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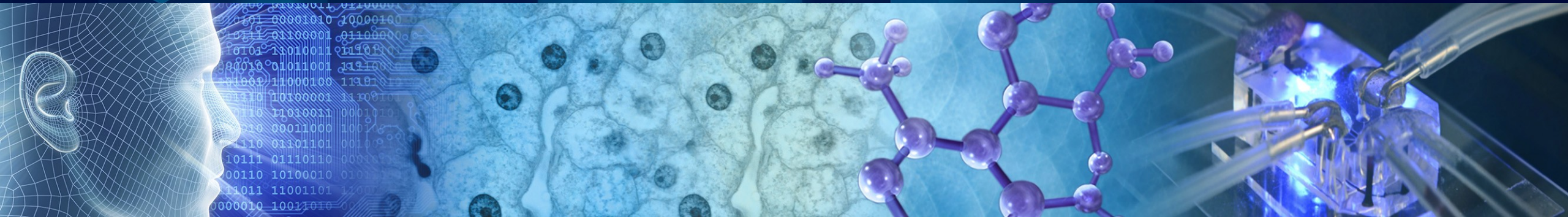

Updates to the Integrated Chemical Environment (ICE)

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

SACATM 2025

Outline

ice.ntp.niehs.nih.gov

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

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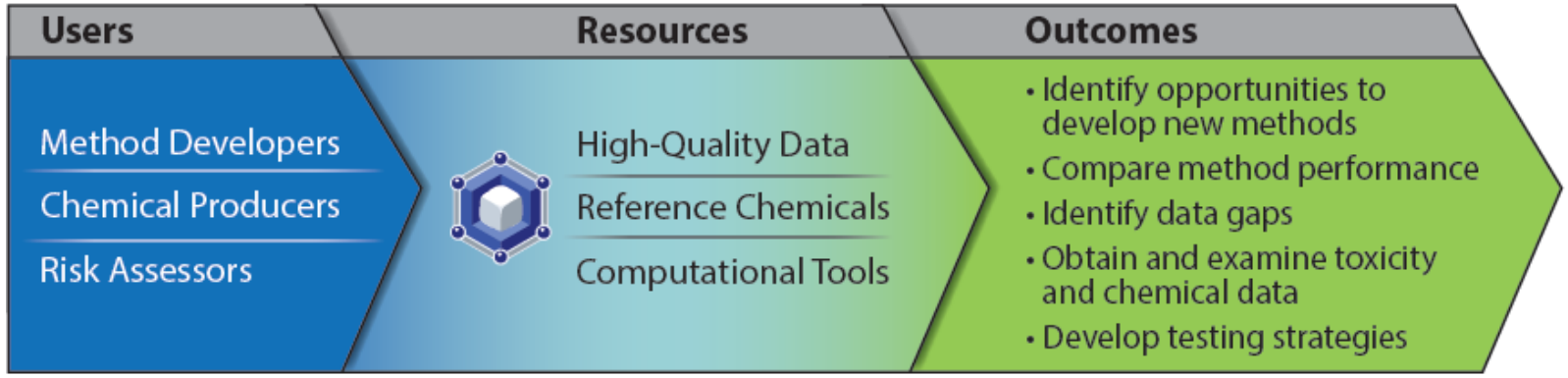
ICE: Integrated Chemical Environment

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)

Findable Accessible Interoperable Reusable



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

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

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

Curated High-Throughput Screening Data

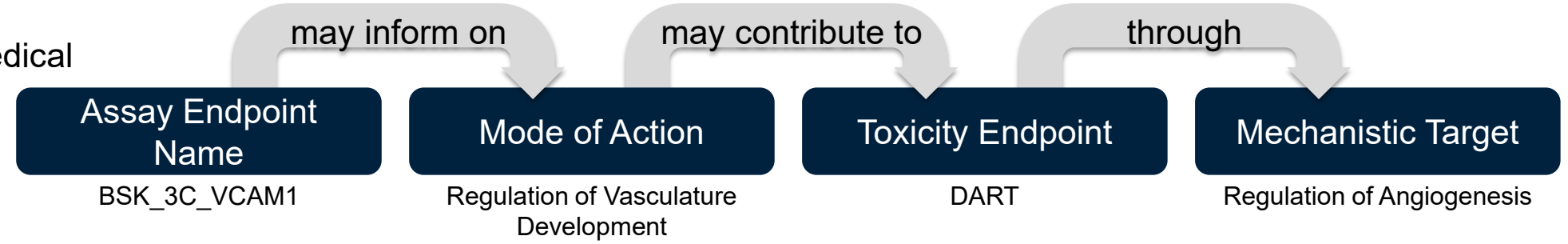
- ICE's curated high-throughput screening (cHTS) data set contains data from the U.S. federal Tox21 collaboration and EPA's ToxCast program for ~10000 chemicals.
- ICE cHTS data align with the EPA's invitrodb.

Updated in ICE v4.2

ICE cHTS Pipeline

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.

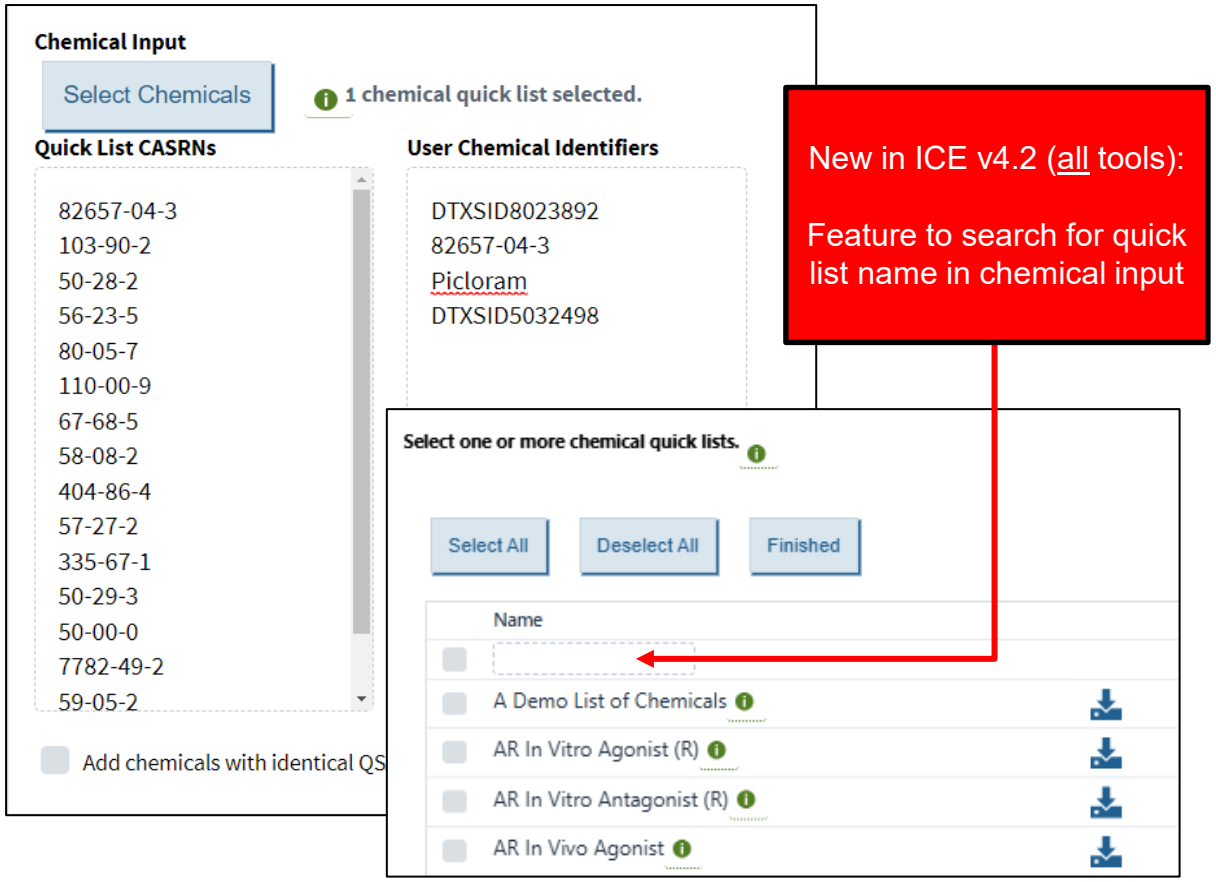
Reference Chemical Lists
AR In Vitro Agonist
AR In Vitro Antagonist
ER In Vivo Agonist
ER In Vitro Agonist
Eye Irritation-Corrosion
Genotoxicity
OECD Defined Approach to Skin Sensitization: Human
OECD Defined Approach to Skin Sensitization: LLNA
Skin Corrosion

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.

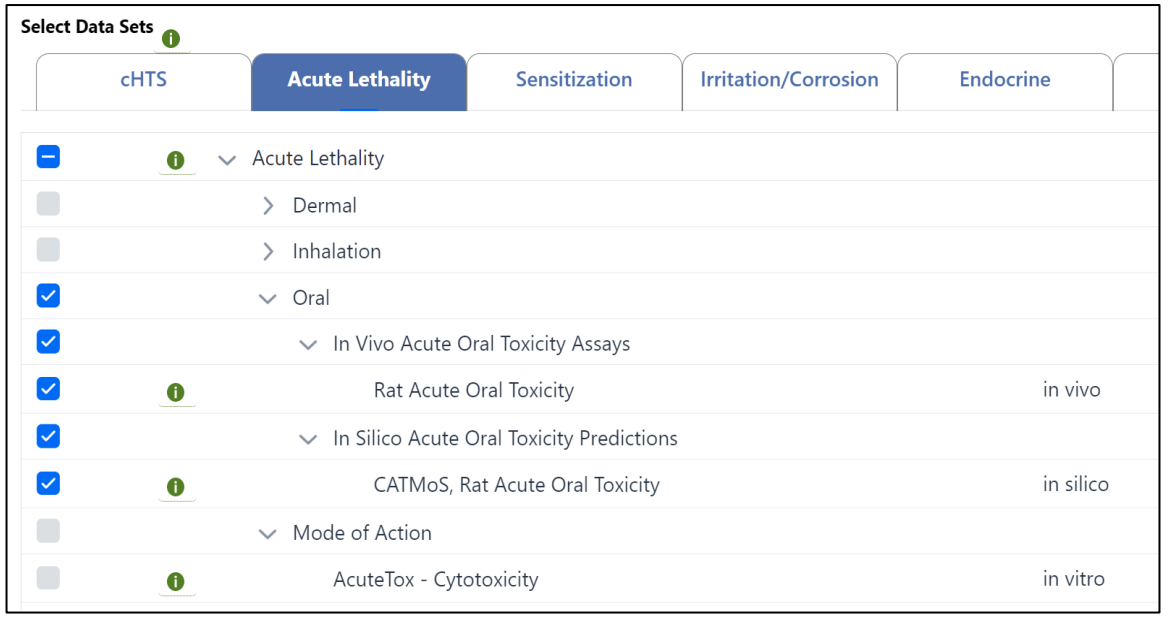
Chemical Input



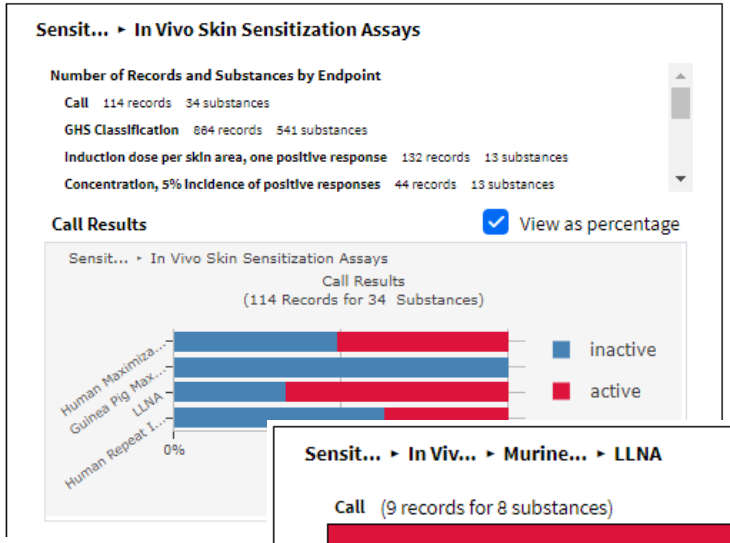
New in ICE v4.2 (all tools):

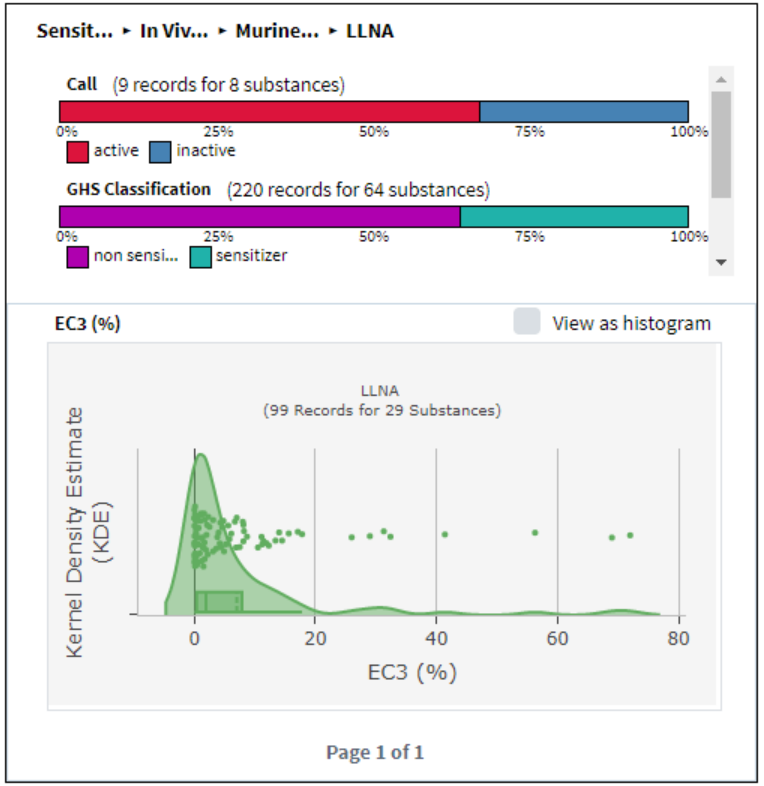
Feature to search for quick list name in chemical input

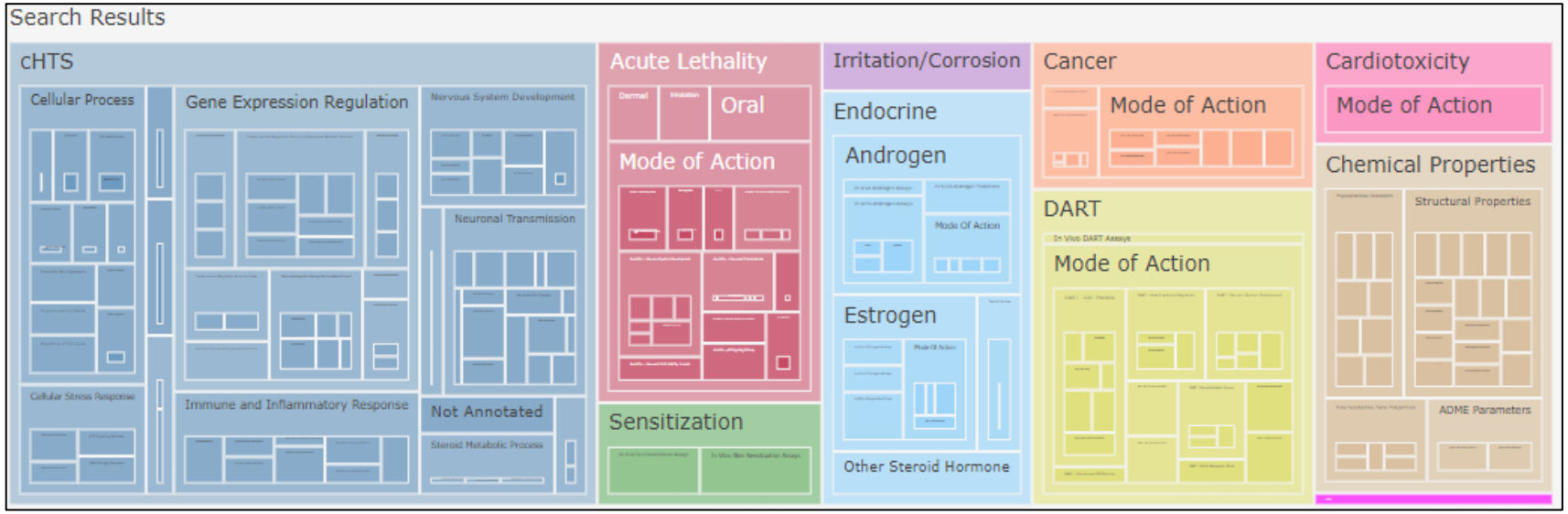
Data Input



- 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.

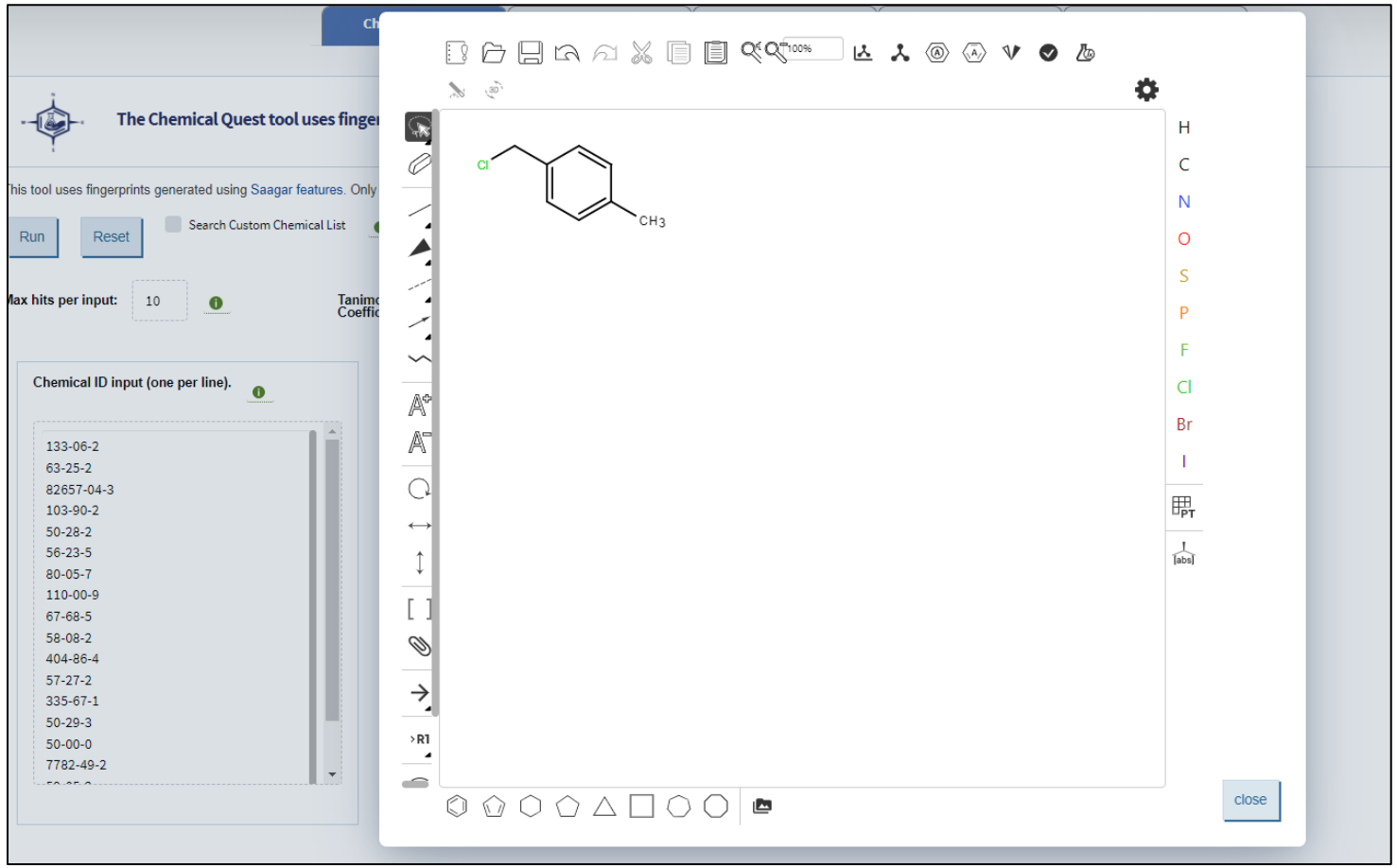


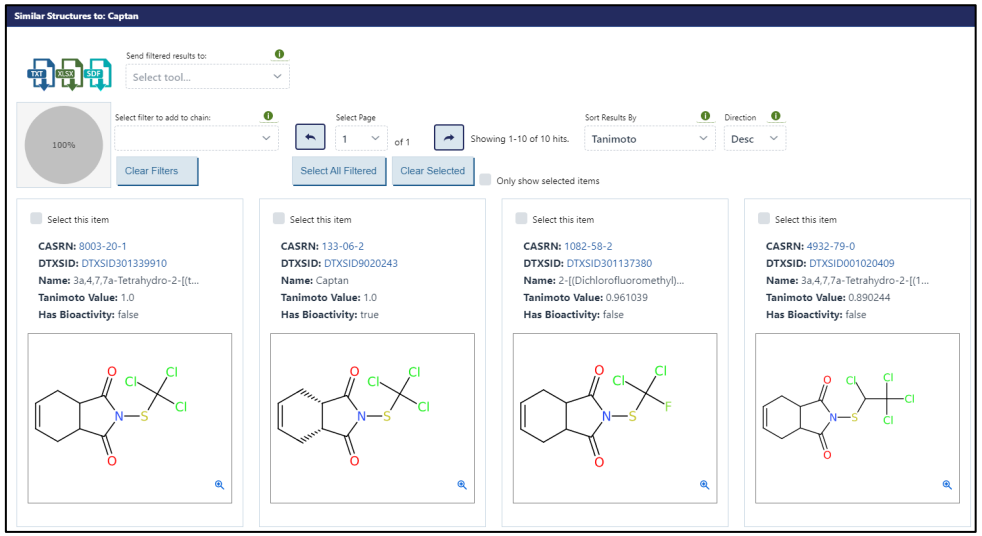


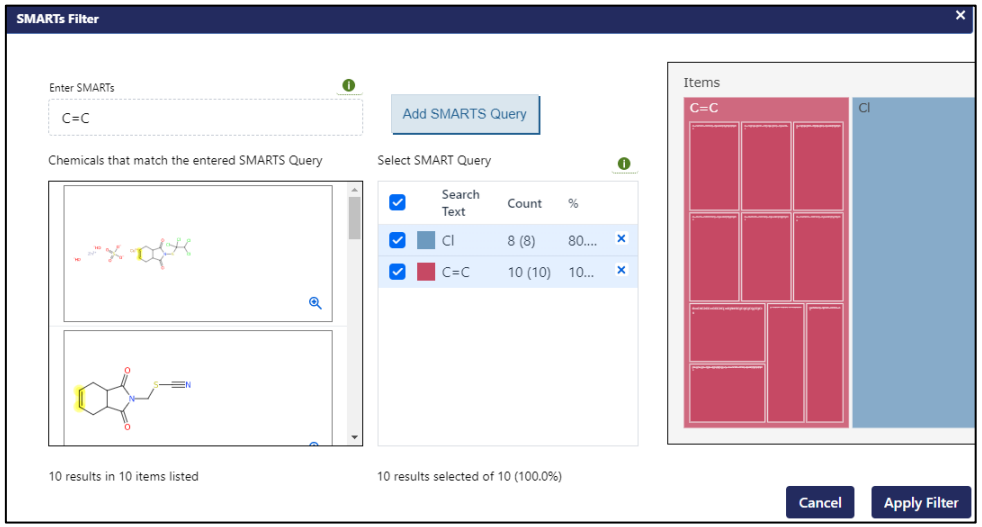


Chemical Quest

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





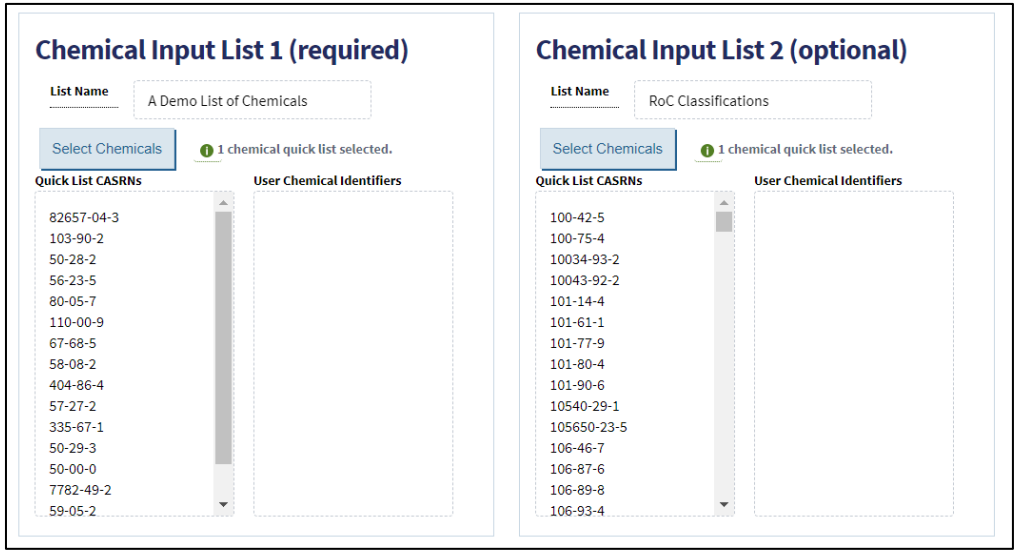


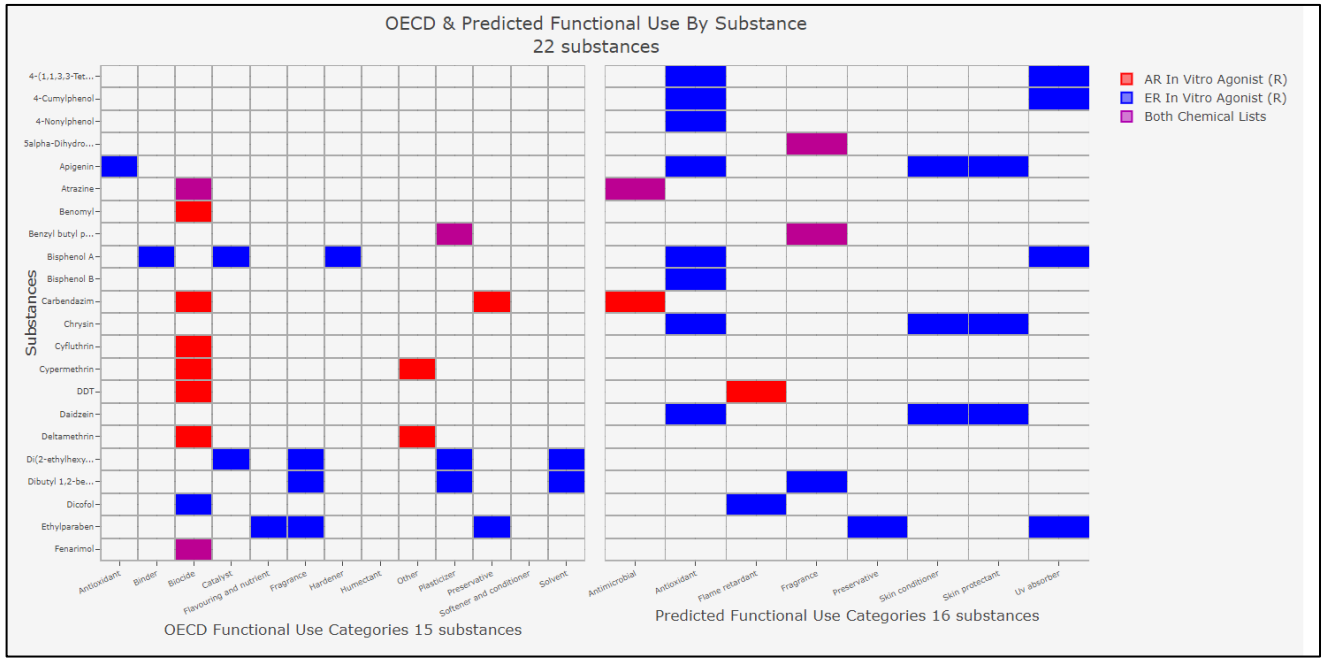
https://doi.org/10.1021/acs.chemrestox.0c00464

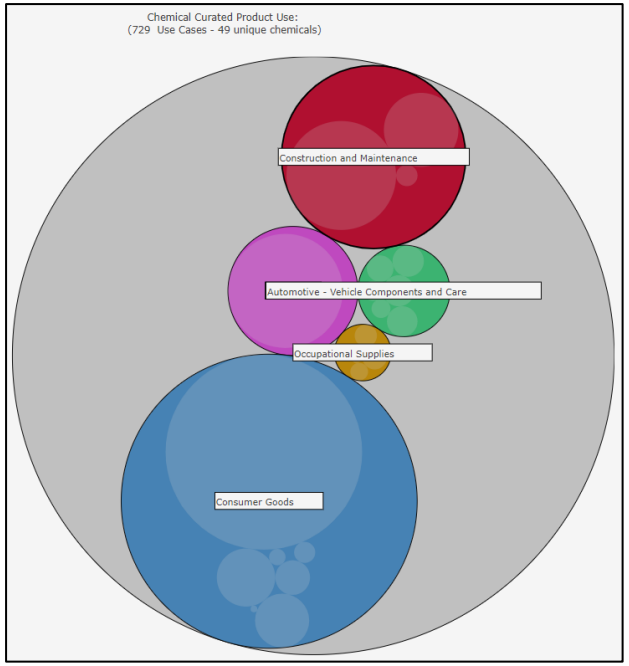
Chemical Characterization

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.







CPDat v3
(Williams, 2017)

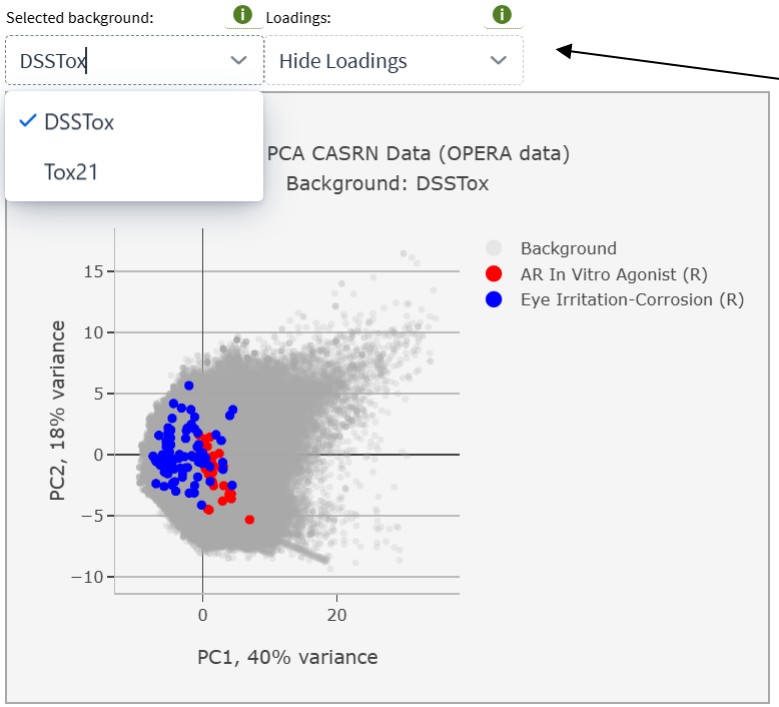
Interactive principal component analysis (PCA) plots

Updated in ICE v4.2

Static PCA plot

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

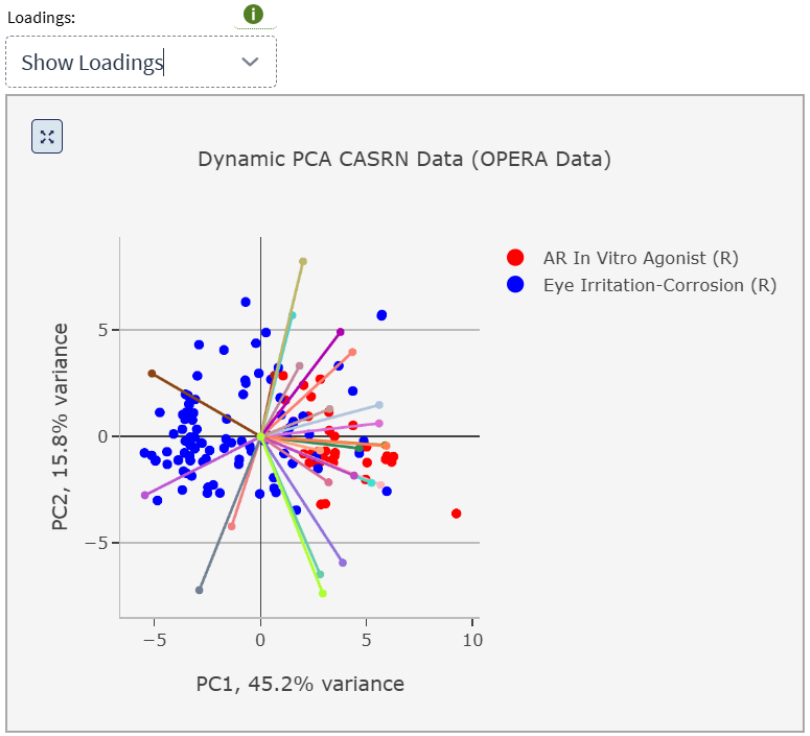
DSSTox and Tox21 backgrounds are available to allow users to compare their lists to two different chemical spaces.



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.

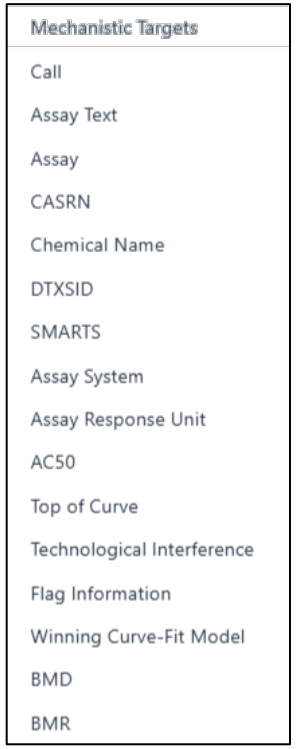


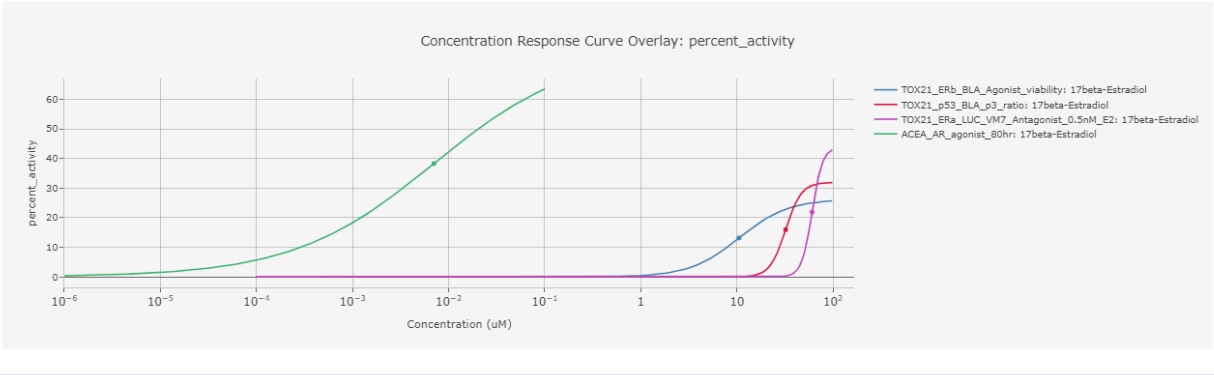
OPERA v2.8 (*Mansouri et al. J Cheminform 2018*)

Curve Surfer

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.

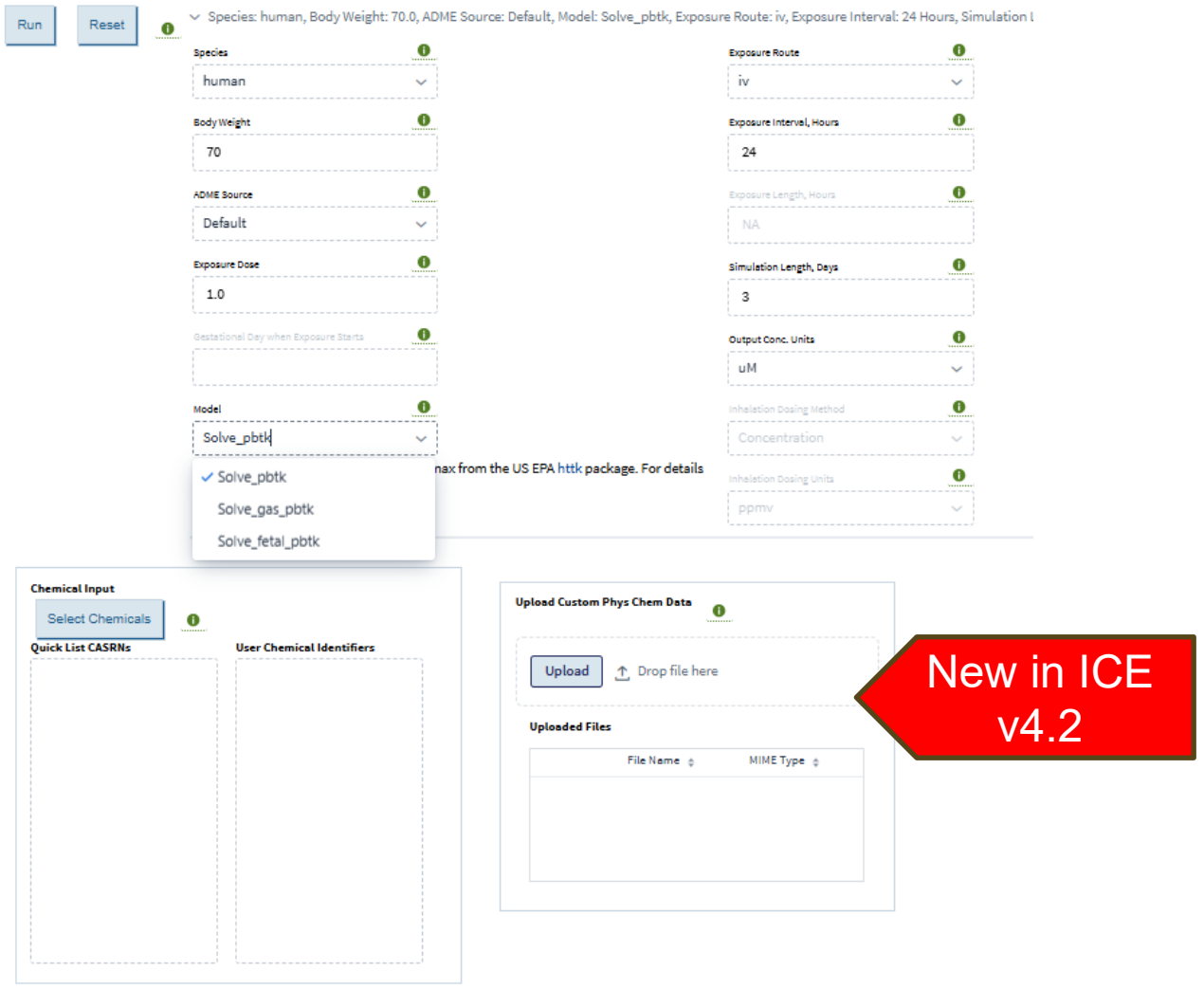




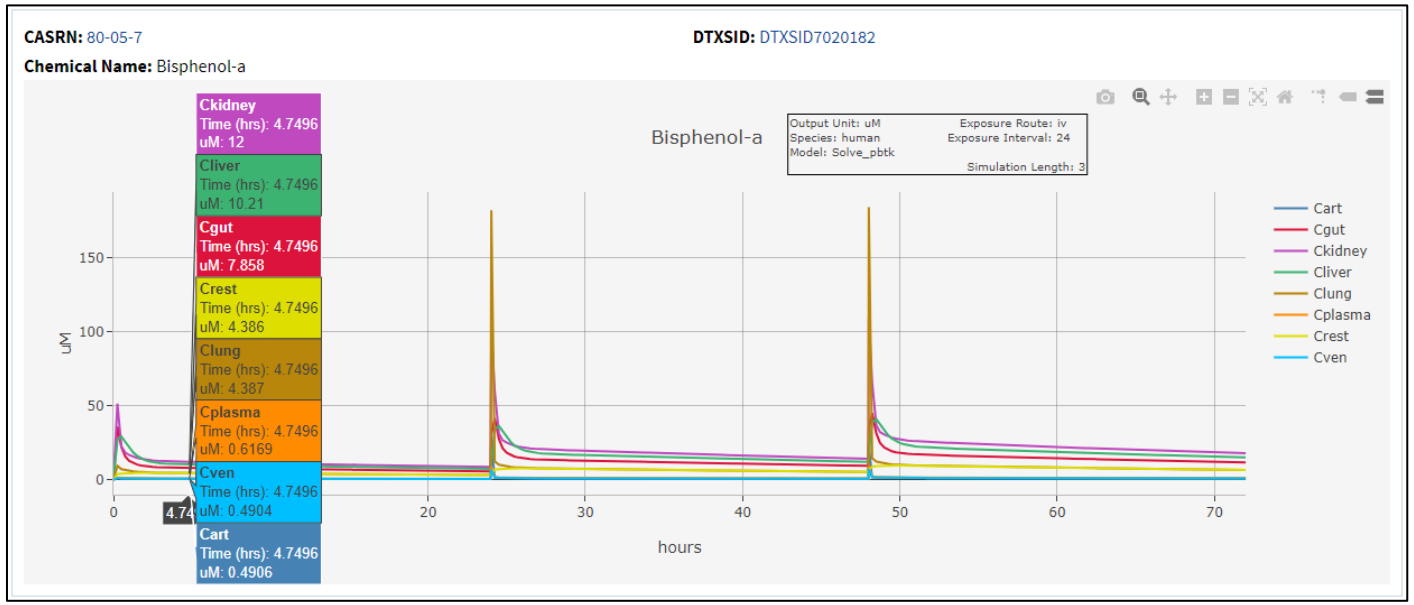
The **PBPK** tool enables modeling of tissue-specific chemical concentrations over time following a dosing event.

- Solve_pbtk: Predictions following oral or IV exposure
- Solve_gas_pbtk: Predictions following inhalation (gas) exposure
- Solve_fetal_pbtk: 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.

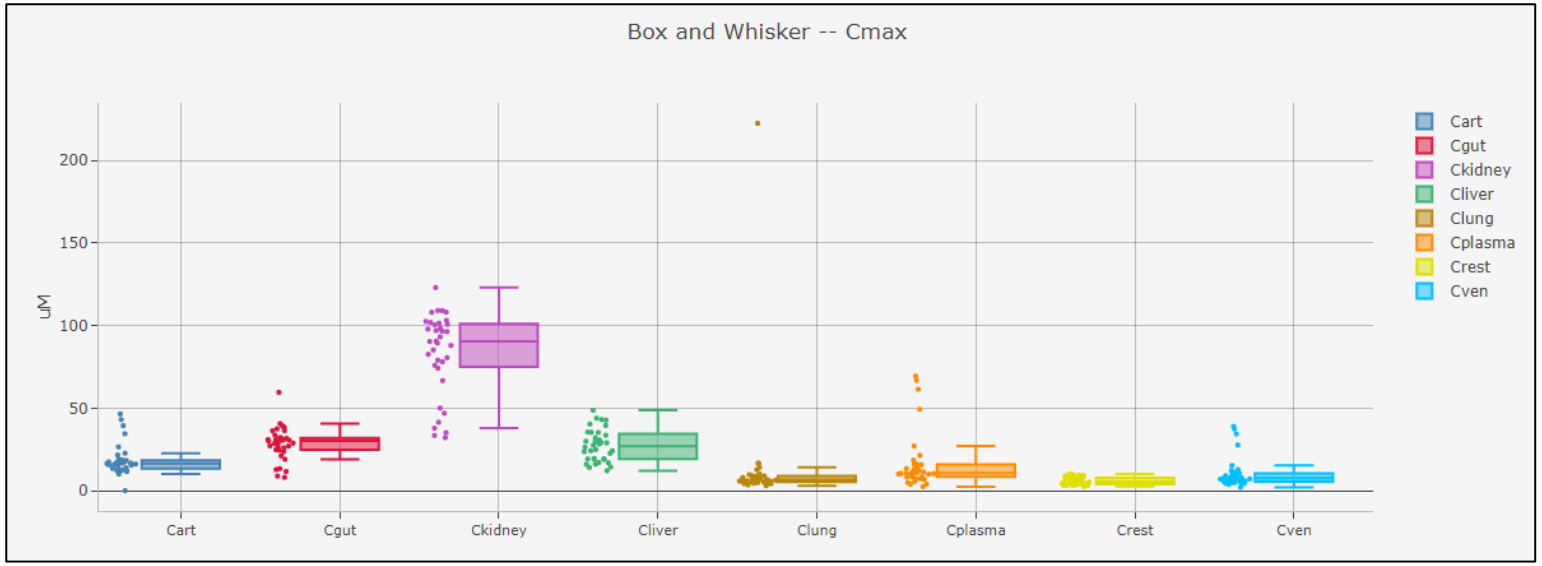


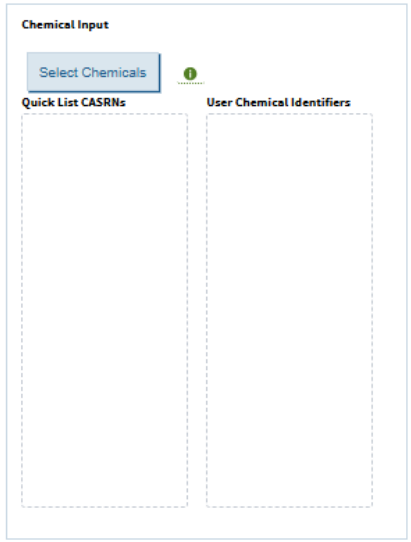
httk v2.2.2
(Pearce et al. J Stat Softw 2017)

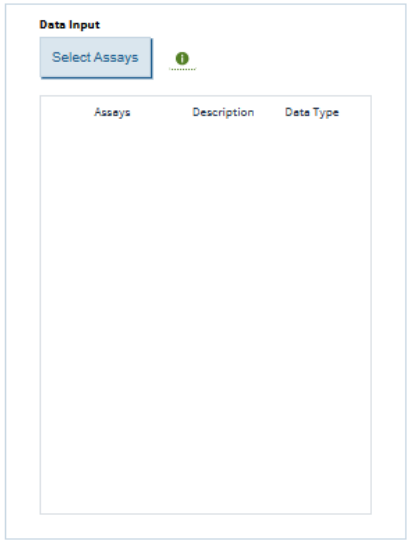


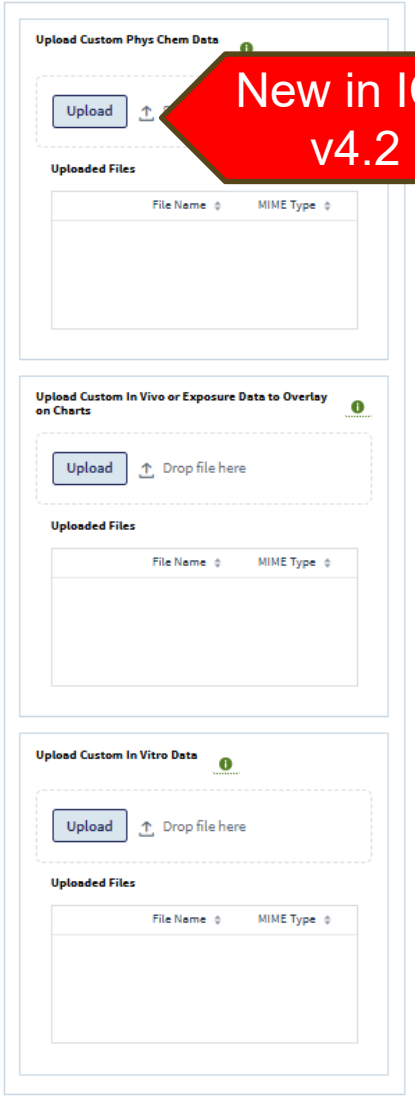
Concentration profile (time series) graphs may be visualized in the PBPK tool.

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

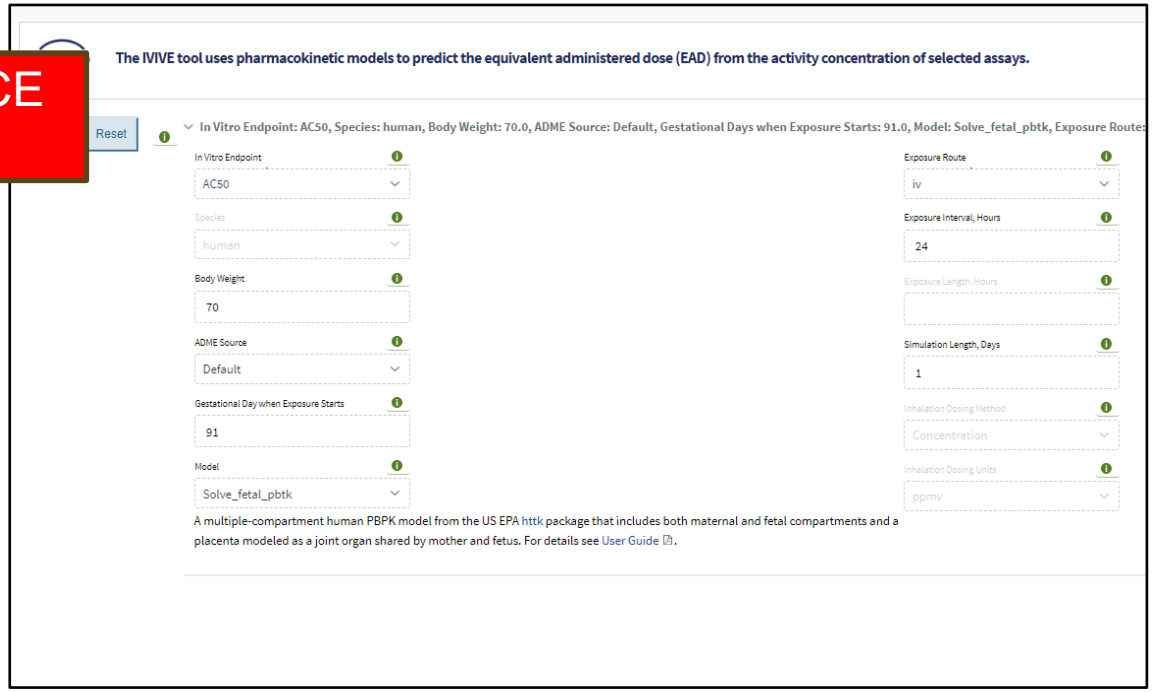






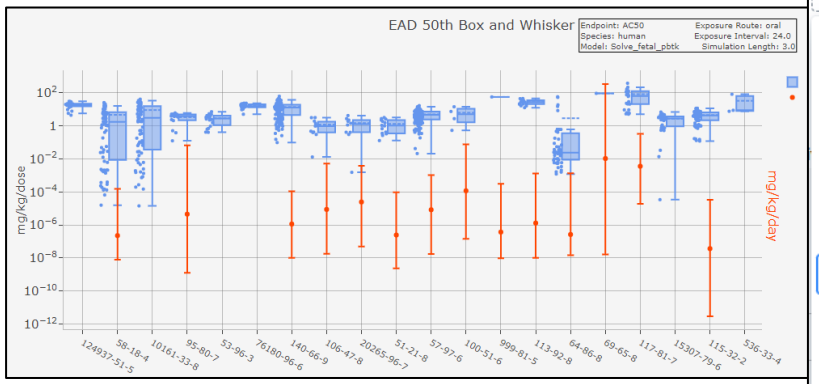


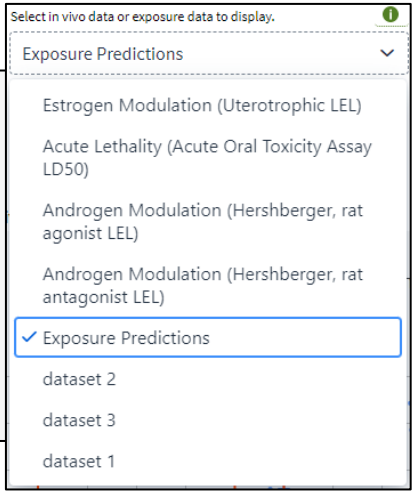
New in ICE v4.2



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.

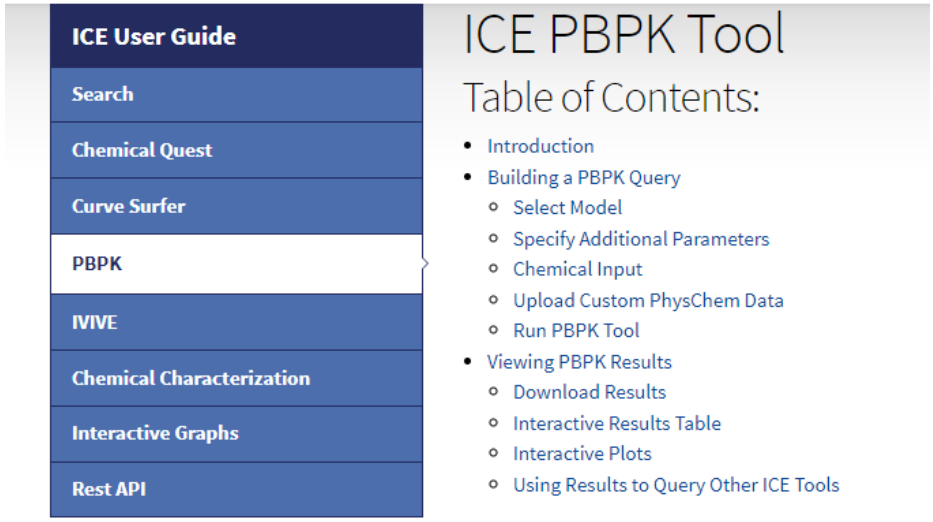


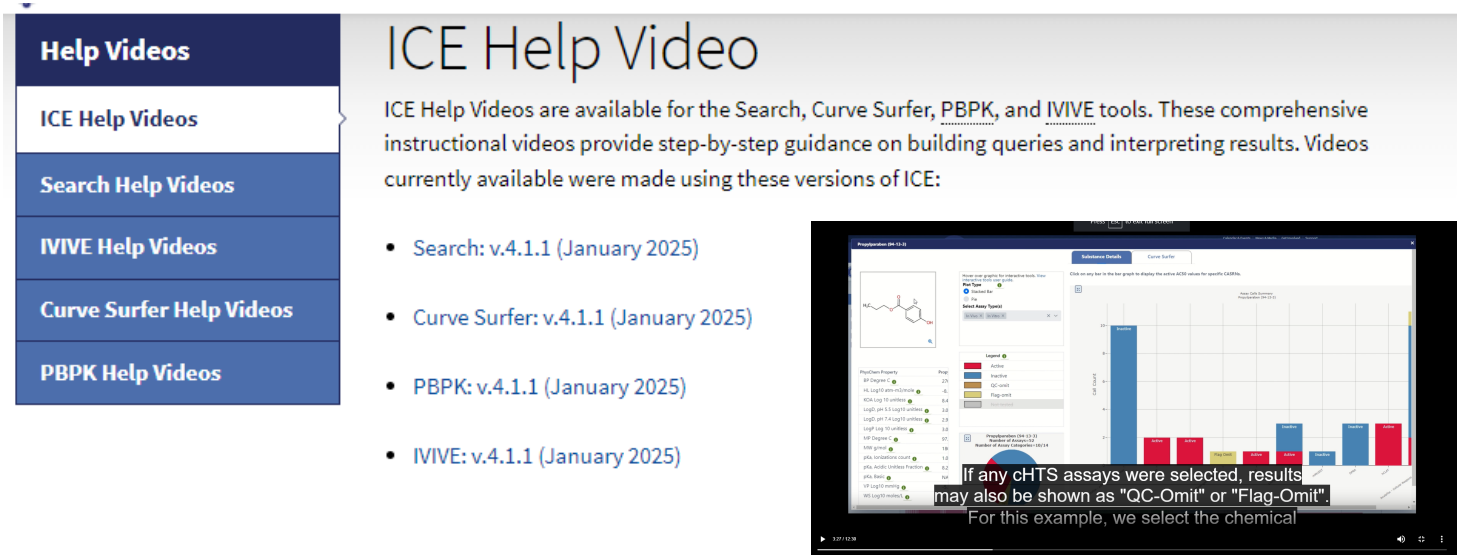


httk v2.2.2
(Pearce et al. J Stat Softw 2017)

Additional ICE Support

- 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





Summary

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

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!

National Institute of Environmental Health Sciences
Division of Translational Toxicology

Acknowledgments and Resources

The NICEATM Group

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

Integrated Chemical Environment

ice.ntp.niehs.nih.gov

OPERA OPEn (q)saR App

github.com/NIEHS/OPERA

CEBS Chemical Effects in Biological Systems

cebs.niehs.nih.gov/cebs

United States Environmental Protection Agency

comptox.epa.gov/dashboard

inotiv analyze. answer. advance.

sciome

sciome.com

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