

Open-access Data and Computational Tools to Investigate Chemical Bioactivity

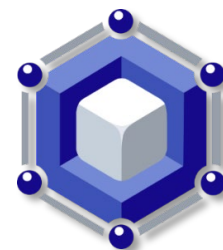
12th ASCCT Annual Meeting
2023-10-25

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

Inotiv, contractor's supporting NICEATM

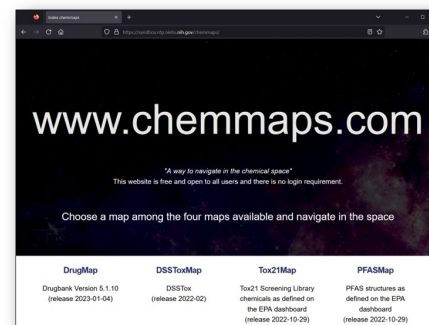
*Disclaimer: Inotiv staff provide technical support for NICEATM,
but do not represent NIEHS, NTP, DTT, or the official positions of any federal agency.*

- Gain an understanding of the data within ICE and how to use ICE tools for data interpretation and exploration.
- Discover the utility of ChemMaps.com for supporting read-across analysis, risk assessment, and the exploration of unknown chemicals.
- Understand the purpose and functionality of the DASS App.

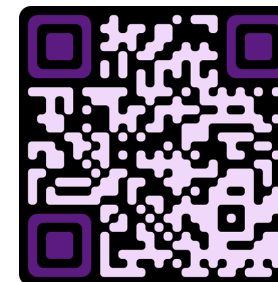


Integrated
Chemical
Environment

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



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



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



1. First Presentation: (30 mins)

- Title: Overview of NICEATM's Integrated Chemical Environment (ICE) with detailed insight into its Search and structural similarity prediction tools.
- Speaker: Aswani Unnikrishnan

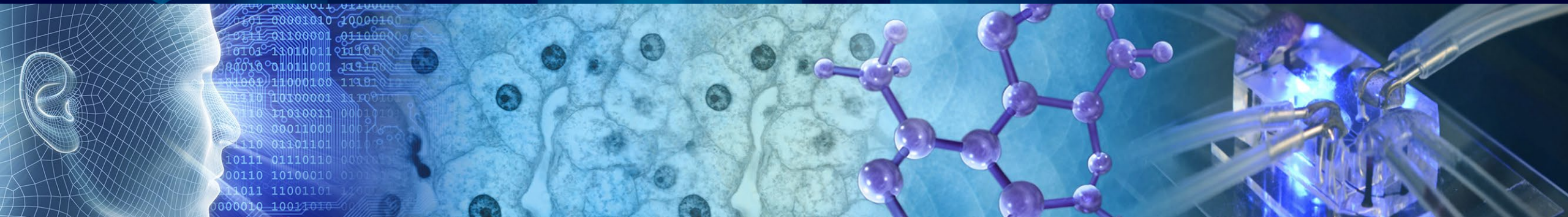
2. Second Presentation: (30 mins)

- Title: Using the Integrated Chemical Environment (ICE) to access interoperable computational tools and inform chemical hazard.
- Speaker: Victoria Hull

3. ICE Q & A (10 mins)**4. Recess: (10 mins)****5. Third Presentation: (30 mins)**

- Title 1: ChemMaps.com v2.0 – Exploring the Environmental Chemical Universe
- Title 2: DASS App: A Web Application for Applying Defined Approaches for Skin Sensitization to Predict Hazard and Potency Categorization.
- Speaker: Kim To

6. ChemMaps & Dass App Q & A (5 mins)



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

**12th ASCCT Annual Meeting
2023-10-25**

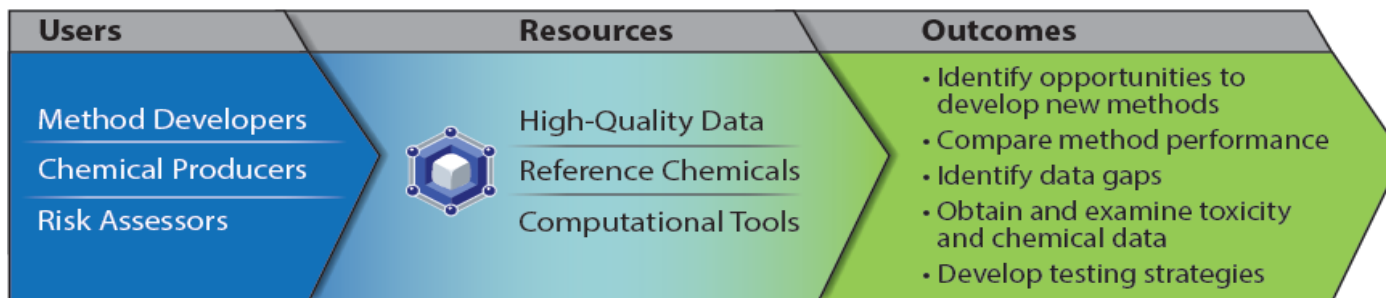
**Presented by Aswani Unnikrishnan, Inotiv, contractor supporting NICEATM
ICE-support@niehs-nih.gov**

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

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






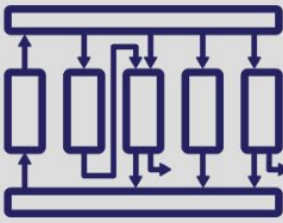


Integrated Chemical Environment

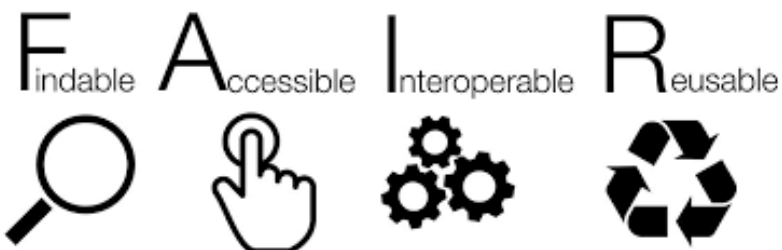


Releases in 2023:

ICE v4.0 (March)

ICE v4.0.1 (August)

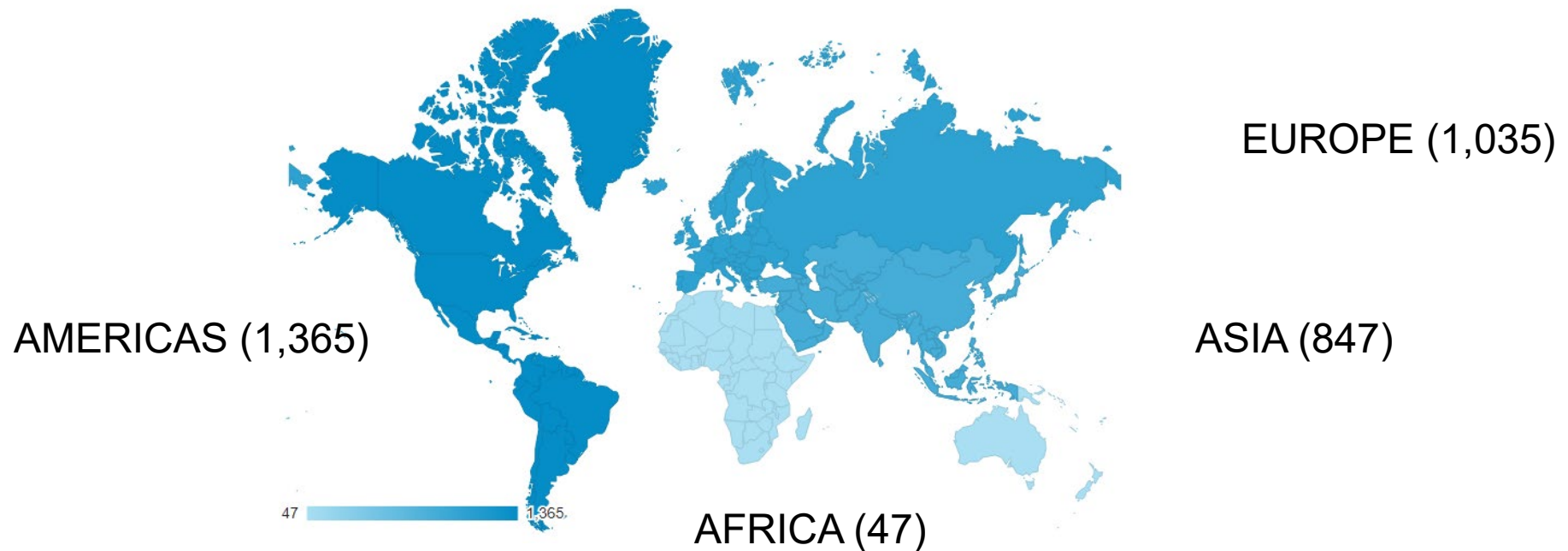
 Search ›	 Chemical Quest ›	 Curve Surfer ›	 PBPK ›
 IVIVE ›	 Chemical Characterization ›	 Data ›	 Help Videos ›



ICE: Site Visits January 2023 – October 2023

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

Users From Around The World



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

Toxicity Endpoints
Chemical Parameters
ADME Parameters
Acute Toxicity
Cancer
DART

Toxicity Endpoints
Skin Sensitization
Skin Irritation
Eye Irritation
Endocrine
cHTS
Exposure

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

		MOA		TE		MT		
A	B	C	D	E	F	G	H	I
1 AssayEndpointName	Assay_MOA	ModeofAction	MOA_ToxicityEndpoint	ToxicityEndpoint	Assay_MechanisticTarget	MechanisticTarget	MT_NCIm_term	MT_NCIm_term_ID
2 APR_HepG2_MicrotubuleCSK_1h_dn	mayInformOn	AcuteTox - Cytotoxicity	mayContributeTo	Acute Lethality	throughMechanisticTarget	Cell Morphology	Cell Viability Process	CUI:C1516362
3 APR_HepG2_MicrotubuleCSK_1h_up	mayInformOn	AcuteTox - Cytotoxicity	mayContributeTo	Acute Lethality	throughMechanisticTarget	Cell Morphology	Cell Viability Process	CUI:C1516362
4 APR_HepG2_MitoMass_1h_dn	mayInformOn	AcuteTox - Energy Metabolism Process	mayContributeTo	Acute Lethality	throughMechanisticTarget	Mitochondrial Function	Energy Metabolism Process	CUI:C0014272
5 APR_HepG2_MitoMass_1h_up	mayInformOn	AcuteTox - Energy Metabolism Process	mayContributeTo	Acute Lethality	throughMechanisticTarget	Mitochondrial Function	Energy Metabolism Process	CUI:C0014272
6 APR_HepG2_MitoMembPot_1h_dn	mayInformOn	AcuteTox - Energy Metabolism Process	mayContributeTo	Acute Lethality	throughMechanisticTarget	Mitochondrial Function	Energy Metabolism Process	CUI:C0014272
7 APR_HepG2_MitoMembPot_1h_up	mayInformOn	AcuteTox - Energy Metabolism Process	mayContributeTo	Acute Lethality	throughMechanisticTarget	Mitochondrial Function	Energy Metabolism Process	CUI:C0014272
8 APR_HepG2_p53Act_1h_dn	mayInformOn	AcuteTox - p53 Signaling Pathway	mayContributeTo	Acute Lethality	throughMechanisticTarget	p53 Modulation	p53 Signaling Pathway	CUI:C2984306
9 APR_HepG2_p53Act_1h_up	mayInformOn	AcuteTox - p53 Signaling Pathway	mayContributeTo	Acute Lethality	throughMechanisticTarget	p53 Modulation	p53 Signaling Pathway	CUI:C2984306
10 APR_HepG2_CellLoss_24h_dn	mayInformOn	AcuteTox - Cytotoxicity	mayContributeTo	Acute Lethality	throughMechanisticTarget	Cell Viability	Cell Viability Process	CUI:C1516362
11 APR_HepG2_MicrotubuleCSK_24h_up	mayInformOn	AcuteTox - Cytotoxicity	mayContributeTo	Acute Lethality	throughMechanisticTarget	Cell Morphology	Cell Viability Process	CUI:C1516362
12 APR_HepG2_MitoMass_24h_dn	mayInformOn	AcuteTox - Energy Metabolism Process	mayContributeTo	Acute Lethality	throughMechanisticTarget	Mitochondrial Function	Energy Metabolism Process	CUI:C0014272



Data

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

Harmonized and updated datasets!

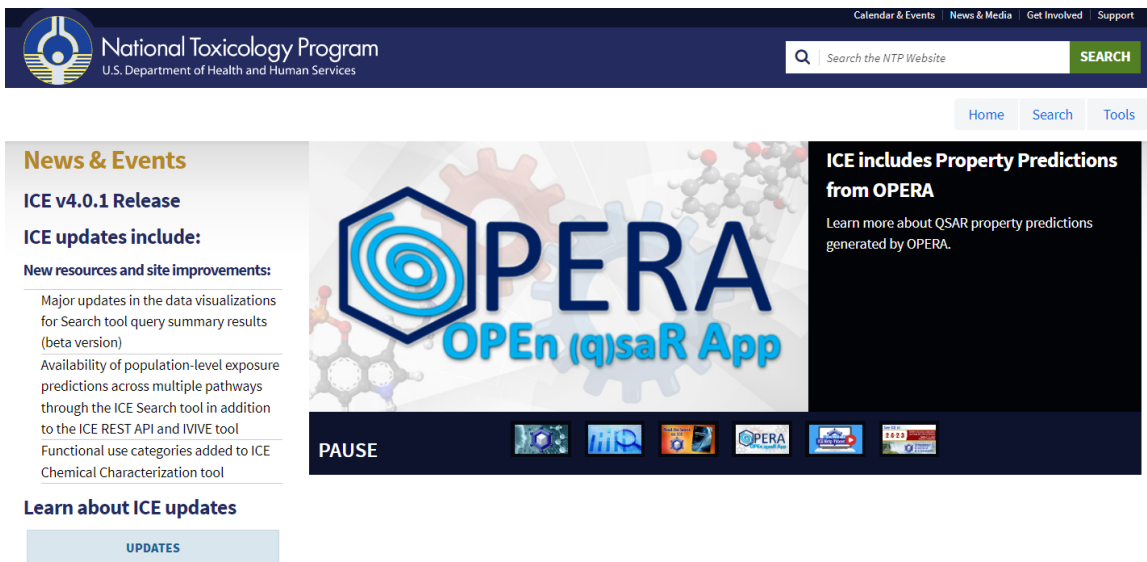


Data

ICE Data (In Silico Models/Integrated Approaches)

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

New exposure predictions!



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

Search the NTP Website SEARCH

Home Search Tools

News & Events

ICE v4.0.1 Release

ICE updates include:

New resources and site improvements:


- Major updates in the data visualizations for Search tool query summary results (beta version)
- Availability of population-level exposure predictions across multiple pathways through the ICE Search tool in addition to the ICE REST API and IVIVE tool
- Functional use categories added to ICE Chemical Characterization tool

Learn about ICE updates

UPDATES

ICE includes Property Predictions from OPERA

Learn more about QSAR property predictions generated by OPERA.



PAUSE

Open Structure-Activity/Property Relationship App (OPERA)

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



Search



Chemical
characterization



Data

Research article | [Open access](#) | Published: 08 March 2018

OPERA models for predicting physicochemical properties and environmental fate endpoints

[Kamel Mansouri](#) , [Chris M. Grulke](#), [Richard S. Judson](#) & [Antony J. Williams](#)

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

20k Accesses | 261 Citations | 25 Altmetric | [Metrics](#)

<https://github.com/NIEHS/OPERA>

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

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

Reference Chemical List

AR In Vitro Agonist

AR In Vitro Antagonist

ER In Vivo Agonist

ER In Vitro Agonist

Eye Irritation-Corrosion

Genotoxicity

OECD Defined Approach to Skin
Sensitization: Human

OECD Defined Approach to Skin
Sensitization: LLNA

Skin Corrosion

Non-reference Chemical List

AR In Vivo Agonists

AR In Vivo Antagonists

EPA Pesticide Active Ingredients

EPA Pesticide Inert Ingredients, Food and
Nonfood Use

EPA IRIS Cancer Assessment

EPA IRIS Non-Cancer Assessment

IARC Classifications

Mixtures and Formulations in ICE

NTP Cancer Bioassay Chemicals

RoC Classifications

Steroidogenesis - Androgen

Steroidogenesis - Estrogen

Thyroid

Tox21

ToxCast Phase I, Phase II, and e1k

**New quick
lists!**





Data

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



National Toxicology Program
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SEARCH

[Home](#) | [Search](#) | [Tools](#) | [Data](#) | [About](#) | [Help](#)

News & Events

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Learn about ICE updates

UPDATES

ICE version 4.0.1 Released August 2023

Visit News page for more information.

PAUSE

- ICE Data Sets
- Data Sets
- Acute Lethality
- Cancer
- Cardiotoxicity
- DART
- Endocrine
- Irritation-Corrosion
- Sensitization
- cHTS
- Chemical Parameters
- Exposure Predictions
- Other Datasets

Data Sets

ICE contains data sets curated for targeted toxicity endpoints by NICEATM, ICCVAM, and their partner organizations. ICE also contains other data sets that may be useful in evaluating or developing new approaches for assessing chemical safety.

The data available in ICE are described in detail under the corresponding ICE Data Sets section in the left sidebar. Each Data Sets page contains information on the assays and their endpoints that make up the data set. Assays and chemicals included in each data set can be selected to query data in Search or run workflows in Tools.

Data in ICE are mostly organized around toxicity endpoints of regulatory interest and assay type. ICE also includes a data set drawn from cHTS data, and a data set of physicochemical parameters. The cHTS data set contains data from assays run by laboratories participating in the Tox21 Consortium (including ToxCast data). These data have been annotated based on their mechanistic target to simplify querying and to allow linkage to other toxicity endpoints through modes of action.

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)
Acute Inhalation Toxicity <ul style="list-style-type: none"> 1556 Chemicals 3 Endpoints 5956 Records 	In vivo data that describe toxic effects occurring within a short period after a single uninterrupted exposure to a test substance by inhalation. Includes data on mixtures and active ingredients. Learn more	<ul style="list-style-type: none"> Download Query (Search, REST API)

Search >

Chemical Quest >

Curve Surfer >

PBPK >

IVIVE >

Chemical Characterization >

Data >

Help Videos >

- For one or more chemical ids, return a list of Assay/Endpoint objects.
 - Query one chemical id using GET
 - Query multiple chemicals using POST
 - Results are formatted in JSON
 - Same data structure for POST and GET REST requests.
 - Array of Assay/Endpoint objects per chemical.
- <https://ice.ntp.niehs.nih.gov/api/v1/search>

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



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:		"MKXKFYHWDHIYRV-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"



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

Integrated Chemical Environment

News & Events

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- Availability of population-level exposure predictions across multiple pathways through the ICE Search tool in addition to the ICE REST API and IVIVE tool
- Functional use categories added to ICE Chemical Characterization tool

Learn about ICE updates

UPDATES

Home Search **Tools** Data About Help

ICE version 4.0.1 Released August 2023
Visit News page for more information.

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

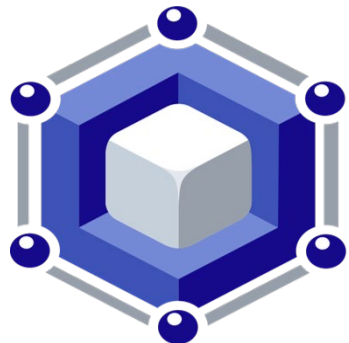
Search and other tools can also be accessed through the search tab and tools tab, respectively.



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

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

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



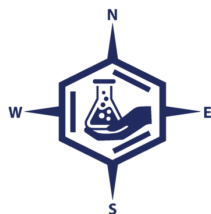
Integrated Chemical Environment

Perform a
search



Search

Expand
inventory:
Identify
similar
chemicals



Chemical Quest

Characterize
chemical
inventory



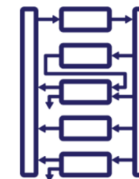
Chemical
characterization

Review
in vitro
data details



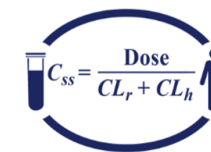
Curve Surfer

Generate
chemical
concentration
predictions



PBPK

Predict
equivalent
administered
dose from in
vitro data



IVIVE



National Institute of
Environmental Health Sciences
Division of Translational Toxicology

Demo

Exploring ICE



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



Integrated Chemical Environment

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

Perform a
search



Search

Expand
inventory:
Identify
similar
chemicals



Chemical Quest

Characterize
chemical
inventory



Chemical
characterization

Review
in vitro
data details



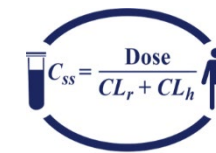
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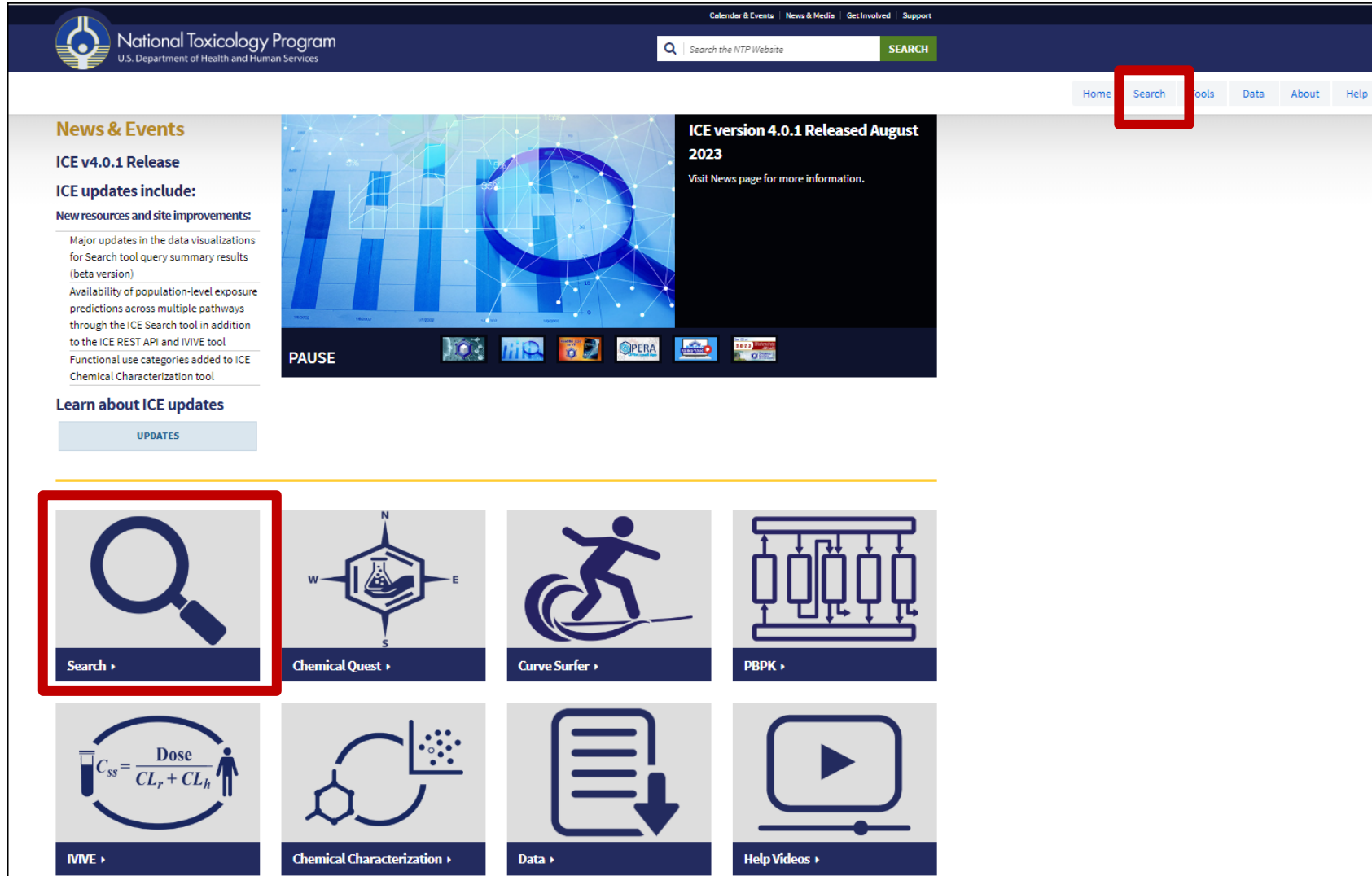


PBPK

Predict
equivalent
administered
dose from in
vitro data



IVIVE



The screenshot shows the National Toxicology Program website. At the top left is the NIH logo and the text "National Institute of Environmental Health Sciences, Division of Translational Toxicology". At the top right is a search icon and the text "Search". Below this is a navigation bar with "Home", "Search", "Tools", "Data", "About", and "Help". The "Search" link is highlighted with a red box. Below the navigation bar is a "News & Events" section with a "ICE v4.0.1 Release" announcement. Below this is a "Learn about ICE updates" section with a "UPDATES" button. At the bottom is a grid of icons for various tools: Search (highlighted with a red box), Chemical Quest, Curve Surfer, PBPK, IVIVE, Chemical Characterization, Data, and Help Videos.

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U.S. Department of Health and Human Services

Search the NTP Website SEARCH

Home Search Tools Data About Help

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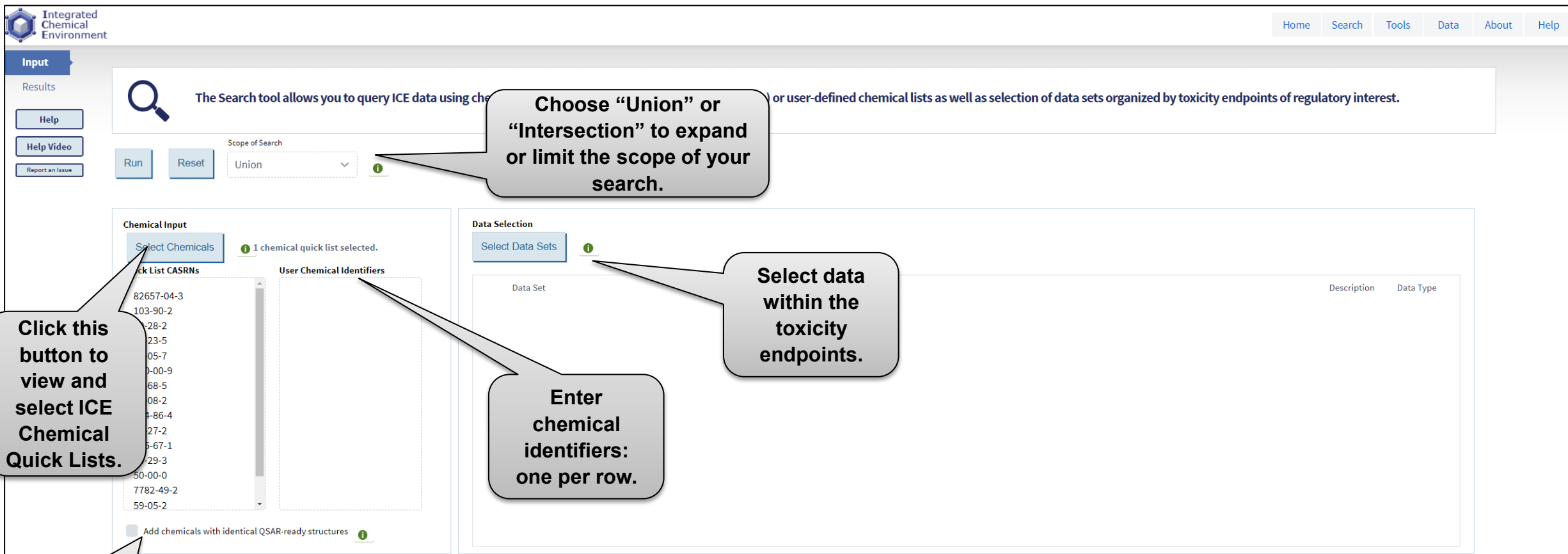
Chemical Characterization

Data

Help Videos

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





The screenshot shows the 'Search Input View' interface. At the top left is the 'Integrated Chemical Environment' logo. A navigation bar contains 'Home', 'Search', 'Tools', 'Data', 'About', and 'Help'. The main content area has a search bar with a magnifying glass icon and the text 'The Search tool allows you to query ICE data using chemical names, chemical identifiers, or user-defined chemical lists as well as selection of data sets organized by toxicity endpoints of regulatory interest.' Below the search bar are 'Run' and 'Reset' buttons. A 'Scope of Search' dropdown menu is set to 'Union'. Below this are two main sections: 'Chemical Input' and 'Data Selection'. The 'Chemical Input' section has a 'Select Chemicals' button and a '1 chemical quick list selected.' indicator. It contains a list of 'Quick List CASRNs' (e.g., 82657-04-3, 103-90-2, etc.) and a 'User Chemical Identifiers' text input field. The 'Data Selection' section has a 'Select Data Sets' button and a table with columns 'Data Set', 'Description', and 'Data Type'. Callout boxes provide instructions: 'Click this button to view and select ICE Chemical Quick Lists.' points to the 'Select Chemicals' button; 'Choose "Union" or "Intersection" to expand or limit the scope of your search.' points to the 'Scope of Search' dropdown; 'Enter chemical identifiers: one per row.' points to the 'User Chemical Identifiers' field; and 'Select data within the toxicity endpoints.' points to the 'Select Data Sets' button. At the bottom left, another callout box says 'Add chemicals available in ICE to your query that have the same QSAR structure as a chemical you have specified.' pointing to a checkbox labeled 'Add chemicals with identical QSAR-ready structures'.

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

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

Enter chemical identifiers: one per row.

Select data within the toxicity endpoints.

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

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 [?](#)

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 [?](#)

OECD Defined Approach to Skin Sensitization Human (R) [?](#)

OECD Defined Approach to Skin Sensitization LLNA (R) [?](#)

RoC Classifications [?](#)

Skin Corrosion (R) [?](#)

Steroidogenesis - Androgen [?](#)

Steroidogenesis - Estrogen [?](#)

Thyroid [?](#)

Tox21 [?](#)

ToxCast Phase I, Phase II, and e1k [?](#)

Finished

ICE Chemical Quick Lists

ICE Chemical Quick Lists

Reference Chemical Lists

Non-reference Chemical Lists

Chemical Quick Lists

ICE Chemical Quick Lists can be used to quickly populate an ICE query. ICE Chemical Quick Lists are lists of chemicals that may be useful for searching ICE for data relevant to endpoints or activities of interest. Most lists were compiled during evaluations of novel testing approaches or for initiatives such as [Tox21](#).

- Reference Chemical Quick Lists** include chemicals that cause a specified well-characterized biological effect and therefore can be used to assess the performance of an assay designed to measure that effect.
- Non-reference Chemical Quick Lists** have inclusion criteria that are less restrictive than those of reference chemical lists, so these lists may include chemicals with uncharacterized or ambiguous biological effects.

If a chemical appears in multiple quick lists selected for an ICE query, it will only be returned once in the results. Reference chemical lists are indicated by "(R)" in the Select Chemical box.

Download Chemical Quick Lists

Quick List	Description	Reference Chemical List
AR In Vitro Agonist (R)	37 chemicals with androgen receptor agonist activity characterized in in vitro assays. Learn more	Yes
AR In Vitro Antagonist (R)	28 chemicals with androgen receptor antagonist activity characterized in in vitro assays. Learn more	Yes
AR In Vivo Agonist	26 chemicals with androgen receptor agonist activity characterized in in vivo assays. Learn more	No
AR In Vivo Antagonist	23 chemicals with androgen receptor antagonist activity characterized in in vivo assays. Learn more	No
EPA Pesticide Active Ingredients	510 chemicals identified by EPA as active ingredients in pesticides. Learn more	No
EPA Pesticide Inert Ingredients, Food and Nonfood Use	1654 chemicals identified by EPA as inert pesticide ingredients, "Food and Nonfood Use". Learn more	No
EPA IRIS Cancer Assessment	94 chemicals classified for weight of evidence of carcinogenicity according to the EPA Guidelines for Carcinogen Risk Assessment. Learn more	No

Home Search Tools Data About Help

Data Sets

Chemical Quick Lists



Integrated Chemical Environment

Home Search

Input

Results

Help
Help Video
Report an Issue

Run Reset

Chemical Input

Select Chemicals

Quick List CASRNs

Add chemicals with

Finished

Select Data Sets

cHTS Acute Lethality Sensitization Irritation/Corrosion Endocrine Cancer Cardiotoxicity DART Chemical Properties Exposure

cHTS
 Abnormal Growth and Differentiation
 Angiogenic Process
 Cellular Processes
 Cellular Stress Response
 Endocrine-Related Processes
 Energy Metabolism Process
 Epigenetic Process
 Gene Expression
 Immune and Inflammatory Response
 Neuronal Transmission
 Xenobiotic Metabolism
 Unannotated

in vitro
in vitro
in vitro

Each tab represents an assay category.

Select Data Sets

cHTS **Acute Lethality** Sensitization Irritation/Corrosion Endocrine Cancer Cardiotoxicity DART

Acute Lethality
 Dermal
 Inhalation
 Oral
 In Vivo Acute Oral Toxicity Assays
 In Silico Acute Oral Toxicity Predictions
 Mode of Action
 AcuteTox - Cytotoxicity
 AcuteTox - Energy Metabolism Process
 AcuteTox - Immune and Inflammatory Response
 AcuteTox - Neuronal Transmission
 AcuteTox - Oxidative Stress
 AcuteTox - p53 Signaling Pathway
 AcuteTox - Steroid Hormone Metabolism

in vitro
in vitro
in vitro
in vitro
in vitro
in vitro
in vitro
in vitro
in vitro
in vitro

Finished

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



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

B Download Send filtered results to: Select tool... Clear Filter Long View Number of chemicals = 61

Substance Name	Substance Type	CASRN (CEBS Link)	DTXSID (Dashboard Link)	QSAR Ready ID	Abnormal Growth and Differentiation Call (# Assays=6)	Angiogenic Process Call (# Assays=28)	Cell Death Process Assays=12	Cell Cycle Call (# Assays=68)	Cell Proliferation Call (# Assays=6)	Cell Viability Call (# Assays=1...)	Extracell... Matrix Call (# Assays=22)	DNA Dama Call (# Assays=1...)
1-Naphthalenol, 1-(N-methylcarbamate)	Chemical	63-25-2	DTXSID020247	VOXZDWN... UHFFFAOY... N	QC-Omit(N=6)	QC-Omit(N=2... Tested(N=6)	QC-Omit(N=5... Tested(N=7)	QC-Omit(N=5... Tested(N=...)	QC-Omit(N=6)	Active(N=2... Omit(N=8... Tested(N=...)	QC-Omit(N=22)	Activ
17beta-Estradiol	Chemical	50-28-2	DTXSID0020573	VOXZDWN... UHFFFAOY... N	Active, Not Tested(N=5)	Active(N=3... Tested(N=6)	Inactive(N... Tested(N=7)	Active(N=6... Tested(N=...)	Inactive(N...)	Active(N=3... Omit(N=7... Tested(N=...)	Active(N=2...)	Activ

C Filter icons for each column header.

A

Send filtered results to: Select tool... Clear Filter

- Curve Surfer
- PBPK
- IVIVE
- Chemical Quest
- Chem Characterization
- Copy CASRNs
- Copy DTXSIDs
- Copy SMILES
- Copy Qsar-Ready SMILES

View Details 1

17beta-Estradiol

B

C

Click icons to view substance details.

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

Click icons to filter results.

B

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 ACSO values for assays with an "Active" chemical. Call values are returned for assays with no active chemicals.

Close

C

Abnormal Growth and Differentiation Call (# Assays=6) Count: 5

Abnormal Growth and Differentiation Call (# Assays=6)

- Active
- Flag-Omit
- Inactive
- Not Tested
- QC-Omit

Close

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



Summary Data

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

Plot Type

- Stacked Bar
- Pie

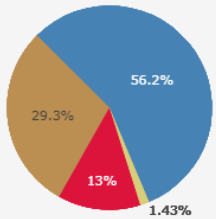
Select Assay Type(s)

- In Vivo x
- In Silico x
- In Vitro x

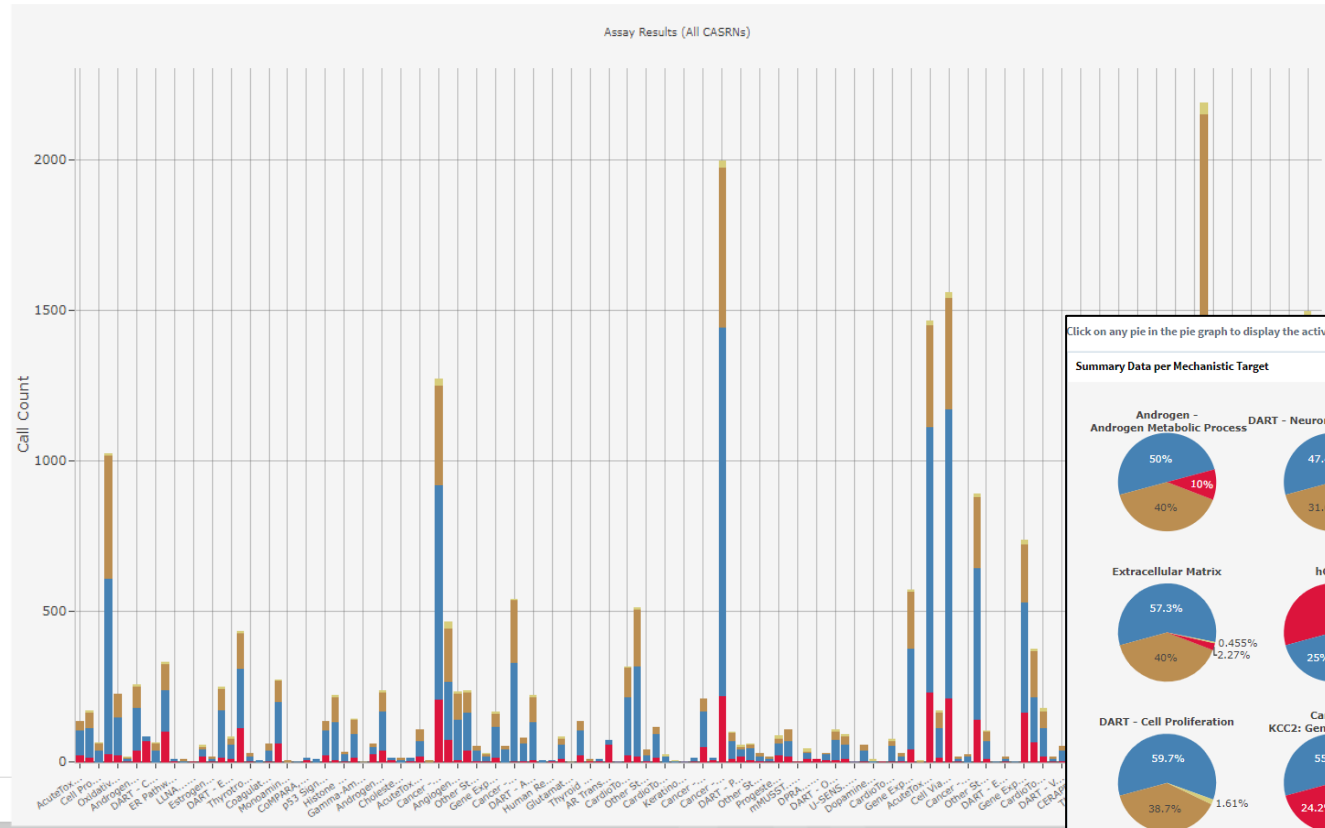
Legend

- Active
- Inactive
- QC-omit
- Flag-omit
- Not tested

All Query Data
Number of Calls=41374
Number of Assay Categories=132

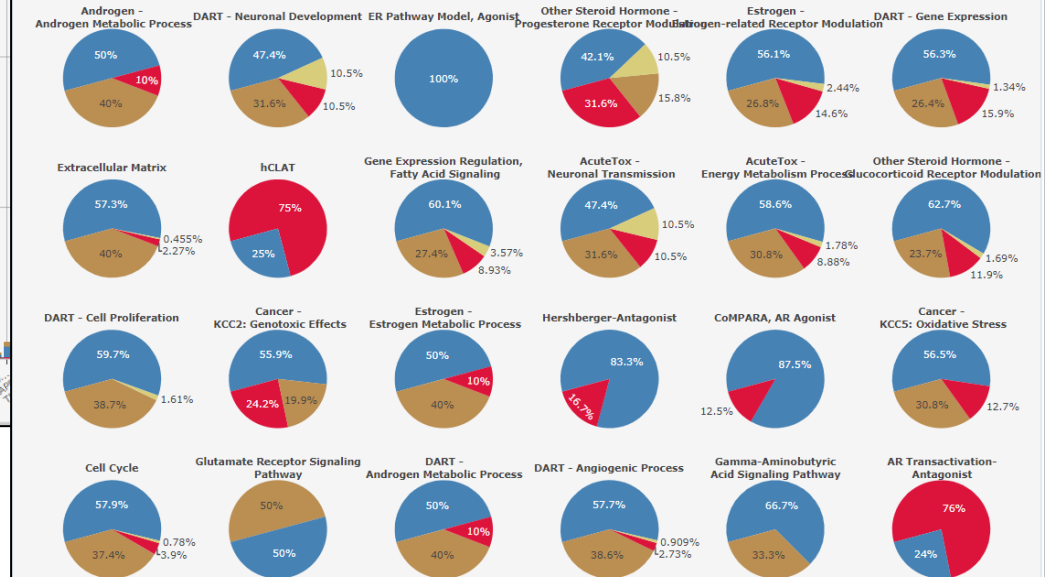


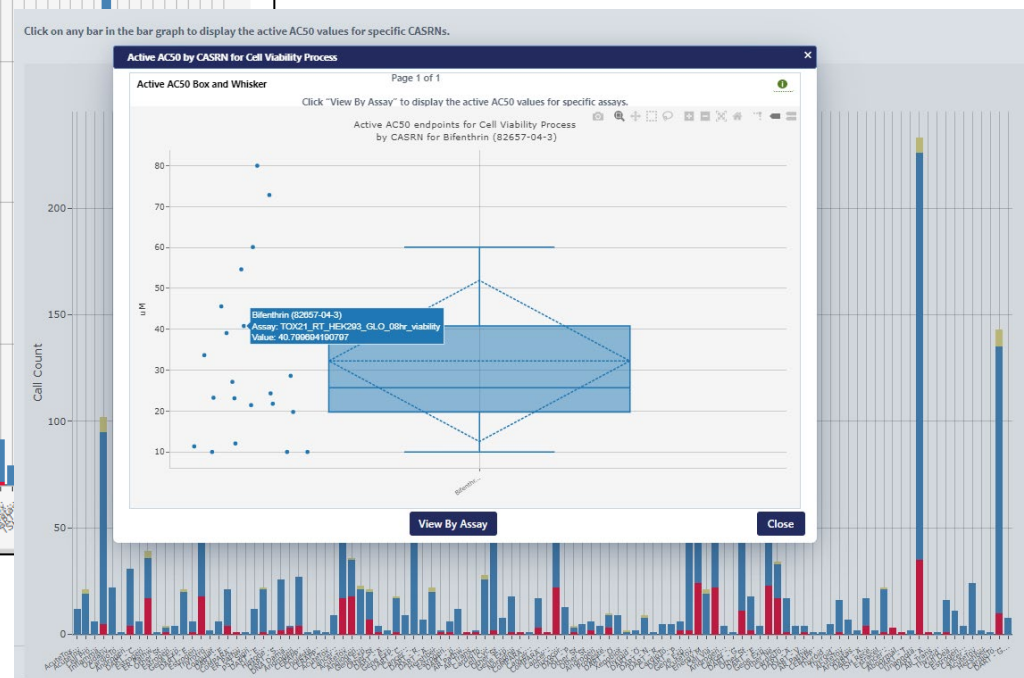
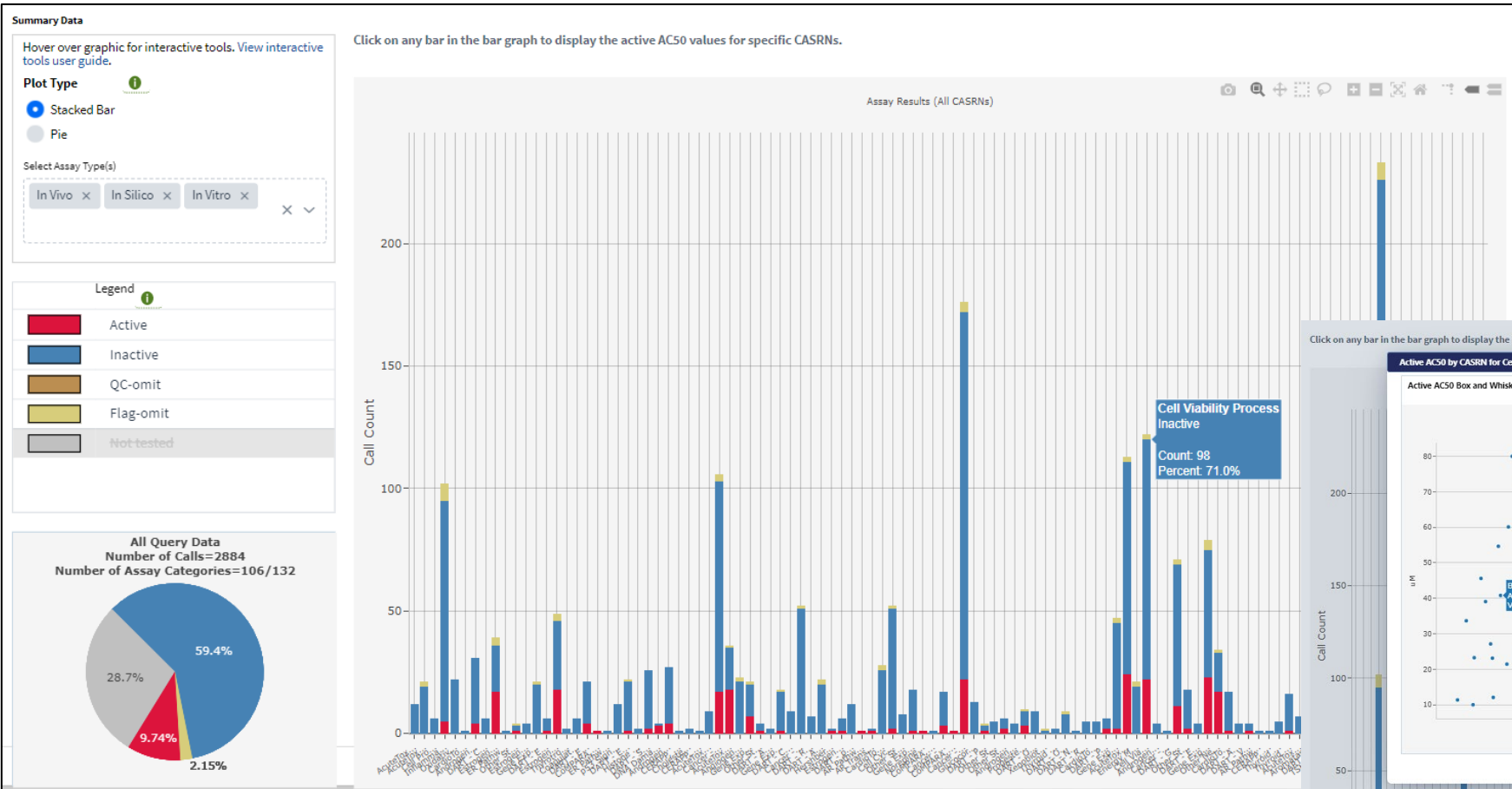
Click on any bar in the bar graph to display the active AC50 values for specific CASRNs.



Click on any pie in the pie graph to display the active AC50 values for specific CASRNs.

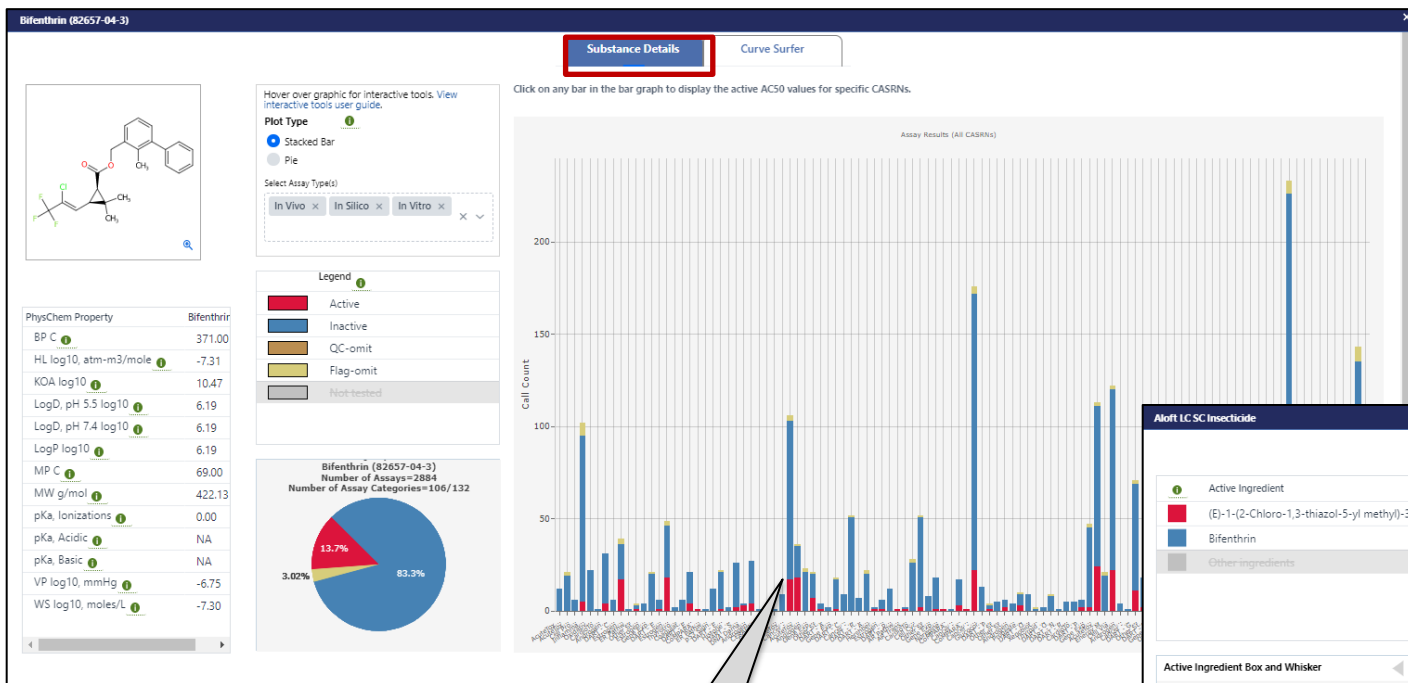
Summary Data per Mechanistic Target



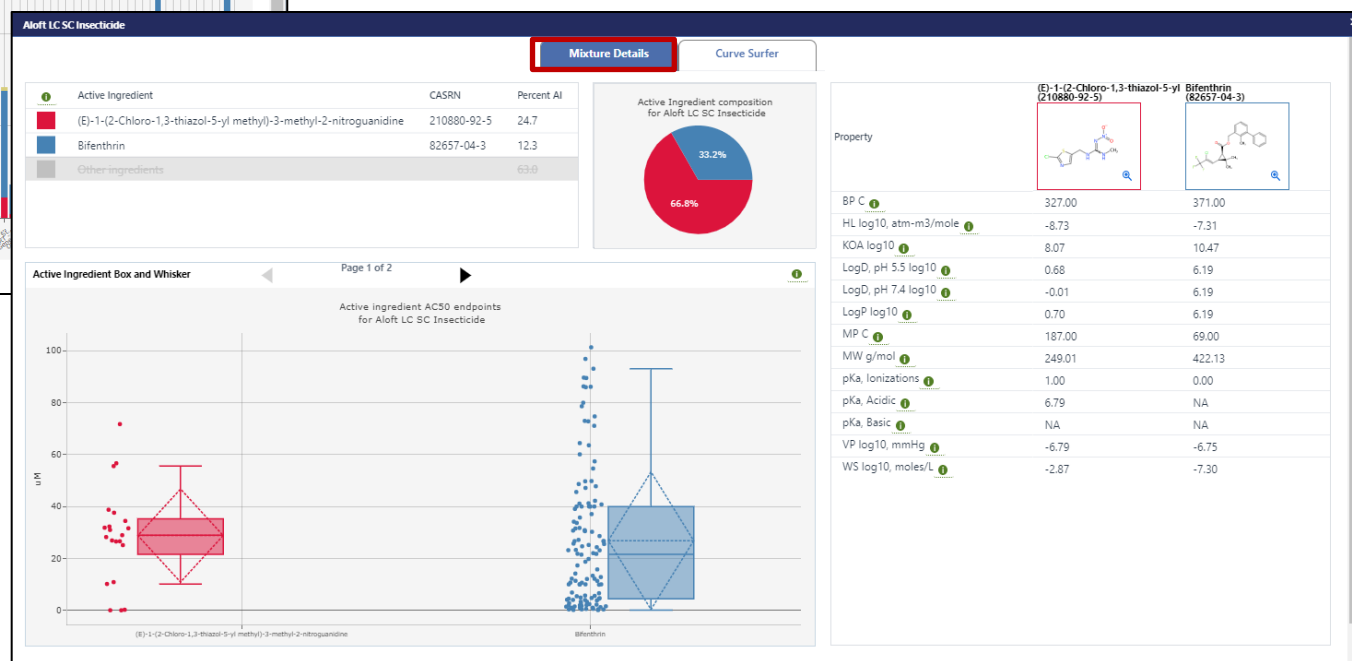


Active AC50 Plot for Assay Chemical Combo

Detail View for Single Chemical



Detail View for Mixtures



Bifenthrin (82657-04-3)

Substance Details
Curve Surfer

Select Filter to add to chain: 1

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

Select All Filtered

Only show selected

Select this item

Select Page: 1 of 34

Showing 1-10 of 338 curves.

Sort Results By: Chemical Name

Direction: Asc

Overlay Selected 1 | Overlay Filtered

ACEA_AR_agonist_AUC_viability
82657-04-3

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

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

ACEA_AR_antagonist_80hr
82657-04-3

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

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



Send filtered results to: Download Select tool... Clear Filter **Long View** Number of chemicals = 61

View Details

Details

Clear Filter Endpoint Record Count: 16399

Record ID	Chemical Name	Substance Type	CASRN	DTXSID	QSAR Ready ID	Assay	Endpoint	Response	Unit	Species	Receptor Species	Route
R_328211...	1-Naphthalenol, 1-(N-methylcarbamate)	Chemical	63-25-2	DTXSID9020247	CVXBEEM... UHFFFAO... N	OPERA, Number of rings	nbRing	2.0	count			
R_000001...	1-Naphthalenol, 1-(N-methylcarbamate)	Chemical	63-25-2	DTXSID9020247	CVXBEEM... UHFFFAO... N	OPERA, Boiling Point	BP	315.0	C			
R_406241...	1-Naphthalenol, 1-(N-methylcarbamate)	Chemical	63-25-2	DTXSID9020247	CVXBEEM... UHFFFAO... N	TOX21_DT...	Top of curve	93.3395	% activity			
R_406241...	1-Naphthalenol, 1-(N-methylcarbamate)	Chemical	63-25-2	DTXSID9020247	CVXBEEM... UHFFFAO... N	TOX21_PX...	Top of curve					
R_406241...	1-Naphthalenol, 1-(N-methylcarbamate)	Chemical	63-25-2	DTXSID9020247	CVXBEEM... UHFFFAO... N	TOX21_A...	Top of curve					
R_406241...	1-Naphthalenol, 1-(N-methylcarbamate)	Chemical	63-25-2	DTXSID9020247	CVXBEEM... UHFFFAO... N	TOX21_C...	Top of curve					
R_406241...	1-Naphthalenol, 1-(N-methylcarbamate)	Chemical	63-25-2	DTXSID9020247	CVXBEEM... UHFFFAO... N	TOX21_DT...	Top of curve					
R_406241...	1-Naphthalenol, 1-(N-methylcarbamate)	Chemical	63-25-2	DTXSID9020247	CVXBEEM... UHFFFAO... N	TOX21_ER...	Top of curve					

Summary Data

Hover over graphic for interactive tools user guide.

Plot Type

- Stacked Bar
- Pie

Select Assay Type(s)

In Vivo In Silico

Legend

- Active
- Inactive
- QC-omit

4/18 chemicals -> Active
 (TOX21_RT_HEK293_GLO_08hr_viability)

Details

Clear Filter Endpoint Record Count: 16399

Record ID	Chemical Name	Substance Type	CASRN	DTXSID	QSAR Ready ID	Assay	Endpoint	Response	Unit	Species	Receptor Species	Route
R_328211...	1-Naphthalenol, 1-(N-methylcarbamate)	Chemical	63-25-2	DTXSID9020247	CVXBEEM... UHFFFAO... N	OPERA, Number of rings	nbRing	2.0	count			
R_000001...	1-Naphthalenol, 1-(N-methylcarbamate)	Chemical	63-25-2	DTXSID9020247	CVXBEEM... UHFFFAO... N	OPERA, Boiling Point	BP	315.0	C			
R_406241...	1-Naphthalenol, 1-(N-methylcarbamate)	Chemical	63-25-2	DTXSID9020247	CVXBEEM... UHFFFAO... N	TOX21_DT...	Top of curve	93.3395	% activity			
R_406241...	1-Naphthalenol, 1-(N-methylcarbamate)	Chemical	63-25-2	DTXSID9020247	CVXBEEM... UHFFFAO... N	TOX21_PX...	Top of curve					
R_406241...	1-Naphthalenol, 1-(N-methylcarbamate)	Chemical	63-25-2	DTXSID9020247	CVXBEEM... UHFFFAO... N	TOX21_A...	Top of curve					
R_406241...	1-Naphthalenol, 1-(N-methylcarbamate)	Chemical	63-25-2	DTXSID9020247	CVXBEEM... UHFFFAO... N	TOX21_C...	Top of curve					
R_406241...	1-Naphthalenol, 1-(N-methylcarbamate)	Chemical	63-25-2	DTXSID9020247	CVXBEEM... UHFFFAO... N	TOX21_DT...	Top of curve					
R_406241...	1-Naphthalenol, 1-(N-methylcarbamate)	Chemical	63-25-2	DTXSID9020247	CVXBEEM... UHFFFAO... N	TOX21_ER...	Top of curve					
R_406241...	1-Naphthalenol, 1-(N-methylcarbamate)	Chemical	63-25-2	DTXSID9020247	CVXBEEM... UHFFFAO... N	TOX21_RT...	Top of curve	30.4428	% activity			
R_406241...	1-Naphthalenol, 1-(N-methylcarbamate)	Chemical	63-25-2	DTXSID9020247	CVXBEEM... UHFFFAO... N	TOX21_RT...	Top of curve	32.808	% activity			
R_406241...	1-Naphthalenol, 1-(N-methylcarbamate)	Chemical	63-25-2	DTXSID9020247	CVXBEEM... UHFFFAO... N	TOX21_RT...	Top of curve	53.2365	% activity			
R_406241...	1-Naphthalenol, 1-(N-methylcarbamate)	Chemical	63-25-2	DTXSID9020247	CVXBEEM... UHFFFAO... N	TOX21_RT...	Top of curve	111.3169	% activity			
R_406241...	1-Naphthalenol, 1-(N-methylcarbamate)	Chemical	63-25-2	DTXSID9020247	CVXBEEM... UHFFFAO... N	TOX21_ER...	Top of curve	32.6558	% activity			

Assay Count: 1179, Selected Rows = 1

- TOX21_RT_HEK293_FLO_40hr...
- TOX21_RT_HEK293_GLO_00hr...
- TOX21_RT_HEK293_GLO_08hr...
- TOX21_RT_HEK293_GLO_16hr...
- TOX21_RT_HEK293_GLO_24hr...
- TOX21_RT_HEK293_GLO_32hr...
- TOX21_RT_HEK293_GLO_40hr...
- TOX21_RT_HEPG2_FLO_00hr...
- TOX21_RT_HEPG2_FLO_08hr...
- TOX21_RT_HEPG2_FLO_16hr...

Close



Input

Results

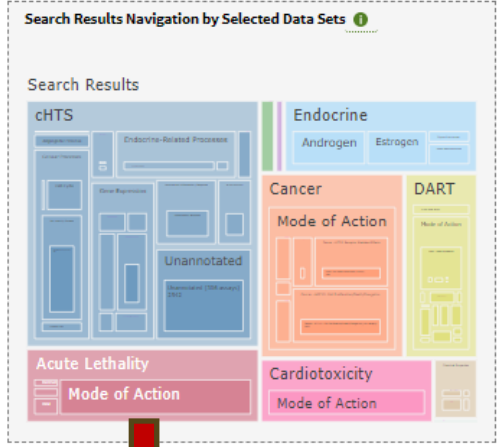
Help

Help Video

Report an Issue

> Search Results Info

Data Summary **Query Summary (Beta)**



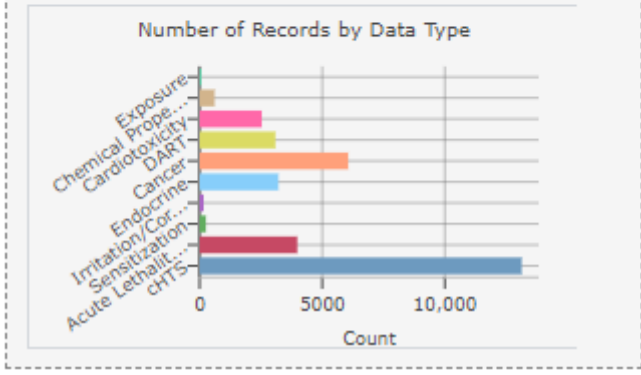
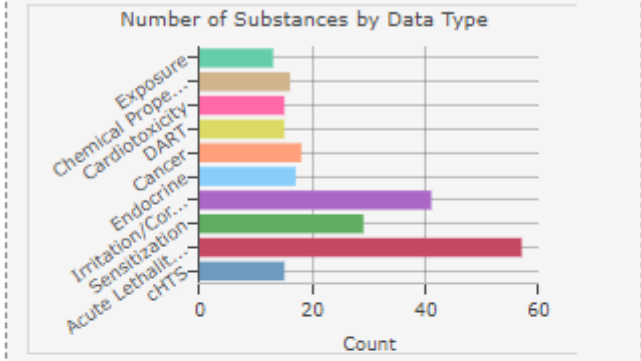
Results Distribution by Chemical Reference List (0 substances queried)

Chemical List	Queried	Chemicals	Mixtures	Not Return...	Number of Records

Search Results by DTXSID, CASRN (14405 records for 61 substances)

Name	Type	CASRN	DTXSID	Number of Records
Enhance AW(19.55)	Mixtu...	ICE_31...	NA	1
The Andersons 0.058...	Mixtu...	ICE_10...	NA	1
Cisplatin	Che...	15663-...	DTXSID40...	1
Dimethyl sulfoxide	Che...	67-68-5	DTXSID20...	1
Alllectus SC Insecticide	Mixtu...	ICE_41...	NA	1

Substance and Record View



Acute Lethality

Assay Call Results (Acute Lethality)

Page 1 of 1

AcuteTox - Energy Metabolism Process (21 assays)

Call (26 records for 15 substances)

Page 1 of 1

AcuteTox - Cytotoxicity (122 assays)

Call (148 records for 15 substances)

Page 1 of 1



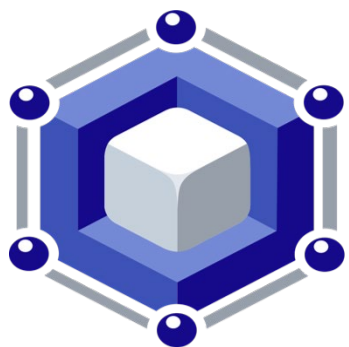
Demo

Exploring ICE Search using “A Demo
List of Chemicals”



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

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



Integrated Chemical Environment

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

Perform a
search



Search

Expand
inventory:
Identify
similar
chemicals



Chemical Quest

Characterize
chemical
inventory



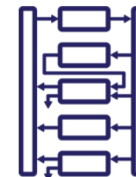
Chemical
characterization

Review
in vitro
data details



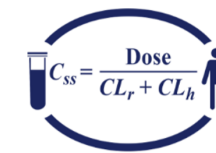
Curve Surfer

Generate
chemical
concentration
predictions



PBPK

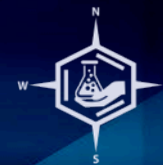
Predict
equivalent
administered
dose from in
vitro data



IVIVE



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



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

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Search the NTP Website SEARCH

Home Search **Tools** Data About Help

News & Events

ICE v4.0.1 Release

ICE updates include:

New resources and site improvements:

- Major updates in the data visualizations for Search tool query summary results (beta version)
- Availability of population-level exposure predictions across multiple pathways through the ICE Search tool in addition to the ICE REST API and IVIVE tool
- Functional use categories added to ICE Chemical Characterization tool

Learn about ICE updates

UPDATES

ICE version 4.0.1 Released August 2023
Visit News page for more information.

PAUSE

Search

Chemical Quest

Curve Surfer

PBPK

IVIVE

Chemical Characterization

Data

Help Videos

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

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



Send filtered results to:

Download Select tool... Clear Filter

View Details

- Curve Surfer
- PBPK
- IVIVE
- Chemical Quest**
- Chem Characterization
- Copy CASRNs
- Copy DTXSIDs
- Copy SMILES
- Copy Qsar-Ready SMILES

17beta-Estradiol



The screenshot shows the Chemical Quest web application interface. The main page has a navigation bar with tabs for 'Chemical Quest', 'Curve Surfer', 'PBPK', 'IVIVE', and 'Chemical Characterization'. The 'Chemical Quest' tab is active. Below the navigation bar, there is a header section with the text: 'The Chemical Quest tool uses fingerprints to calculate structure similarity.' and 'This tool uses fingerprints generated using Saagar features. Only 50 input chemical ids/structures allowed at a time.' Below this, there are 'Run' and 'Reset' buttons, and a checkbox for 'Search Custom Chemical List'. There are also input fields for 'Max hits per input:' (set to 10) and 'Tanimoto Coefficient:' (set to 0.7 or greater). Below these are two main input areas: 'Chemical ID input (one per line.)' and 'Smiles Structures for similarity search'. The 'Chemical ID input' area contains a list of chemical IDs: 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. The 'Smiles Structures for similarity search' area has 'Draw' and 'Enter' buttons, and a 'Chemical Structure' dropdown menu. Below this is a 'Run' and 'Reset' button, and another 'Chemical ID input' area. A red arrow points from the 'Enter' button in the 'Smiles Structures for similarity search' area to a callout box titled 'Easy selection of common ring structures'. This callout box shows a chemical structure editor with a benzene ring substituted with a chlorine atom and a methyl group. Below the editor is a 'close' button. Another red arrow points from the 'Enter' button in the 'Smiles Structures for similarity search' area to a callout box titled 'Easy element selection'. This callout box shows a list of chemical elements: H, C, N, O, S, P, F, Cl, Br, I, Pt, [Na]. Below the list is a 'close' button. A third red arrow points from the 'Max hits per input:' and 'Tanimoto Coefficient:' input fields to a callout box titled 'Specify number of returned chemicals and desired Tanimoto value'. A fourth red arrow points from the 'Chemical ID input (one per line.)' area to a callout box titled 'Easy element selection'. The callout box titled 'Easy element selection' also shows a 'close' button.

Specify number of returned chemicals and desired Tanimoto value

Easy selection of common ring structures

Easy element selection



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

Input
Results

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.

Run | Reset | Search Custom Chemical List

Help | Report an Issue

Tanimoto Coefficient: or greater

Chemical ID input (one per line).

Smiles Structures for similarity search
+ Draw | + Enter
Chemical Structure

Custom Chemical Search Targets
Select Chemicals
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

Search for similar structures within specified chemical lists

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
- 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



Input
Results

Chemical Quest Results

Send filtered results to:
Select tool... [Clear Filter](#)

Help
Report an Issue

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

Chemical Name	CASRN	DTXSID	Tanimoto	Hit Count	Passed Filter(s)	Selected Item(s)
Acetaminophen	103-90-2	DTXSID2020006	top 10 hits and >0.7	10	10/10	0/10
Perfluorooctanoic acid	335-67-1	DTXSID8031865	top 10 hits and >0.7	10	10/10	0/10
DDT	50-29-3	DTXSID4020375	top 10 hits and >0.7	10	10/10	0/10
Caffeine	58-08-2	DTXSID0002032	top 10 hits and >0.7	10	10/10	0/10

View Results

View Results

View Results

View Results



There are several filter options including filtering by specific substructures (SMARTS)

Similar Structures to: Captan

Send filtered results to: Select tool...

Select Filter to add to chain: [Dropdown]

Showing 1-10 of 10 hits: Tanimoto Desc

CASRN	DTXSID	Name	Tanimoto Value	Has Bioactivity
8003-20-1	DTXSID01339910	3a,4,7,7a-Tetrahydro-2-[(1...	1.0	false
133-06-2	DTXSID9020243	Captan	1.0	true
1092-58-2	DTXSID01137380	2-[(Dichlorofluoromethyl)...	0.961039	false
4932-79-0	DTXSID001020409	3a,4,7,7a-Tetrahydro-2-[(1...	0.890244	false
2425-06-1	DTXSID4020242	Captafol	0.888889	true
75045-72-6	DTXSID00996550	Copper(2+) zinc hydroxid...	0.888889	false
2939-80-2	DTXSID7034418	cis-Captafol	0.888889	false
86199-24-8	DTXSID10280992	(1,3-Dioxo-1,3,3a,4,7,7a-H...	0.75641	false
155967-70-7	DTXSID01153421	1H-Indazole-1,3(2H)-dio...	0.75641	false

Similar Structures to: Captan

Send filtered results to: Select tool...

Select Filter to add to chain: [Dropdown]

Select Page: 1 of 1

Select All Filtered

Select this item

CASRN: 8003-20-1
DTXSID: DTXSID01339910
Name: 3a,4,7,7a-Tetrahydro-2-[(1...

SMARTS Filter

Enter SMARTS

Add SMARTS Query

Chemicals that match the entered SMARTS Query

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

Items

10 results in 10 items listed

10 results selected of 10 (100.0%)

Close

When specifying SMART strings, the substructure will be highlighted for easy identification



Demo

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



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



Supports identification of information for data poor chemicals

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

The NICEATM Group



Integrated
Chemical
Environment

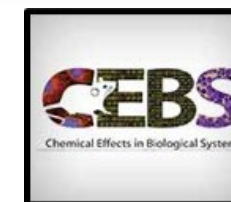


<https://github.com/>



Sciome

<https://www.sciome.com/>



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

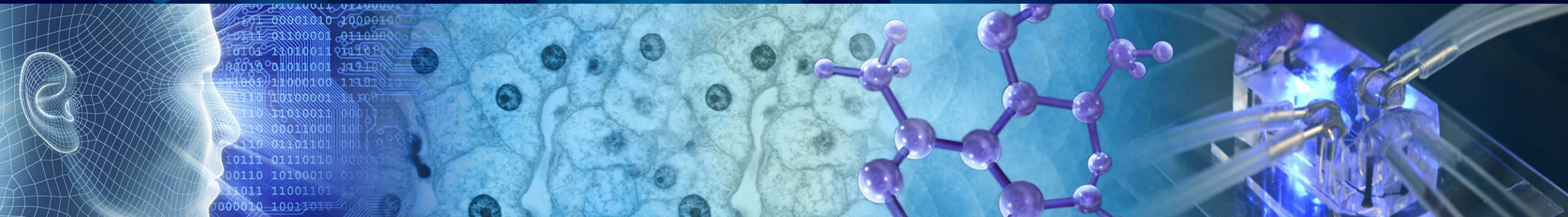


<https://comptox.epa.gov/dashboard>



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





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

12th ASCCT Annual Meeting
2023-10-25

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

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

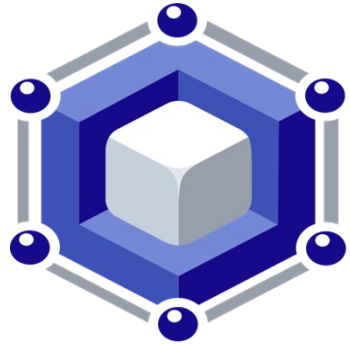
Presentation Outline

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

Introduction

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

ICE Tools Workflow



Integrated Chemical Environment

Perform a
search



Search

Expand
inventory:
Identify
similar
chemicals



Chemical Quest

Characterize
chemical
inventory



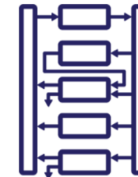
Chemical
characterization

Review
in vitro
data details



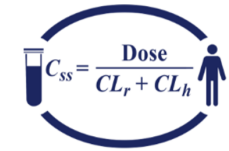
Curve Surfer

Generate
chemical
concentration
predictions



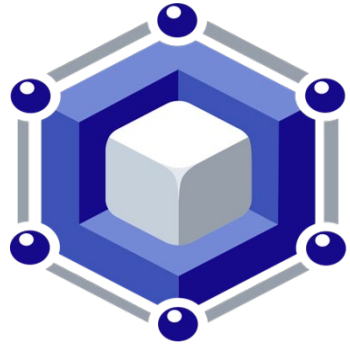
PBPK

Predict
equivalent
administered
dose from in
vitro data



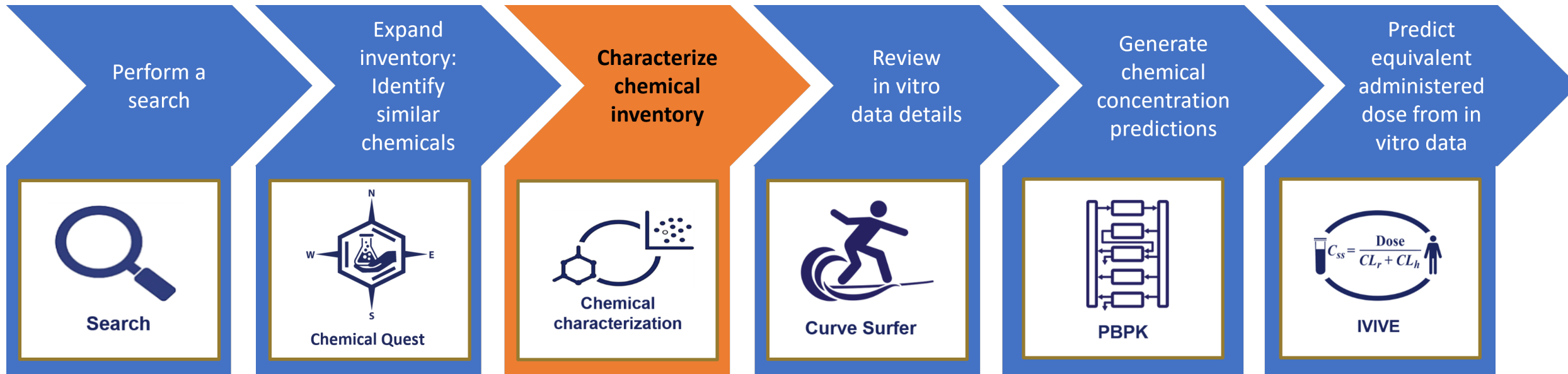
IVIVE

ICE Tools Workflow



Integrated Chemical Environment

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



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

The screenshot displays the Chemical Characterization tool interface. At the top, a navigation menu includes 'Input', 'Results', 'Help', and 'Report an Issue'. 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 is divided into two panels, each representing a chemical list. The left panel is titled 'A Demo List of Chemicals' and the right panel is titled 'AR In Vitro Agonist (R)'. Both panels feature a 'Select Chemicals' button and a status indicator '1 chemical quick list selected.' Each panel contains two columns: 'Quick List CASRNs' and 'User Chemical Identifiers'. The 'Quick List CASRNs' column in the left panel lists 15 CASRNs, and the right panel lists 15 different CASRNs. Callout boxes highlight the 'Input Demo List of Chemicals' and 'Insert a second chemical list'.

Input Demo List of Chemicals

Insert a second chemical list

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:

List Name: AR In Vitro Agonist (R)

Select Chemicals 1 chemical quick list selected.

Quick List CASRNs:

- 427-51-0
- 76-43-7
- 10161-33-8
- 51-98-9
- 58-18-4
- 58-22-0
- 68-22-4
- 797-63-7
- 965-93-5
- 10540-29-1
- 10605-21-7
- 129453-61-8
- 13311-84-7
- 17804-35-2
- 1912-24-9

User Chemical Identifiers:


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

Chemical Properties Summary i

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

Lists: Both Chemical Lists

Send filtered results to: Select tool...



OPERA v2.8
(Mansouri et al., 2018)

Users can toggle results to show results for one or both lists

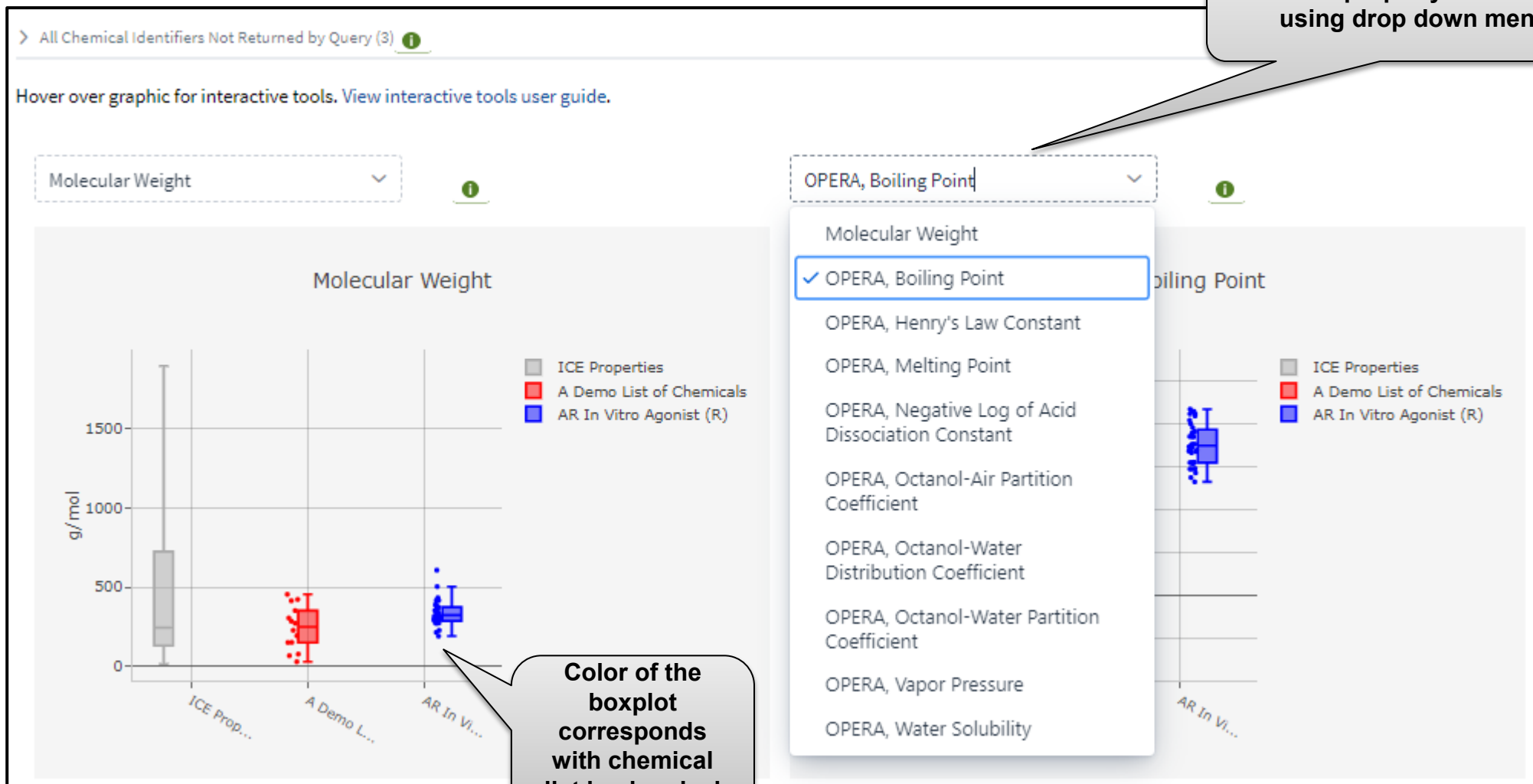
Click icons to download results

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	Cocaine	141-97-4	DTXSID0020004	305.100	310.0	0.0	25.0	10.00	0.01	0.00	0.00	0.00	4.47

Chemical List Statistical Summary of (OPERA) Predictions i

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

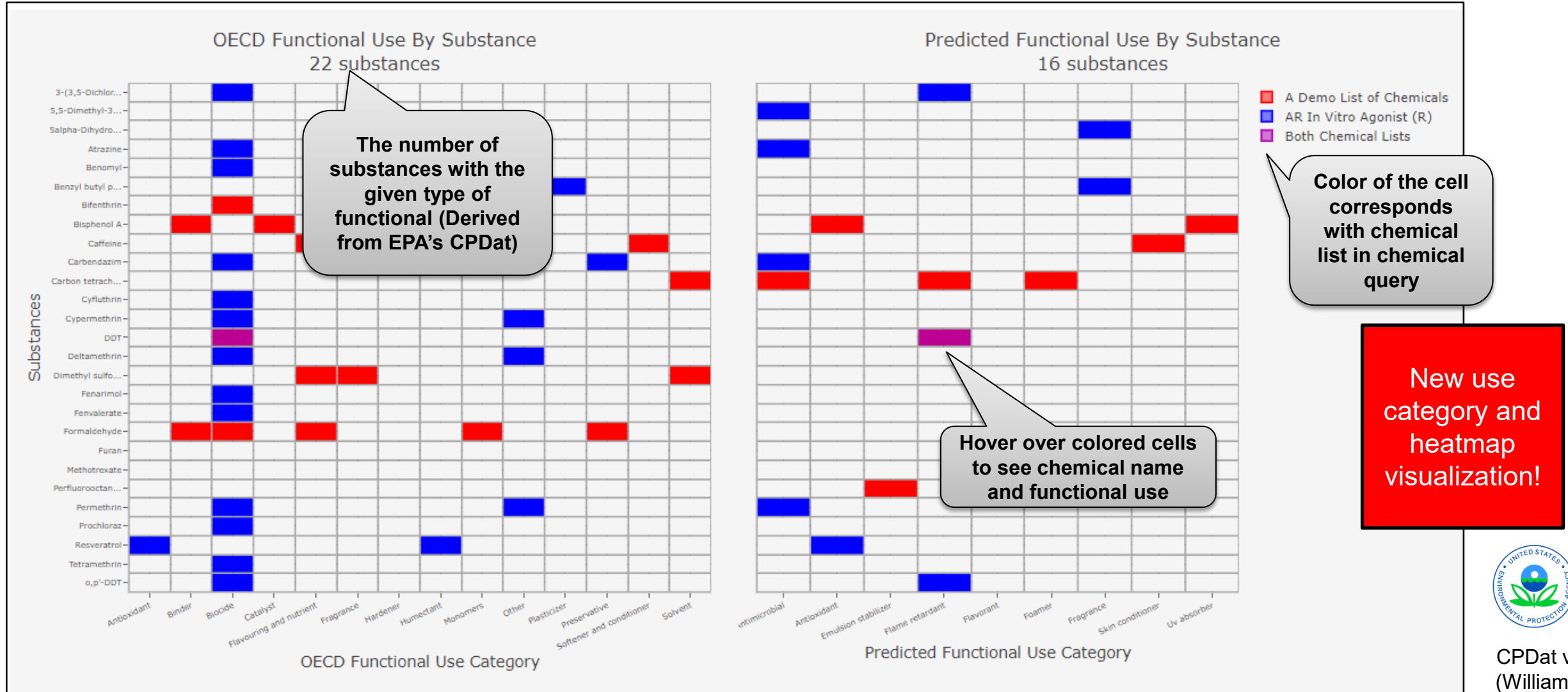
Visualize physicochemical properties



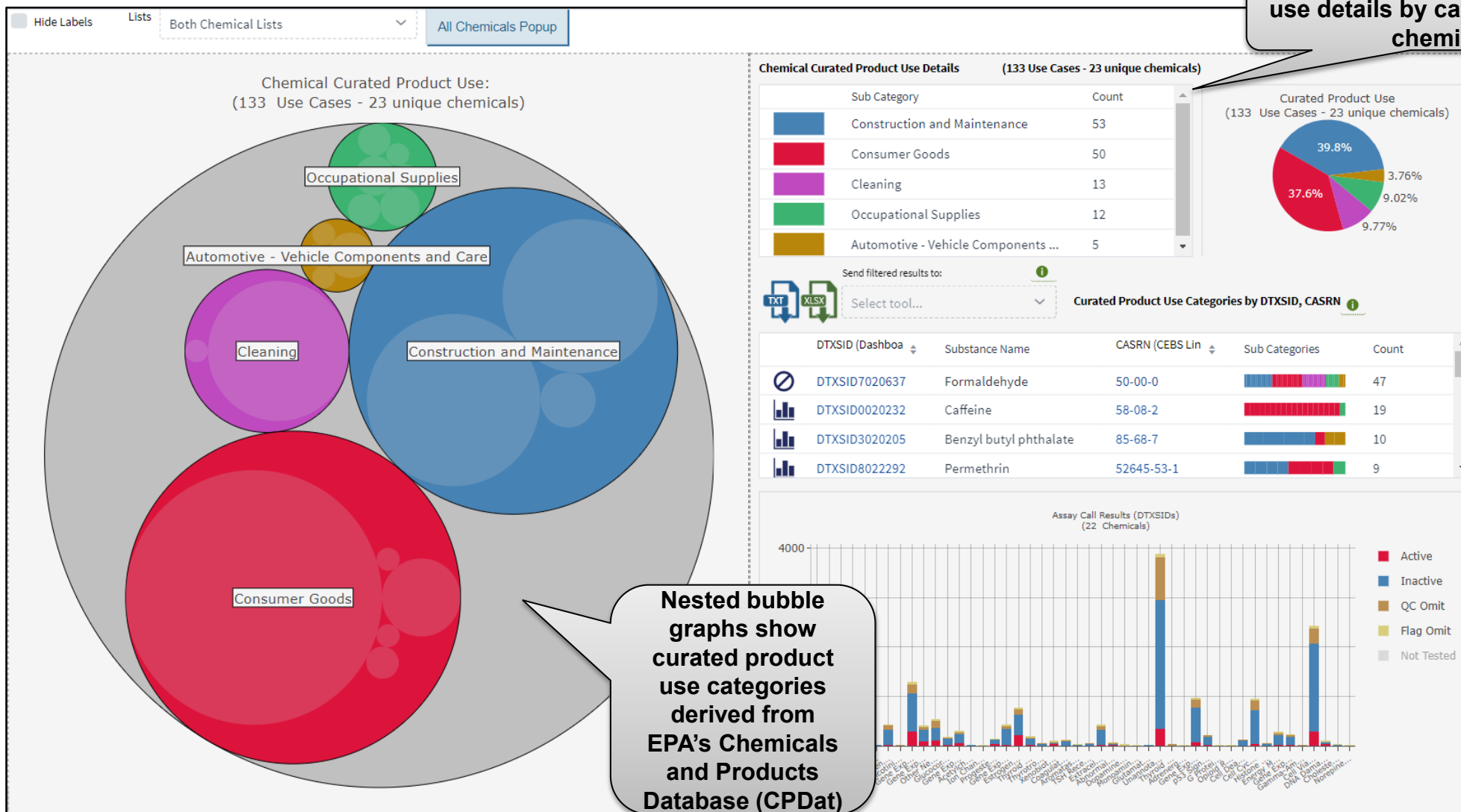
Choose property to visualize using drop down menu

Color of the boxplot corresponds with chemical list in chemical query

Explore Functional Use Categories



Explore Curated Product Use Categories



Summary details show product use details by category and by chemical

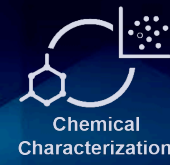
Nested bubble graphs show curated product use categories derived from EPA's Chemicals and Products Database (CPDat)

Consumer use categories are now called curated product use categories!





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Division of Translational Toxicology



Chemical Characterization

Demo

Chemical Characterization



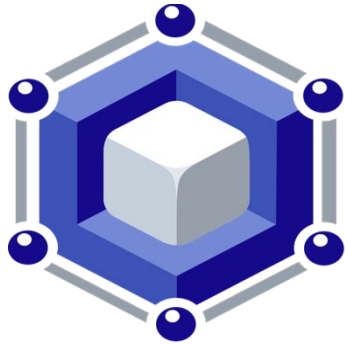
<https://ice.ntp.niehs.nih.gov/>

Chemical Characterization Summary

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

ICE User Guide	<h2>Chemical Characterization Tool</h2> <h3>Table of Contents:</h3> <ul style="list-style-type: none">• Introduction• Building a Chemical Characterization Query<ul style="list-style-type: none">◦ Chemical Input◦ Run Chemical Characterization Tool• Viewing Chemical Characterization Results<ul style="list-style-type: none">◦ Chemical Properties Summary◦ Download Results◦ Visualization of Chemical Properties◦ Interactive PCA Plots<ul style="list-style-type: none">▪ Static PCA Plots▪ Dynamic PCA Plots◦ Functional Use Explorer◦ Curated Product Use Explorer<ul style="list-style-type: none">▪ Chemical Curated Product Use Circle Plot▪ Chemical Curated Product Use Details◦ Using Results to Query Other ICE Tools
Search	
Chemical Quest	
Curve Surfer	
PBPK	
IVIVE	
Chemical Characterization	
Interactive Graphs	
Rest API	

ICE Tools Workflow



**Integrated
Chemical
Environment**

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

Perform a search



Search

Expand inventory:
Identify similar chemicals



Chemical Quest

Characterize chemical inventory



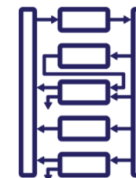
Chemical characterization

Review cHTS concentration-response curves



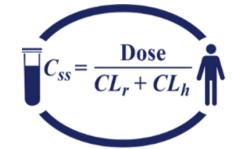
Curve Surfer

Generate chemical concentration predictions



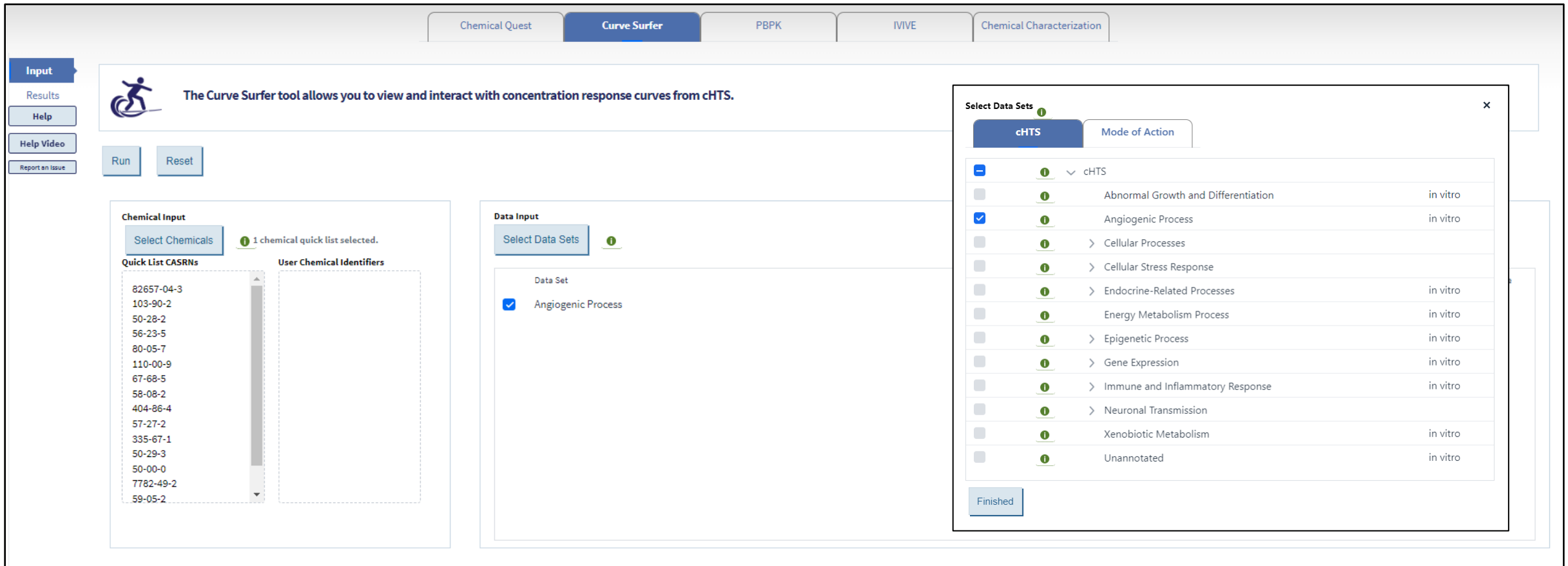
PBPK

Predict equivalent administered dose from in vitro data



IVIVE

Select chemical list and assay mechanistic target



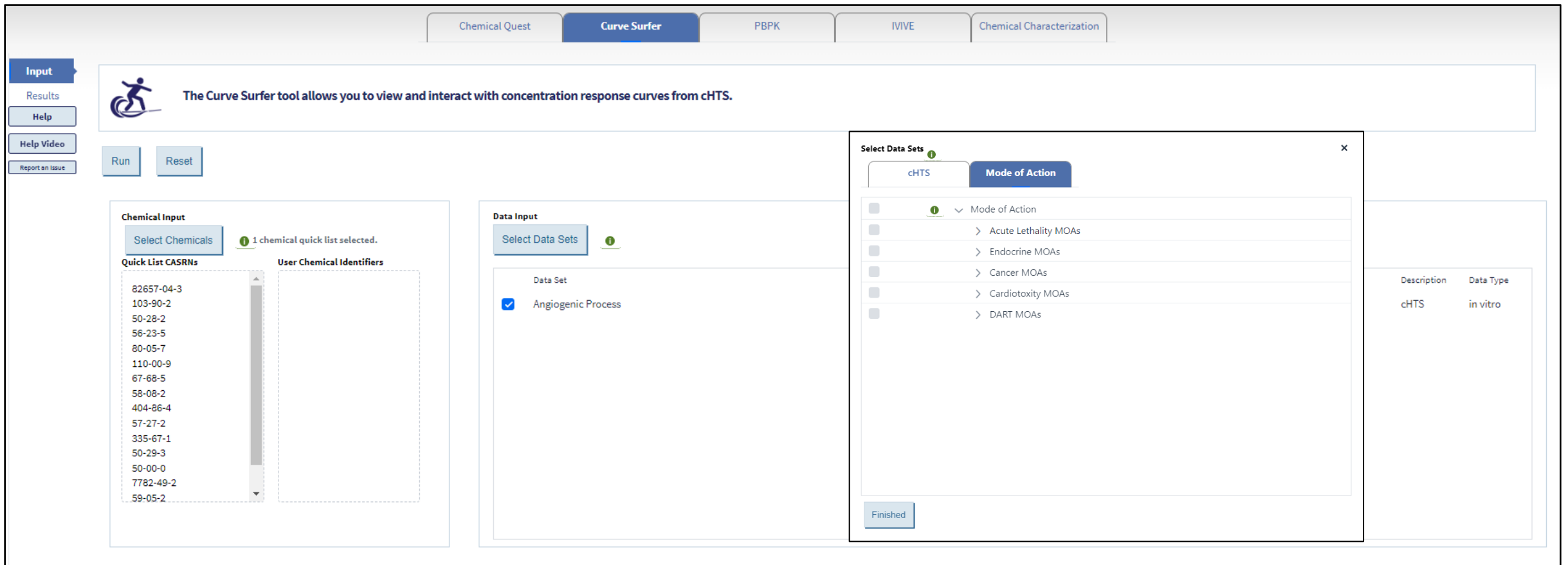
The Curve Surfer tool allows you to view and interact with concentration response curves from cHTS.

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

Data Input
Select Data Sets 1
Data Set: Angiogenic Process

Select Data Sets (Modal Window)
cHTS Mode of Action
cHTS
 Abnormal Growth and Differentiation in vitro
 Angiogenic Process in vitro
 Cellular Processes
 Cellular Stress Response
 Endocrine-Related Processes in vitro
 Energy Metabolism Process in vitro
 Epigenetic Process in vitro
 Gene Expression in vitro
 Immune and Inflammatory Response in vitro
 Neuronal Transmission
 Xenobiotic Metabolism in vitro
 Unannotated in vitro
Finished

Select chemical list and assay mode of action



The screenshot displays the Curve Surfer web application interface. At the top, there are navigation tabs: "Chemical Quest", "Curve Surfer" (active), "PBPK", "IVIVE", and "Chemical Characterization". On the left, a sidebar contains "Input", "Results", "Help", "Help Video", and "Report an Issue" buttons. Below the sidebar, there are "Run" and "Reset" buttons. The main content area features a header with the Curve Surfer logo and the text: "The Curve Surfer tool allows you to view and interact with concentration response curves from cHTS." Below this, there are two main input sections: "Chemical Input" and "Data 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

User Chemical Identifiers

Data Input

Select Data Sets 1

Data Set

- Angiogenic Process

Select Data Sets Modal Window

Mode of Action

- Mode of Action
- > Acute Lethality MOAs
- > Endocrine MOAs
- > Cancer MOAs
- > Cardiotoxicity MOAs
- > DART MOAs

Finished

Table

Description	Data Type
cHTS	in vitro

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

Send filtered results to:

Select tool...

Select Filter to add to chain:

100%

Clear Filters

Select All Filtered

Clear Selected

Only show selected items

Select Page

1 of 3

Showing 1-10 of 28 curves.

Sort Results By

Chemical Name

Direction

Asc

Overlay Selected

Overlay Filtered

Selected Item(s): 0/28

Select this item

BSK_3C_VCAM1_down
50-28-2

Assay: BSK_3C_VCAM1_down
CASRN: 50-28-2
Chemical Name: 17beta-Estradiol
LOEC (uM): NA
Call: Inactive

Mechanistic Target: Angiogenic Process,Inflammatory Response
DTXSID: DTXSID0020573
Winning Curve-Fit Model: Hill
Top of Curve: NA

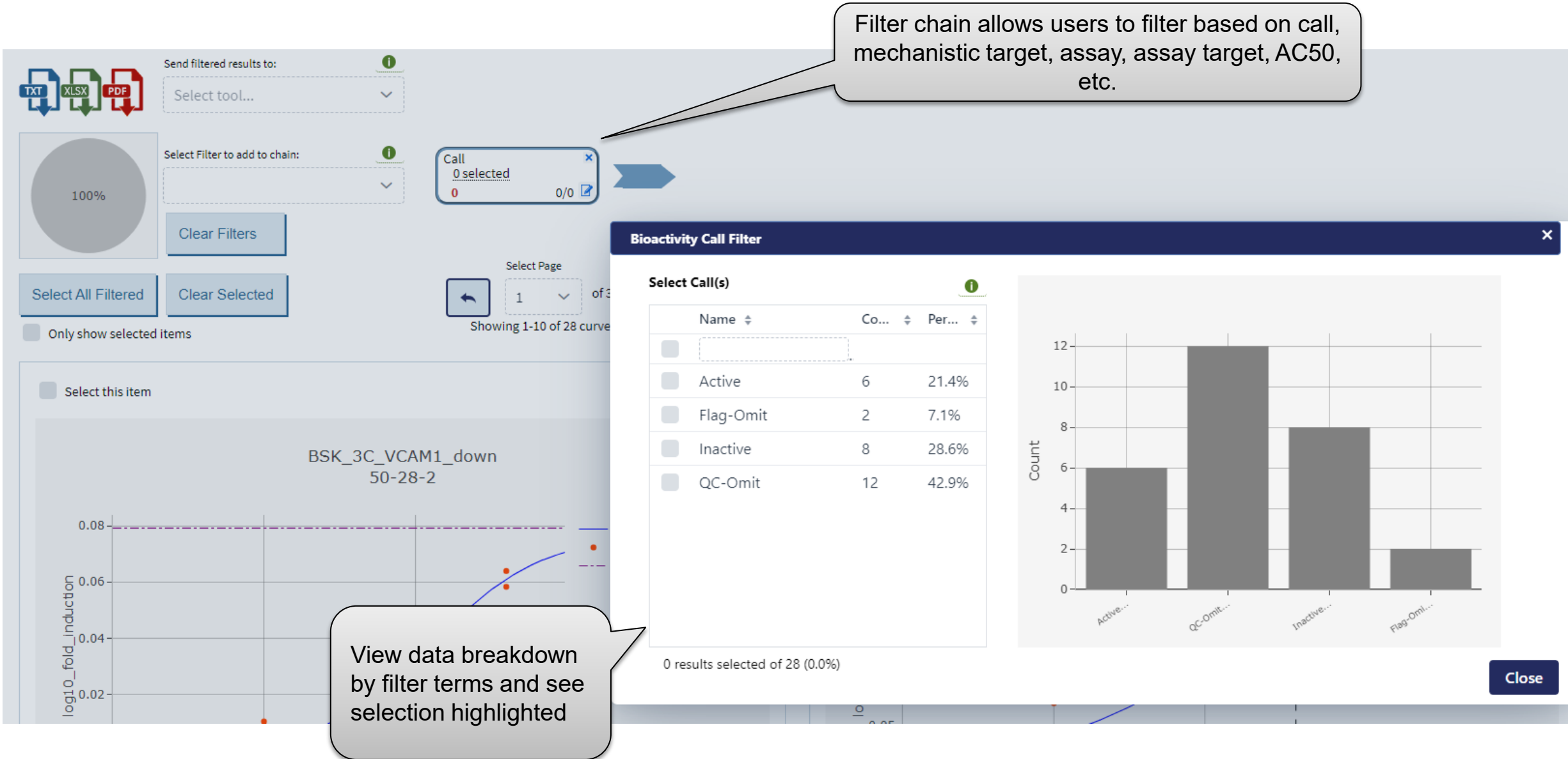
Select this item

BSK_4H_MCP1_down
50-28-2

Assay: BSK_4H_MCP1_down
CASRN: 50-28-2
Chemical Name: 17beta-Estradiol
LOEC (uM): 40.0
Call: Active

Mechanistic Target: Angiogenic Process,Inflammatory Response
DTXSID: DTXSID0020573
Winning Curve-Fit Model: Hill
Top of Curve: 0.31

Plots have key features highlighted and details for assay and chemical information are provided below



The screenshot displays the Curve Surfer interface. At the top left, there are options to export filtered results to TXT, XLSX, or PDF. Below this is a 'Send filtered results to:' dropdown menu. A 'Select Filter to add to chain:' dropdown is currently empty. A 'Call' filter is selected in the chain, showing '0 selected' and '0/0'. A blue arrow points from this filter to a 'Bioactivity Call Filter' dialog box.

The 'Bioactivity Call Filter' dialog box has a title bar and a 'Select Call(s)' section. It contains a table with the following data:

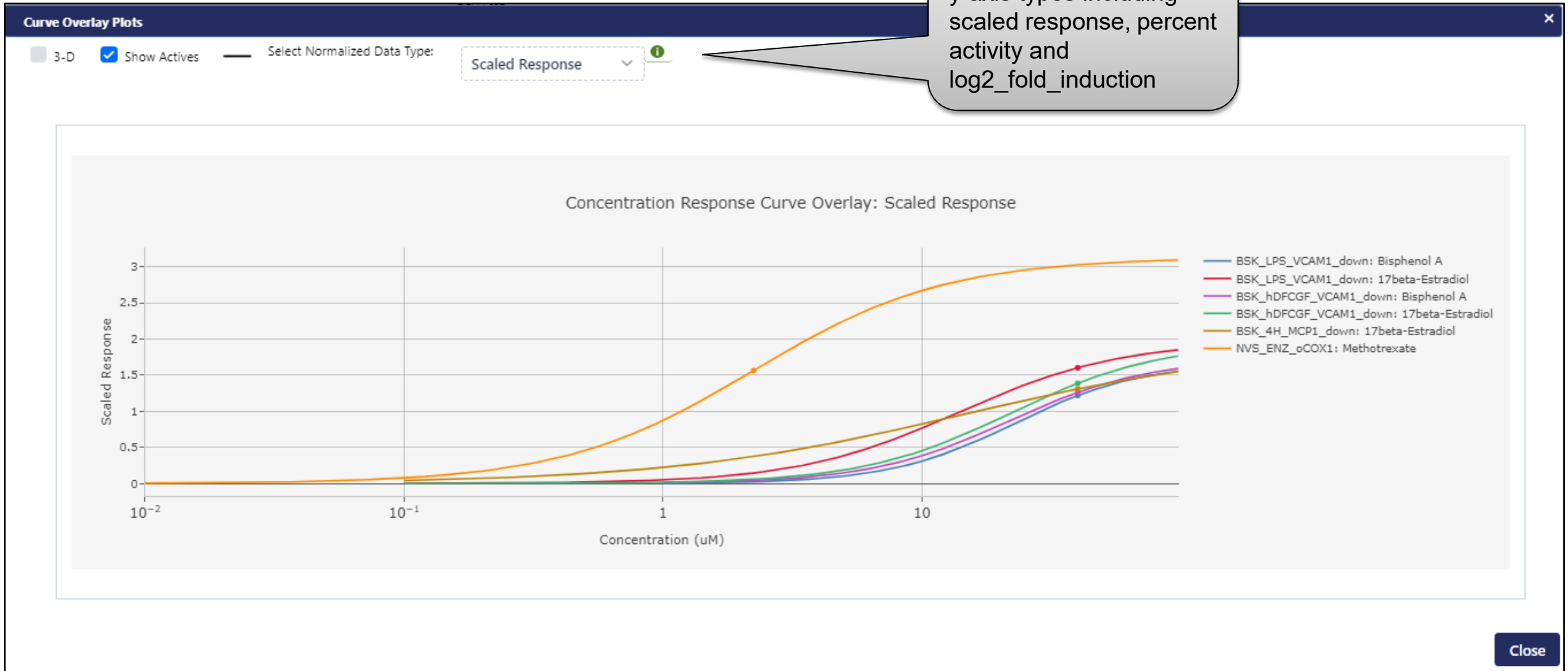
Name	Co...	Per...
Active	6	21.4%
Flag-Omit	2	7.1%
Inactive	8	28.6%
QC-Omit	12	42.9%

Below the table, it shows '0 results selected of 28 (0.0%)'. To the right of the dialog is a bar chart showing the count for each call type: Active (6), QC-Omit (12), Inactive (8), and Flag-Omit (2).

In the background, a plot titled 'BSK_3C_VCAM1_down 50-28-2' shows log10_fold_induction on the y-axis. A call is highlighted in the plot, and a callout box points to it with the text: 'View data breakdown by filter terms and see selection highlighted'.

Another callout box points to the 'Call' filter in the chain with the text: 'Filter chain allows users to filter based on call, mechanistic target, assay, assay target, AC50, etc.'

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



Demo

Curve Surfer



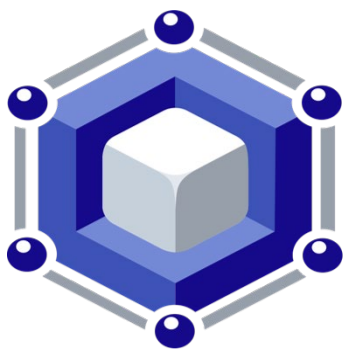
<https://ice.ntp.niehs.nih.gov/>

Curve Surfer Summary

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

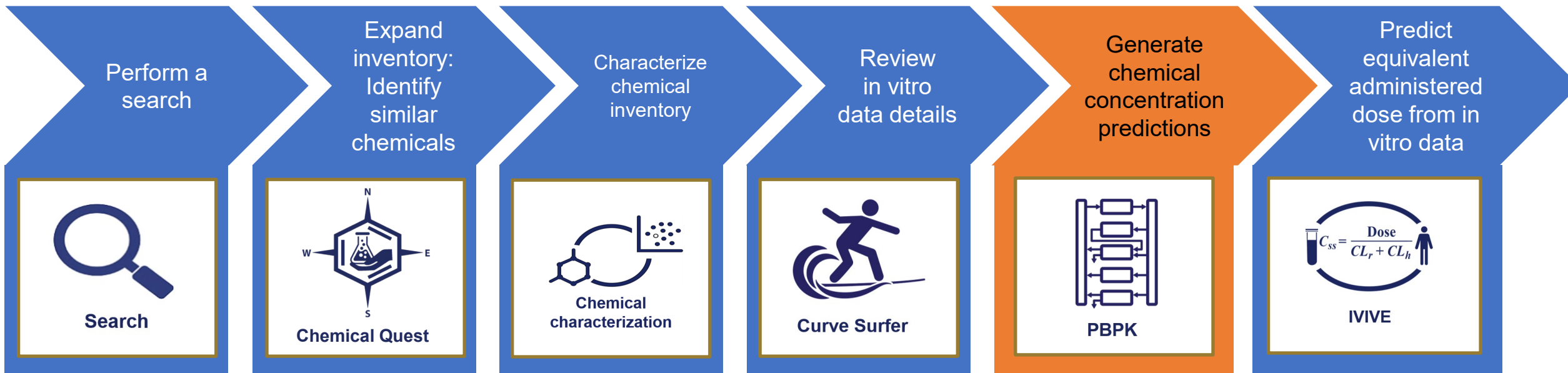
ICE User Guide	<h2>Curve Surfer</h2> <h3>Table of Contents:</h3> <ul style="list-style-type: none">• Introduction• Building a Curve Surfer Query<ul style="list-style-type: none">◦ Chemical Input◦ Data Input◦ Run Curve Surfer Tool• Viewing Curve Surfer Results<ul style="list-style-type: none">◦ Interactive Plots◦ Sort, Filter, and Select Curves◦ Overlay Curves◦ Download Results◦ Using Results to Query Other ICE Tools• Accessing Curve Surfer from Other ICE Tools
Search	
Chemical Quest	
Curve Surfer	
PBPK	
IVIVE	
Chemical Characterization	
Interactive Graphs	
Rest API	

ICE Tools Workflow



Integrated Chemical Environment

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



Parameterize PBPK models for a chemical list

Choose human or rat (fetal model only allows human)

Measured: experimental values for ADME parameters
In Silico: QSAR predictions
Default: experimental data where available + in silico predictions

Choose from 3 PBPK models sourced from US EPA's httk package

Customize model parameters such as Exposure Dose, Exposure Route, Exposure Length, and Simulation Length

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

Species: human, Body Weight: 70.0, ADME Source: Default, Exposure Dose: 1.0, Gestational Day when Exposure Starts: 91, Model: Solve_fetal_pbtk, Exposure Route: iv, Exposure Interval, Hours: 24, Exposure Length, Hours: 0.25, Simulation Length, Days: 3, Output Conc. Units: uM, Inhalation Dosing Method: Concentration, Inhalation Dosing Units: ppmv

Model from the US EPA httk package that includes both maternal and fetal compartments and is used by mother and fetus. For details see [User Guide](#).

Chemical Input: Select Chemicals, Quick List CASRNs, User Chemical Identifiers: 80-05-7, 50-28-2, 59-05-2



View PBPK results in an interactive table


Input


Results


Help

Help Video



Report an Issue


 PBPK workflow results

> Download PBPK Files 

Interactive PBPK Results 

Send filtered results to:

  Select tool...

Number of rows = 60
Number of chemicals = 3 

Chemical	CASRN (CEBS Link)	DTXSID (Dashboard Link)	Compartment	CSS	Cmax
Bisphenol-a	80-05-7	DTXSID7020182	Cadipose	0.0	7.933
Bisphenol-a	80-05-7	DTXSID7020182	Cart	0.0	5.211
Bisphenol-a	80-05-7	DTXSID7020182	Cfart	0.0	4.941
Bisphenol-a	80-05-7	DTXSID7020182	Cfbrain	0.0	8.895
Bisphenol-a	80-05-7	DTXSID7020182	Cfgut	0.0	19.96
Bisphenol-a	80-05-7	DTXSID7020182	Cfkidney	0.0	30.09
Bisphenol-a	80-05-7	DTXSID7020182	Cfliver	0.0	27.86

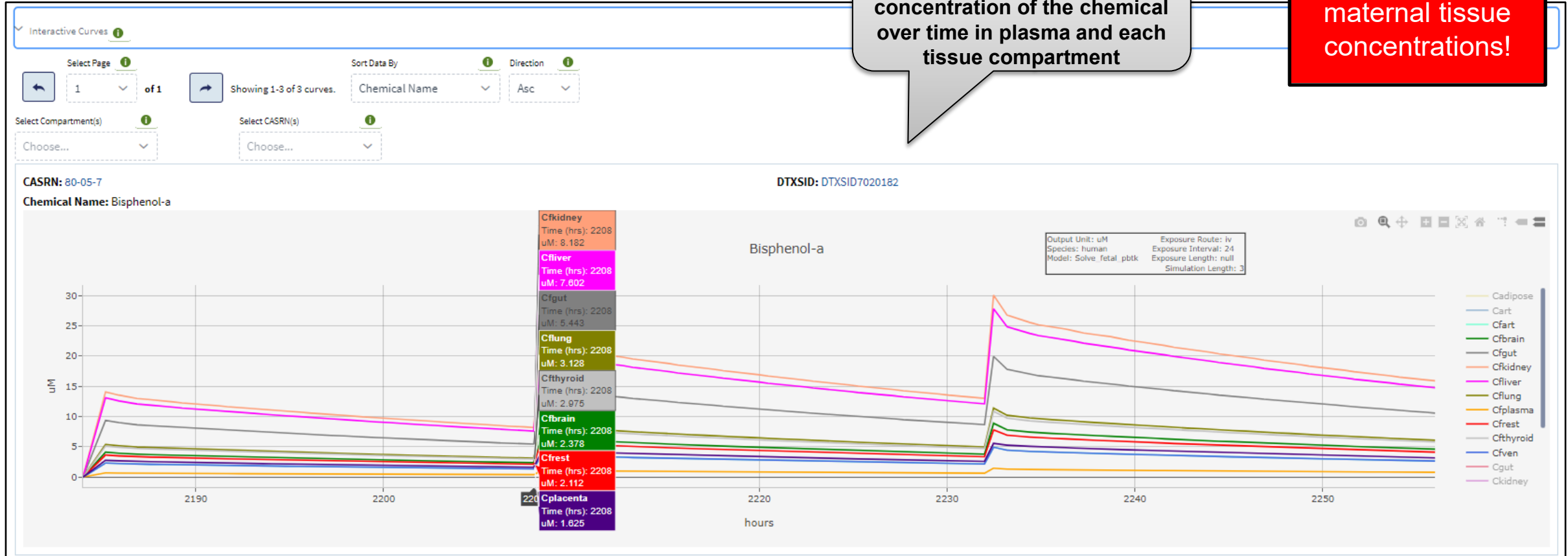
Result download provides full time series for each chemical and compartment along with all parameters and sources

Summary results CSS and Cmax for each compartment.

Visualize PBPK results

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

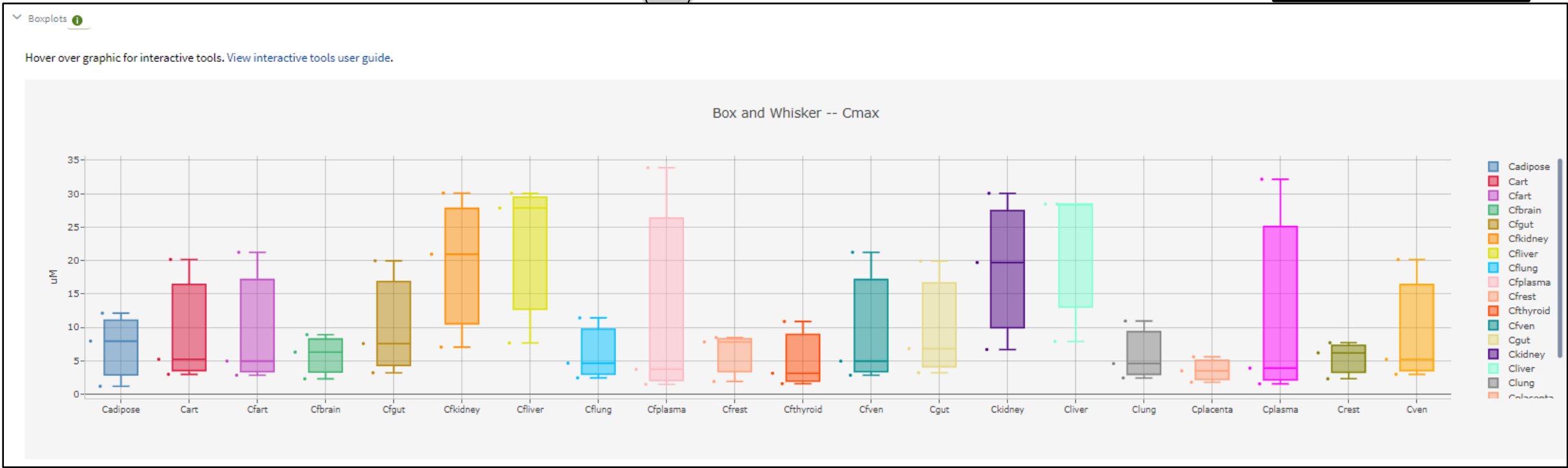
Visualize fetal and maternal tissue concentrations!



Visualize PBPK results

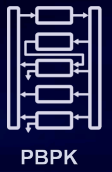
Boxplots show the Cmax distribution across all returned chemicals for each compartment

Visualize fetal and maternal tissue concentrations!





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PBPK

PBPK

Demo

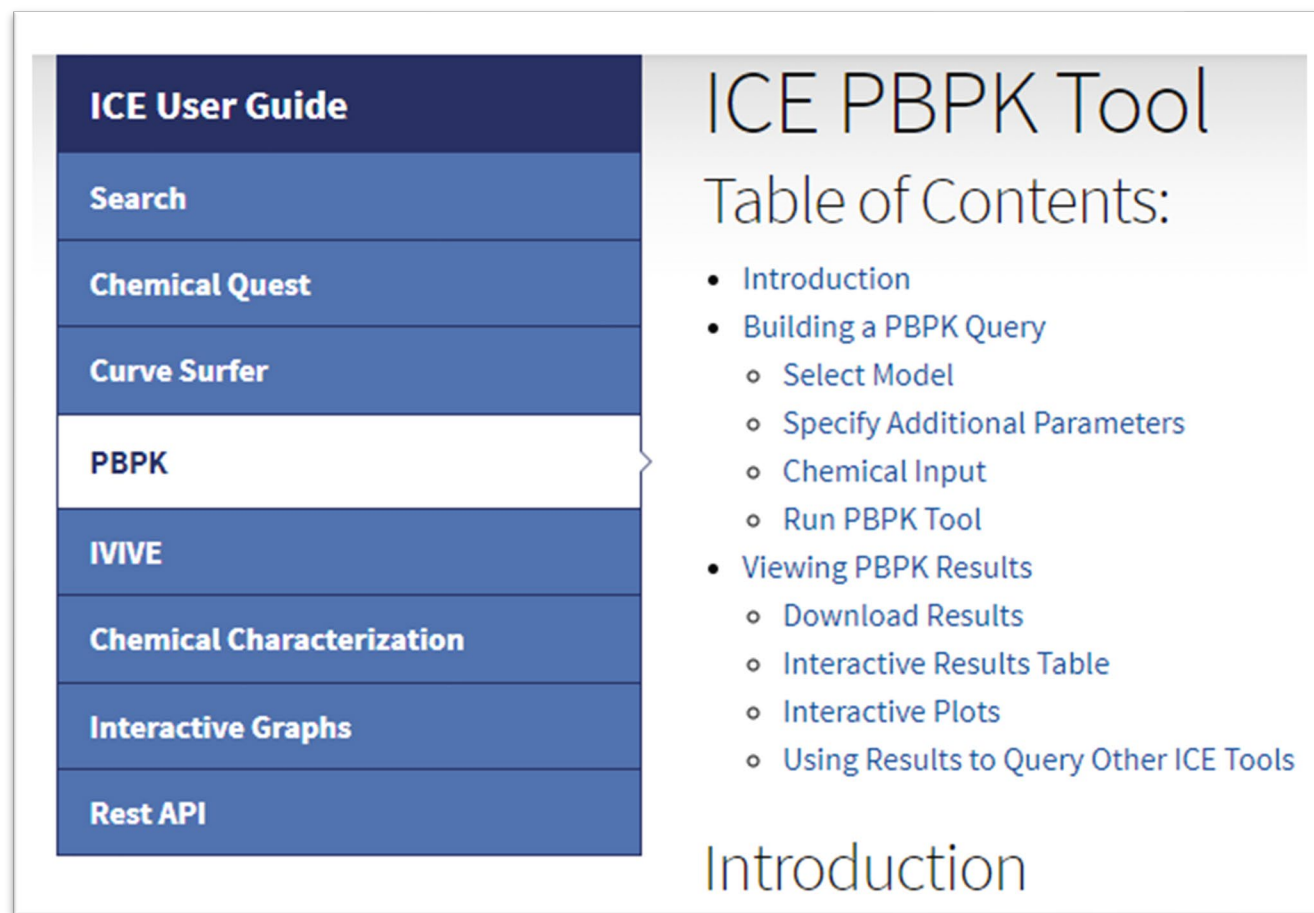
PBPK



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

PBPK Demo

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



The screenshot displays the ICE PBPK Tool interface. On the left is a vertical navigation menu with the following items: ICE User Guide, Search, Chemical Quest, Curve Surfer, PBPK (highlighted with a white background and a right-facing curly bracket), IVIVE, Chemical Characterization, Interactive Graphs, and Rest API. On the right, the main content area is titled "ICE PBPK Tool" and "Table of Contents:". Below the title is a bulleted list of sections: Introduction, Building a PBPK Query (with sub-items: Select Model, Specify Additional Parameters, Chemical Input, Run PBPK Tool), and Viewing PBPK Results (with sub-items: Download Results, Interactive Results Table, Interactive Plots, Using Results to Query Other ICE Tools). At the bottom right of the content area, the word "Introduction" is displayed in a large font.

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

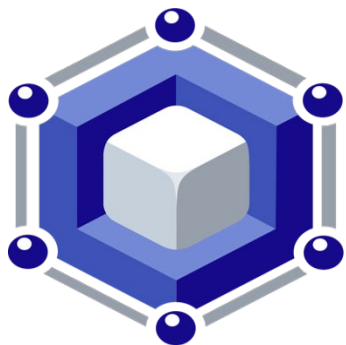
ICE PBPK Tool

Table of Contents:

- Introduction
- Building a PBPK Query
 - Select Model
 - Specify Additional Parameters
 - Chemical Input
 - Run PBPK Tool
- Viewing PBPK Results
 - Download Results
 - Interactive Results Table
 - Interactive Plots
 - Using Results to Query Other ICE Tools

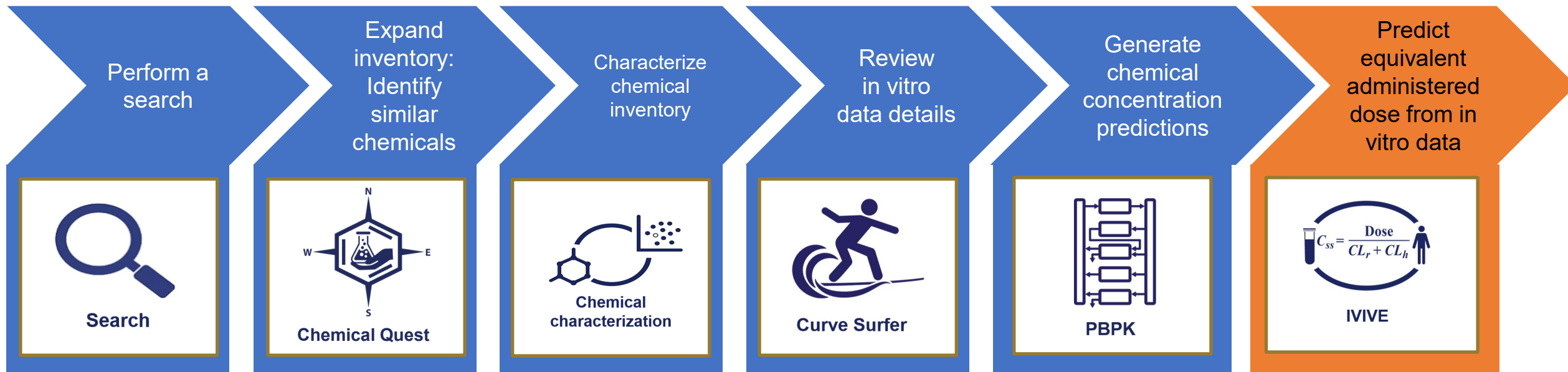
Introduction

ICE Tools Workflow



Integrated Chemical Environment

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



Parameterize IVIVE models for a chemical list

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: AC50, 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 ?

AC50 ?

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 ?

A multiple-compartment human PBPK model from the US EPA htk 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](#).

Chemical Input

Select Chemicals

Quick List CASRNs

User Chemical Identifiers

Data Input

Select Data Sets

Data Set	Description	Data Type
<input checked="" type="checkbox"/>	Unannotat...	cHTS in vitro
<input checked="" type="checkbox"/>	Xenobiotic Metabolism	cHTS in vitro
<input checked="" type="checkbox"/>	Serotonin Receptor Signaling Pathway	cHTS in vitro
<input type="checkbox"/>	Opioid Receptor	

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

Help | Help Video | Report an Issue

Type of activity conc. –
AC50 or ACC

New fetal pbtck model!
Inhalation model now accepts concentration units of ppmv!

Upload custom in vivo data to overlay on charts or upload custom in vitro data to run through IVIVE



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

View and download IVIVE results


Input

Results

Help

Help Video

Report an Issue



IVIVE workflow results

> Download IVIVE Files ?

∨ IVIVE Results

Send filtered results to:





Select tool...

?

Clear Filter

Number of rows = 449

Number of chemicals = 3 ?

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

Summary results for AC50 and EAD for each assay and chemical.

Visualize IVIVE results



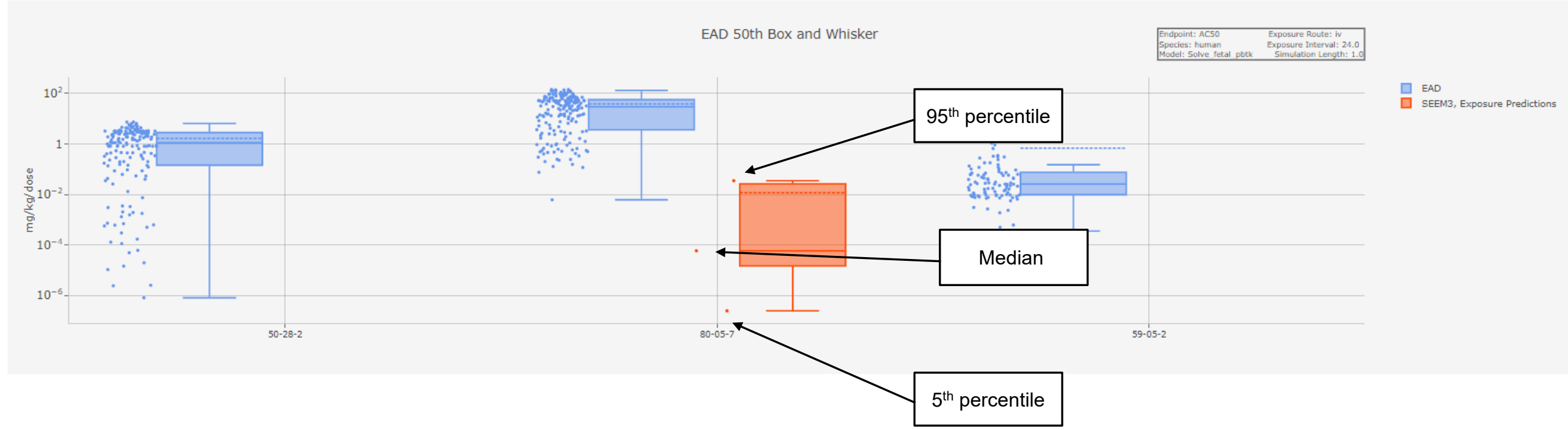
IVIVE Results Visualizations

Select EAD to visualize: EAD 50th
 Select in vivo data or exposure data to display: Exposure Predictions
 Log Axis Show Name

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

Overlay new exposure predictions from EPA's SEEM3!

Hover over graphic for interactive tools. [View interactive tools user guide.](#)



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
Data Set: Angiogenic Process, Description: cHTS, Data Type: in vitro

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

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

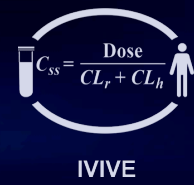
Upload Custom In Vitro Data
To load user assay data into your model, click "Upload." Supported file types: comma-delimited (csv), plain text (txt), and Excel (xlsx). To view example templates of data formats, click the links below.
Template In Vitro Assay File for IVIVE (Text)
Template In Vitro Assay File for IVIVE (Excel)
Close

Custom In vitro data template

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

Custom In vitro data template

casn	dxsid	chem name	dataset	assay1	assay2	assay3	assay4	assay5	assay6	assay7	assay8	assay9	assay10	assay11
115-32-2	dtxsid1	17-Methyltestosterone	dataset 1	1	23	4	213	8	9		98	9	9	
117-81-7	dtxsid2	Testosterone	dataset 1	55	65	55	4	3	466		66	88	8	986
120-47-8	dtxsid2	17beta-Trenl	dataset 1	788	887	997	778	997	997	56	7	76	677	2
13311-84-7	dtxsid2	Testosterone	dataset 1	9876	7687	877	679	547	123	234	45	456	67	56
140-66-9	dtxsid1	17-Methyltestosterone	dataset 2	987	76	987	4	54	54	556	456	567	778	23
57-85-2	dtxsid2	Testosterone	dataset 2	98		9	98			98			98	98
10161-33-8	dtxsid2	17beta-Trenl	dataset 2	123		2345	567	567			45		566	6
58-22-0	dtxsid2	Testosterone	dataset 2	876			87		6443	345		678		322
58-18-4	dtxsid1	17-Methyltestosterone	dataset 3	987	234	23	567	775	445	7878	123	456	8	6
57-85-2	dtxsid2	Testosterone	dataset 3	1	23	4	213	8	9		98	9	9	
10161-33-8	dtxsid2	17beta-Trenl	dataset 3	55	65	55	4	3	466		66	88	8	986
58-22-0	dtxsid2	Testosterone	dataset 3	788	887	997	778	997	997	56	7	76	677	2



Demo

IVIVE



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

IVIVE Summary

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

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

IVIVE Tool

Table of Contents:

- Introduction
- Building an IVIVE Query
 - Select In Vitro Endpoint, PK Model Type, and Parameter Settings
 - Chemical Input
 - Data Input
 - Options to Upload Custom Data
 - Run IVIVE Tool
- Viewing IVIVE Results
 - Download Results
 - Interactive Results Table
 - Interactive Plots
 - Using Results to Query Other ICE Tools

Summary

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



The NICEATM Group



NIEHS/DTT Contributors



Subscribe to NICEATM News

<https://list.nih.gov/cgi-bin/wa.exe?SUBED1=niceatm-I&A=1>



Integrated
Chemical
Environment

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



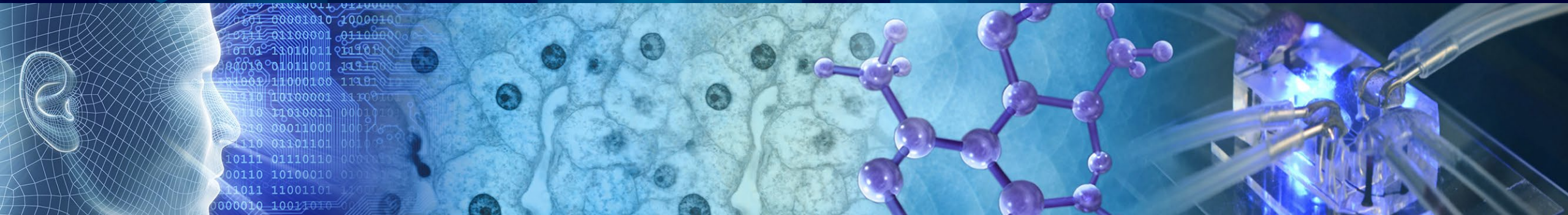
<https://github.com/NIEHS/OPERA>



National Institute of
Environmental Health Sciences
Division of Translational Toxicology

Questions?

Contact: ICE-support@niehs.nih.gov



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

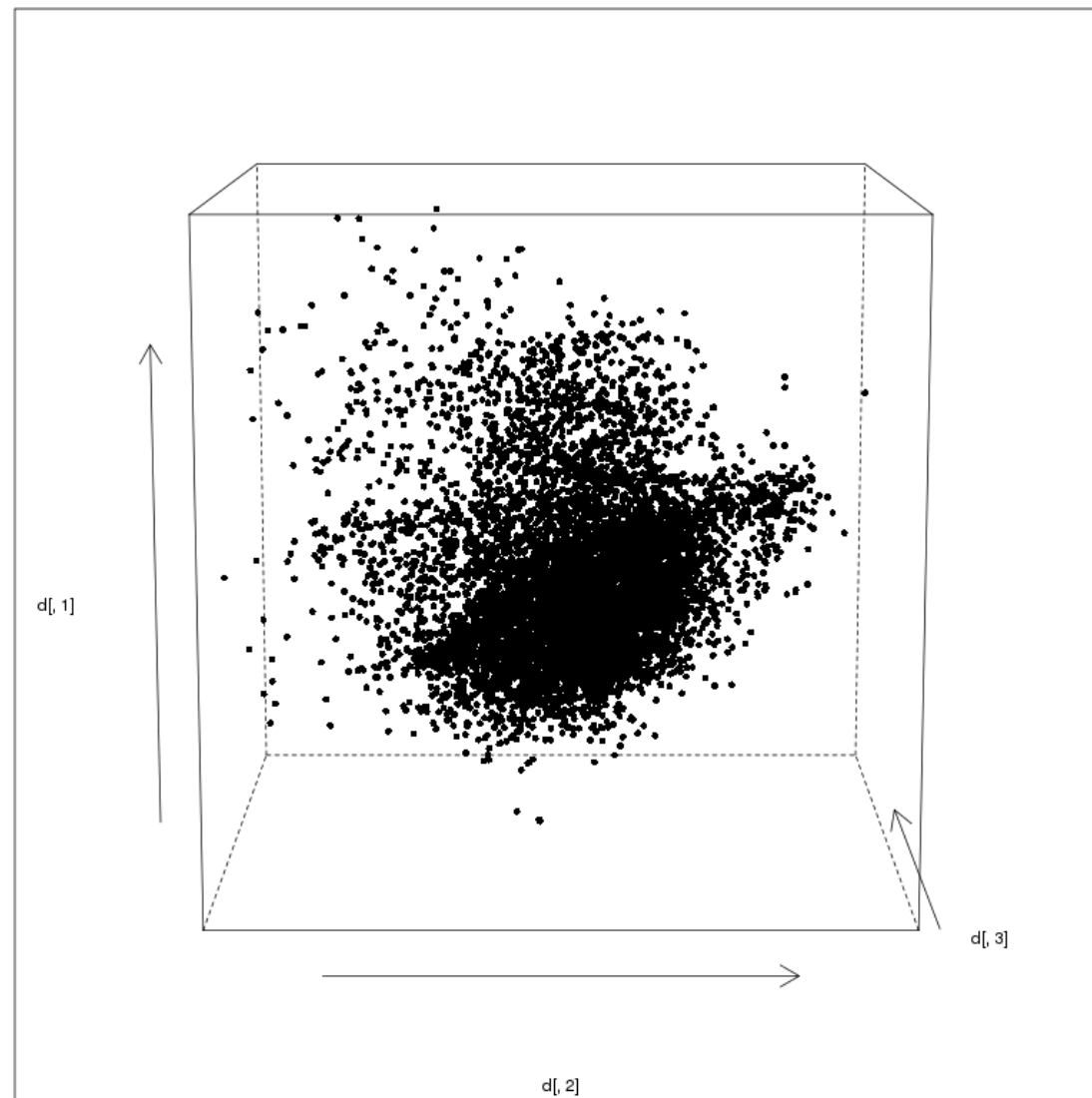
12th ASCCT Annual Meeting
2023-10-25

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

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

The Chemical Space

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



The Chemical Space

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

 DRUGBANK



CompTox
Chemicals Dashboard

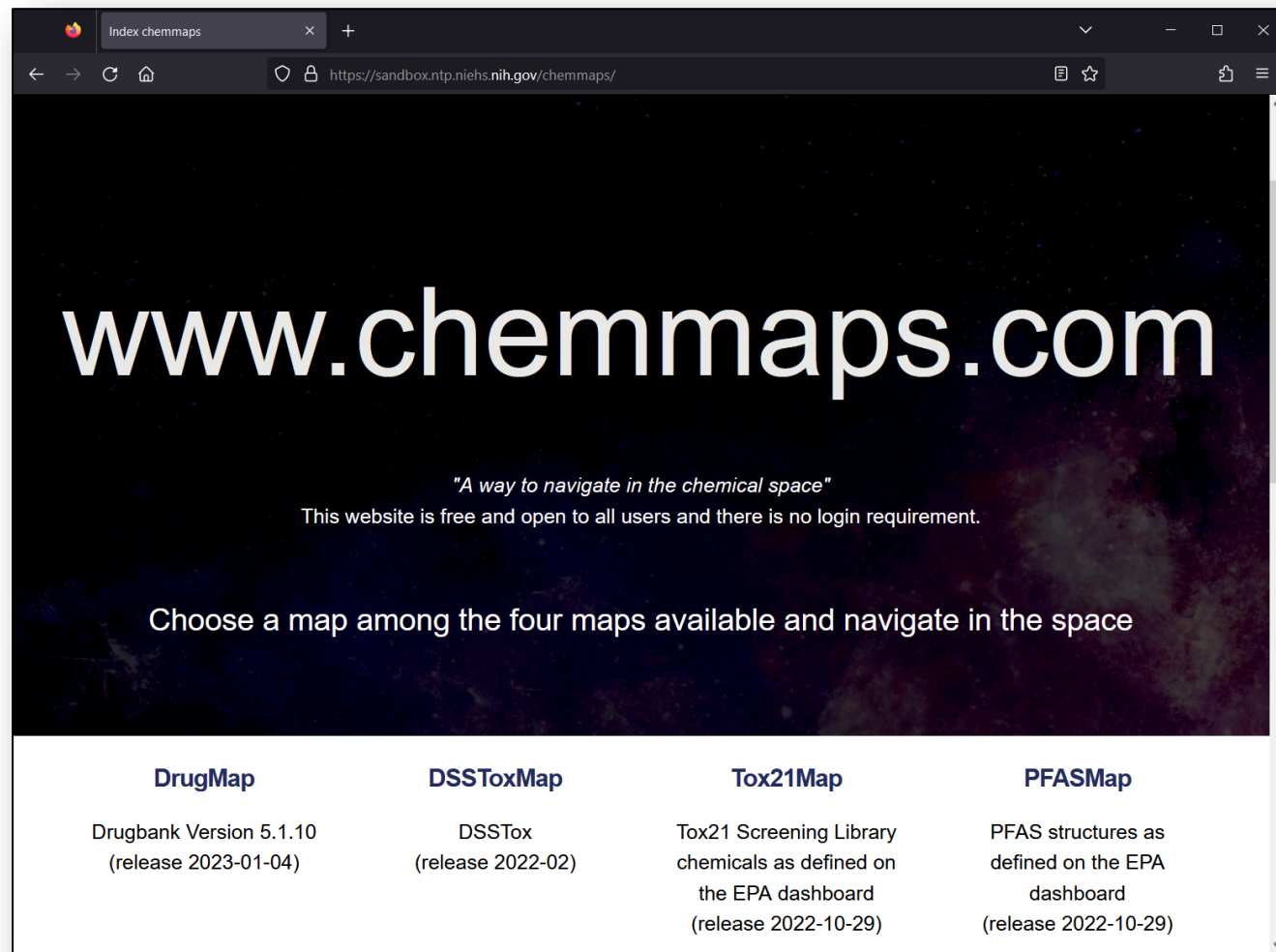
Tox21

ChemMaps.com

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



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



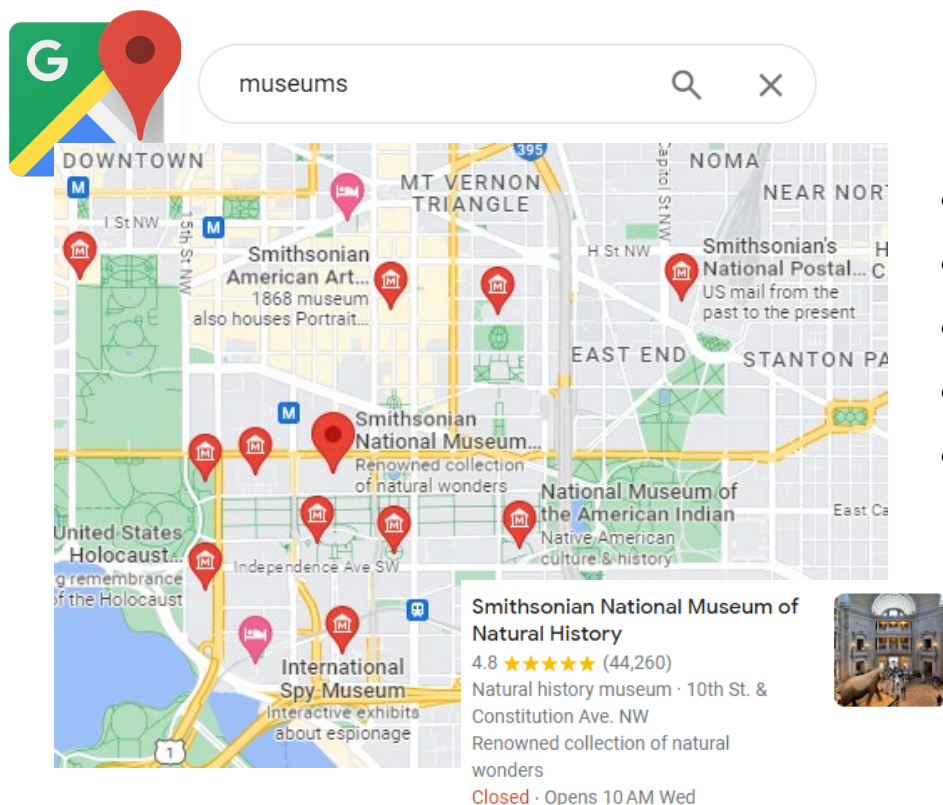
The screenshot shows a web browser window with the URL <https://sandbox.ntp.niehs.nih.gov/chemmaps/>. The main heading is **www.chemmaps.com**. Below the heading, it says: "A way to navigate in the chemical space" and "This website is free and open to all users and there is no login requirement." The instruction "Choose a map among the four maps available and navigate in the space" is followed by a grid of four map options:

DrugMap	DSSToxMap	Tox21Map	PFASMap
Drugbank Version 5.1.10 (release 2023-01-04)	DSSTox (release 2022-02)	Tox21 Screening Library chemicals as defined on the EPA dashboard (release 2022-10-29)	PFAS structures as defined on the EPA dashboard (release 2022-10-29)

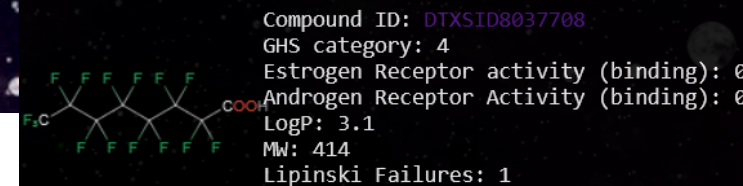
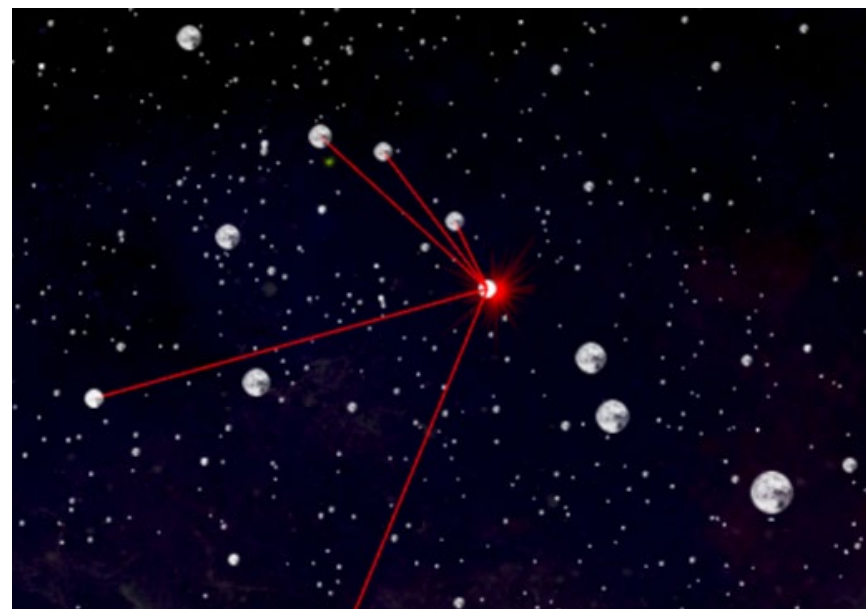


ChemMaps.com

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



- Interactive
- Easy to use
- Informative
- Responsive
-



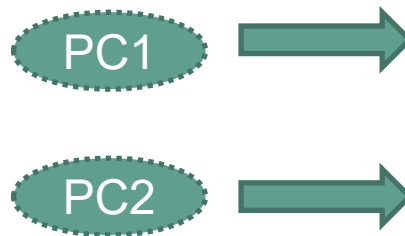


ChemMaps.com: Mapping chemicals

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

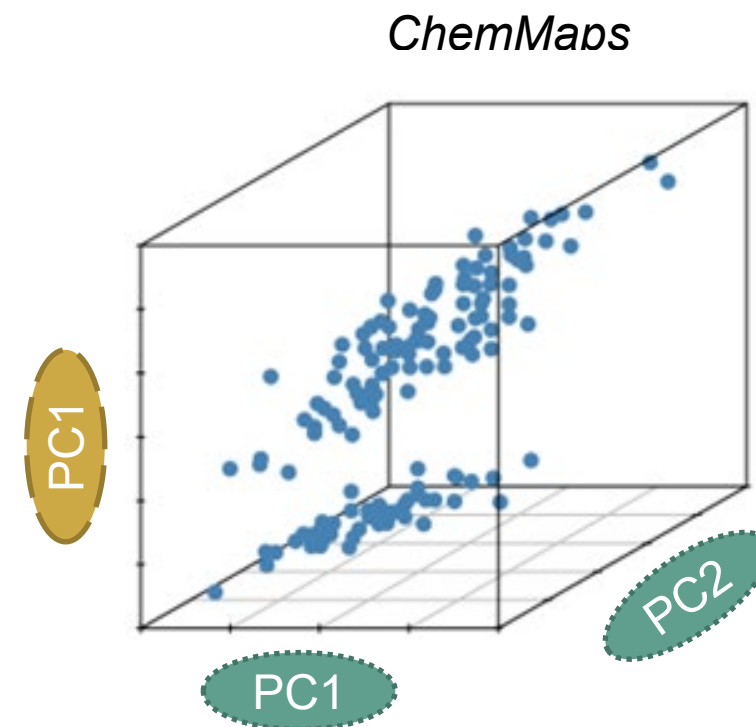
1D/2D descriptors

1D/2D descriptors			



3D descriptors

3D descriptors			





ChemMaps.com

DrugMap

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



DSSToxMap

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



PFASMap

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

Tox21Map

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



National Institute of
Environmental Health Sciences
Division of Translational Toxicology

“Demo”

Exploring the PFOA chemical space

PFOA on DSSToxMap

The screenshot shows a web browser window with the URL <https://sandbox.ntp.niehs.nih.gov/chemmaps/>. The main heading is **www.chemmaps.com**. Below the heading, it states: *"A way to navigate in the chemical space"* and *This website is free and open to all users and there is no login requirement.* The instruction *Choose a map among the four maps available and navigate in the space* is followed by a grid of four map options:

DrugMap	DSSToxMap	Tox21Map	PFASMap
Drugbank Version 5.1.10 (release 2023-01-04)	DSSTox (release 2022-02)	Tox21 Screening Library chemicals as defined on the EPA dashboard (release 2022-10-29)	PFAS structures as defined on the EPA dashboard (release 2022-10-29)

A purple arrow points to the DSSToxMap option.



PFOA on DSSToxMap

Generate the DsstoMap

Select up to 5 features you would like put on the map:

Chemical classification

- EPA category
- LD50 (mg/kg)

Toxicology prediction

- Acute Tox (very toxic)
- Acute Tox (no toxic)
- Acute Tox (EPA)
- Acute Tox (GHS)
- Acute Tox (LD50)
- Estrogen Receptor activity (Agonist)
- Estrogen Receptor activity (binding)
- Hepatic clearance

- Androgen Receptor Activity (Antagonist)
- Androgen Receptor Activity (binding)

Physicochemical prediction

- Plasma fraction unbound
- Henry's Law constant (atm-mol³/mole)
- KM (biotransformation rate)
- Log Octanol/air partition coefficient
- Log Soil adsorption coefficient (L/Kg)
- Log Fish bioconcentration factor
- LogD
- LogP

- Melting Point (C)

- Pka acid
- Pka basic

- Biodegradability
- HPLC retention time
- Log vapor pressure (mmHg)

- Log Water solubility
- Log Atmospheric constant (cm³/molsec)
- Biodegradation half-life
- Boiling Point

Descriptors

- MW
- Lipinski Failures

Chemical in the center of the map (DTXSID):

DTXSID8031865

Generate DSSToxMap

DSSToxMap displays
projections for 10,000
chemicals

Hide Chemicals

Classified

No classified

Added chemicals

Draw structures

Colors by

GHS category

Lipinski Failures

Androgen Receptor Activity (binding)

Estrogen Receptor activity (binding)

MW

LogP

Axes

Set a pivot point

Reset view

Reset map

Help

Save map view

Close Controls

9874 chemicals



Compound ID: DTXSID8031865

GHS category: NA

Lipinski Failures: 1

Androgen Receptor Activity (binding): 0

Estrogen Receptor activity (binding): 0

MW: 414

LogP: 3.1

Connect 1

Extract 1

Draw chemical

Download neighbors

[Link to DSSTOXMap](#)

Chemicals are represented by planets or stars.

Stars indicate that the chemical has acute toxicity information available.

Hide Chemicals

Classified

No classified

Added chemicals

Draw structures

Colors by

GHS category

Estrogen Receptor activity (binding)

Androgen Receptor Activity (binding)

LogP

MW

Lipinski Failures

Axes

Set a pivot point

Reset view

Reset map

Help

Save map view

Close Controls

9874 chemicals



Compound ID: DTXSID8031865

GHS category: NA

Estrogen Receptor activity (binding): 0

Androgen Receptor Activity (binding): 0

LogP: 3.1

MW: 414

Lipinski Failures: 1

Connect 1

Extract 1

Draw chemical

Download neighbors

[Link to DSSTOxMap](#)

DTXSID8031865

Search bar to locate specific chemicals

Navigation panel allows visualization of previously selected features or chemical structure

Hide Chemicals

Classified

No classified

Added chemicals

Draw structures

Colors by

GHS category

Estrogen Receptor activity (binding)

Androgen Receptor Activity (binding)

LogP

MW

Lipinski Failures

Axes

Set a pivot point

Reset view

Reset map

Help

Save map view

Close Controls

Information panel updates in real time while navigating the map

9874 chemicals

Compound ID: DTXSID8031865

GHS category: NA

Estrogen Receptor activity (binding): 0

Androgen Receptor Activity (binding): 0

LogP: 3.1

MW: 414

Lipinski Failures: 1


Connect 1

Extract 1

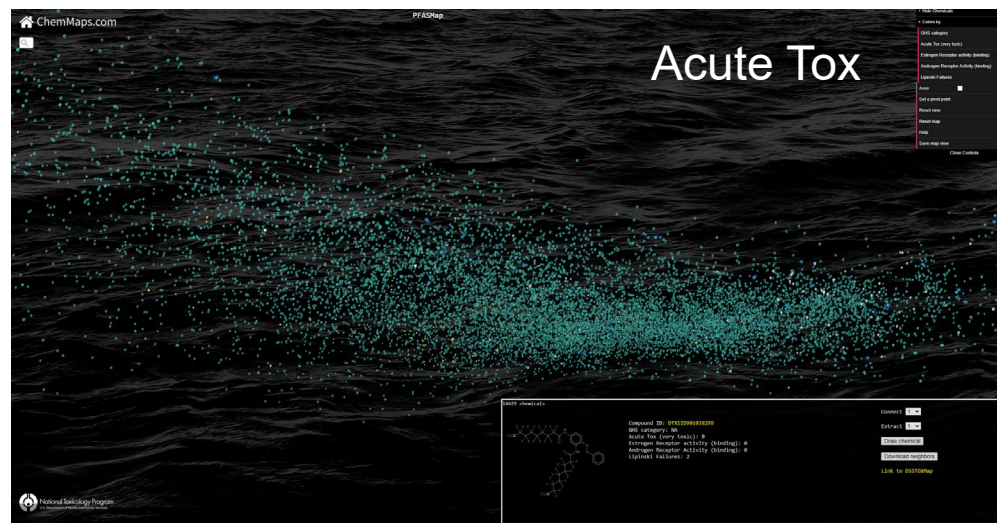
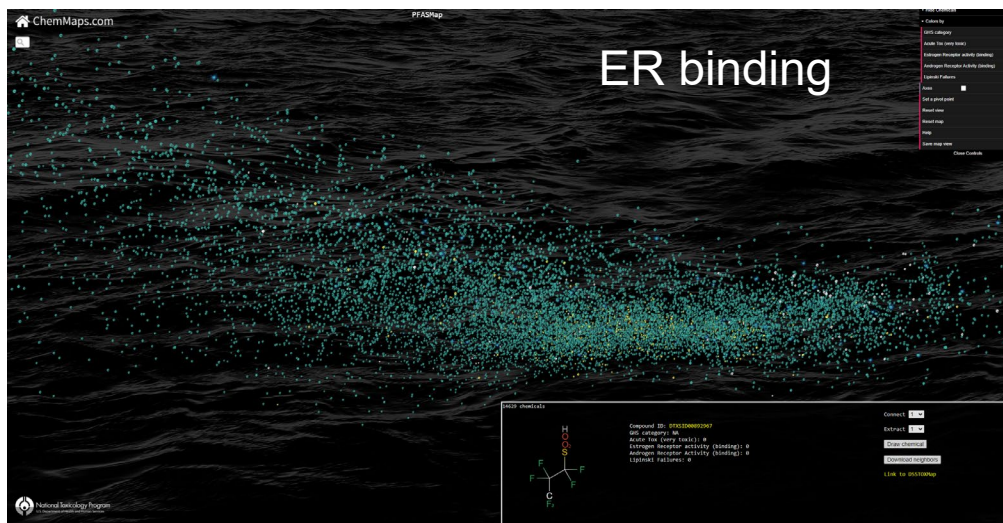
Draw chemical

Download neighbors

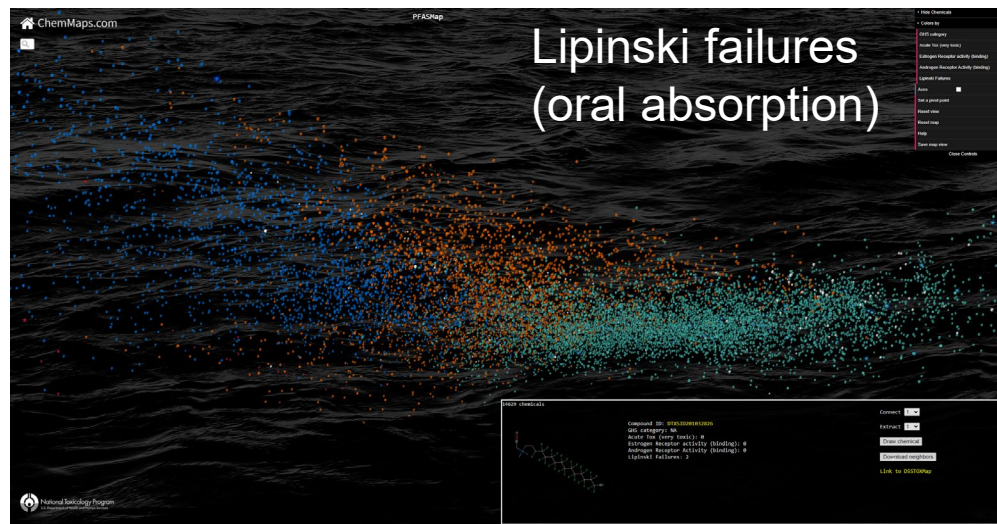
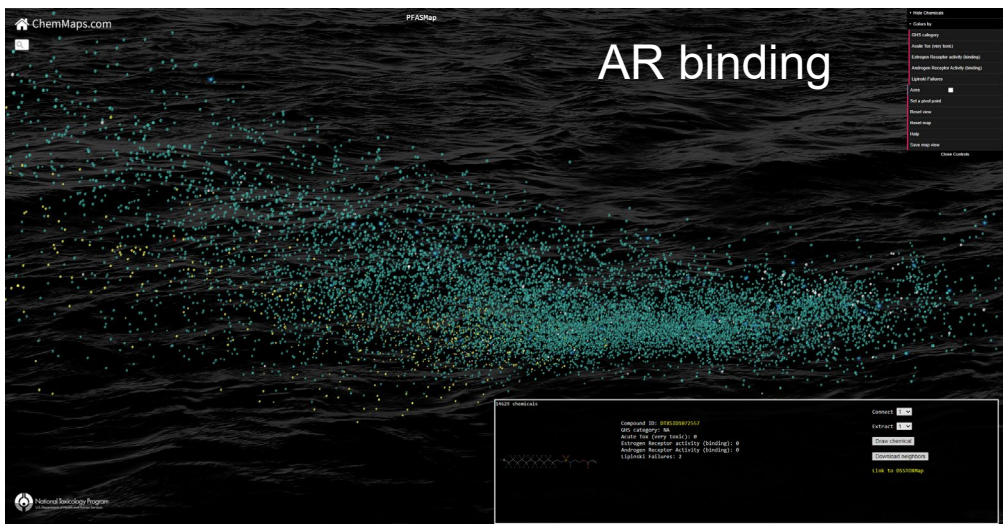
Link to DSSTOxMap



Visualizing Features



- Inactive
- Active



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

Hide Chemicals

Classified

No classified

Added chemicals

Draw structures

Colors by

Axes

Set a pivot point

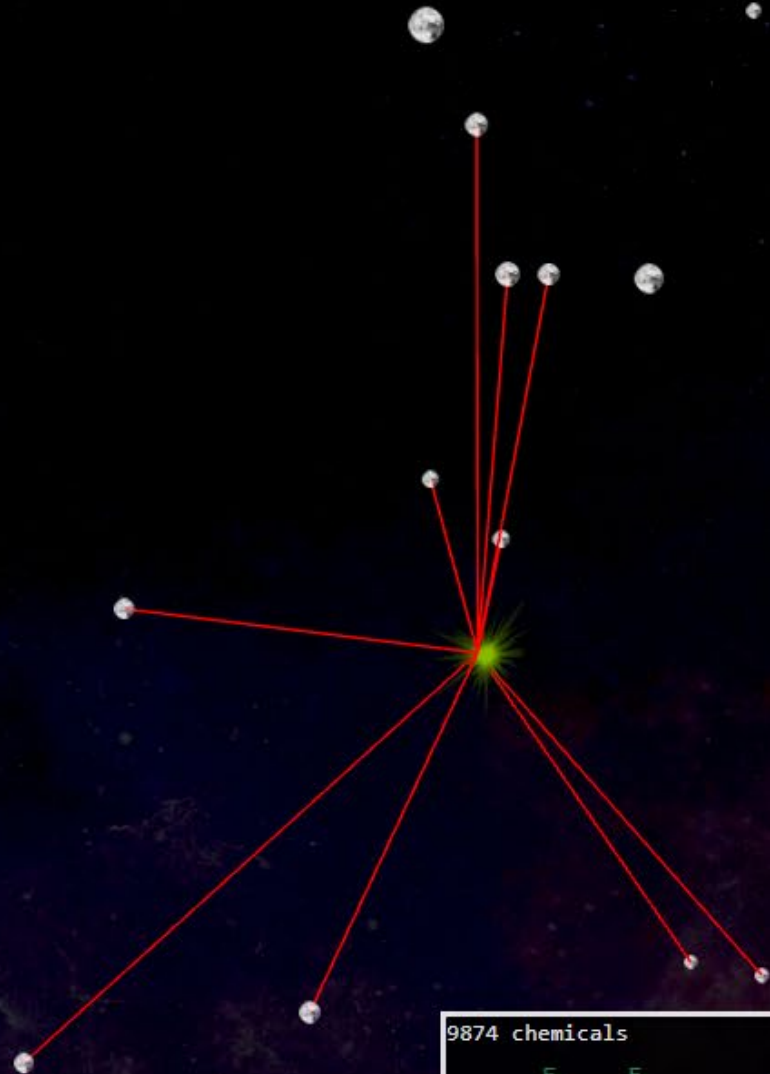
Reset view

Reset map

Help


Save map view

Close Controls



Highlight closest PFOA neighbors

9874 chemicals



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

Connect

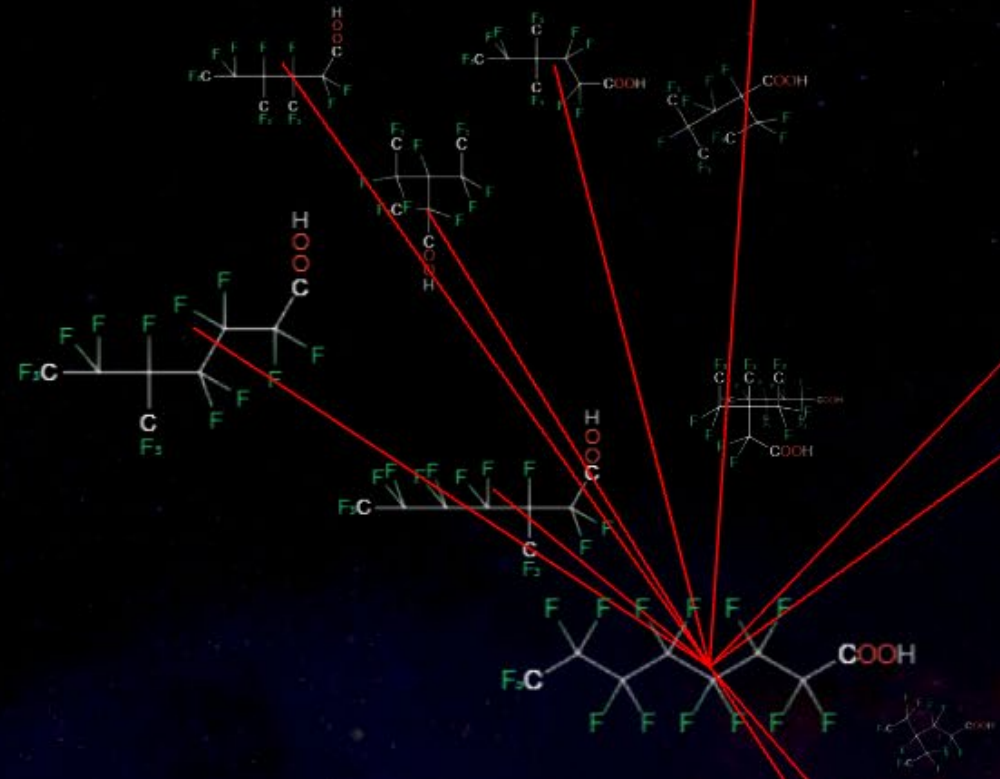
Extract

Draw chemical

Download neighbors

[Link to DSSTOXMap](#)

Center chemical: DTXSID8031865



Toggle visualization of chemical structures

Hide Chemicals

Classified

No classified

Added chemicals

Draw structures

Colors by

GHS category

Estrogen Receptor activity (binding)

Androgen Receptor Activity (binding)

LogP

MW

Lipinski Failures

Axes

Set a pivot point

Reset view

Reset map

Help

Save map view

Close Controls

9874 chemicals

Compound ID: **DTXSID70896654**

GHS category: NA

Estrogen Receptor activity (binding): 0

Androgen Receptor Activity (binding): 0

LogP: 3.2

MW: 396

Lipinski Failures: 0

Connect

Extract

[Draw chemical](#)

[Download neighbors](#)

[Link to DSSTOxMap](#)

PFOA on Tox21Map

The screenshot shows a web browser window with the URL <https://sandbox.ntp.niehs.nih.gov/chemmaps/>. The main content area features the text **www.chemmaps.com** and a subtitle *"A way to navigate in the chemical space"*. Below this, it states "This website is free and open to all users and there is no login requirement." and "Choose a map among the four maps available and navigate in the space".

DrugMap	DSSToxMap	Tox21Map	PFASMap
Drugbank Version 5.1.10 (release 2023-01-04)	DSSTox (release 2022-02)	Tox21 Screening Library chemicals as defined on the EPA dashboard (release 2022-10-29)	PFAS structures as defined on the EPA dashboard (release 2022-10-29)



Tox21Map

Project Tox21 assay results

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

Assay	Species	Tissue	Cell line	Gene	Mechanistic target
ACEA_ER_80hr	human	breast	cell line(T47D)	ESR1	CardioTox_ER Alpha,Estrogen Re...
APR_HepG2_MicrotubuleCSK_1h_dn	human	liver	cell line(HepG2)	TUBA1A	Cell Morphology
APR_HepG2_MicrotubuleCSK_1h_up	human	liver	cell line(HepG2)	TUBA1A	Cell Morphology
APR_HepG2_MitoticArrest_1h_dn	human	liver	cell line(HepG2)	H3F3A	Cell Cycle
APR_HepG2_MitoticArrest_1h_up	human	liver	cell line(HepG2)	H3F3A	Cell Cycle
APR_HepG2_P-H2AX_1h_dn	human	liver	cell line(HepG2)	H2AFX	Oxidative Stress
APR_HepG2_P-H2AX_1h_up	human	liver	cell line(HepG2)	H2AFX	Oxidative Stress
APR_HepG2_p53Act_1h_dn	human	liver	cell line(HepG2)	p53	p53 Modulation
APR_HepG2_p53Act_1h_up	human	liver	cell line(HepG2)	p53	p53 Modulation
APR_HepG2_StressKinase_1h_dn	human	liver	cell line(HepG2)	JUN	Oxidative Stress
APR_HepG2_StressKinase_1h_up	human	liver	cell line(HepG2)	JUN	Oxidative Stress
APR_HepG2_MicrotubuleCSK_24h_dn	human	liver	cell line(HepG2)	TUBA1A	Cell Morphology
APR_HepG2_MicrotubuleCSK_24h_up	human	liver	cell line(HepG2)	TUBA1A	Cell Morphology

Project assays with the same target gene

Project a unique assay result

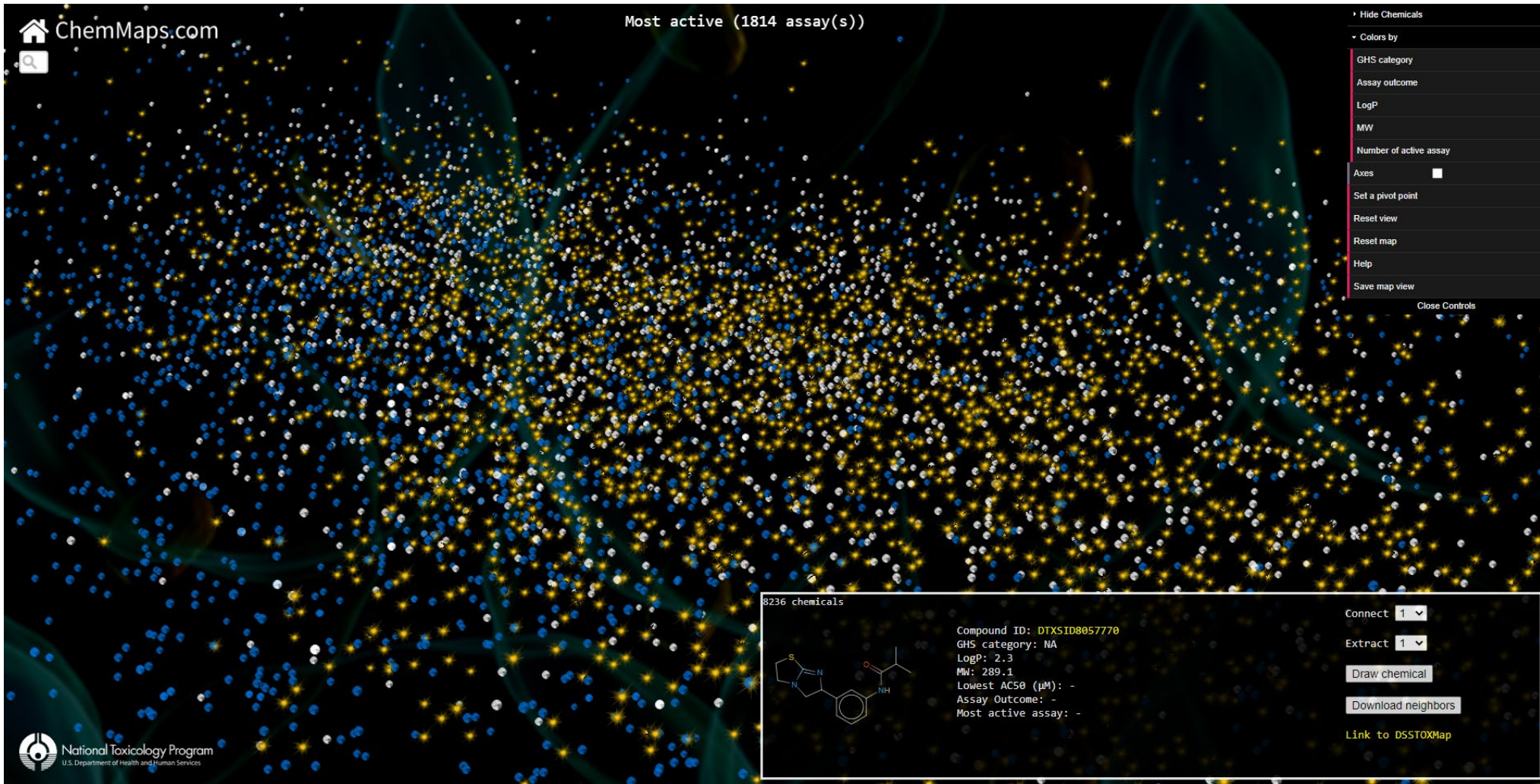
Project by chemical the most active assay

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

Tox21Map with lowest AC50 by chemicals

Project the assay result with the lowest AC50

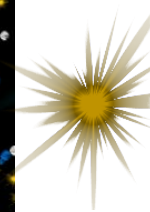
Tox21Map – Lowest AC50



Inactive

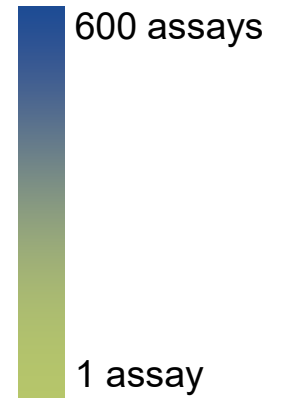
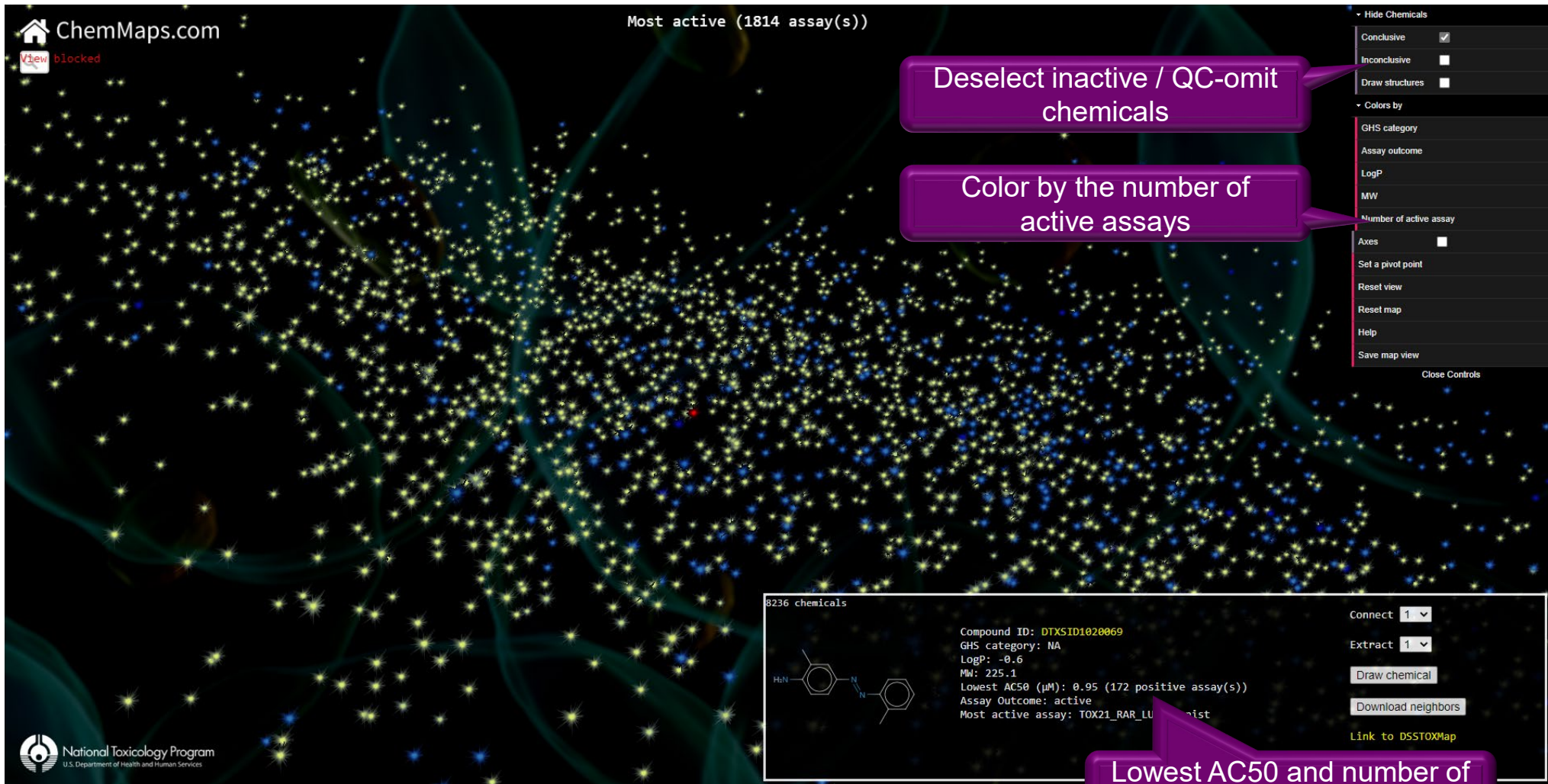


QC omit



At least one assay active

Tox21Map – Lowest AC50

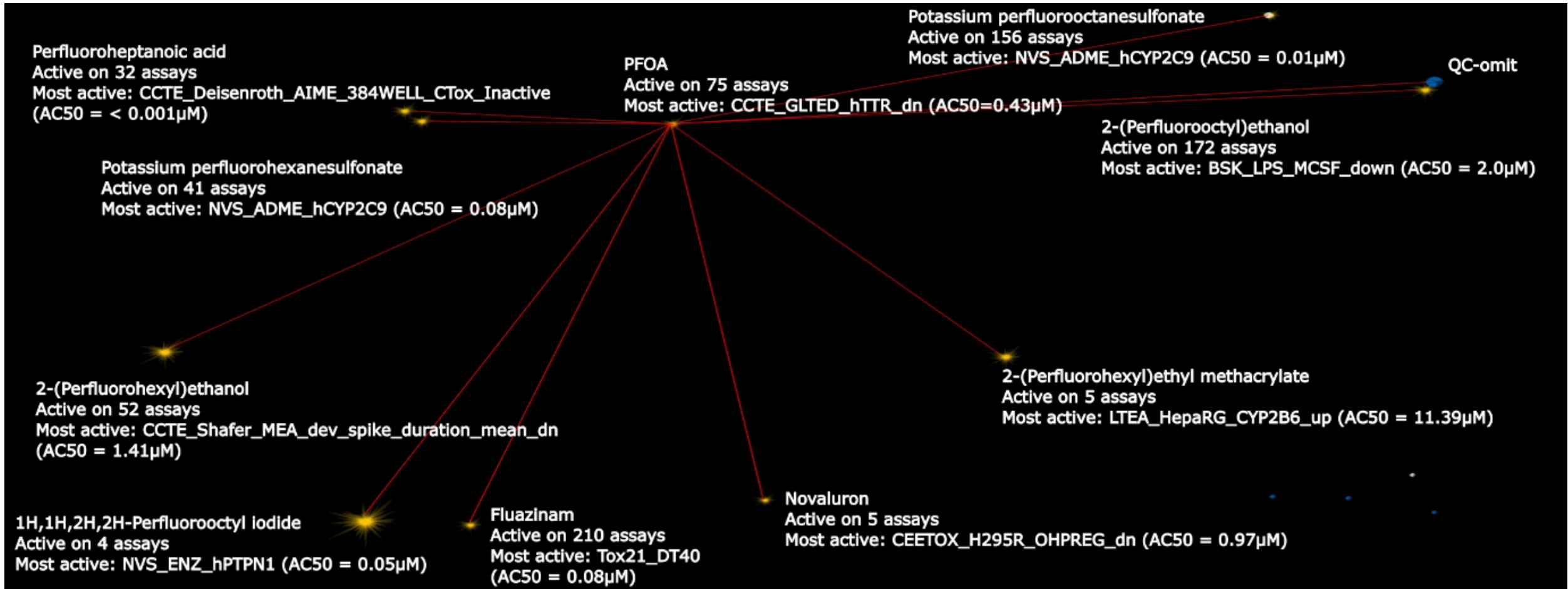


Deselect inactive / QC-omit chemicals

Color by the number of active assays

Lowest AC50 and number of active assay

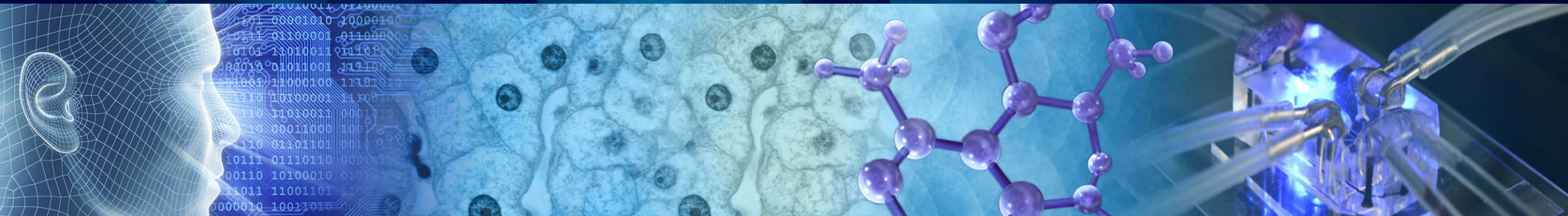
PFOA on Tox21Map



Summary

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

For more information, contact:
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The DASS App: A Web Application to Predict Skin Sensitization Using Defined Approaches

12th ASCCT Annual Meeting
2023-10-25

Presented by Kim To, Inotiv, contractor supporting NICEATM

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

Skin Sensitization

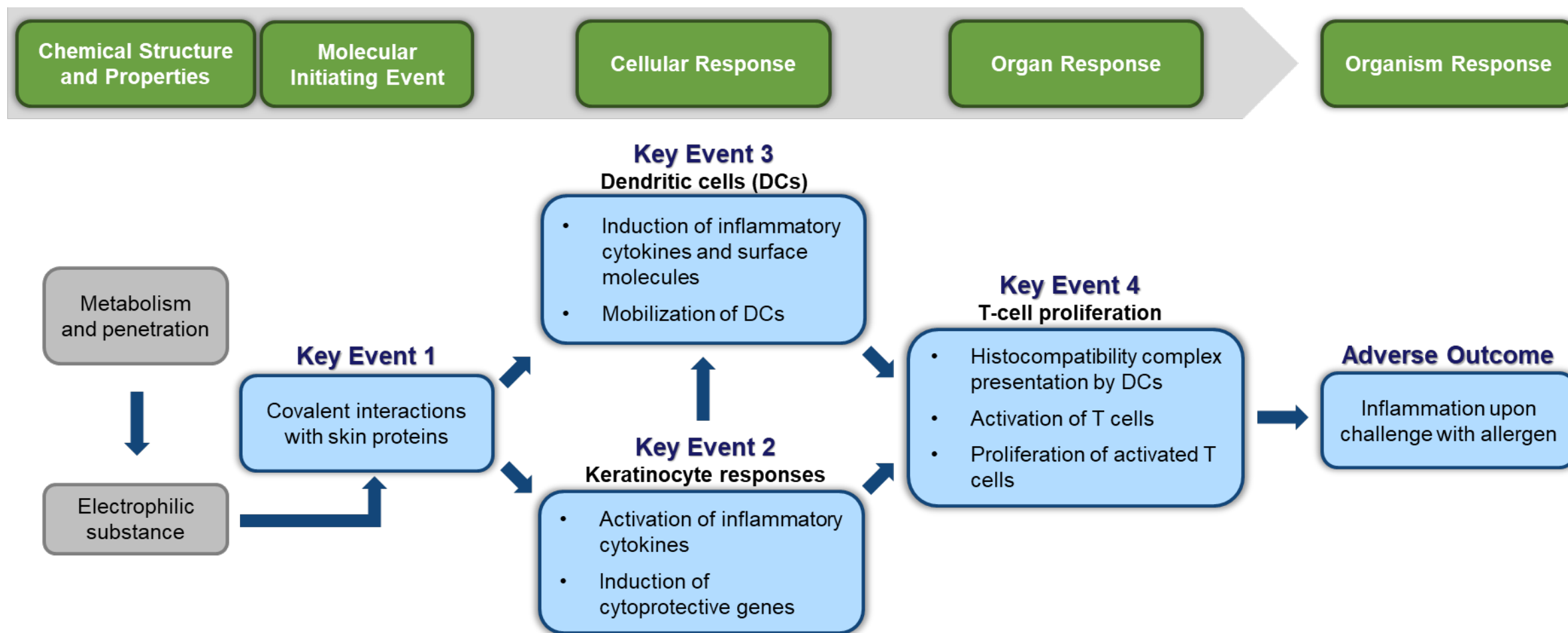
- Up to 20% of the population suffer from skin sensitization reactions¹.
- Historically, skin sensitization has been tested using in vivo methods such as the local lymph node assay (LLNA) or the guinea pig maximization test (gPMT).
- Regulatory frameworks, e.g., REACH, ask for information on predicting skin sensitization potential in humans.



¹Adler & DeLeo, *JAMA Dermatol.* 2021

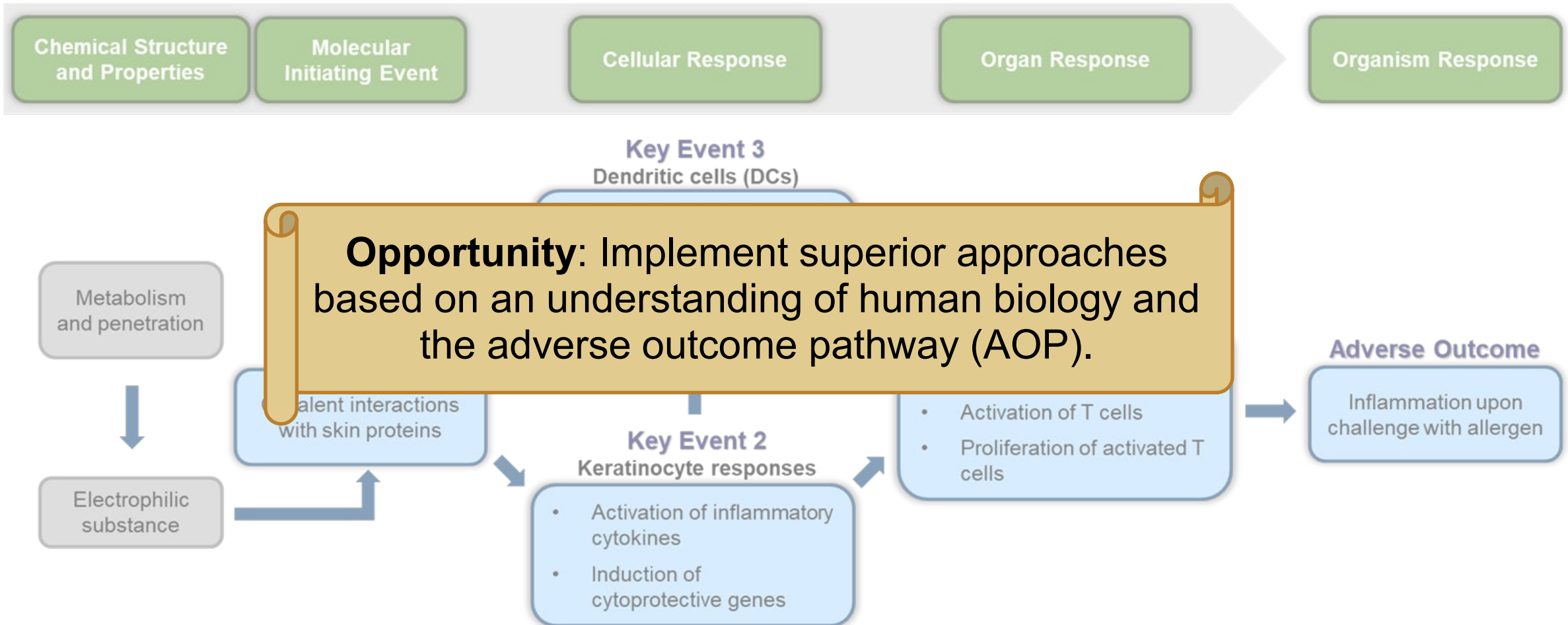
Adverse Outcome Pathway for Skin Sensitization

For sensitization initiated by covalent binding to proteins



Adverse Outcome Pathway for Skin Sensitization

For sensitization initiated by covalent binding to proteins

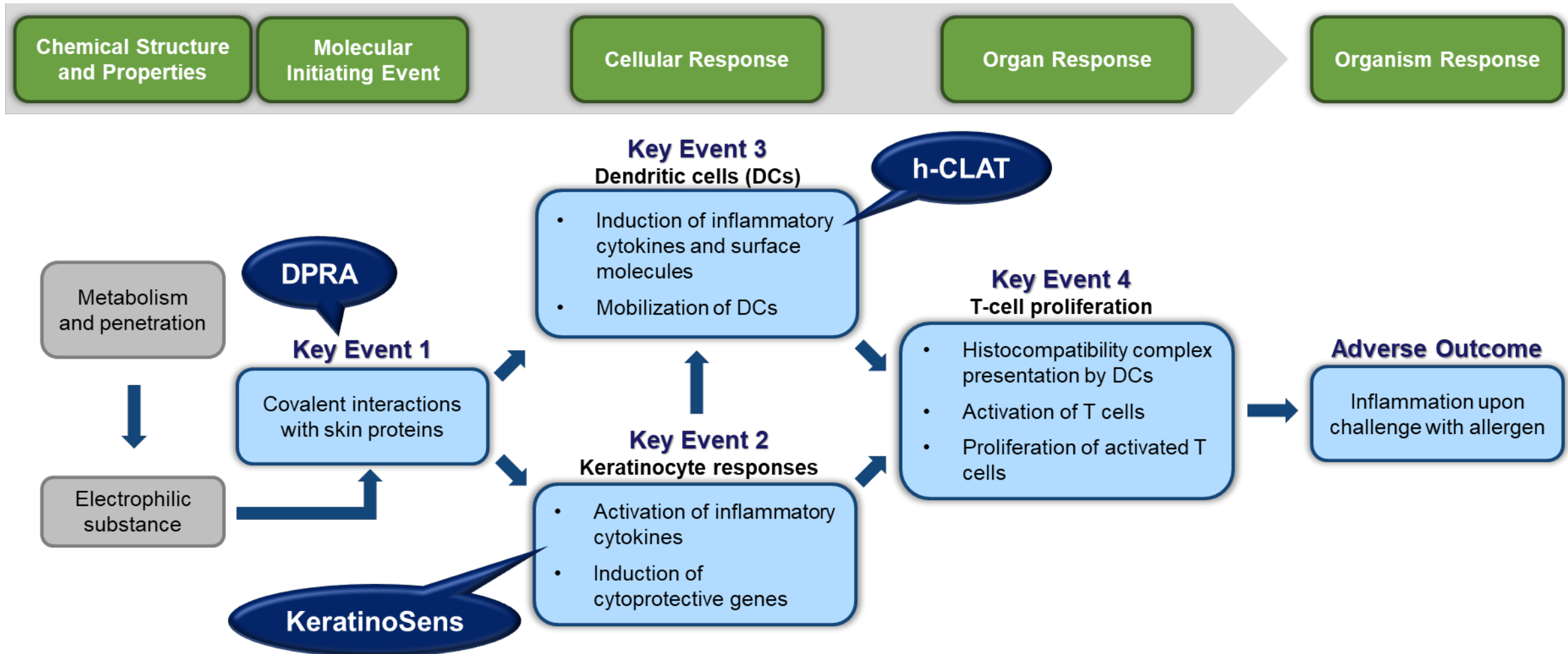


Non-animal methods for evaluating skin sensitization

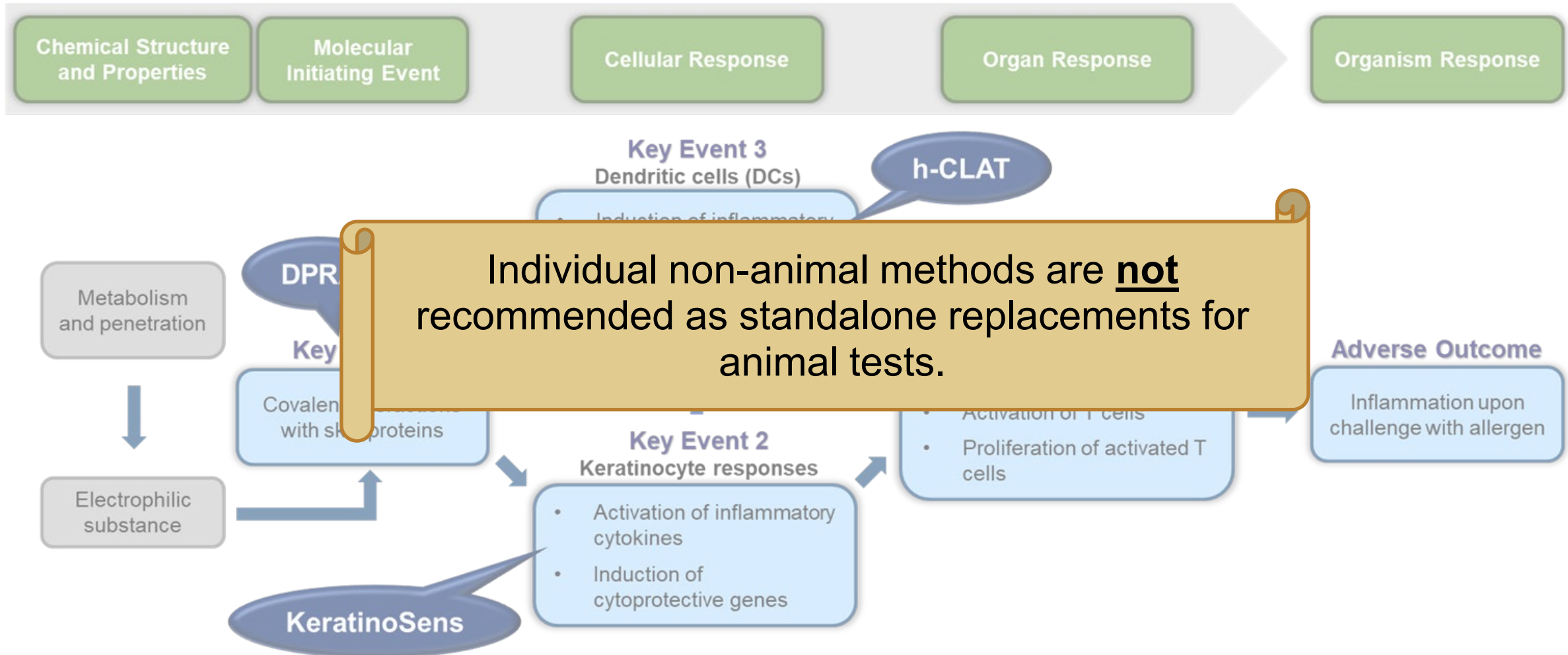
- Mechanistically based methods that address key events in the skin sensitization AOP
 - Direct peptide reactivity assay (DPRA)
 - KeratinoSens™ (KS)
 - Human cell line activation test (h-CLAT)



Non-animal methods for evaluating skin sensitization

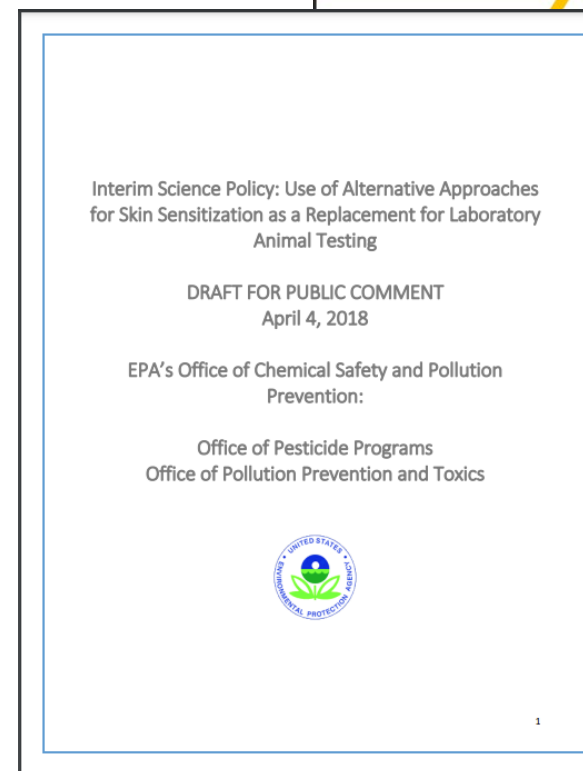


Non-animal methods for evaluating skin sensitization



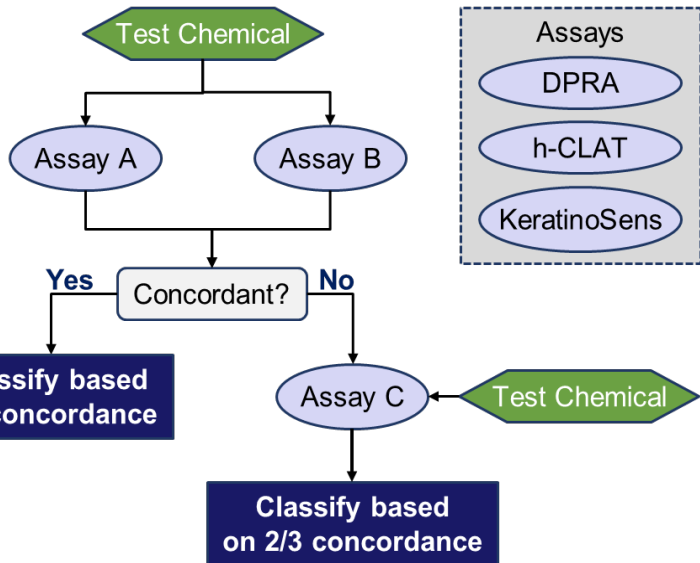
Defined Approaches

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



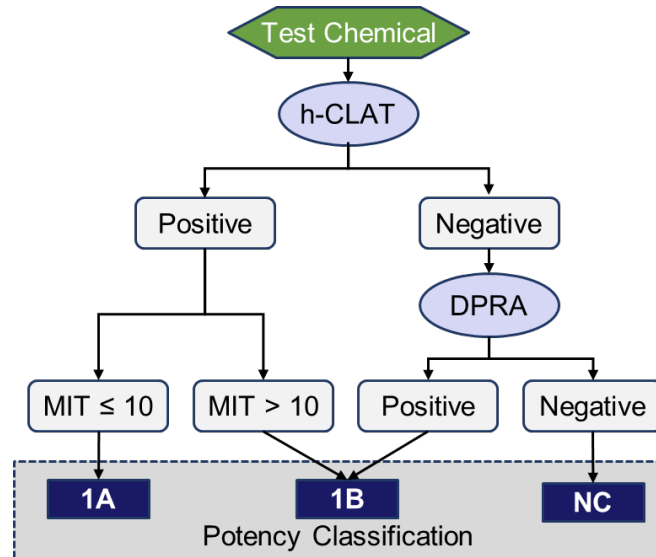
Defined Approaches for Skin Sensitization (DASS)

2 out of 3 (2o3)



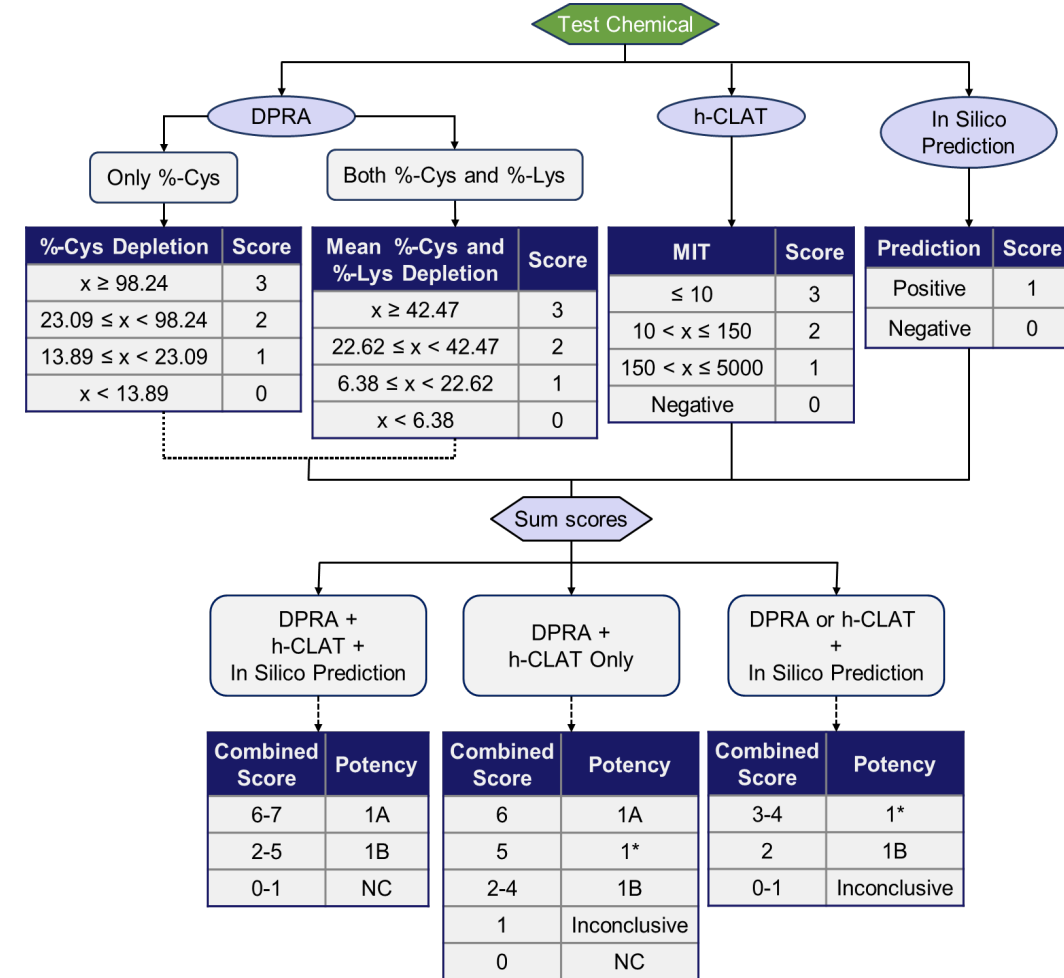
- Assays
- DPRA
 - h-CLAT
 - KeratinoSens

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



- Potency Classification
- 1A
 - 1B
 - NC

Integrated Testing Strategy (ITS)



%-Cys Depletion	Score
$x \geq 98.24$	3
$23.09 \leq x < 98.24$	2
$13.89 \leq x < 23.09$	1
$x < 13.89$	0

Mean %-Cys and %-Lys Depletion	Score
$x \geq 42.47$	3
$22.62 \leq x < 42.47$	2
$6.38 \leq x < 22.62$	1
$x < 6.38$	0

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

Prediction	Score
Positive	1
Negative	0

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

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

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

Accuracy of Methods Against Human Reference Data

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

Hazard Identification

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

Potency

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

The DASS App

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

Welcome to the DASS App!

The DASS App applies defined approaches on skin sensitization (DASS) that are described in OECD Guideline No. 497 [↗](#) and the U.S. EPA's Interim Science Policy: Use of Alternative Approaches for Skin Sensitization as a Replacement for Laboratory Animal Testing [↗](#). The defined approaches (DAs) predict skin sensitization hazard (either a sensitizer or non-sensitizer) and potency by integrating data from in vitro assays that represent key events in the Adverse Outcome Pathway (AOP) for Skin Sensitisation Initiated by Covalent Binding to Proteins [↗](#) and in silico hazard predictions.

More details are available in the User Guide [↗](#).

For more information or to report a problem with the app, please contact NICEATM at ICE-support@niehs.nih.gov.

Access the DASS App

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





National Institute of
Environmental Health Sciences
Division of Translational Toxicology

Demo

Evaluating data from OECD GL497



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



DASS App Demo

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

Step 1: Select the Defined Approaches to Apply

To begin, select the DAs to be implemented. Click on the green information buttons to view a description of the DA and the test methods required to implement the DA.

Select All | Deselect All


- 2 out of 3 (203) ⓘ
- Integrated Testing Strategy (ITS) ⓘ
- Key Event 3/1 (KE 3/1) Sequential Testing Strategy (STS) ⓘ



DASS App Demo

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

Step 2: Upload Data

 Before uploading your file, ensure that the data meet the **data and formatting requirements**.

A table template is provided in tab-delimited or Excel format. The template contains columns for every possible assay endpoint. If an assay endpoint will not be used, the corresponding column can be deleted but that is not required. Using the template is not required.

[Download Data Template \(.xlsx\)](#)
[Download Data Template \(.txt\)](#)

Use demo data



DASS App Demo

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

Step 3: Select Data Columns for Predictions

The assay endpoints that are required for the selected DAs are shown below. Use the dropdown lists to select the columns from your data that correspond to the given endpoints. Columns are automatically selected for an endpoint if the column name matches the corresponding column name in the data template. A column must be selected for each endpoint shown. When you are finished, click 'Done'.

Click on the information buttons next to the assay endpoint names to view information about the endpoints and data formatting requirements. Values that are incorrectly formatted or invalid will be treated as missing data and may affect the results. More details are given in the User Guide.

DPRA Call

Data Source

- Use DPRA Binary Call
 Use %-Depletion Values

DPRA Binary Call Column

dpra_call

DPRA % Depletion

DPRA %-Cysteine Depletion Column

dpra_pC

DPRA %-Lysine Depletion Column

dpra_pK

h-CLAT Binary Call

h-CLAT Binary Call Column

hCLAT_call



DASS App Demo

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

Step 4: Review Selection

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

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

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

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

Run

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

Run **Cancel**



DASS App Demo

10. DA predictions are appended to the original data.

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

Download Results ▾

Column visibility ▾

CASRN	SMILES	DA ITS Call	DA ITS Potency	DA 2o3 Call	DA KE 3/1 STS Call	DA KE 3/1 STS Potency
514-10-3	<chem>CC(C)C1CC[C@H]2C(=CC[C@@H]3[C@]2(C)CCC[C@@]3(C)C(O)=O)C=1</chem>	1	1B	1	1	1B
100-06-1	<chem>COc1ccc(cc1)C(C)=O</chem>	0	NC	0	0	NC
874-23-7	<chem>CC(=O)C1CCCC1=O</chem>	1	1B	1	1	1B
140-67-0	<chem>COc1ccc(CC=C)cc1</chem>	1	1B	1	1	1B
7493-74-5	<chem>C=CCOC(=O)COc1ccccc1</chem>	0	NC	0	0	NC
150-13-0	<chem>Nc1ccc(cc1)C(O)=O</chem>	0	NC	0	0	NC
2835-99-6	<chem>Cc1cc(O)ccc1N</chem>	1	1A	1	1	1B
2835-95-2	<chem>Cc1ccc(N)cc1O</chem>	1	1A	1	1	1B
95-55-6	<chem>Nc1ccccc1O</chem>	1	1A	1	1	1A
591-27-5	<chem>Nc1cccc(O)c1</chem>	1	1B	0	1	1B



DASS App Demo

11. Users may supply reference data to evaluate the DA results. The demo data include LLNA and Human reference data. In the Performance Metrics module, select:

- Type of comparison: Hazard
- Prediction columns: DA ITS Call, DA 2o3 Call, DA KE 3/1 STS Call
- Reference columns: LLNA.Call, Basketter_human_Call

12. Click the “Compare” button.

Supplemental: Compare Results

The dropdown menus show column names from your uploaded data and column names from the DA output. You may calculate accuracy of a DA result against reference data. Reference data should be included in your uploaded data. Select the prediction and reference columns to be compared.

Select type of comparison

Hazard
 Potency

Select Prediction Column(s)

DA ITS Call DA 2o3 Call
DA KE 3/1 STS Call

Select Reference Column(s)

LLNA.Call Basketter_human_Call

Compare



DASS App Demo

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

Select Output

llnacall_daitscall

- llnacall_daitscall
- llnacall_da2o3call
- llnacall_dake3/1stscall
- basketter_human_call_daitscall
- basketter_human_call_da2o3call
- basketter_human_call_dake3/1stscall

Confusion Matrix and Performance Metrics

Reference Column: LLNA.Call

Prediction Column: DA ITS Call

		Reference	
		0	1
Predicted	0	23	15
	1	10	117

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

Download Performance

Select tables to download

- llnacall_daitscall
- llnacall_da2o3call
- llnacall_dake3/1stscall
- basketter_human_call_daitscall
- basketter_human_call_da2o3call
- basketter_human_call_dake3/1stscall

[Download](#)

[Close](#)

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



Summary

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

Conclusion

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

The NICEATM Group



NIEHS/DTT Contributors



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



<https://github.com/NIEHS/OPERA>



ChemMaps.com

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



The DASS App

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