated in
ICE v4.2



Knowledge Organization Structure

Open Biological and Biomedical
Ontology (OBO) Foundry
(<http://obofoundry.org/>).



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-Relevant Data

Endpoint	# of Chemicals
Exposure Predictions (Ring 2019. Environ Sci Technol)	479,791
Curated Product Use Categories (Isaacs 2020. J Expo Sci Environ Epidemiol)	4893
Reported Functional Use Categories	9395
Predicted Functional Use Categories (Phillips 2017. Green Chem)	~200000

Chemical Taxonomy

New in ICE v4.1.1

- ClassyFire Chemical Taxonomy download
 - A structure-based, automated chemical taxonomy developed by the Wishart Research group at the University of Alberta (Djoumbou Feunang et al. 2016).
 - Download contains chemical taxonomies for over one million chemicals.
 - There are 4825 classifications across 11 hierarchical levels.

Hierarchical Level	Classifications
Level 1: Kingdom	organics and inorganics
Level 2: SuperClass	26 organic and 5 inorganic categories
Level 3: Class	764 categories
Level 4: SubClass	1729 categories
Level 5-11	2296 additional categorizations prioritized in order of chemical weight

Chemical Quick Lists

- Chemical quick lists can be used to populate queries across ICE tools.
 - Reference chemical lists comprise chemicals that cause a specified, well-characterized biological effect.
 - Non-reference chemical lists have less restrictive inclusion criteria.

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

Non-reference Chemical Lists	
AR In Vivo Agonist	Mixtures and Formulations in ICE
AR In Vivo Antagonist	NTP Cancer Bioassay Chemicals
EPA Pesticide Active Ingredients	RoC Classifications
EPA Pesticide Inert Ingredients, Food and Nonfood Use	Steroidogenesis - Androgen
EPA PFAS Master List V2	Steroidogenesis - Estrogen
EPA IRIS Cancer Assessment	Thyroid
EPA IRIS Non-Cancer Assessment	Tox21*
IARC Classifications	ToxCast Phase I, Phase II, & e1k

***Updated in ICE v4.2 to align with U.S. EPA's invitrodb v4.2**

The **Search** tool enables users to query the ICE data by specifying chemicals and/or data sets.

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 identical QS

User Chemical Identifiers

DTXSID8023892
82657-04-3
Picloram
DTXSID5032498

Select one or more chemical quick lists.

Select All Deselect All Finished

	Name	
☐		
☐	A Demo List of Chemicals	
☐	AR In Vitro Agonist (R)	
☐	AR In Vitro Antagonist (R)	
☐	AR In Vivo Agonist	

New in ICE v4.2 (all tools):
Feature to search for quick list name in chemical input

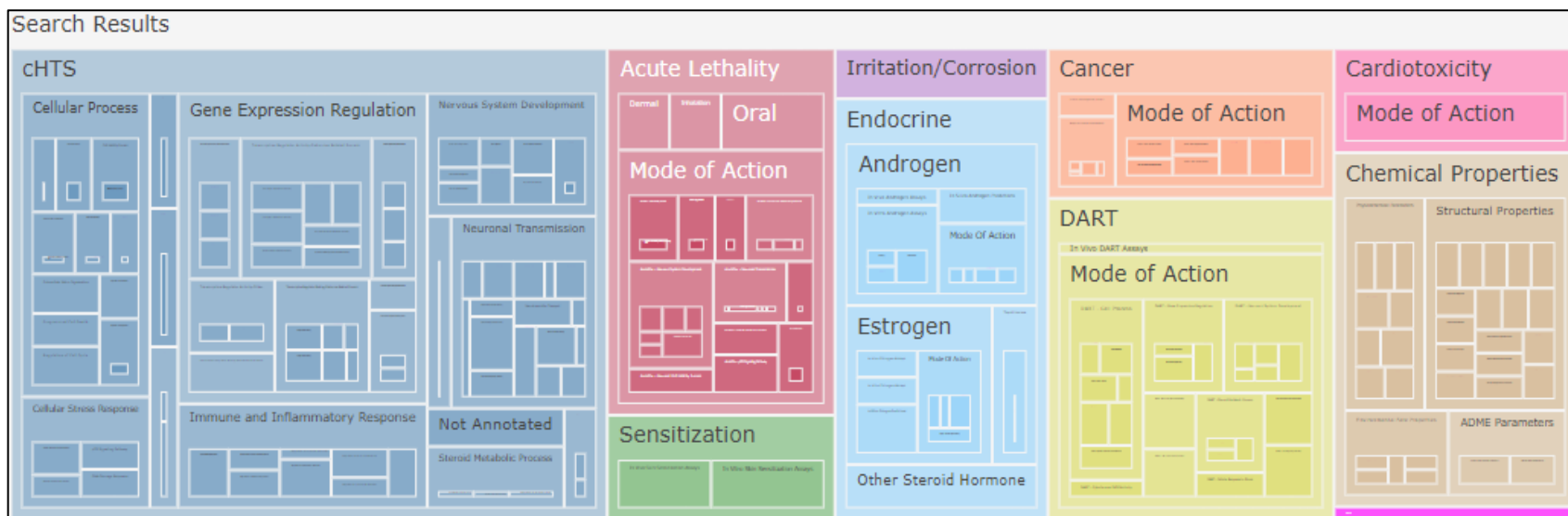
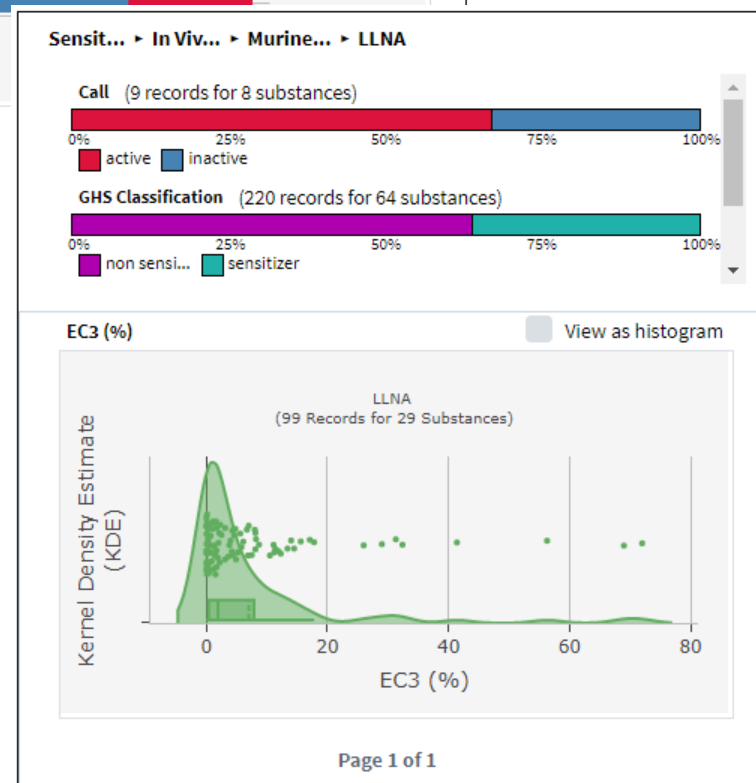
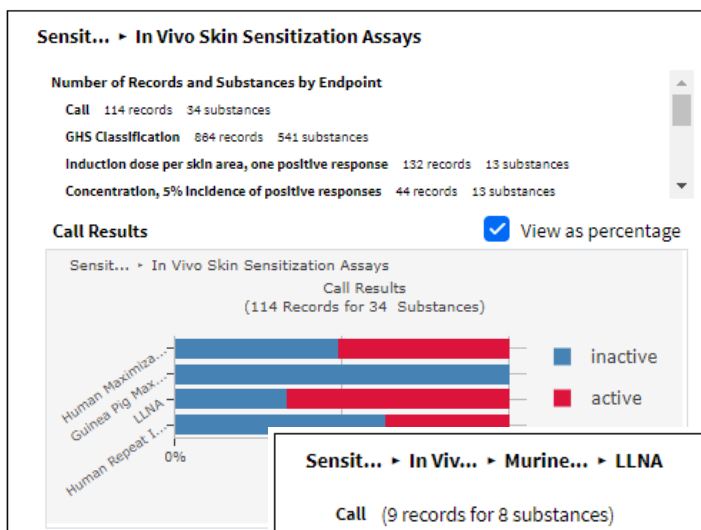
Data Input

Select Data Sets

cHTS Acute Lethality Sensitization Irritation/Corrosion Endocrine

☐	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

- Results can be explored using the navigation map that organizes results based on assay/data set.
- Data visualizations aggregate results by data set/subset based on the user's position in the navigation map.





The **Chemical Quest** tool allows users to query by chemical ID or SMILES structure to identify similar chemicals within the ICE database.

The Chemical Quest tool uses fingerprints generated using Saagar features. Only this tool uses fingerprints generated using Saagar features. Only

Run Reset Search Custom Chemical List

Max hits per input: 10

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

Chemical structure: ClCc1ccc(C)cc1

close

Similar Structures to: Captan

Send filtered results to: Select tool...

Select filter to add to chain: 100%

Clear Filters

Select Page: 1 of 1

Showing 1-10 of 10 hits.

Sort Results By: Tanimoto Direction: Desc

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: 4932-79-0
DTXSID: DTXSID001020409
Name: 3a,4,7,7a-Tetrahydro-2-[[t...
Tanimoto Value: 0.890244
Has Bioactivity: false

SMARTs Filter

Enter SMARTs: C=C

Add SMARTs Query

Chemicals that match the entered SMARTs Query

Select SMART Query

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

Items

C=C

Cl

10 results in 10 items listed

10 results selected of 10 (100.0%)

Cancel Apply Filter

Exploring physicochemical properties and chemical use categories for a set of chemicals or

Compare results between two sets of chemicals. Users may also explore chemical properties data.

Chemical Input List 1 (required)

List Name A Demo List of Chemicals

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

Chemical Input List 2 (optional)

List Name RoC Classifications

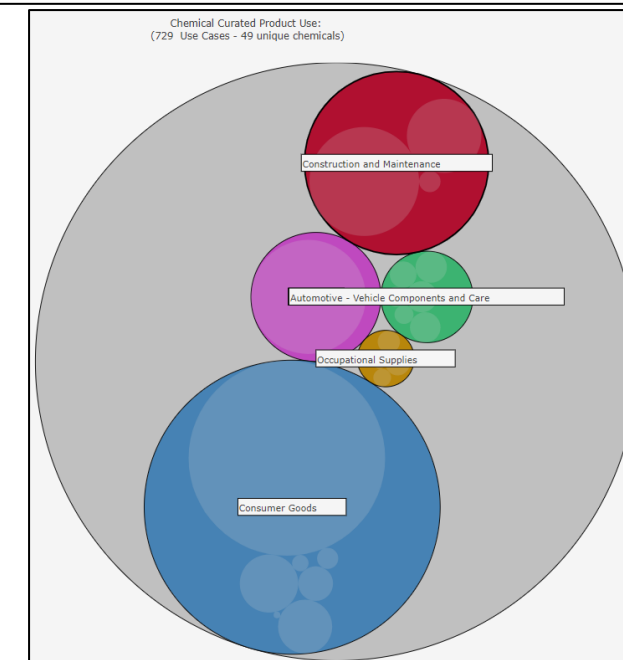
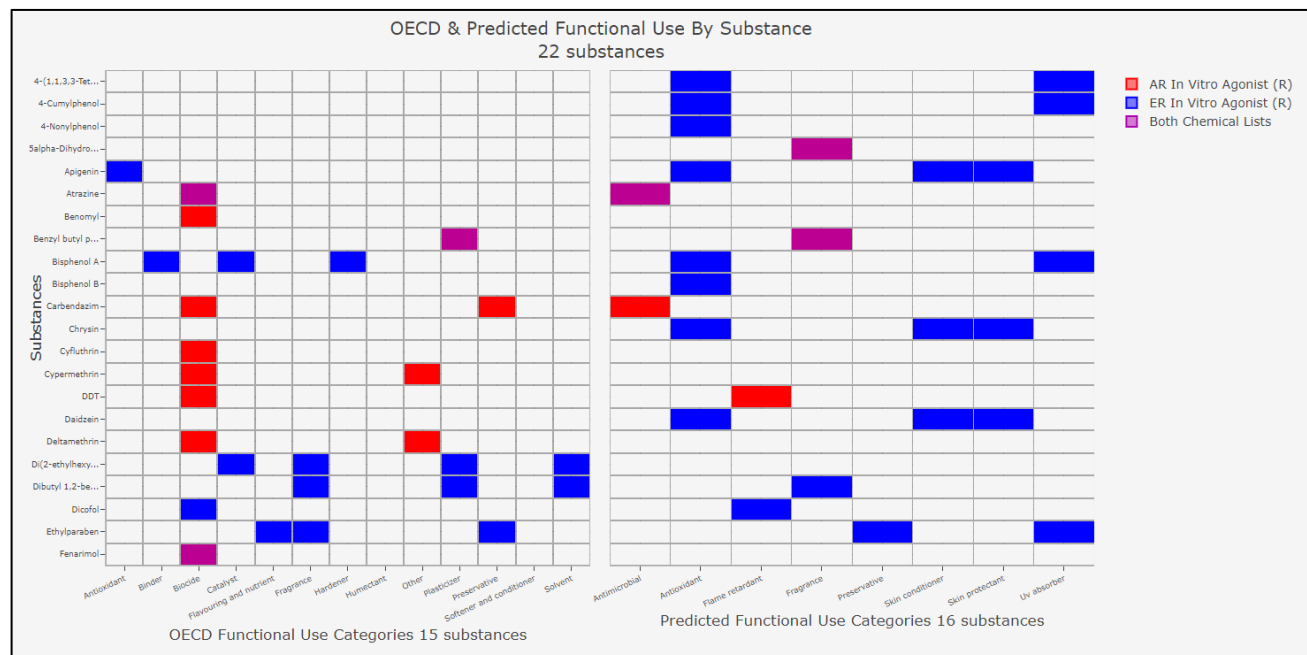
Select Chemicals

1 chemical quick list selected.

Quick List CASRNs

100-42-5
100-75-4
10034-93-2
10043-92-2
101-14-4
101-61-1
101-77-9
101-80-4
101-90-6
10540-29-1
105650-23-5
106-46-7
106-87-6
106-89-8
106-93-4

User Chemical Identifiers



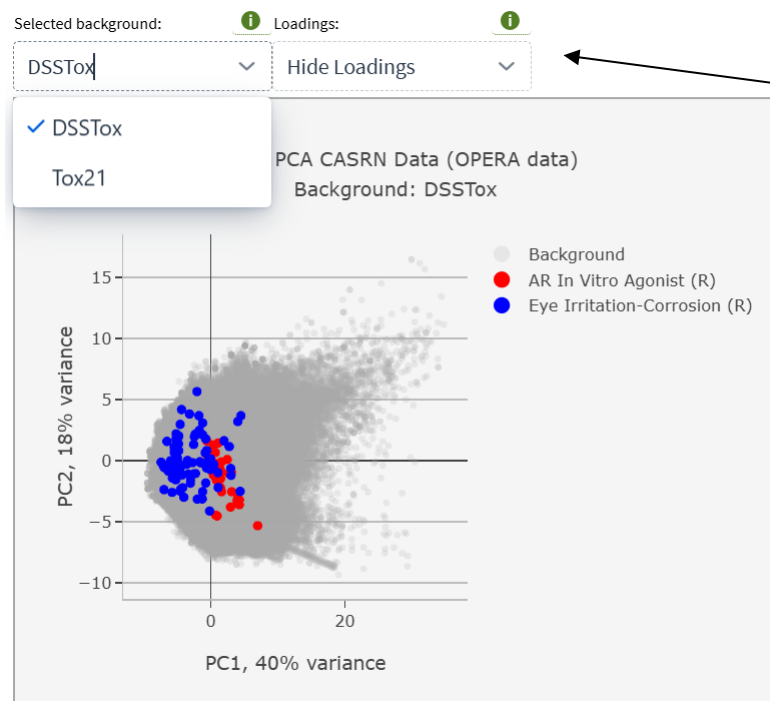
Interactive principal component analysis (PCA) plots

Updated in ICE v4.2

Static PCA plot

Derived from a PCA with all chemicals in the selected background chemical set.

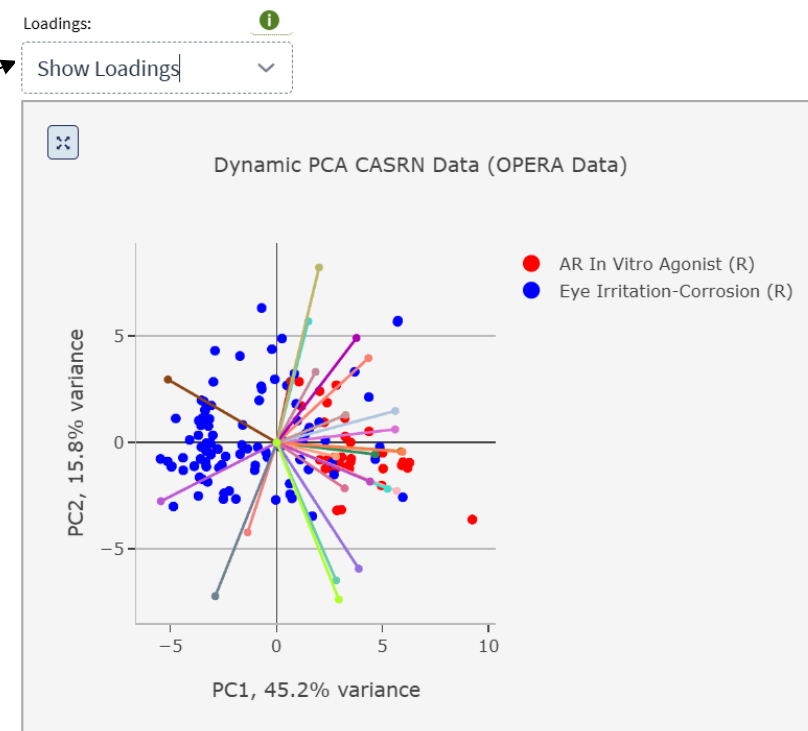
DSSTox and Tox21 backgrounds are available to allow users to compare their lists to two different chemical spaces.



Show or hide loadings
(vectors that represent the
correlation between each
property/descriptor and
principal components).

Dynamic PCA plot

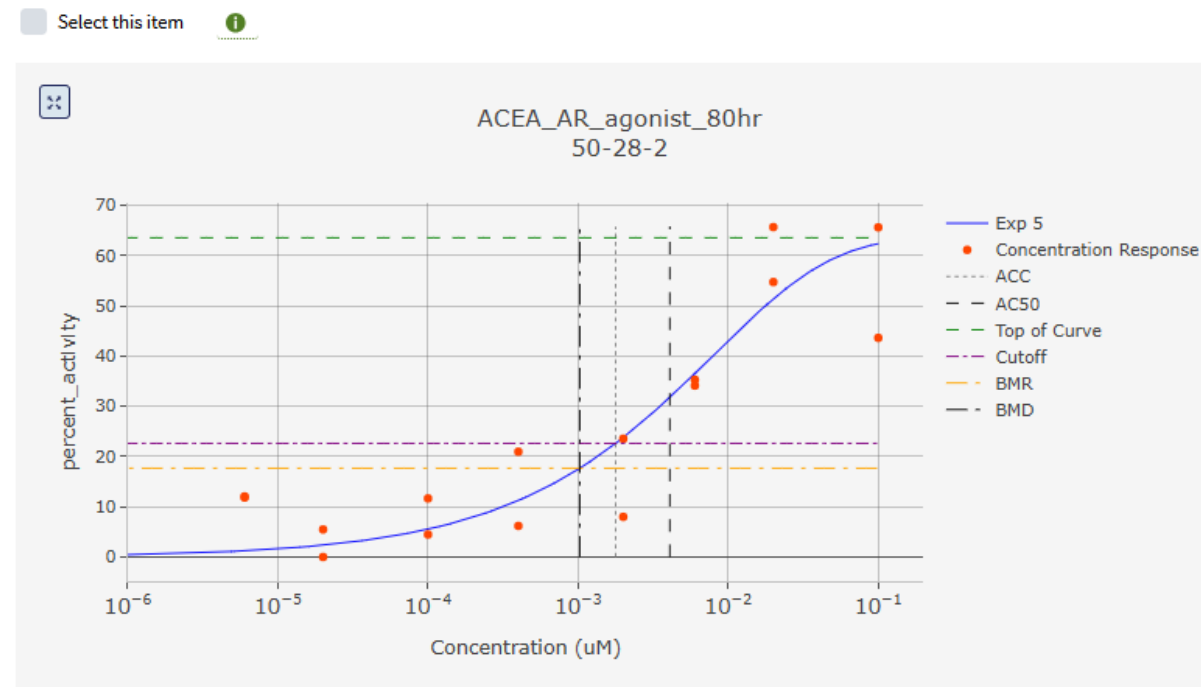
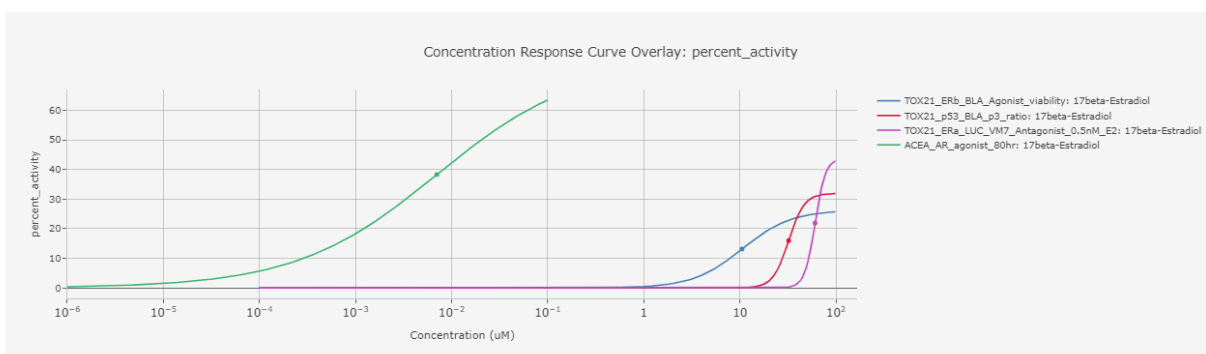
Derived from a PCA with chemicals in query.



The **Curve Surfer** tool allows users to visualize concentration-response curves from the cHTS data.

- Curve Surfer cards enhanced in ICE v4.2 with new curves and points of departure (benchmark dose) to reflect Invitrodb v4.2 updates.

Mechanistic Targets
Call
Assay Text
Assay
CASRN
Chemical Name
DTXSID
SMARTS
Assay System
Assay Response Unit
AC50
Top of Curve
Technological Interference
Flag Information
Winning Curve-Fit Model
BMD
BMR



Assay: ACEA_AR_agonist_80hr

CASRN: 50-28-2

Chemical Name: 17beta-Estradiol

AC50 (uM): 0.0041

BMD (uM): 0.001

Top of Curve: 63.57

Technological Interference: No interference flag

Mechanistic Target: Androgen Receptor Activity

DTXSID: DTXSID0020573

Winning Curve-Fit Model: exp5

ACC (uM): 0.0018

BMR: 17.68

Call: Active

Flag Information: No flag information

**New in ICE
v4.2**

The **PBPK** tool enables modeling of tissue-specific chemical concentrations over time following a dosing event.

- Solve_pbt_k: Predictions following oral or IV exposure
- Solve_gas_pbt_k: Predictions following inhalation (gas) exposure
- Solve_fetal_pbt_k: Predictions for maternal and fetal compartments following oral or IV exposure
- Experimental and/or in silico ADME parameter values can be selected as model inputs.
- Users can customize model parameters such as Exposure Dose, Exposure Route, and Simulation Length.
- New feature added in ICE v4.2 that allows users to upload custom data for selected physicochemical and ADME parameters.

The screenshot displays the PBPK tool interface. At the top, a status bar shows: "Species: human, Body Weight: 70.0, ADME Source: Default, Model: Solve_pbt_k, Exposure Route: iv, Exposure Interval: 24 Hours, Simulation Length: 3 Days". Below this, there are two columns of input fields, each with a green information icon (i).

Left Column Inputs:

- Species: human (dropdown)
- Body Weight: 70 (text input)
- ADME Source: Default (dropdown)
- Exposure Dose: 1.0 (text input)
- Gestational Day when Exposure Starts: (empty text input)
- Model: Solve_pbt_k (dropdown menu is open, showing options: Solve_pbt_k (checked), Solve_gas_pbt_k, Solve_fetal_pbt_k)

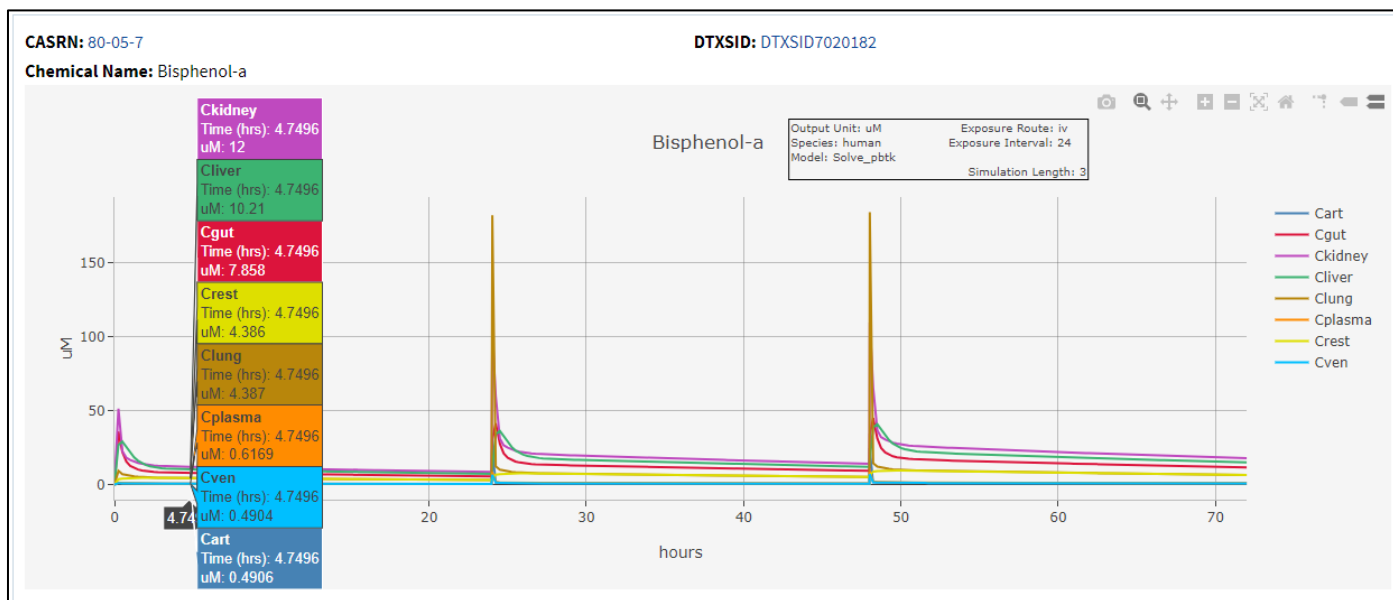
Right Column Inputs:

- Exposure Route: iv (dropdown)
- Exposure Interval, Hours: 24 (text input)
- Exposure Length, Hours: NA (text input)
- Simulation Length, Days: 3 (text input)
- Output Conc. Units: uM (dropdown)
- Inhalation Dosing Method: Concentration (dropdown)
- Inhalation Dosing Units: ppmv (dropdown)

Below the main input fields, there are two additional sections:

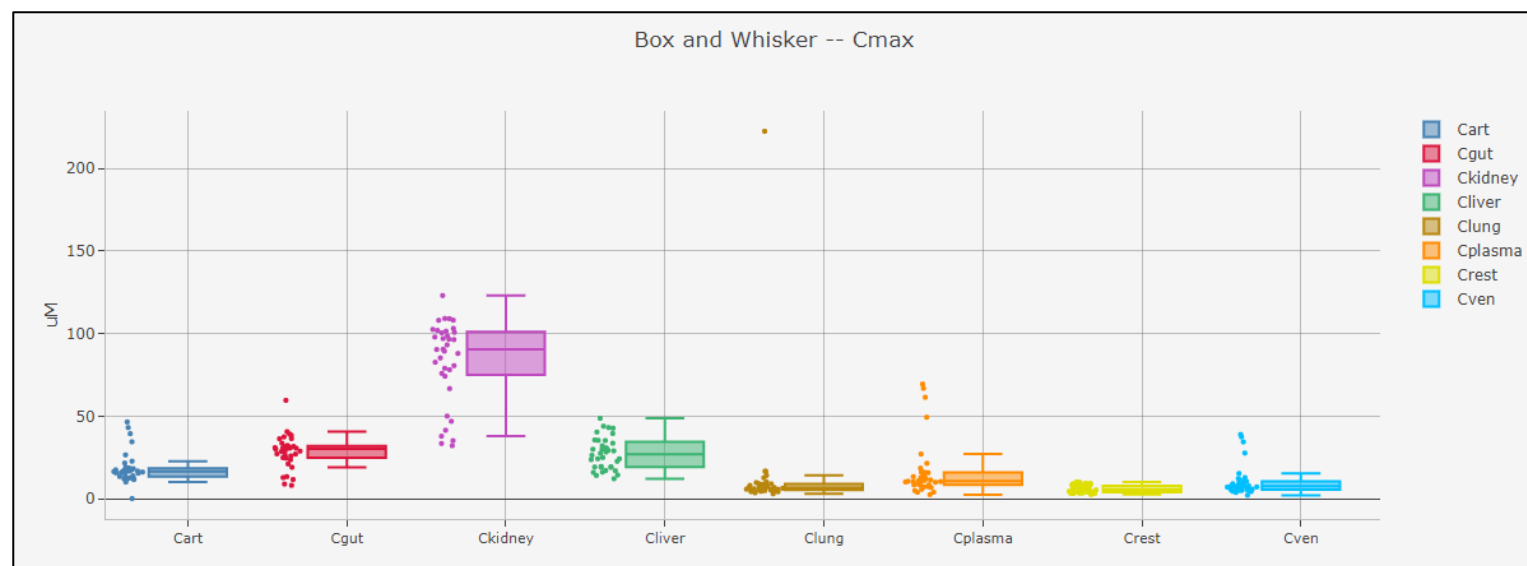
- Chemical Input:** Includes a "Select Chemicals" button and two large empty text areas labeled "Quick List CASRNs" and "User Chemical Identifiers".
- Upload Custom Phys Chem Data:** Includes an "Upload" button, a "Drop file here" area, and a table for "Uploaded Files" with columns for "File Name" and "MIME Type".

A red arrow points to the "Upload Custom Phys Chem Data" section with the text "New in ICE v4.2".



Concentration profile (time series) graphs may be visualized in the PBPK tool.

Box plots with the distribution of Cmax values for each compartment across the chemicals in the query.



Chemical Input

Select Chemicals

Quick List CASRNs

User Chemical Identifiers

Data Input

Select Assays

Assays	Description	Data Type

Upload Custom Phys Chem Data

Upload

Uploaded Files

File Name	MIME Type

Upload Custom In Vivo or Exposure Data to Overlay on Charts

Upload

Drop file here

Uploaded Files

File Name	MIME Type

Upload Custom In Vitro Data

Upload

Drop file here

Uploaded Files

File Name	MIME Type

**New in ICE
v4.2**

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

Reset

In Vitro Endpoint: AC50, Species: human, Body Weight: 70.0, ADME Source: Default, Gestational Days when Exposure Starts: 91.0, Model: Solve_fetal_pbtok, Exposure Route: iv

Exposure Route: iv

Exposure Interval, Hours: 24

Exposure Length, Hours:

Simulation Length, Days: 1

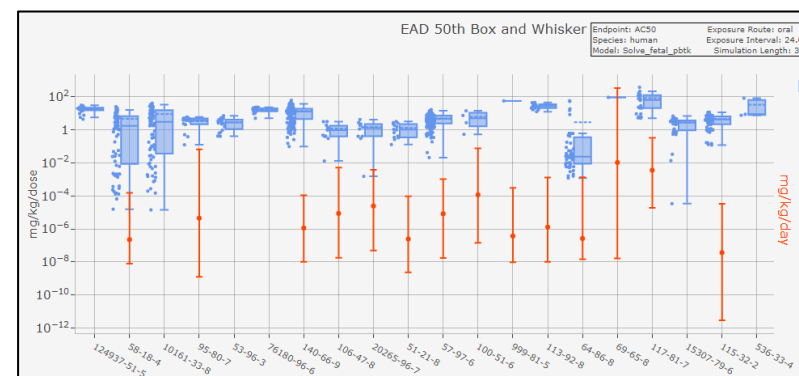
Inhalation Dosing Method: Concentration

Inhalation Dosing Units: ppmv

A multiple-compartment human PBPK model from the US EPA httk package that includes both maternal and fetal compartments and a placenta modeled as a joint organ shared by mother and fetus. For details see User Guide.

The **IVIVE** tool generates estimates 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.

- New feature added in ICE v4.2 that allows users to upload custom data for selected physicochemical and ADME parameters.



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

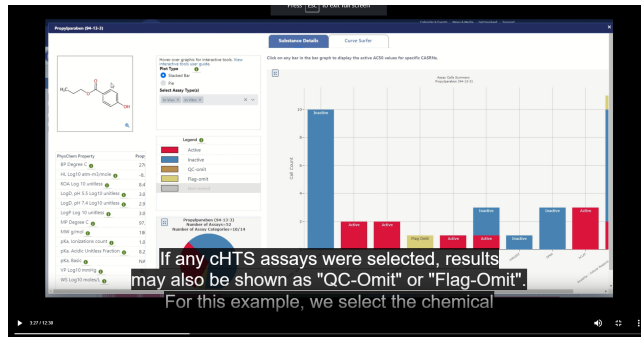
dataset 3

dataset 1

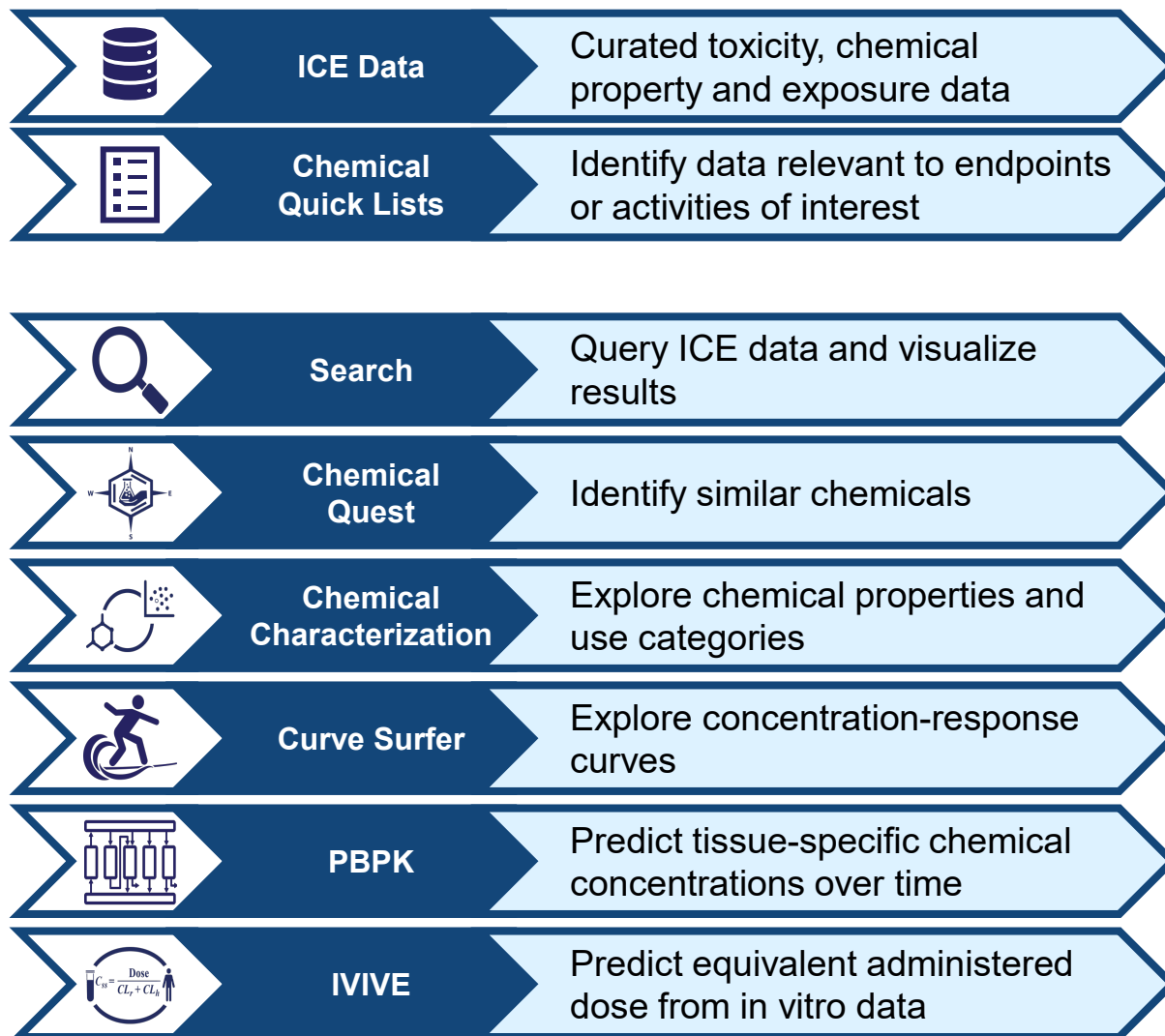
- User guides and data sets descriptions are updated with each release to aid in the navigation of ICE.
- **ICE help videos were updated in ICE v4.1.1.** Updated in ICE v4.1.1
- The ICE support email is monitored frequently to ensure any additional questions are answered: **ICE-support@niehs.nih.gov**
- Hands on trainings are available upon request

ICE User Guide	ICE PBPK Tool
Search	Table of Contents:
Chemical Quest	• Introduction • Building a PBPK Query ◦ Select Model ◦ Specify Additional Parameters ◦ Chemical Input ◦ Upload Custom PhysChem Data ◦ Run PBPK Tool • Viewing PBPK Results ◦ Download Results ◦ Interactive Results Table ◦ Interactive Plots ◦ Using Results to Query Other ICE Tools
Curve Surfer	
PBPK	
IVIVE	
Chemical Characterization	
Interactive Graphs	
Rest API	

Help Videos	ICE Help Video
ICE Help Videos	ICE Help Videos are available for the Search, Curve Surfer, PBPK, and IVIVE tools. These comprehensive instructional videos provide step-by-step guidance on building queries and interpreting results. Videos currently available were made using these versions of ICE:
Search Help Videos	• Search: v.4.1.1 (January 2025)
IVIVE Help Videos	• Curve Surfer: v.4.1.1 (January 2025)
Curve Surfer Help Videos	• PBPK: v.4.1.1 (January 2025)
PBPK Help Videos	• IVIVE: v.4.1.1 (January 2025)



If any cHTS assays were selected, results may also be shown as "QC-Omit" or "Flag-Omit". For this example, we select the chemical



Ongoing ICE Projects

- Continuous development of data visualizations in Search tool
- Continuous curation and harmonization of ICE data
- Update ChemQuest to improve functionality and introduce endpoint-specific similarity searches
- Expand PBPK and IVIVE tools to include more species and allow for flexibility in dosing scenarios
- Integrate chemical taxonomies into ICE tools to allow for more targeted exploration of chemical space
- Improve chemical QC flags in cHTS data using new analytical QC results from EPA

Let us know what you
would like to see next!

The NICEATM Group



Contact Us: ICE-support@niehs.nih.gov



**Integrated
Chemical
Environment**



ice.ntp.niehs.nih.gov



github.com/NIEHS/OPERA



cebs.niehs.nih.gov/cebs



inotiv
analyze. answer. advance.

Sciome

comptox.epa.gov/dashboard

sciome.com

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