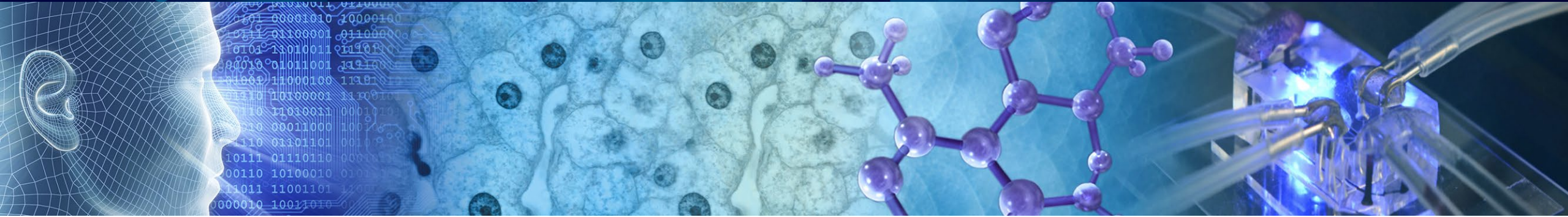




National Institute of
Environmental Health Sciences
Division of Translational Toxicology



The Integrated Chemical Environment (ICE): An open-access tool to support chemical evaluations

Victoria Hull, M.S.

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

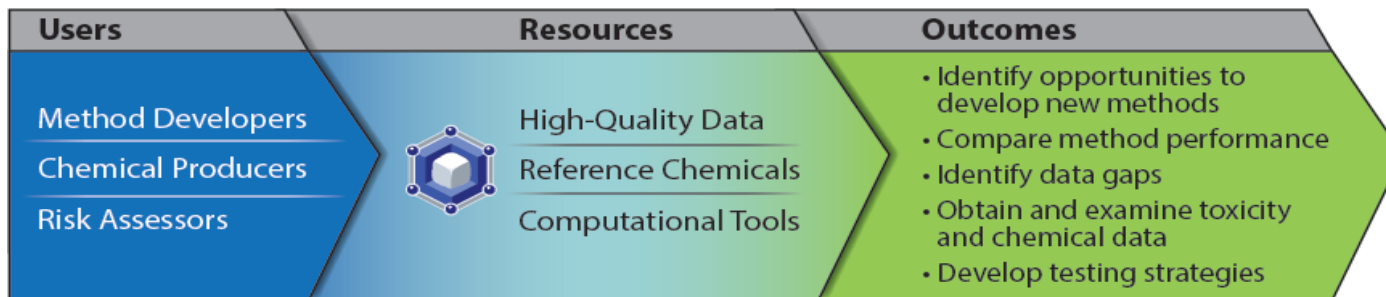
SACATM 2023

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

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



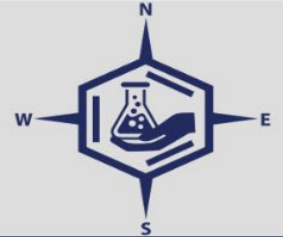

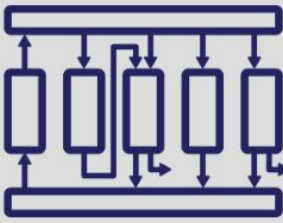
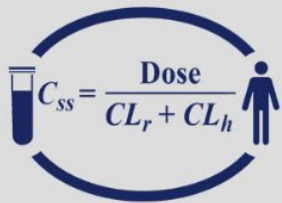



Integrated Chemical Environment

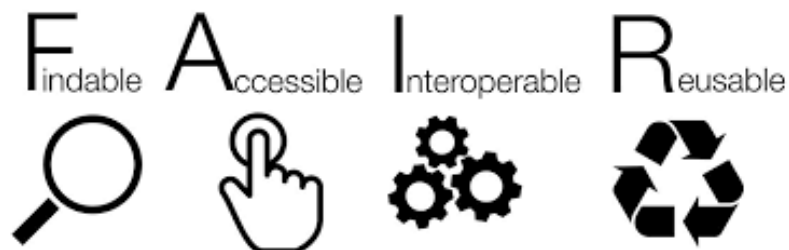


Releases in 2023:

ICE v4.0 (March)

ICE v4.0.1 (August)

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



Accessing ICE Data and Tools

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

Integrated Chemical Environment

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

ICE version 4.0.1 Released August 2023

Visit News page for more information.

PAUSE

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

- News
- News
- Release Notes

ICE Updates

ICE 4.0.1 Release Notes

ICE version 4.0.1 (August 2023) includes updates on data and tools:

- Availability of population-level exposure predictions across multiple pathways through the ICE Search tool in addition to the ICE REST API and IVIVE tool.
- Major updates in the data visualizations for Search tool query summary results (beta version).
- Addition of new quicklists:
 - Mixtures and Formulations in ICE
 - ToxCast Phase I, Phase II, and e1k
- Functional use categories added to ICE Chemical Characterization tool..
- "Consumer Use Explorer" in ICE Chemical Characterization tool Improved and rebranded as "Curated Product Use Explorer".
- Improved support for chemical name searching in all ICE tools.
- Harmonization of structure and data fields in the dermal irritation/corrosion data set to make data computationally accessible and facilitate interoperability on the ICE user interface.
- Multiple bug fixes to optimize functioning of the ICE website.

[ICE 4.0 Release Notes](#)

ICE version 4.0 (March 2023) includes new data and updated tools:

- New interactive data visualizations for Search results summary.
- New Exposure Predictions data set providing population-level exposure predictions from EPA's SEEM3 model.
- Updates to the PBPK and IVIVE tools:
 - Tools use models from httk R package [version 2.2.2](#) (released February 2023).
 - A human gestational model from httk v2.2.2 has been added to both tools.
 - A new chemical concentration unit, ppmv , has been added when modeling chemical exposure as gas.
 - Predicted half-life and area under curve values are available in PBPK models output.
 - Exposure Predictions are available as an overlay option in the IVIVE results.
- Acceptance of chemical names and synonyms as input.

Learn about ICE updates

UPDATES

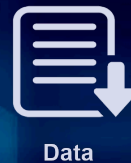
- Search
- Chemical Quest
- Curve Surfer
- PBPK
- IVIVE
- Chemical Characterization
- Data
- Help Videos

- ICE Database Access via REST API
 - <https://ice.ntp.niehs.nih.gov/api/v1/search>
 - For one or more chemical ids, return a list of Assay/Endpoint objects

ICE Data (In Vivo and In Vitro)

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!



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!

ICE Chemical Quick Lists

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!



ICE Tools Workflow



Integrated Chemical Environment

Perform a
search



Search

Expand
inventory:
Identify
similar
chemicals



Chemical Quest

Characterize
chemical
inventory



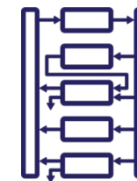
Chemical
characterization

Review
in vitro
data details



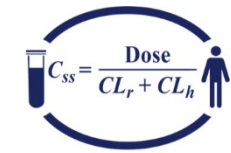
Curve Surfer

Generate
chemical
concentration
predictions



PBPK

Predict
equivalent
administered
dose from in
vitro data



IVIVE



Input

Results

The Search tool allows you to query ICE data using chemical quick list selections (chemical names and synonyms) and a selection of data sets organized by toxicity endpoints of regulatory interest.

Run Reset Scope of Search Union

Help Help Video Report an Issue

Chemical Input

Select Chemicals

Quick List CASRNs

User Chemical Identifiers

133-06-2
63-25-2
DTXSID9020160
BPA
17alpha-Ethinylestradiol

Data Selection

Select Data Sets

Set

Select Data Sets	Description	Data Type
cHTS		
<input type="checkbox"/>	Abnormal Growth and Differentiation	in vitro
<input type="checkbox"/>	Angiogenic Process	in vitro
<input type="checkbox"/>	Cellular Processes	
<input type="checkbox"/>	Cellular Stress Response	
<input type="checkbox"/>	Endocrine-Related Processes	in vitro
<input type="checkbox"/>	Energy Metabolism Process	in vitro
<input type="checkbox"/>	Epigenetic Process	in vitro
<input type="checkbox"/>	Gene Expression	in vitro
<input type="checkbox"/>	Immune and Inflammatory Response	in vitro
<input type="checkbox"/>	Neuronal Transmission	
<input type="checkbox"/>	Xenobiotic Metabolism	in vitro
<input type="checkbox"/>	Unannotated	in vitro

Finished

Click "Select Data Sets" to select assays organized by toxicity endpoint

Click this button to view and select ICE Chemical Quick Lists

Enter one chemical identifier per row. Identifiers can now include names and synonyms!

Chemical input now accepts chemical names and synonyms! Access new and improved datasets!



Explore new datasets!

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

Send filtered results to other ICE tools

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

View Details	Substance Name	Substance Type	CASRN (CEBS Link)	DTXSID (Dashboard Link)	QSAR Ready ID	Abnormal Growth and Differenti... Call (# Assays=6)	Angiogenic Process Call (# Assays=28)	Cell Death Process Call (# Assays=12)	Cell Cycle Call (# Assays=68)	Cell Proliferat... Call (# Assays=6)	Cell Viability Process Call (# Assays=1...	Extra: Matric: (# Assay)
	17-Methyltestosterone	Chemical	58-18-4	DTXSID1033664	GCKMFJB... UHFFFAOY... N	Active,Not Tested(N=5)	Inactive(N... Tested(N=6)	Inactive(N... Tested(N=7)	Active(N=1... 11	Inactive(N... 11	Active(N=1... Tested(N=...	Activ Omit
	17alpha-Estradiol	Chemical	57-91-0	DTXSID8022377	VOXZDWN... UHFFFAOY... N	Active,Not Tested(N=5)	Active(N=3... Omit(N=2)... Tested(N=6)	Inactive(N... Tested(N=7)	Omit(N=1)... Tested(N=...	Inactive(N... 11	ve(N=3... Omit(N=8)... Tested(N=...	Activ

Click icons to view substance details

Click icons to filter results



Perform a search

Expand Inventory:
Identify similar chemicals

Characterize chemical inventory

Review in vitro data details

Generate chemical concentration predictions

Predict equivalent administered dose

The Chemical Quest tool uses fingerprints to calculate structural similarity. This tool uses fingerprints generated using Saagar features. Only 50 input chemical IDs/structures are allowed.

Draw 2D structures or input chemical SMILES

Max hits per input: 10 | Tanimoto Coefficient: 0.7 or greater

Chemical ID input (one per line):
63-25-2
80-05-7
133-06-2
57-63-6
82657-04-3

Smiles Structures for similarity search:
Draw | Enter
Chemical Structure: C(C)1=CC=C(C(C)C)C=C1

Results show number of similar structures identified for each input chemical or structure

Chemical Name: Captan
CASRN: 133-06-2
DTXSID: DTXSID9020243
Tanimoto: top 10 hits and >0.7
Hit Count: 10
Passed Filter(s): 10/10
Selected Item(s): 0/10

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

Similar Structures to: Captan

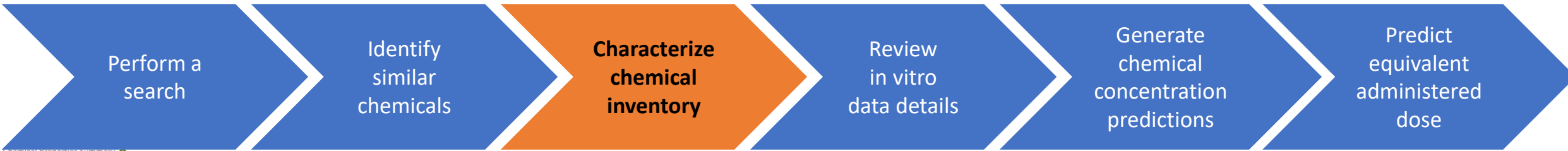
Send filtered results to: Select tool...
Select Filter to add to chain:
CASRN
Chemical Name
DTXSID
Name
Tanimoto Value
Has Bioactivity

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

SMARTS Filter: Enter SMARTS: C-Br
Add SMARTS Query

Search Text	Count	%
<input checked="" type="checkbox"/> C=C	10 (10)	100.0%
<input checked="" type="checkbox"/> C-F	1 (1)	10.0%

Items: C=C, C-F



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

Lists: Both Chemical Lists

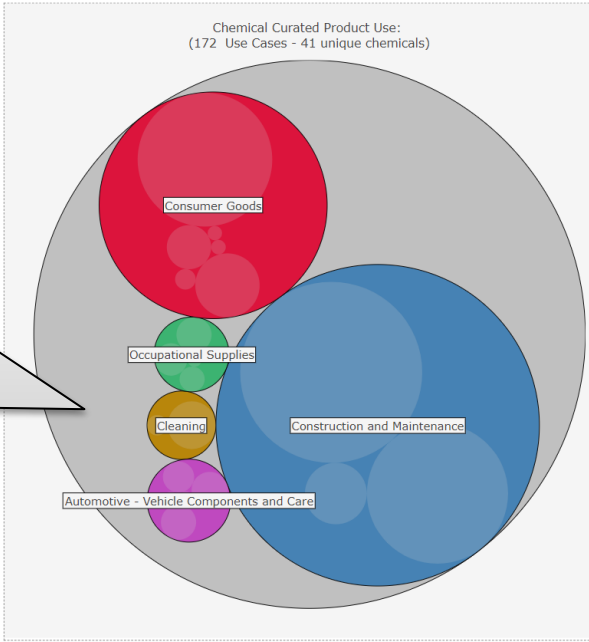
Send filtered results to: Select tool...

Chemical List (OPERA) Predictions by Input List, CASRN

Users can input one or two lists of chemicals and toggle results to show one or both lists

List	Substance Name	CASRN (CEBS Link)	DTXSID (Dashboard Link)	Molecular Weight, g/mol	OPERA, Boiling Point, C	OPERA, Henry's Law Constant, atm-m ³ /mol
Custom Chemical List 1	Carbaryl	63-25-2	DTXSID9020247	201.221	314.943	-7.86
Custom Chemical List 1	Captan	133-06-2	DTXSID9020243	300.589	302.104	-5.43
Custom Chemical List 1	(+)-cis-Permethrin	54774-45-7	DTXSID5052208	391.288	401.446	-7.62

Summary details show product use details by category and by chemical



Chemical Curated Product Use Details (172 Use Cases - 41 unique chemicals)

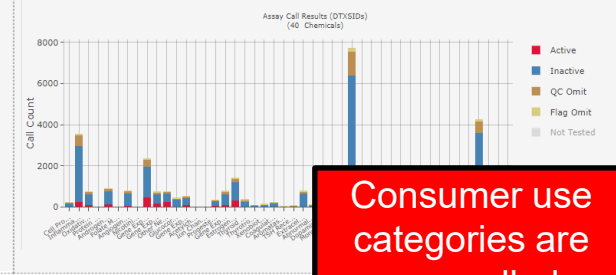
Sub Category	Count
Construction and Maintenance	104
Consumer Goods	36
Automotive - Vehicle Components a...	12
Occupational Supplies	12
Cleaning	8

DTXSID (Dashboard)	Substance Name	CASRN (CEBS Link)	Sub Categories	Count
DTXSID8021482	Acetone	67-64-1	[Construction and Maintenance, Consumer Goods, Automotive - Vehicle Components a..., Occupational Supplies, Cleaning]	57
DTXSID3020205	Benzyl butyl phthalate	85-68-7	[Construction and Maintenance, Consumer Goods, Automotive - Vehicle Components a..., Occupational Supplies, Cleaning]	10
DTXSID8022292	Permethrin	52645-53-1	[Construction and Maintenance, Consumer Goods, Automotive - Vehicle Components a..., Occupational Supplies, Cleaning]	9
DTXSID2021781	Dibutyl 1,2-benzenedi...	84-74-2	[Construction and Maintenance, Consumer Goods, Automotive - Vehicle Components a..., Occupational Supplies, Cleaning]	8

Chemical List Statistical Summary of (OPERA) Predictions

Endpoint	Min	25th	Median	Mean	75th	Max
OPERA, Water Solubility, log ₁₀ , moles/L	-10.4	-4.35	-2.33	-2.81	-0.869	1.355
Molecular Weight, g/mol	30.026	120.17	197.446	214.652	268.352	1202.611
OPERA, Octanol-Air Partition Coefficient, KOA log ₁₀	0.969	3.854	7.843	6.883	9.383	11.757

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!

Perform a search

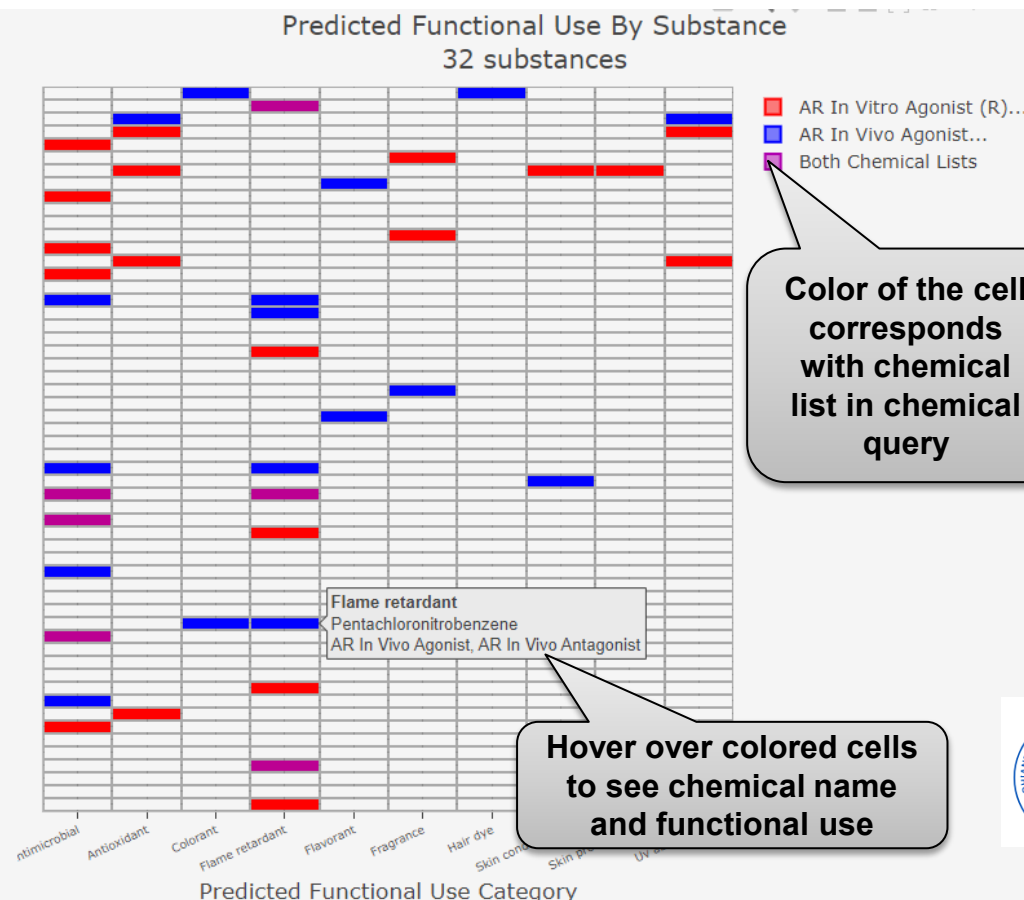
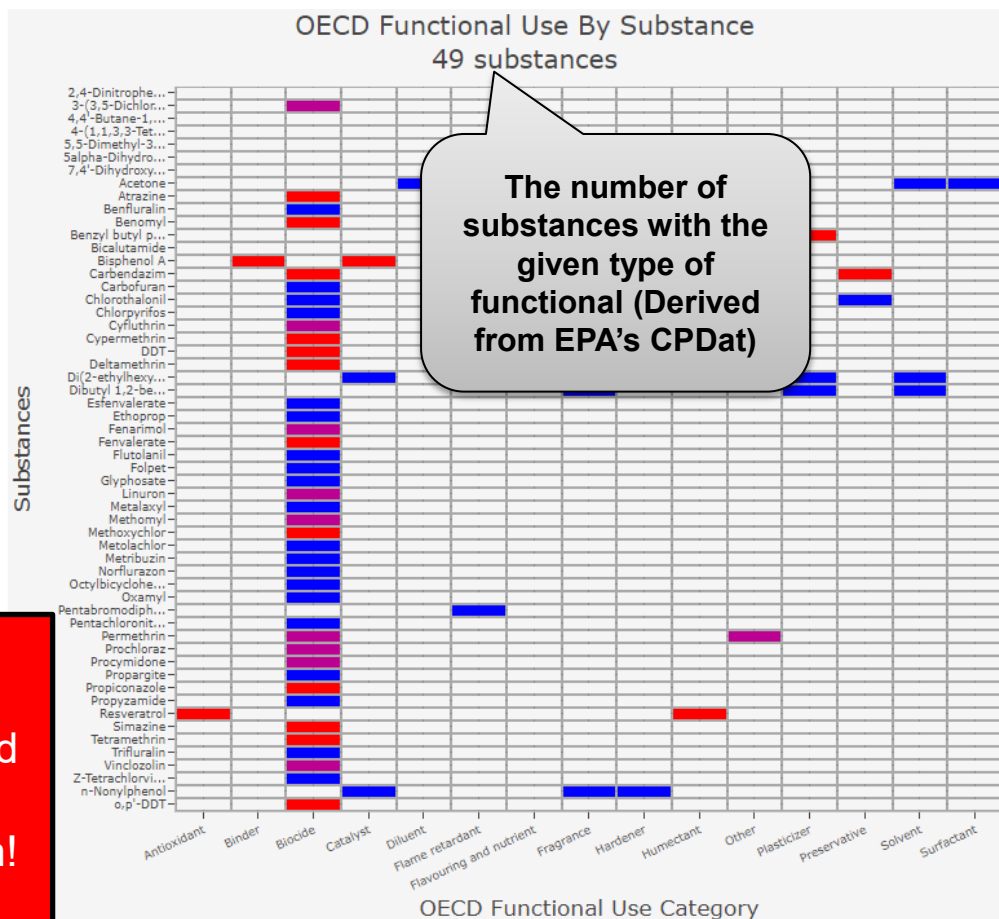
Identify similar chemicals

Characterize chemical inventory

Review in vitro data details

Generate chemical concentration predictions

Predict equivalent administered dose



New use category and heatmap visualization!

Hover over colored cells to see chemical name and functional use



Perform a search

Identify similar chemicals

Characterize chemical inventory

Review cHTS concentration-response curves

Generate chemical concentration predictions

Predict equivalent administered dose

The screenshot displays the Curve Surfer web application interface. At the top, there are search and filter options, including a pie chart showing the distribution of results (54.5%, 27%, 18.5%). Below this, there are buttons for 'Select All Filtered', 'Clear Selected', and 'Only show selected items'. The main area shows two assay plots side-by-side, each with a detailed information panel below it. The left plot is for 'ACEA_AR_agonist_AUC_viability' and the right plot is for 'ACEA_AR_antagonist_80hr'. Both plots show 'Percent Activity' vs 'Concentration (uM)' on a log scale. The information panels provide details such as Assay, CASRN, Chemical Name, ACS0 (uM), Top of Curve, and Mechanistic Target. A callout box points to the filter options, stating 'to filter based on assay, assay target, C.'. Another callout box points to the data breakdown, stating 'View data breakdown by filter terms and see selection highlighted'. A third callout box points to the plot information panels, stating 'Plots have key features highlighted and details for assay and chemical information are provided below plots'. On the right, there is an 'AC 50 Filter' window with a slider and a 'Kernel Density Estimate (KDE)' plot showing the distribution of concentrations. The KDE plot has a mean of 30.00 and a standard deviation of 27.05, with 7054 items selected. A 'Close' button is located at the bottom right of the KDE plot.

to filter based on assay, assay target, C.

View data breakdown by filter terms and see selection highlighted

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

AC 50 Filter

Enter Values: Min Value: 0.00001, Max Value: 194.900227, Inverse Mode: [Off]

Mean: 30.00, Std. Dev.: 27.05, Selected: 7054

Kernel Density Estimate (KDE)

Concentration (uM)

Close



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

Choose human or rat (fetal model only allows human)

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

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

Input Results

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

Run Reset

Species: human, ADME Source: Default, Model: Solve_fetal_pbtk, Exposure Route: iv, Exposure Interval: 24 Hours, Exposure Length: 0.25, Simulation Length: 3 Days, Body Weight: 70.0, Gestation Days: 91.0

Species	human	Exposure Route	iv
Body Weight	70	Exposure Interval, Hours	24
ADME Source	Default	Exposure Length, Hours	0.25
Exposure Dose	1.0	Simulation Length, Days	3
Gestational Day when Exposure Starts	91	Output Conc. Units	uM
Model	Solve_fetal_pbtk	Inhalation Dosing Method	Concentration
	Solve_pbtk	Inhalation Dosing Units	ppmv
	Solve_gas_pbtk		
	Solve_fetal_pbtk		

Model from the US EPA's httk package. External and fetal compartments are shared by mother and fetus.

Chemical Input

Select Chemicals

Quick List CASRNs

User Chemical Identifiers

133-06-2
63-25-2
54774-45-7

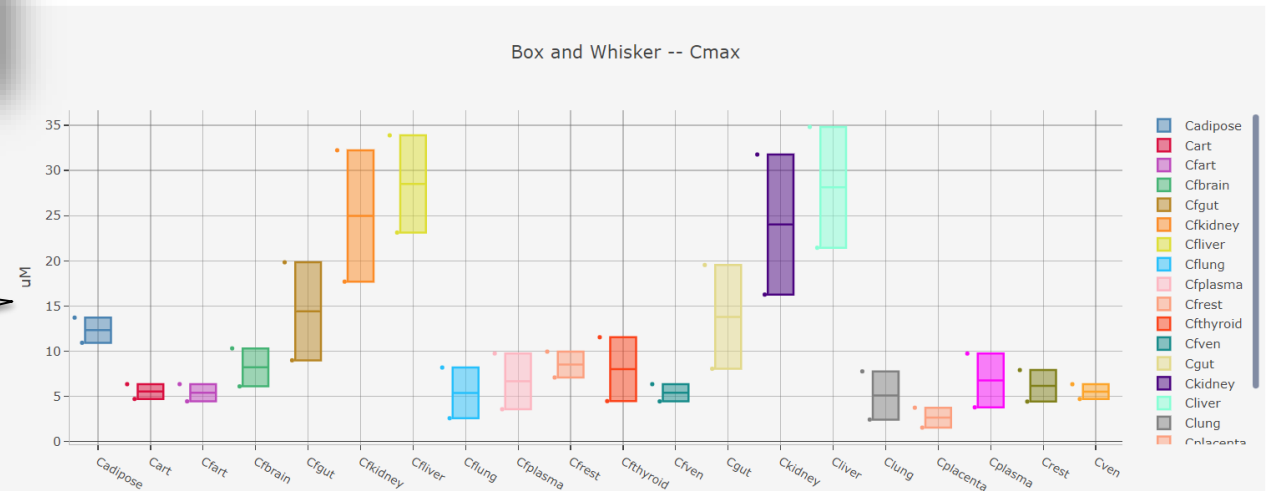




For each input chemical, the results show the concentration of the chemical over time in plasma and each tissue compartment

Visualize fetal and maternal tissue concentrations!

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





Input

Results

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

Run Reset

Endpoint: AC50, Species: human, ADME Source: Default, Model: Solve_fetal_pbtik, Exposure Route: Iv, Exposure Interval: 24.0 Hours, Exposure Length: null, Simulation Length: 3.0 Days, Gestational Days: 91.0, Body Weight: 70.0

In Vitro Endpoint
AC50

Species
human

Body Weight
70

ADME Source
Default

Gestational Day when Exposure Starts
91

Model
Solve_fetal_pbtik

Exposure Route
Iv

Exposure Interval, Hours
24

Exposure Length, Hours

Simulation Length, Days
3

Inhalation Dosing Method
Concentration

Inhalation Dosing Units
ppmv

Chemical Input
Select Chemicals
Quick List CASRNs
User Chemical Identifiers

Data Input
Select Assays
Assay Description Assay Type

Upload Custom In Vivo or Exposure Data to Overlay on Charts
Upload Drop file here
Uploaded Files
File Name MIME Type

Type of activity concentration (AC50 or ACC)

Choose from in house ICE models and models sourced from US EPA's httk Package

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

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

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





IVIVE Results Visualizations

Select EAD to visualize: EAD 50th

Select in vivo data or exposure data to display: Exposure Predictions

Log Axis

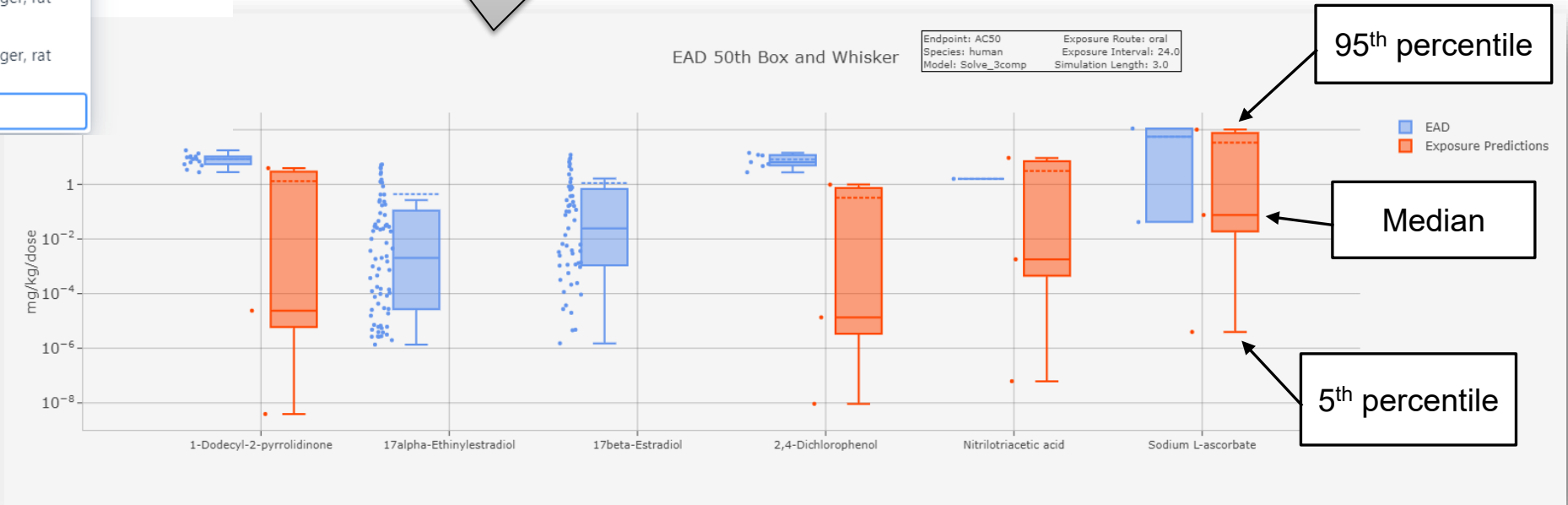
Select Page: 1 of 1

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

Box and whisker plots show Equivalent Administered Dose (EAD) based on in vitro inputs

Overlay new exposure predictions!

Users can now overlay Exposure Predictions from EPA's SEEM3 model



Ongoing Additions – Search Query Summary Results (In Beta)

non-cHTS
assays!

Search Results Info

Data Summary
Query Summary (Beta)

Search Results Navigation by Selected Data Sets

Search Results

cHTS

Cellular Processes

Gene Expression

Unannotated

Acute Lethality

Mode of Action

Endocrine

Androgen

Cancer

Mode of Action

DART

Mode of Action

Cardiotoxicity

Mode of Action

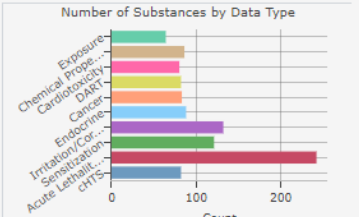
Results Distribution by Chemical Reference List (88 substances queried)

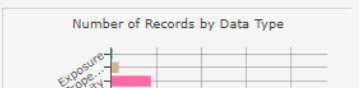
Chemical List	Queried	Chemicals	Mixtures	Not Retur...	Number of Records
AR In Vitro Agonist (R)	37	37	59	0	
AR In Vivo Agonist	26	26	86	0	
AR In Vitro Antagonist (R)	28	28	31	0	

Search Results by DTXSID, CASRN (98101 records for 248 substances)

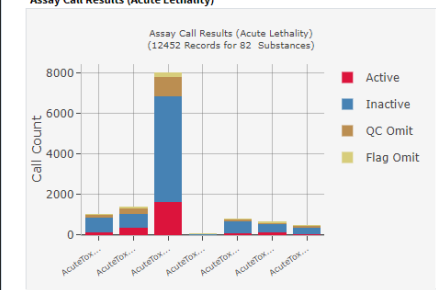
Name	Type	CASRN	DTXSID	Number of Records
Departure Herbicide	Mixture	ICE_41...	NA	
Troysan ALF4	Mixture	ICE_31...	NA	
Fenbutatin oxide				
Gordon's Horse 8				
Abamectin(98%)				

Substance and Record View





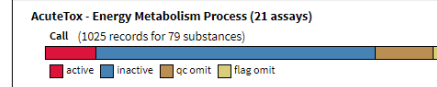
Acute Lethality



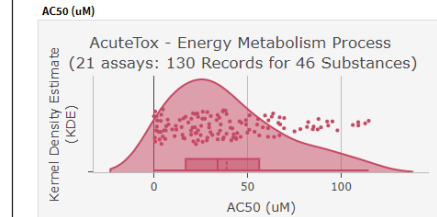
Page 1 of 1

AcuteTox - Energy Metabolism Process (21 assays)

Call (1025 records for 79 substances)



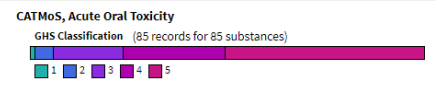
AC50 (uM)



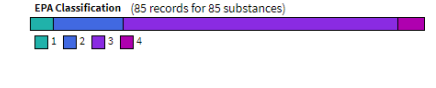
Page 1 of 1

CATMoS, Acute Oral Toxicity

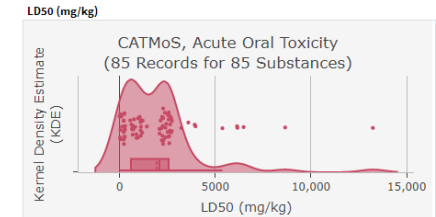
GHS Classification (85 records for 85 substances)



EPA Classification (85 records for 85 substances)



LD50 (mg/kg)



Page 1 of 1

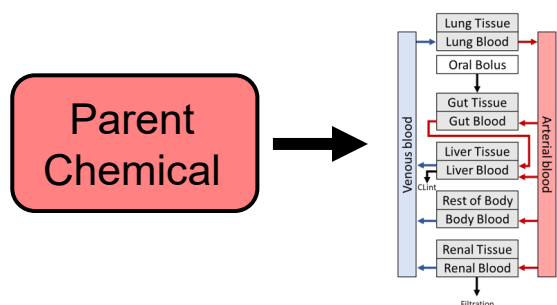
Future Additions – Genetic Enzyme Variability in PBPK Models

Workflow Overview:

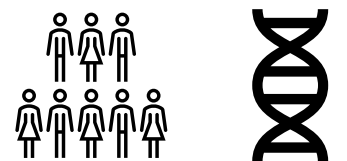
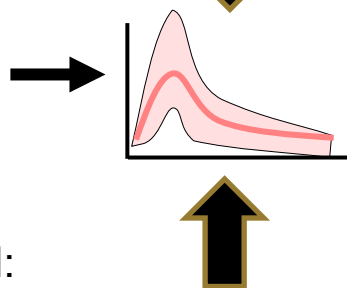
1. Exposure (dose)
2. PBPK parameters
3. Enzyme variability data
 - A. Structure
 - B. % Yield
 - C. Enzyme contribution
4. Metabolite data



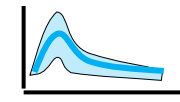
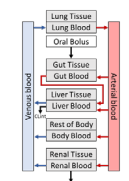
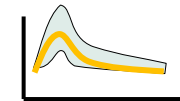
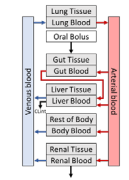
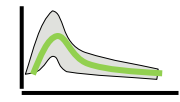
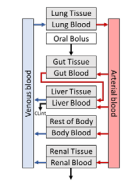
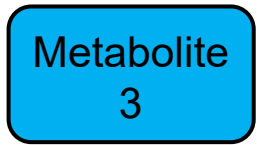
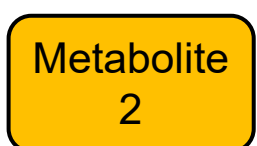
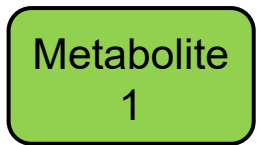
Model Parameters



PBPK model:
ADME



Genetic variability



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
- Future updates will include the incorporation of additional endpoint specific visualizations and the integration of enzyme variability into PBPK models



The NICEATM Group



Integrated
Chemical
Environment

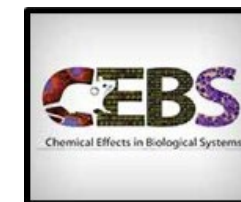


[https://github.com/
NIH/OPERA](https://github.com/NIH/OPERA)



Sciome

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



[https://cebs.niehs.nih.
gov/cebs/](https://cebs.niehs.nih.gov/cebs/)



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



Subscribe to NICEATM News email list
<https://ntp.niehs.nih.gov/go/niceatm>