

Update on NICEATM Computational Resources

SACATM
September 21-22, 2022
Helena Hogberg



Background (WHY?)

Role of Computational Approaches in Chemical Safety Testing

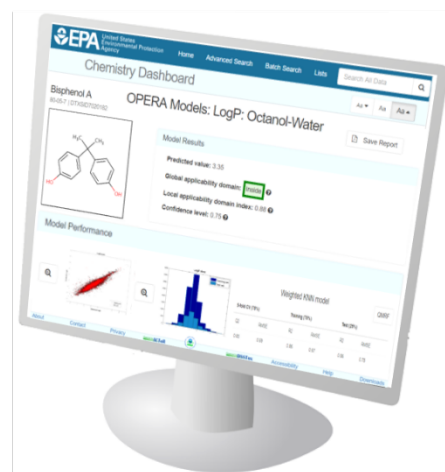
- Computational tools and resources play a critical role in data evaluations:
 - Data aggregation
 - Data curation
 - Mapping data to biological systems and outcomes
 - Generating predicted values
 - Gaining insight into chemical and biological context
 - Chemical properties
 - Chemical use
 - Insight into dose/exposure (IVIVE, PBPK)





OPERA approach

- Curated **open** access datasets (<https://doi.org/10.1186/s13321-018-0263-1>)
- **Open-source** code (github.com/NIEHS/OPERA)
- **Transparent** unambiguous algorithms (<https://qsardb.jrc.ec.europa.eu/qmrf/>)
- **Transparent** validated performances (<https://doi.org/10.1080/1062936X.2016.1253611>)
- **Defined** applicability domain and limitations of the models
- Predictions **available** through:
 - NICEATM's Integrated Chemical Environment (<https://ice.ntp.niehs.nih.gov/>)
 - The EPA's CompTox Dashboard (<https://comptox.epa.gov/dashboard>)
 - Free and open-source standalone application (github.com/NIEHS/OPERA)



Integrated
Chemical
Environment



Running OPERA

OPERA standalone application:

- Free, opensource & open-data
- Single chemical and batch mode
- Multiple platforms (Windows and Linux)
- Embeddable libraries (java, C, C++, Python)
- **Command line & Graphical user interface**

OPERA models:

- Physicochemical properties
- Environmental fate
- ADME properties
- Toxicity endpoints

Input options:

- Structure IDs (CAS, DTXSID, InChIKey)
- Structure files (SMILES, SDF, Mol)

Links:

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

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

<https://jcheminf.biomedcentral.com/articles/10.1186/s13321-018-0263-1>

```
OPERA models for physchem, environmental fate and tox properties.
Version 2.8 (March 2022)

OPERA is a command line application developed in Matlab providing QSAR
models predictions as well as applicability domain and accuracy assessment.

Developed by:
Kamel Mansouri
kamel.mansouri@nih.gov

Usage: OPERA <argument_list>

Examples:
OPERA -s Sample_50.sdf -o predictions.csv -a -x -v 2
opera -d Sample_50_PadelDesc.csv -o predictions.txt -e logP BCF -n -v 1

Type OPERA -h or OPERA --help for more info.

C:\>
```

Input Browse

Output Browse

Models

Physchem properties
 LogP MP BP VP WS HL KOA RT pKa LogD

Environmental fate
 LogBCF AOH Biodeg R-Biodeg KM KOC

Toxicity endpoints
 ER (CERAPP) AR (CoMPARA) AcuteTox (CATMoS)

ADME properties
 FUB Clint Caco2

Standardize: Off On

Output options: Separate files Experimental values Nearest neighbors Include descriptor values Keep full descriptors files

Results summary:

Calculate

OPERA
Open (q)SAR App



OPERA models (version 2.9)

Physchem properties		Chemicals	Version
BP	Boiling Point	7860	2.9
HL	Henry's Law Constant	2233	2.9
LogP	Octanol-water Partition Coefficient	18154	2.9
MP	Melting Point	22554	2.9
VP	Vapor Pressure	6764	2.9
WS	Water Solubility	9943	2.9
pKa	Acid Dissociation Constant	6503	2.6
KOA	Octanol/Air Partition Coefficient	270	2.6

Environmental fate		Chemicals	Version
AOH	Atmospheric Hydroxylation Rate	692	2.6
BCF	Bioconcentration Factor	626	2.6
BioHL	Biodegradation Half-life	150	2.6
RB	Ready Biodegradability	1603	2.6
KM	Fish Biotransformation Half-life	541	2.6
KOC	Soil Adsorption Coefficient	728	2.6

Toxicity endpoints		Chemicals	Version
ER	Estrogen Receptor Activity	32464	2.6
AR	Androgen Receptor Activity	47673	2.6
AcuteTox	Acute Oral Systemic Toxicity	50660	2.6

ADME properties		Chemicals	Version
FUB	Fraction unbound	3229	2.8
Clint	Intrinsic clearance	1346	2.8
CACO2	Caco-2 permeability	4601	2.8

New/updated since 2021



PFAS in OPERA models

	Models	PFAS/Total
BP	Boiling Point	346/7860
LogP	Octanol-water Partition Coef.	97/18154
MP	Melting Point	409/22554
VP	Vapor Pressure	178/6764
WS	Water Solubility	105/9943

VP Vapor Pressure

Deviation of $\log_{10} p$ (Pa) estimates from experimental measurements at 25 °C

	COSMOtherm	EPI Suite	NICEATM	ACD/Labs	TEST	OPERA
MAE	1.22	1.08	1.46	1.53	1.31	0.95
RMSE	1.48	1.48	2.06	1.99	1.91	1.26

LogP Octanol-water Coef

Deviation of octanol-water partition ratio ($\log K_{ow}$) estimates from experimental measurements at 25 °C

	COSMOtherm	EPI Suite	NICEATM	ACD/Labs	OPERA	LSER
MAE	0.41	0.25	0.68	0.61	0.21	0.33
RMSE	0.50	0.29	1.13	0.70	0.28	0.36

WS Water solubility

Deviation of water solubility ($\log S$; mg/L) estimates from experimental measurements at 25 °C

	COSMOtherm	EPI Suite	NICEATM	TEST ^a	OPERA
MAE	0.35	1.82	2.38	0.95	0.23
RMSE	0.41	2.20	2.55	1.36	0.36

Environmental Chemistry

Property Estimation of Per- and Polyfluoroalkyl Substances: A Comparative Assessment of Estimation Methods

Alina Lampic and J. Mark Pamis*

Chemical Properties Research Group (Canadian Environmental Modelling Centre), Department of Chemistry, Trent University, Peterborough, Ontario, Canada



Updates Under Development

OPERA in the OECD Toolbox

The screenshot displays the QSAR Toolbox interface. The top navigation bar includes icons for Input, Profiling, Data, Category definition, Data Gap Filling, and Report. Below this, there are tabs for Gap Filling and Workflow Editor, with sub-options like Trend analysis, Read across, (Q)SAR, Automated, Standardized, New, Import, Export, and Delete. The main workspace shows a chemical structure and a list of properties, with 'Boiling point' selected. The left sidebar shows 'Documents' with 'Document 1' and 'Data Gap Filling Settings' with 'Only endpoint relevant' checked. The right sidebar shows a table of QSAR models.

QSAR name	#	Predicted	Domain	QMRF	Test set	Training set
Boiling Point Adapted Stein and Brown Method (EPISUITE) (1.0)	1	431 °C	No domain available		0	0
Opera BP (2.6)	2	327 °C	No domain available	Q17-12-0021	0	0

<https://repository.qsartoolbox.org/>

Migrate all models to use CDK2 package (OPERA v3.0 coming soon)



ICE v3.7 <https://ice.ntp.niehs.nih.gov/>

News & Events

ICE v3.6 Release

ICE updates include:

New tools and expanded capabilities:

- Enhanced filtering for Curve Surfer and Chemical Quest
- Curve overlay 2-D and 3-D for Curve Surfer
- SMARTS Filtering and Highlighting Chemical Quest Results
- Search custom chemical list Chemical Quest

Learn about ICE updates

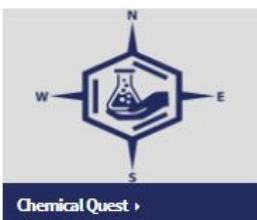
UPDATES



- Bulk query mindset
- Integrated across multiple data types
- Data curated, cleaned, ready-to-use
- Assays annotated to aid interpretation
- FAIR (Findable, Accessible, Interoperable, and Reusable)
- Tools to support data exploration
- Continued development based on stakeholder and SACATM feedback



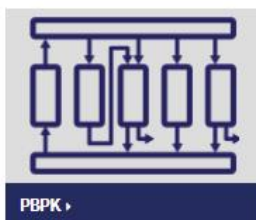
Search >



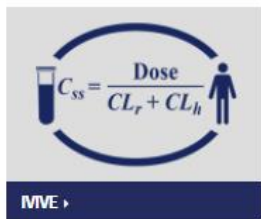
Chemical Quest >



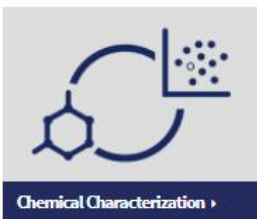
Curve Surfer >



PBPK >



IVIVE >



Chemical Characterization >



Data >



Help Videos >



What Sets ICE Apart from Other Tools?

Intended use

- Target audience is broad, spanning the scientific community, e.g. regulatory decision makers, researchers, model developers, educators, etc.
- Resource for summary-level, high-quality, curated data
- Ease of accessibility
- Interactive and inter-connected tools
- Provides references: links out to other sites for detailed data review (i.e., EPA comptox data dashboard)



In Vivo and In Vitro Data in ICE

Toxicity endpoint	Assays	# of chemicals
Chemical Parameters	Experimental physchem	~20000
ADME Parameters	FUB, intrinsic clearance, Caco2 permeability	~5000
Acute Toxicity	In vivo acute oral, dermal, and inhalation toxicity	~10000
Cancer	In vivo and in vitro Cancer, and Weight of Evidence	3042
DART	In vivo and in vitro DART	607
Skin Sensitization	In vivo and in vitro skin sensitization	2181
Skin Irritation	In vivo and in vitro skin irritation/corrosion	1664
Eye Irritation	In vivo and in vitro eye irritation/corrosion	796
Endocrine	In vivo and low throughput in vitro data on AR and ER agonist and antagonist activity	281
cHTS	Curated ToxCast and Tox21 assays	~9213



In Silico Models/Integrated Approaches

Endpoint	Model	# of chemicals*
Physicochemical Properties	OPEn (q)saR App (OPERA) Mansouri et al. J Cheminform 2018	800,000+
Acute Oral Toxicity	Collaborative Acute Toxicity Modeling Suite (CATMoS) - Rat acute oral toxicity. Mansouri et al. EHP 2021	800,000+
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	800,000+
	Collaborative Modeling Project for Androgen Receptor Activity (COMAPRA). Mansouri et al. EHP 2020	800,000+



ICE Database Access via REST API

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

```
https://ice.ntp.niehs.nih.gov/api/v1/search?chemid=DTXSID7032004
JSON Raw Data Headers
Save Copy Collapse All Expand All (slow) Filter JSON
▶ 1568: {...}
▶ 1569: {...}
▶ 1570: {...}
▶ 1571: {...}
▶ 1572: {...}
▶ 1573: {...}
▼ 1574:
  assay: "Rat Acute Oral Toxicity"
  endpoint: "LD50"
  substanceType: "Chemical"
  casrn: "13311-84-7"
  qsarReadyId: "MKXKFYHWDHIYRV-UHFFFAOYSA-N"
  value: "787.0"
  unit: "mg/kg"
  species: "Rat"
  receptorSpecies: ""
  route: "NA"
  sex: ""
  strain: ""
  lifeStage: ""
  tissue: ""
  lesion: ""
  location: ""
  assaySource: ""
  inVivoAssayFormat: ""
  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"
```



Example R code to query ICE REST API



```
library(httr)
library(jsonlite)

#Query a single chemical using GET Request
results<-GET("https://ice.ntp.niehs.nih.gov/api/v1/search?chemid=DTXSID7032004")
jsonText<-content(results,"text")
jsonResults<-fromJSON(jsonText)

#Query a list of chemicals using POST Request
bodyContent = '{"chemids": ["YPQLFJODEKMJEF-UHFFFAOYSA-N", "DTXSID8020381", "330-55-2"]}'
results <- POST("https://ice.ntp.niehs.nih.gov/api/v1/search",content_type_json(),body=bodyContent);
jsonText<-content(results,"text")
jsonResults<-fromJSON(jsonText)
```



```
import requests
import json

#Query a single chemical using GET Request
response = requests.get("http://ice.ntp.niehs.nih.gov/api/v1/search?chemid=DTXSID7020182")
print(response);
json_object = json.loads(response.text)
print(json.dumps(json_object, indent=4))

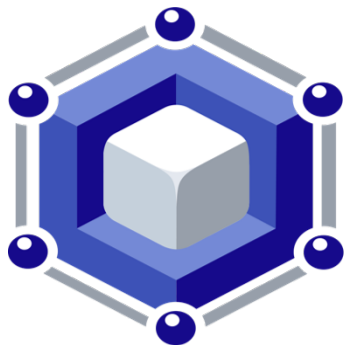
#Query a list of chemicals using POST Request
response = requests.post("http://ice.ntp.niehs.nih.gov/api/v1/search", json={'chemids': ["YPQLFJODEKMJEF-UHFFFAOYSA-N", "DTXSID8020381", "330-55-2"]})
print(response);
json_object = json.loads(response.text)
print(json.dumps(json_object, indent=1))
```



```
curl -XGET https://ice.ntp.niehs.nih.gov/api/v1/search?chemid=DTXSID7032004
curl -XPOST -d '{"chemids": ["YPQLFJODEKMJEF-UHFFFAOYSA-N", "DTXSID8020381", "330-55-2"]}' https://ice.ntp.niehs.nih.gov/api/v1/search?chemid=DTXSID7032004
```

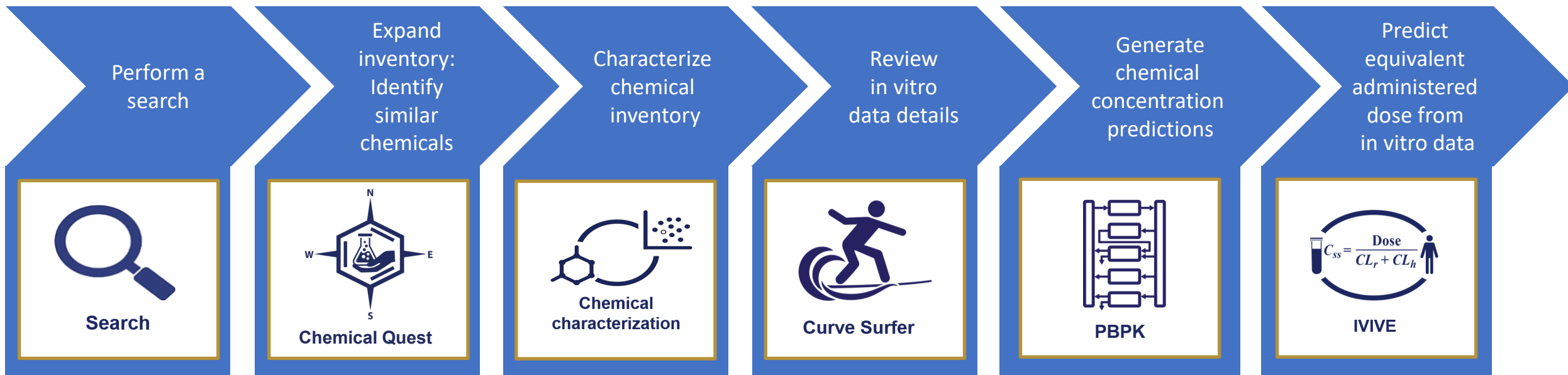


ICE Tools Workflow



**Integrated
Chemical
Environment**

**SACATM 2021 – ICE 3.4
SACATM 2022 – ICE 3.7**





Data and General Updates

- Continued implementation of FAIR and TRUST standards, e.g., implementation of REST APIs
- QC annotations for cHTS data
- Updated acute oral toxicity, skin sensitization, and htk ADME data.
- Addition and harmonization of endocrine data
- New reference Chemical Quick List
- More attractive, up-to-date user interface
- New Publication section
- Updates to supporting documentation
- Help videos



Help Videos

Attend a free virtual training

April 18-19, 2022, 1:00-3:00 PM EDT



ICE, ICE, Data:

Using NICEATM's Integrated Chemical Environment to support chemical evaluations



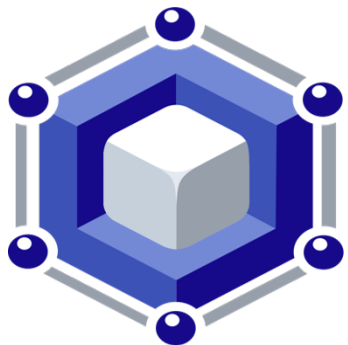
Scan code to register

Recording at

<https://pcrm.widencollective.com/portals/ieooh0ol/ICE> 15



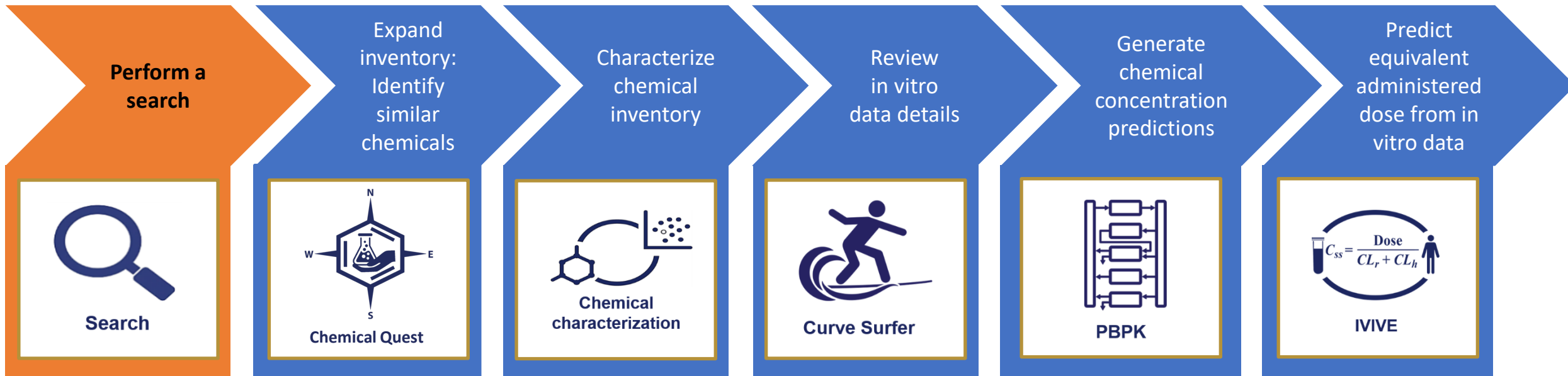
ICE Tools Workflow



**Integrated
Chemical
Environment**

Updates 2022

Updates to results graphics





ICE Tool: Search

Chemical Input

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

Add chemicals with identical QSAR structures

Assay Input

Select Assays 1 chemical quick list selected.

Assay	Description	Assay Type
<input checked="" type="checkbox"/> DART - Cell Proliferation	DART	in vitro

Select Assays

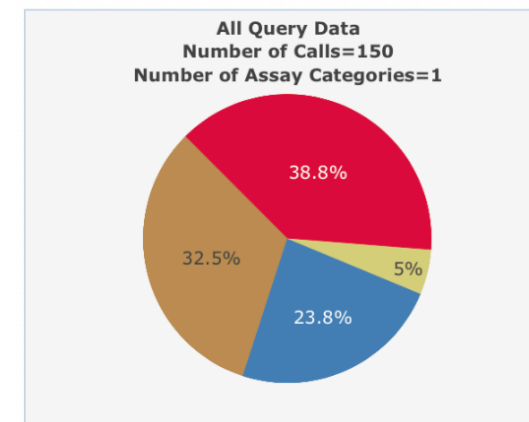
cHTS Acute Lethality Sensitization

Irritation/Corrosion Endocrine Cancer

DART Cardiotoxicity Chemical Parameters

Legend

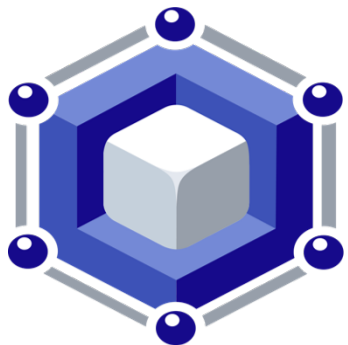
- Active
- Inactive
- QC-omit
- Flag-omit
- Not tested



Users can select from predefined lists of chemicals that are related to specific toxicity endpoints. Reference lists and common chemical sets (e.g., Tox21, pesticide AIs). Users can also enter their own chemical identifiers.



ICE Tools Workflow



**Integrated
Chemical
Environment**

Updates 2022

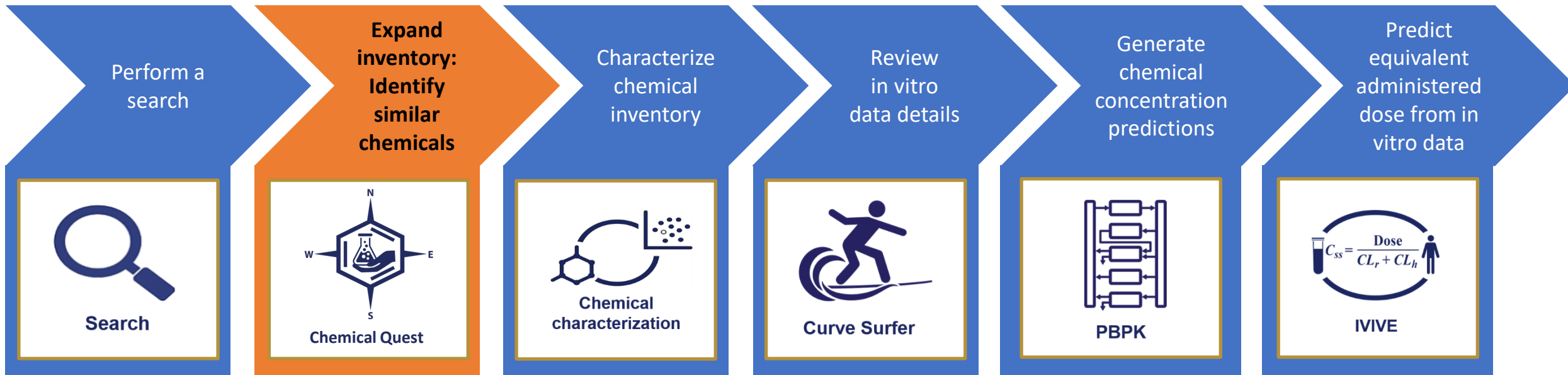
Similarity search based on custom chemical lists and targets

New filtering options

New result selection option

Utilizes Saggart fingerprints for structural similarity searching

Sedykh et al. 2021 Chem Res Tox





ICE Tool: Chemical Quest

Similar Structure Results

Integrated Chemical Environment

HOME SEARCH TOOLS DATA ABOUT

Chemical Quest Curve Surfer PBPK IVIVE Chemical Characterization

Input Results Help Report an issue

Chemical Quest Results

Send filtered results to: []
Select tool...

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

Chemical Name: Carbaryl
CASRN: 63-25-2
DTXSID: DTXSID9020247
Tanimoto: top 10 hits and >0.7
Hit Count: 10
Passed Filter(s): 10/10
Selected Item(s): 0/10

Chemical Name: (+)-cis-Permethrin
CASRN: 54774-45-7
DTXSID: DTXSID052208
Tanimoto: top 10 hits and >0.7
Hit Count: 10
Passed Filter(s): 10/10
Selected Item(s): 0/10

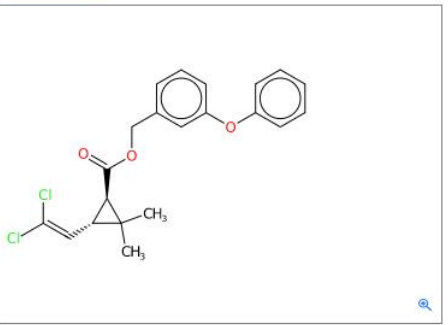
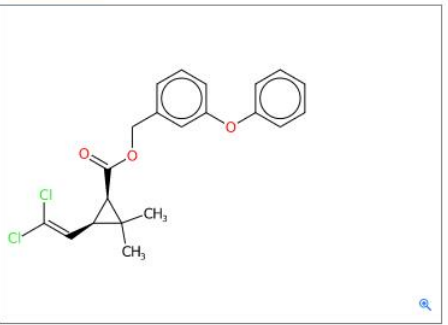
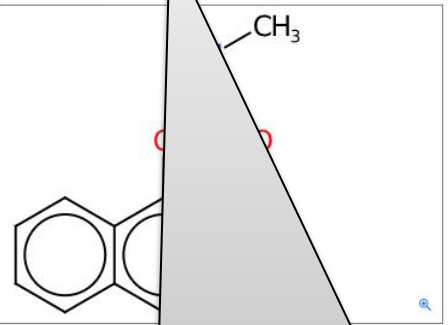
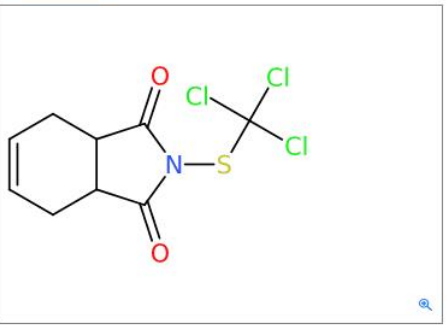
Chemical Name: (+)-trans-Permethrin
CASRN: 51877-74-8
DTXSID: DTXSID0508116
Tanimoto: top 10 hits and >0.7
Hit Count: 10
Passed Filter(s): 10/10
Selected Item(s): 0/10

View Results

View Results

View Results

View Results



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

The result page initial shows the chemical identified from your input with the number of similar structures returned

Chemicals from the input list are shown with the number of similar structures identified. This will influence the data downloads



ICE Tool: Chemical Quest

Seeing The Differences

Multiple filters can be applied and changing the order will change the end results

Can select individual results

The screenshot displays the ICE Tool interface for chemical search. At the top, there are file upload options (TXT, XLSX, SDF) and a 'Select tool...' dropdown. A pie chart shows a 10% filter and a 90% result distribution. The 'Select Filter to add to chain:' section shows 'SMARTS' with '2 selected' and '1' filter. The 'Select Page' is set to '1 of 1', and 'Sort Results By' is set to 'Tanimoto'. Below the filters, there are buttons for 'Select All Filtered', 'Clear Selected', and a checkbox for 'Only show selected items'. The main results area shows five chemical entries, each with a 'Select this item' checkbox, CASRN, DTXSID, Name, Tanimoto Value, and Has Bioactivity status. The first entry is selected. Each entry includes a chemical structure image.

Select this item	CASRN	DTXSID	Name	Tanimoto Value	Has Bioactivity
<input checked="" type="checkbox"/>	133-06-2	DTXSID9020243	Captan	1.0	true
<input type="checkbox"/>	75045-72-6	DTXSID00996550	Copper(2+) zinc hydroxide...	0.888889	false
<input checked="" type="checkbox"/>	2939-80-2	DTXSID7034418	cis-Captafol	0.888889	false
<input type="checkbox"/>	86199-24-8	DTXSID10280992	(1,3-Dioxo-1,3,3a,4,7,7a-he...	0.75641	false
<input checked="" type="checkbox"/>	30922-32-8	DTXSID80718035	2-[(Trichloromethyl)sulfan...	0.755556	false

These selected chemicals differ by one structural feature and the difference are quantified by the Tanimoto value



Send to Another Tool



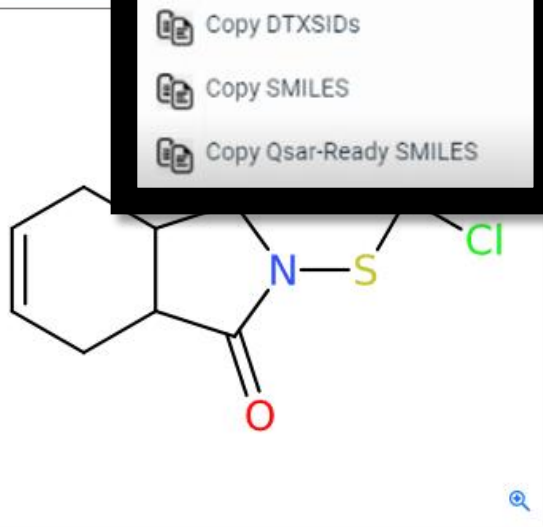
Chemical Quest Results

Send filtered results to: ?

TXT XLSX SDF Select tool... ▼ Clear Filter

Chemical Name: Carbaryl
CASRN: 63-25-2
DTXSID: DTXSID9020247
Tanimoto: top 10 hits and >0.7
Hit Count: 10
Passed Filter(s): 10/10
Selected Item(s): 0/10

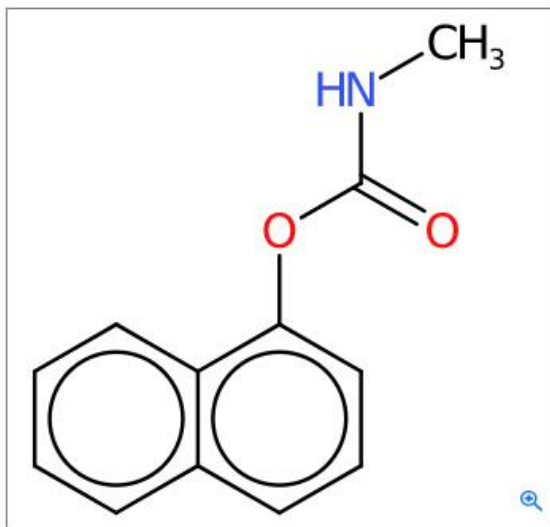
View Results



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

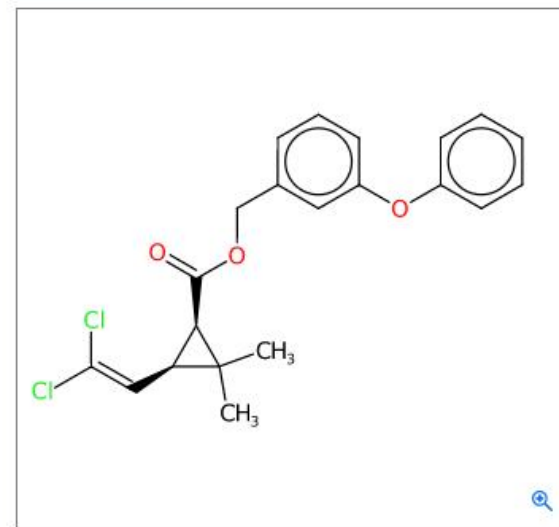
Chemical Name: (+)-cis-Permethrin
CASRN: 54774-45-7
DTXSID: DTXSID5052208
Tanimoto: top 10 hits and >0.7
Hit Count: 10
Passed Filter(s): 10/10
Selected Item(s): 0/10

View Results



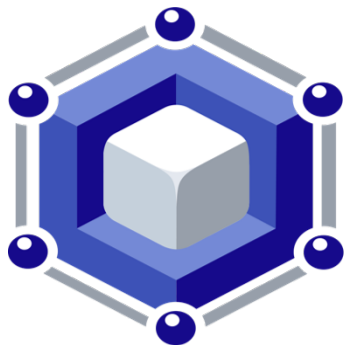
Chemical Name: (+)-cis-Permethrin
CASRN: 54774-45-7
DTXSID: DTXSID5052208
Tanimoto: top 10 hits and >0.7
Hit Count: 10
Passed Filter(s): 10/10
Selected Item(s): 0/10

View Results





ICE Tools Workflow



**Integrated
Chemical
Environment**

Updates 2022

Improvements in Categorical characterization

Updated documentation

Perform a
search



Search

Expand
inventory:
Identify
similar
chemicals



Chemical Quest

**Characterize
chemical
inventory**



Chemical
characterization

Review
in vitro
data details



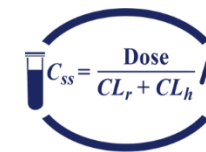
Curve Surfer

Generate
chemical
concentration
predictions



PBPK

Predict
equivalent
administered
dose from in
vitro data



IVIVE



ICE Tool: Chemical Characterization

Consumer Use Explorer

Consumer Use Explorer ?

Graphical distribution of chemical lists across consumer use categories

This tool uses information from the US EPA's Chemical and Products Database (CPDat), Version 3.

Consumer use labels are organized into several categories and subcategories represented by the different circles. The parent category is represented first with subcategories packed within. The size of the circle indicates the number of input chemicals present in that category; this means the larger the circle the more chemicals that fall into that category.

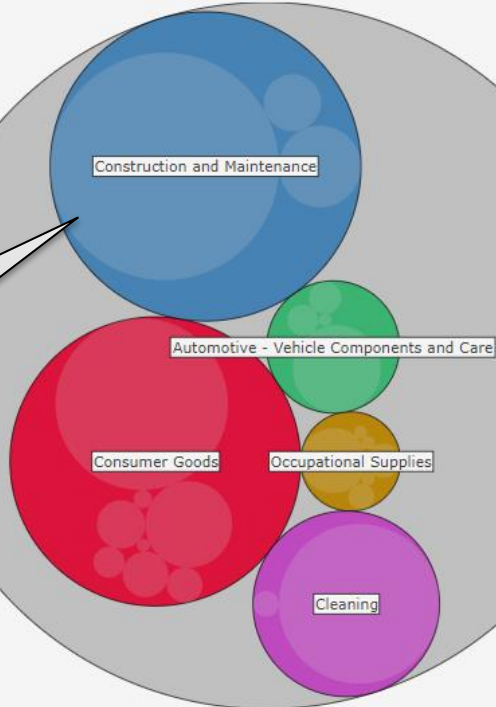
Clicking on the circles allows users to zoom in, and the chart titles and detailed information changes to match the data being shown. To zoom out, click on a previous layer or the back arrow at the top left of the graph. The house icon will reset the plot. Hovering over the title displays the chemical count within the circle.

DTXIDs Not Returned by Query (142) ?

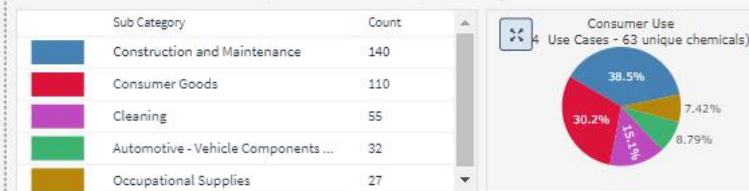
Hide Labels Lists Both Chemical Lists ▼ All Chemicals PopUp

L

Chemical Consumer Use:
(364 Use Cases - 63 unique chemicals)

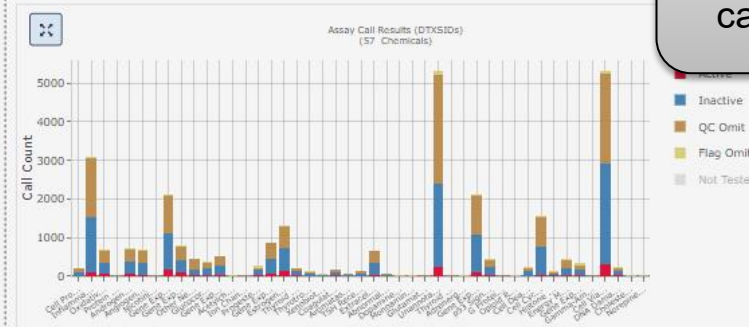


Chemical Consumer Use Details (364 Use Cases - 63 unique chemicals)



Send filtered results to: ?
Select tool...

DTXID (Dashboard)	Substance Name	CASRN (CEBS Link)	Categories	Count
DTXSID7020637	Formaldehyde	50-00-0	Construction and Maintenance	140
DTXSID0020868	Dichloromethane	75-09-2	Consumer Goods	110
DTXSID2021284	Styrene	100-42-5	Cleaning	55
DTXSID5039224	Acetaldehyde	75-07-0	Automotive - Vehicle Components ...	32



Shows product use details for the selected chemical lists from EPA's CPDat database

Nested bubble graphs show consumer use categories and subcategories

Summary details show consumer use details by category and by chemical



ICE Tool: Chemical Characterization

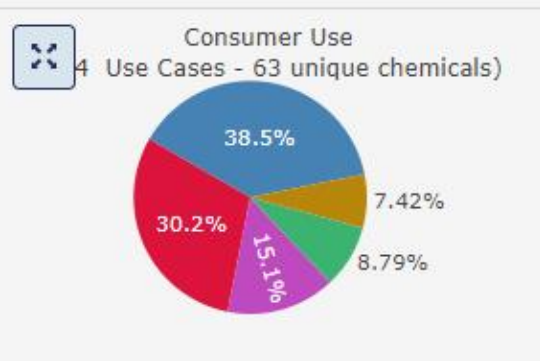
Breakdown Of Product Groups

Clicking on consumer use categories in the bubble graph will update with summary details for the subcategories in view

Chemical Consumer Use Details (364 Use Cases - 63 unique chemicals)

Sub Category	Count
Construction and Maintenance	140
Consumer Goods	110
Cleaning	55
Automotive - Vehicle Components ...	32
Occupational Supplies	27

More use cases than unique chemicals means the same chemical is used in multiple products



Indicates if the chemical has cHTS bioactivity data

Send filtered results to:

Select tool...

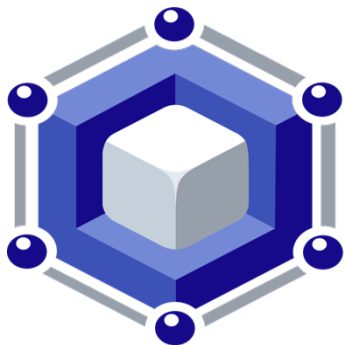
Consumer Use Categories by DTXSID, CASRN

DTXSID (Dashboa	Substance Name	CASRN (CEBS Lin	Sub Categories	Count
DTXSID7020637	Formaldehyde	50-00-0		47
DTXSID0020868	Dichloromethane	75-09-2		33
DTXSID2021284	Styrene	100-42-5		20
DTXSID5039224	Acetaldehyde	75-07-0		20

Table gives you a quick overview of the type of products your chemicals are in



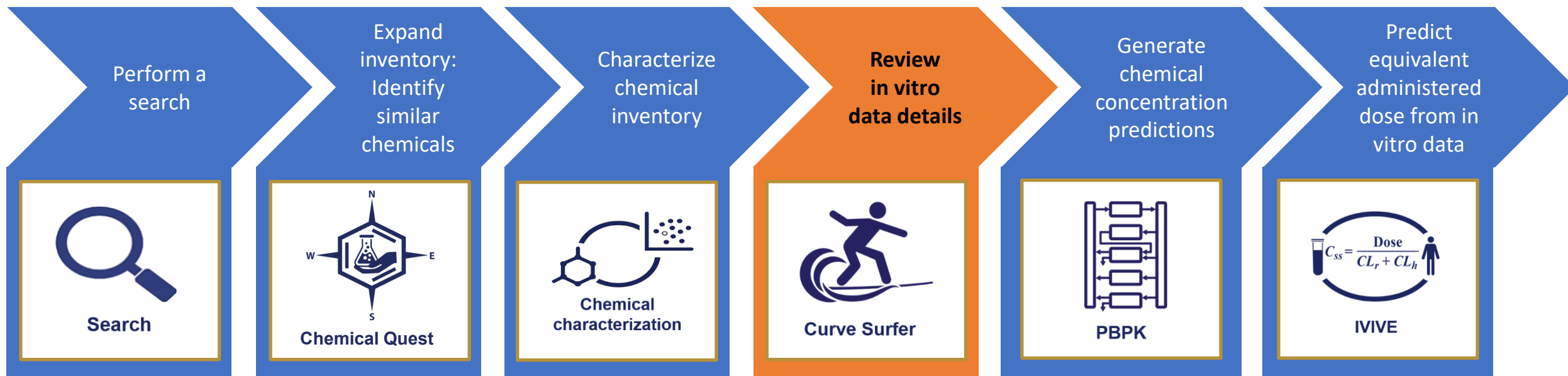
ICE Tools Workflow



Integrated Chemical Environment

Updates 2022

Overlay, 2D, and 3D curve viewing options
New filtering and selection options





ICE Tool: Curve Surfer

View results, filter, and select for overlay

Send filtered results to: 📄 📁 📄

Select Filter to add to chain: ➔ ➔ 213

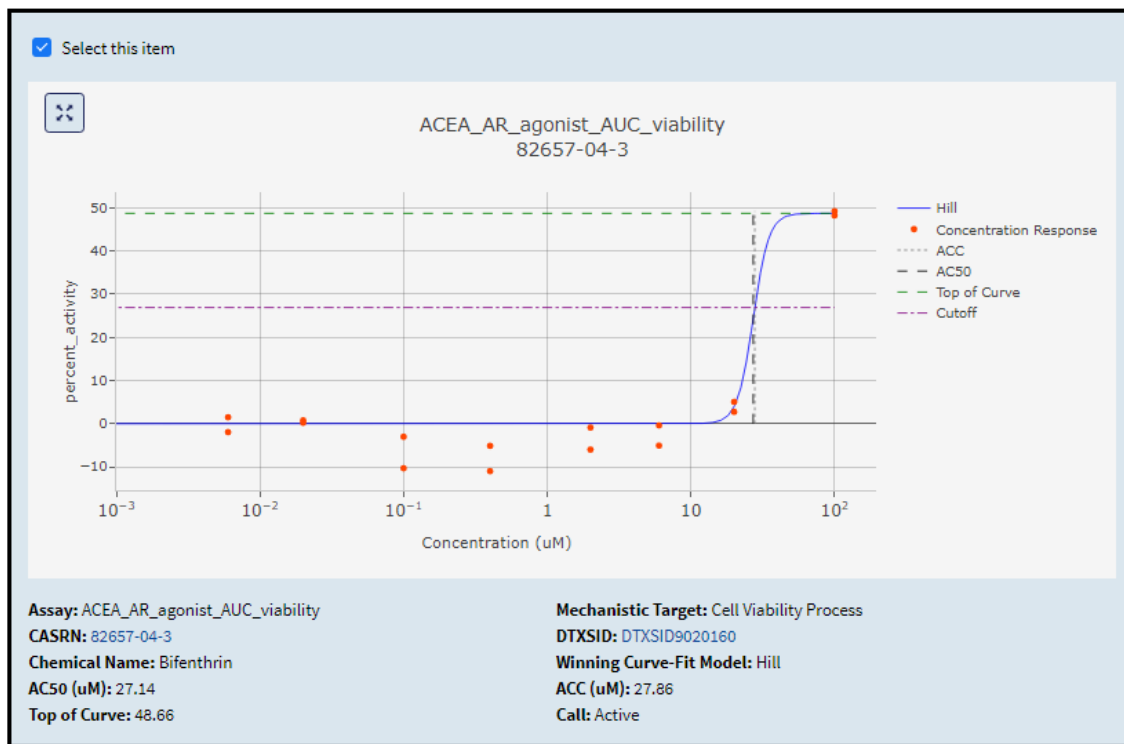
Only show selected items

Select Page: 1 of 22

Showing 1-10 of 213 curves.

Sort Results By: Direction:

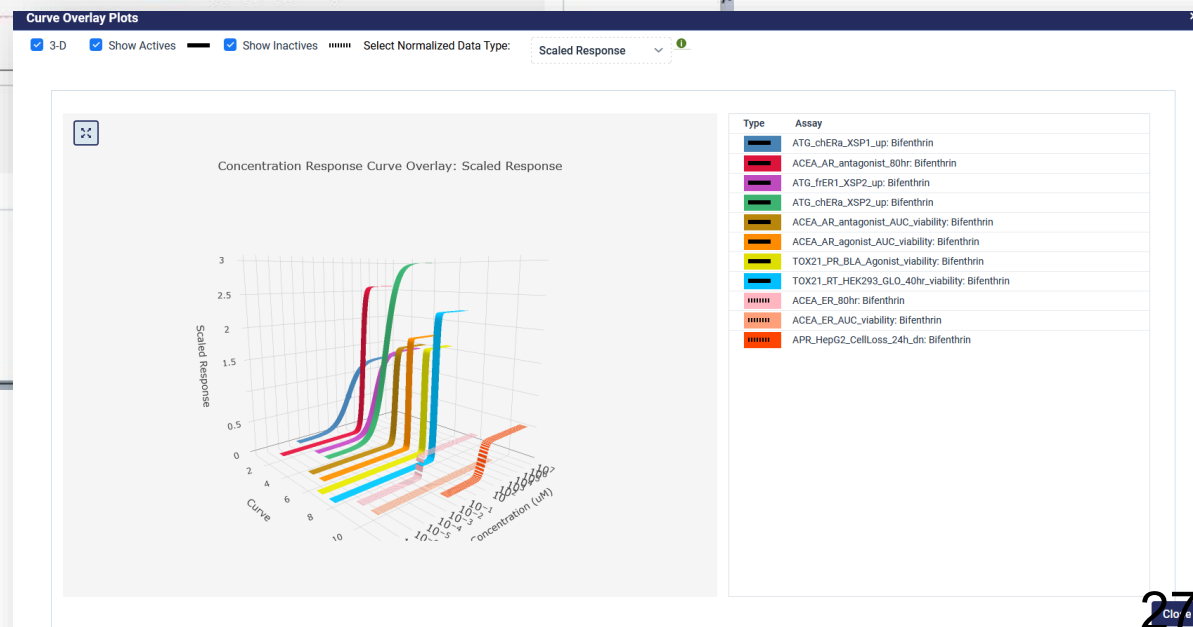
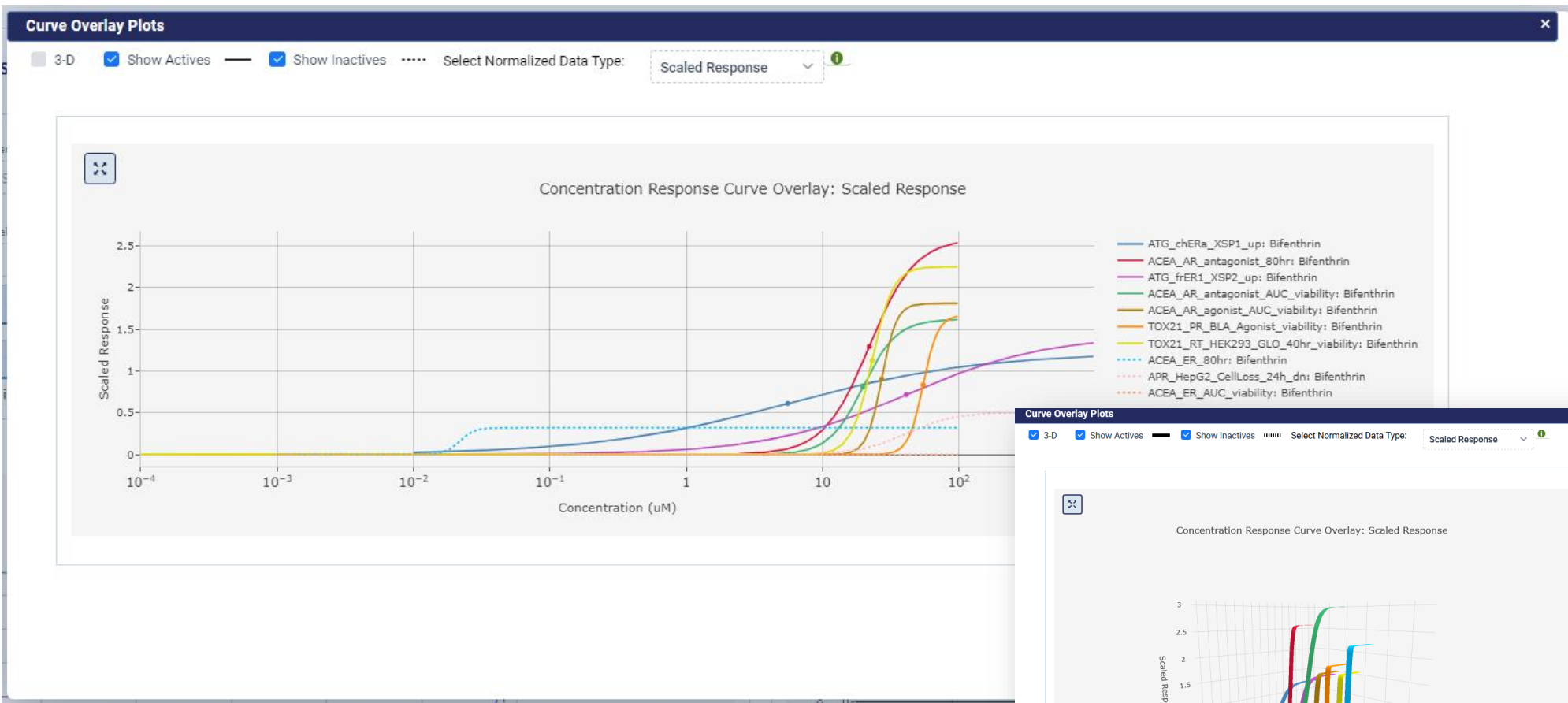
Selected Item(s): 1/1149





ICE Tool: Curve Surfer

Viewing overlay of multiple concentration-response curves





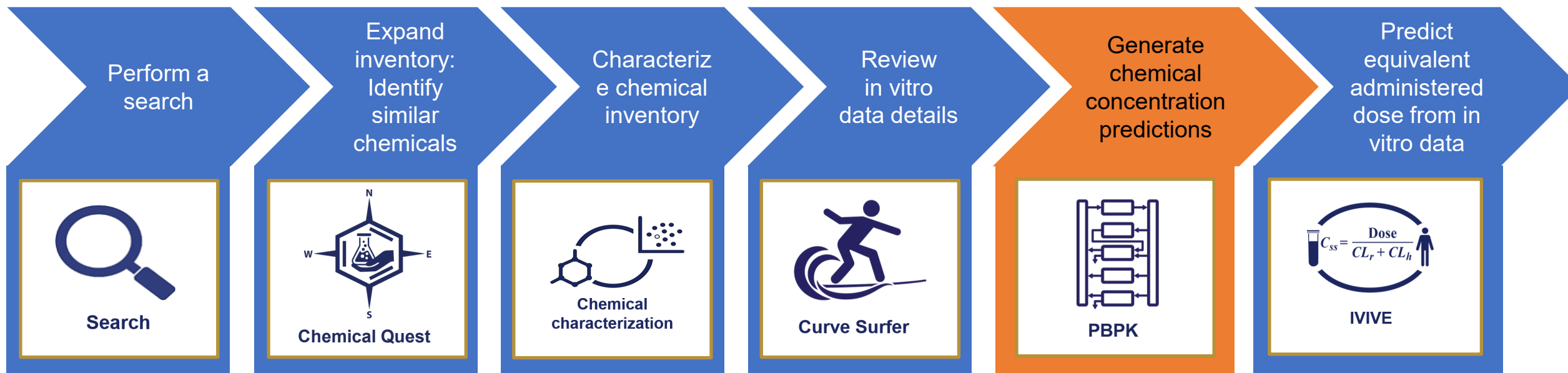
ICE Tools Workflow



**Integrated
Chemical
Environment**

Updates 2022

Updated htkk ADME data



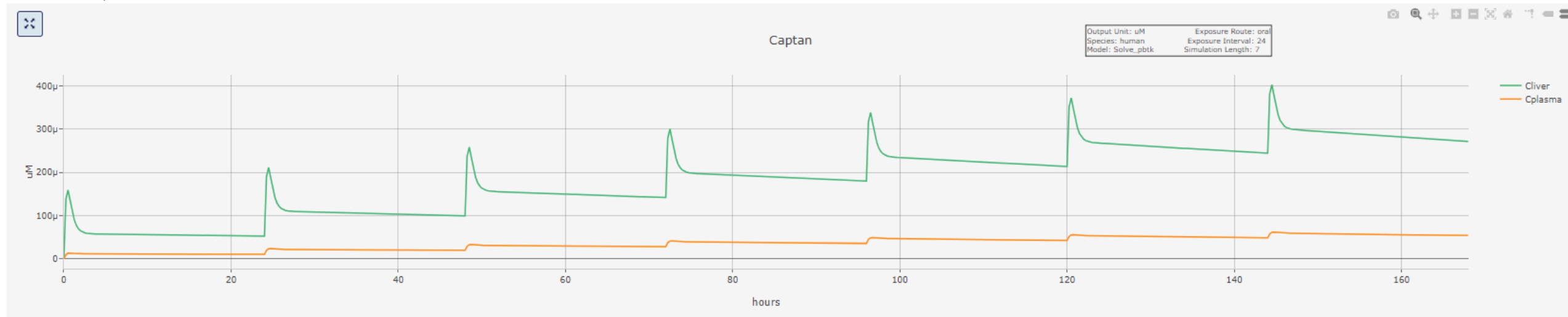


Example of predicted accumulation of chemical after oral exposure

CASRN: 133-06-2

DTXSID: DTXSID9020243

Chemical Name: Captan



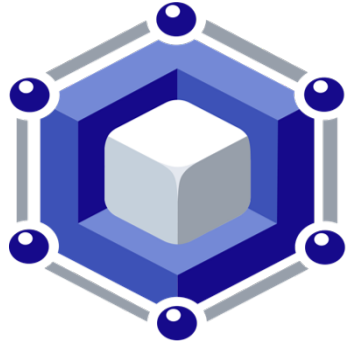


Comparing predicted levels across tissues





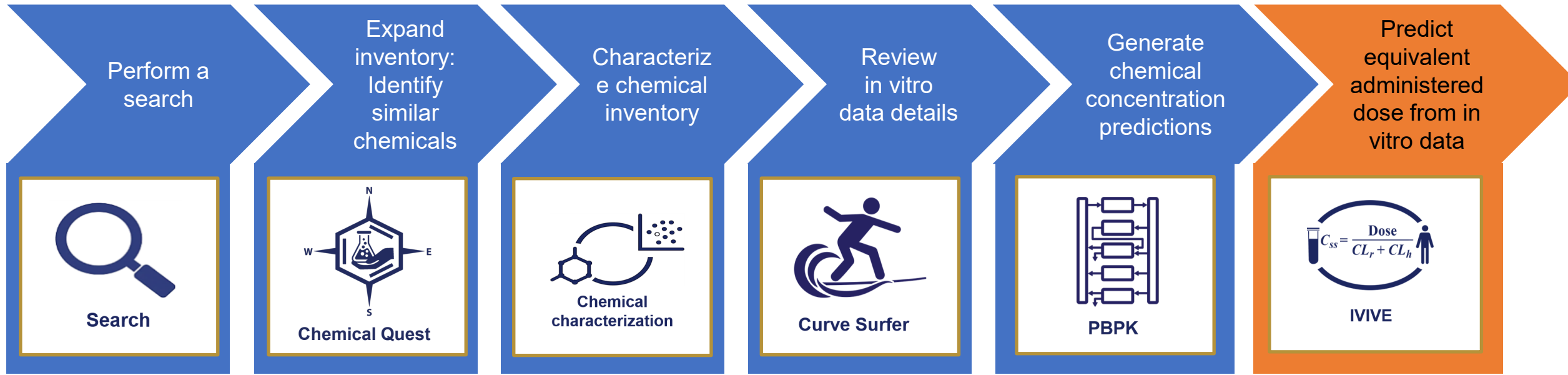
ICE Tools Workflow



**Integrated
Chemical
Environment**

Updates 2022

Uploading custom in vivo and in vitro data





ICE Tool: IVIVE

IVIVE Results Visualizations

Select EAD to visualize:

EAD 95th

Select in vivo data to display:

Acute Lethality (Acute Oral Toxicity Assay LD50)

Log Axis

Show Name



CASRN to
Chemical Name

EAD 50th
EAD 95th

Select Page

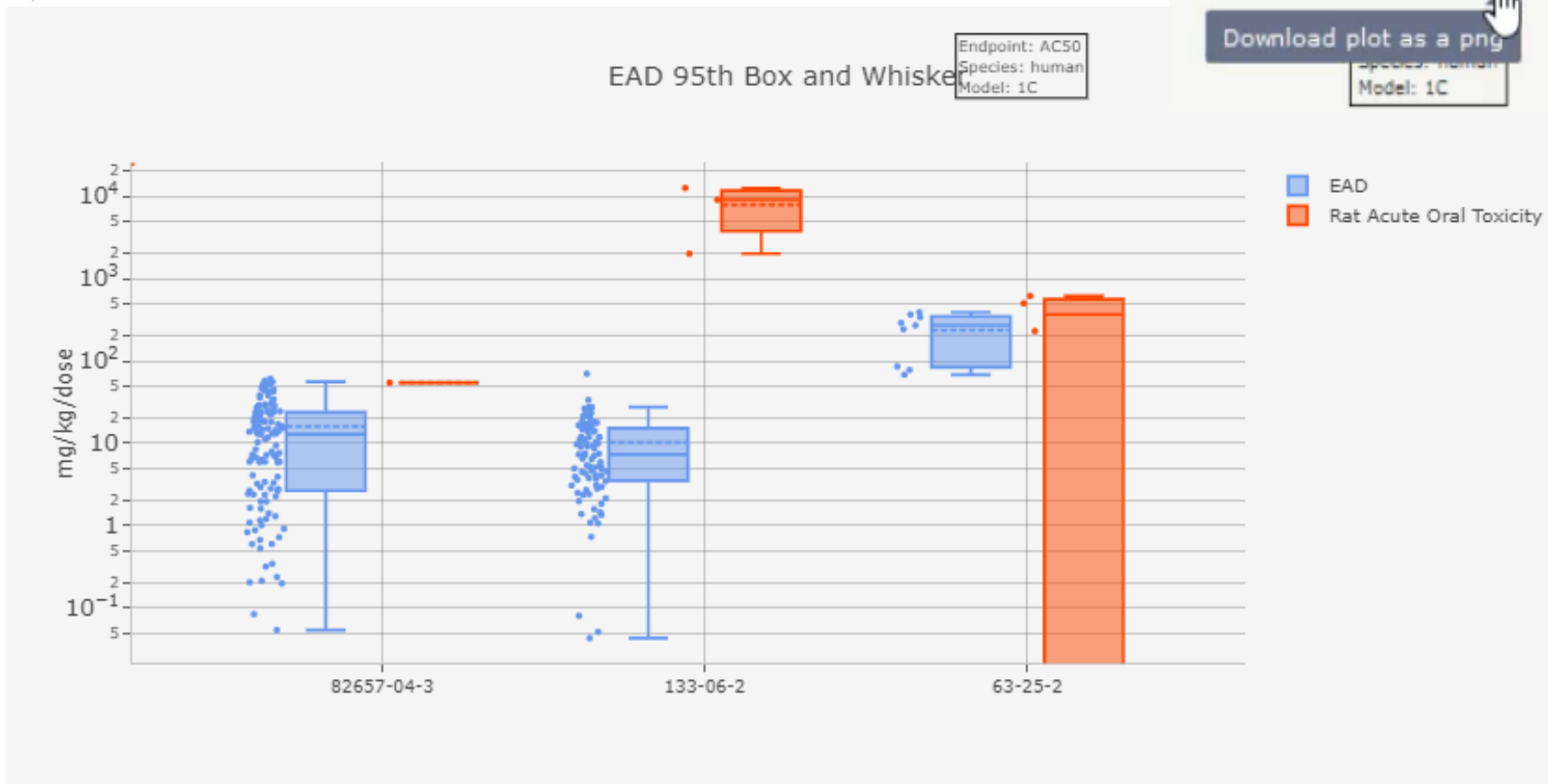


1

of 1

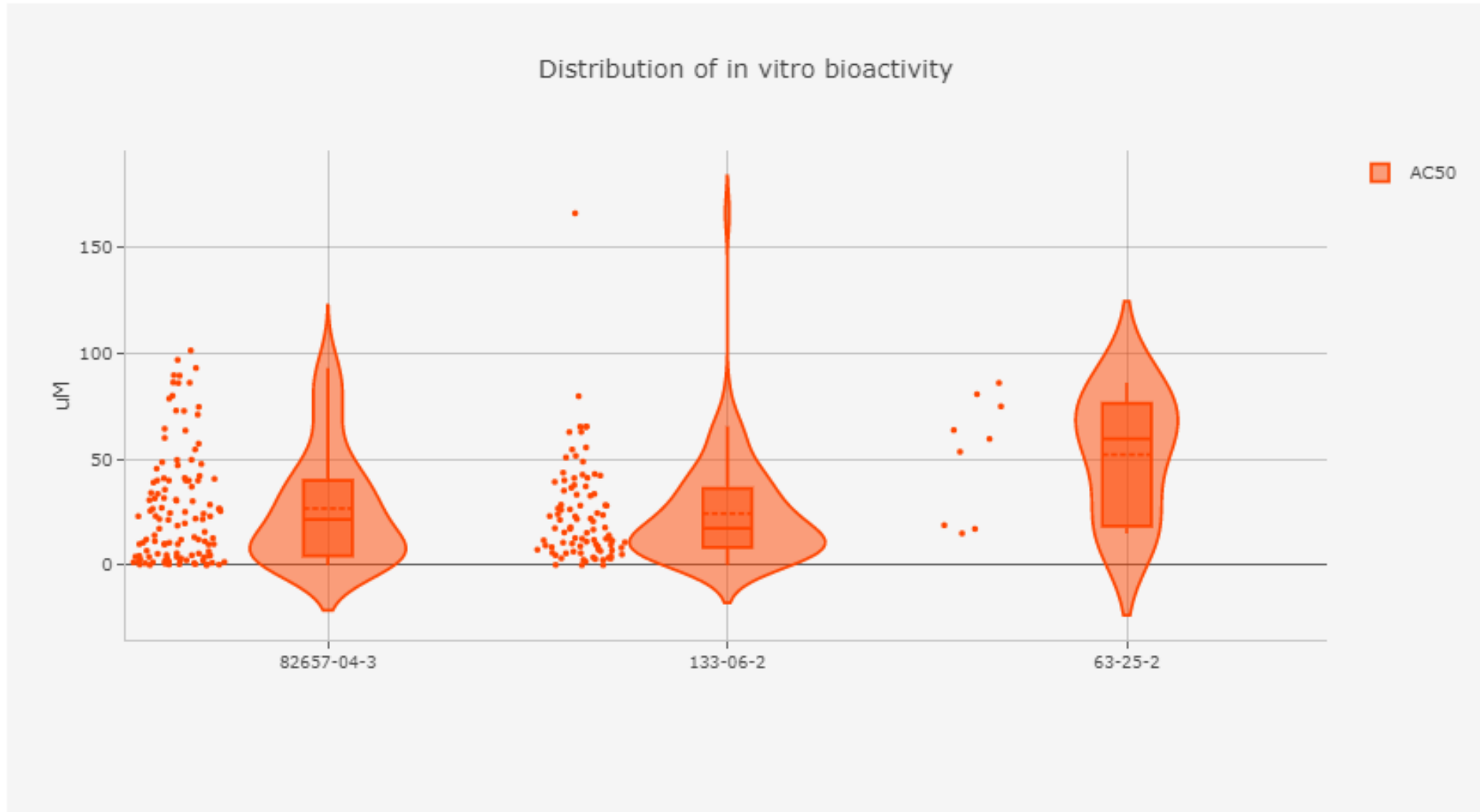


Showing 1-3 of 3 chemicals.





Visualizing Distributions from In Vitro Data

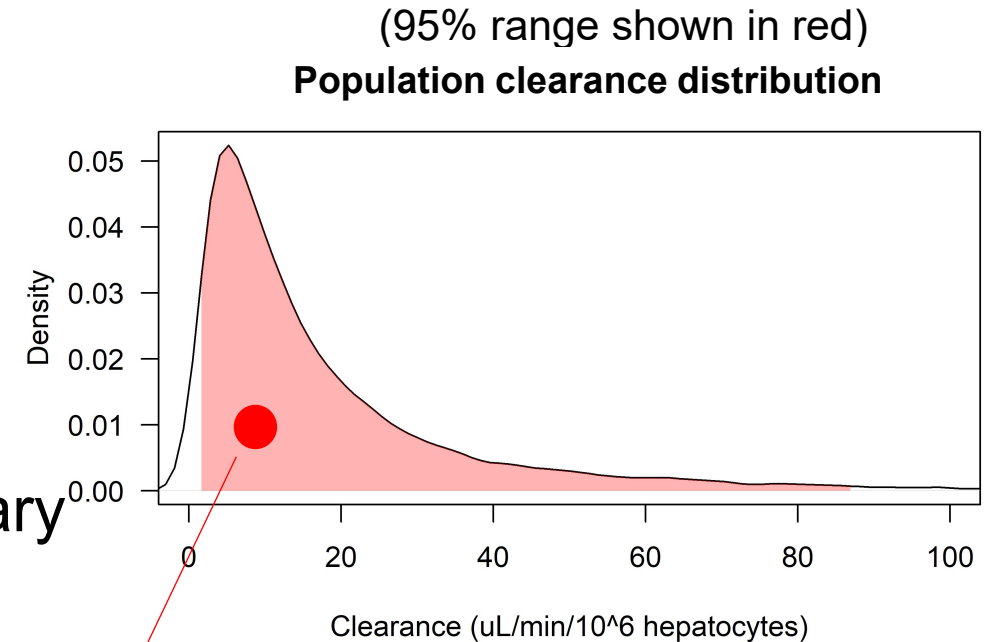




Incorporating Metabolism and Population Variability

Metabolism, enzyme variability, and parameter information are integrated into IVIVE models using the intrinsic clearance (CL_{int}) parameter

1. CL_{int} parameter (measured or OPERA prediction) obtained
2. ADMET Predictor provides **enzymes** involved in metabolism
3. Lognormal CL_{int} coefficient of variation (CV) for **each enzyme** obtained from EFSA summary
4. Lognormal distribution of CL_{int} values assembled around CL_{int} parameter using CV
5. Monte Carlo sampling (n=10,000) used to run *httk* models and describe predicted tissue concentrations resulting from population enzyme variability





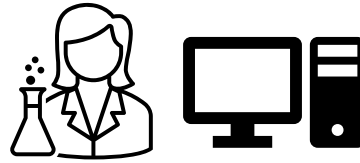
Module Overview

Inputs needed:

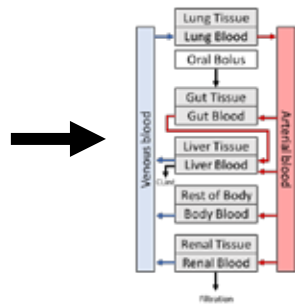
1. Exposure (dose)
2. PBPK parameters
3. Enzyme variability data
 - A. Structure
 - B. % Yield
 - C. Enzyme contribution
4. Metabolite data



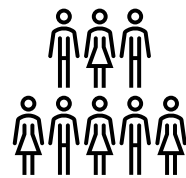
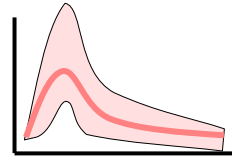
Model Parameters



Parent Chemical



PBPK model:
ADME



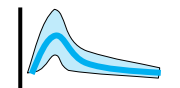
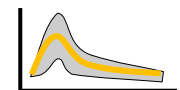
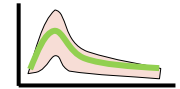
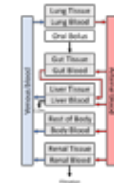
Genetic variability



Metabolite 1

Metabolite 2

Metabolite 3





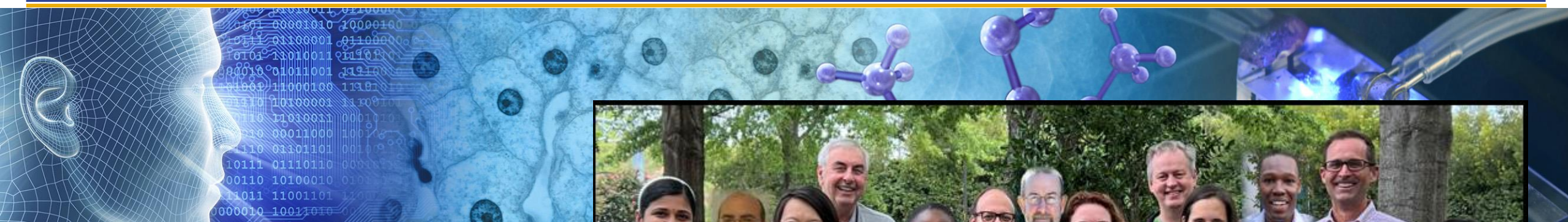
ICE Improvements motivated by SACATM feedback

- Additional data added, including in vivo developmental toxicity data, human skin sensitization data, acute inhalation toxicity data and CaCo2 permeability data
- Simulation of population variability in PBPK
- Removal of outliers from dose-response curves in Curve Surfer and subsequent recalculation of the activity metric
- New molecular descriptors in Chemical Quest
- Continued implementation of FAIR and TRUST standards, e.g., implementation of REST APIs
- Enhanced download formatting
- Targeted training sessions (e.g. via NURA) and help videos



ICE 3.8 Release March 2023 at SOT2023

- Exposure estimates to be included (multiple tools)
- Improved visualization of non cHTS data
- IVIVE/PBPK updates e.g., inhalation model
- Metabolism and population variability
- Data updates
 - OPERA models
 - In vitro Dermal harmonization



ICE

ice.ntp.niehs.nih.gov
ICE-support@niehs-nih.gov

NICEATM

ntp.niehs.nih.gov/go/niceatm