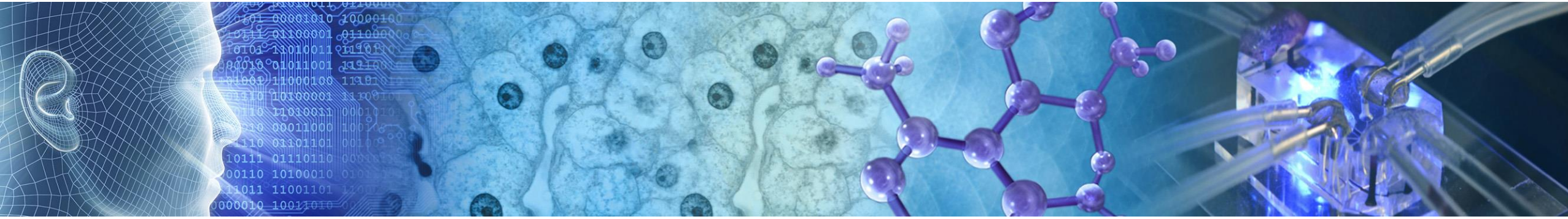
NTP
National Toxicology Program



Update on NICEATM Computational Resources

SACATM
September 21-22, 2022
Helena Hogberg

Background (WHY?)

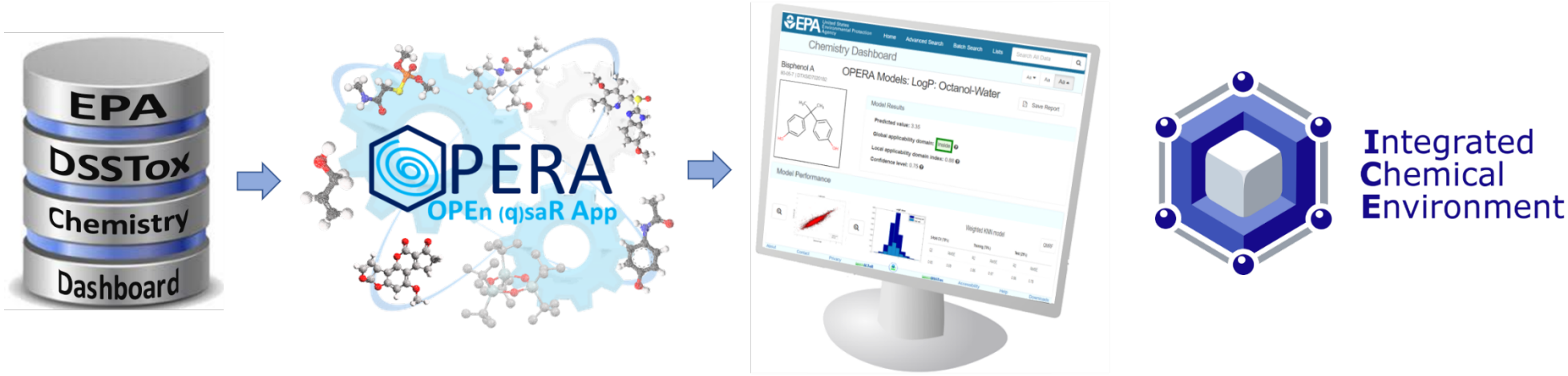
Role of Computational Approaches in Chemical Safety Testing

- 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)

Integrated
Chemical
Environment

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)



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:

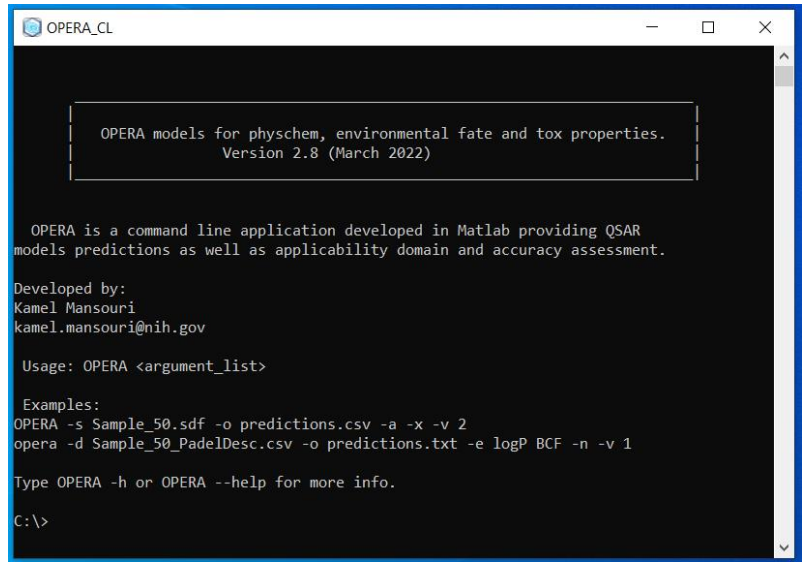
- Physicochemical properties
- Environmental fate
- ADME properties
- Toxicity endpoints

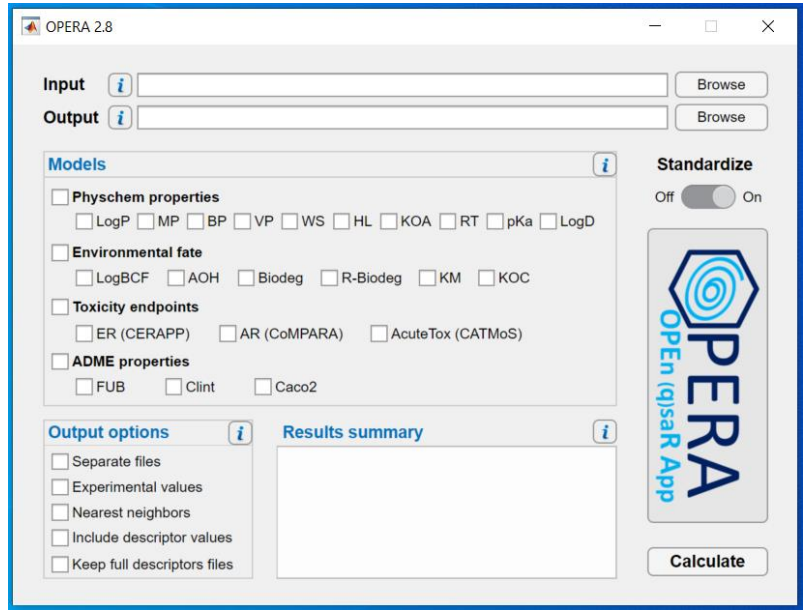
Input options:

- 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 (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^{V}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

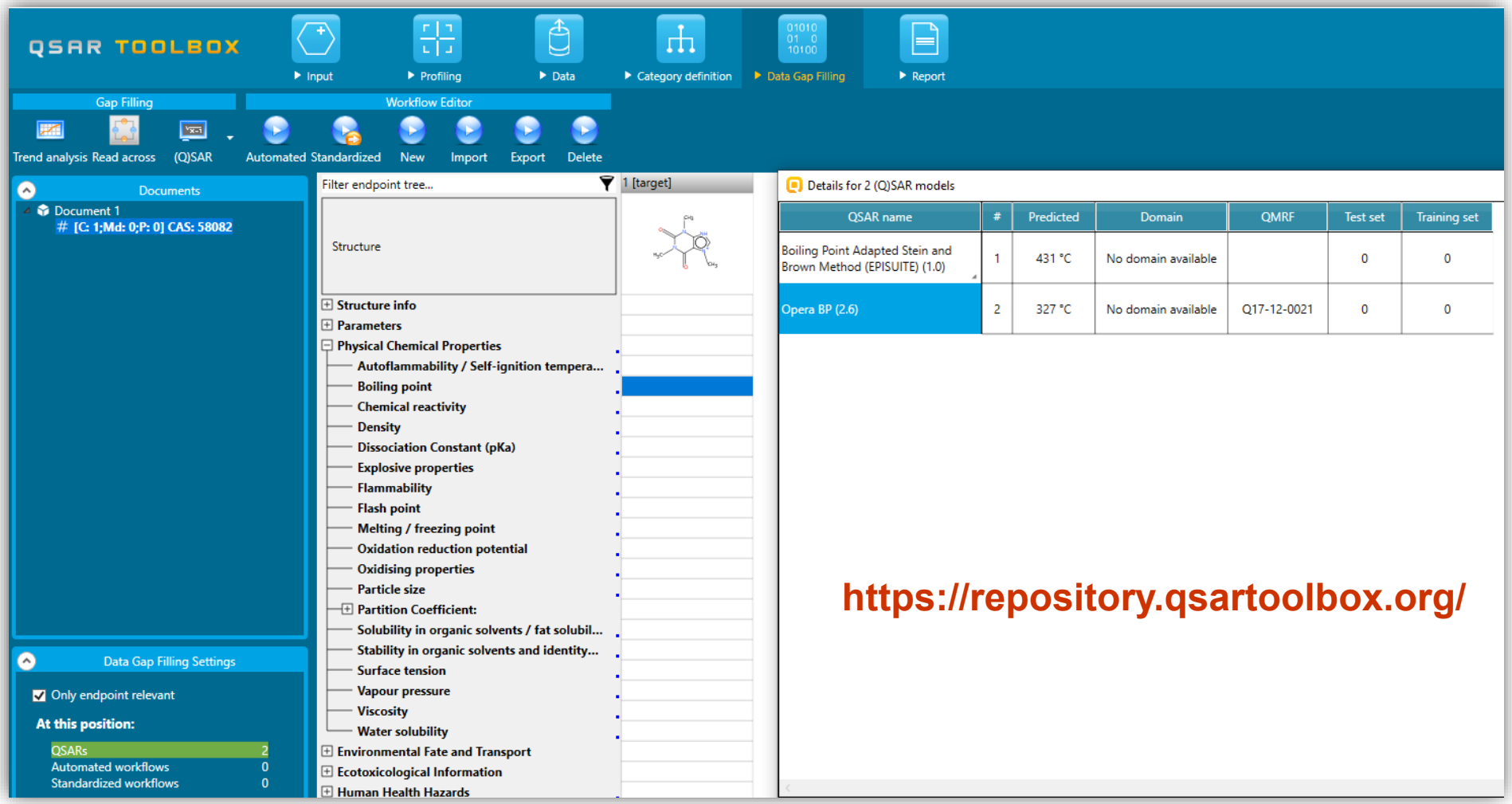
Property Estimation of Per- and Polyfluoroalkyl Substances: A Comparative Assessment of Estimation Methods

Alina Lampic and J. Mark Parnis*

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

Updates Under Development

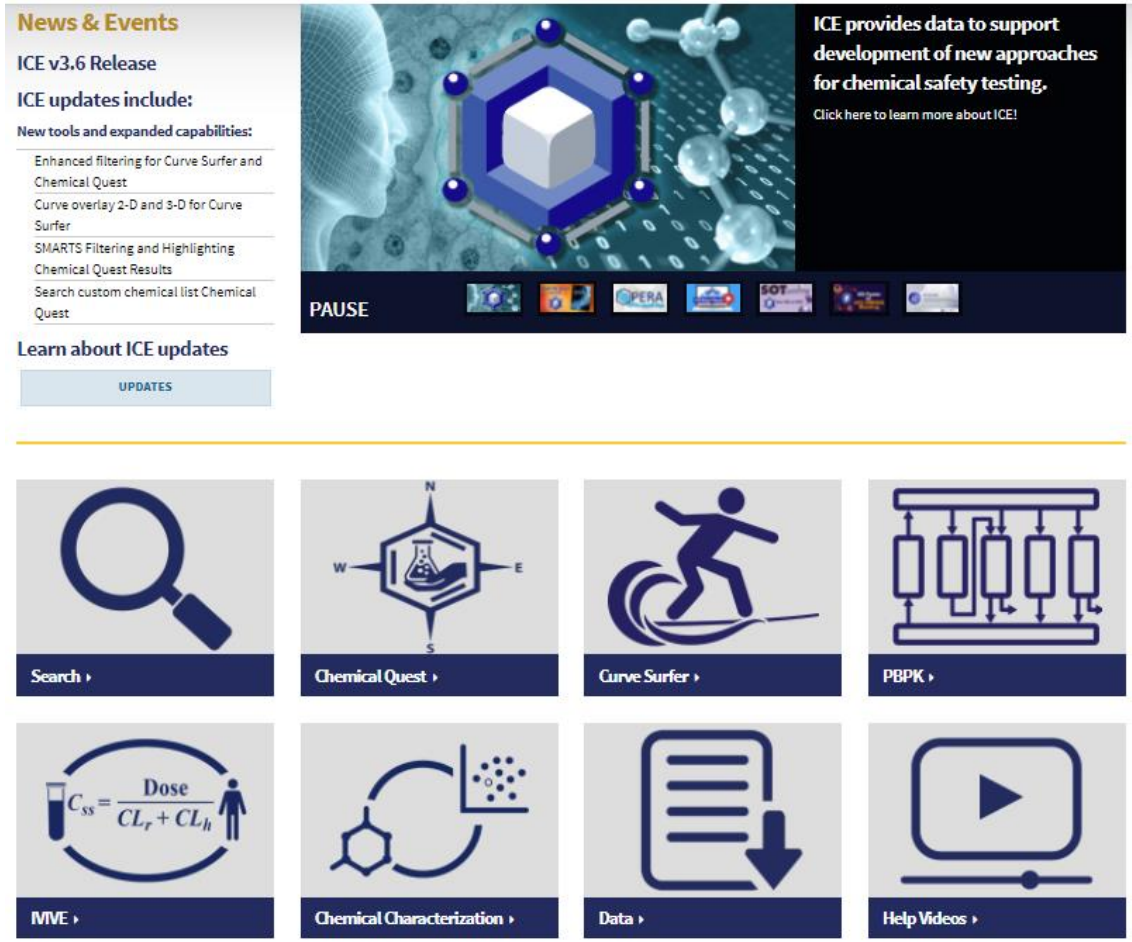
OPERA in the OECD Toolbox



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

Integrated Chemical Environment

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



- 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

Bell et al. 2017 EHP; Bell et al. 2020 Tox In Vitro; Abedini et al. 2021 Comp Tox

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

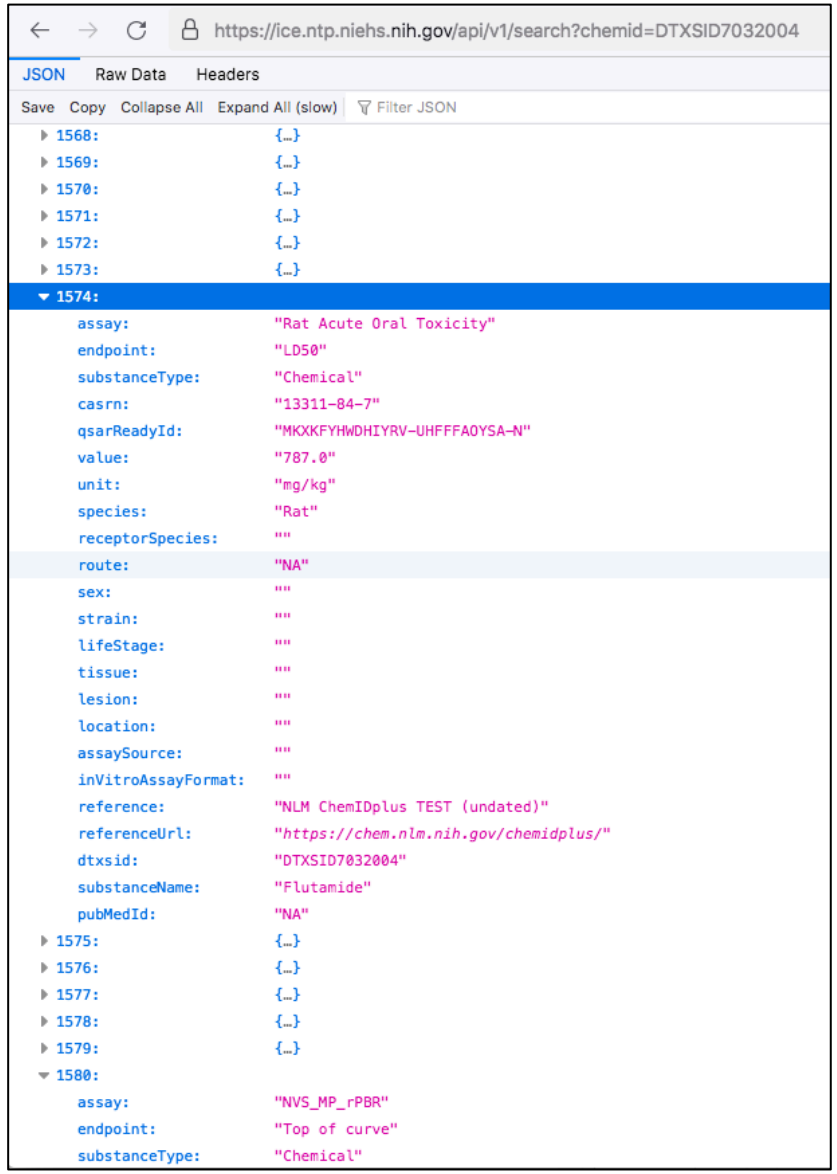
Toxicity endpoint	Assays	# of chemicals
Chemical Parameters	Experimental physchem	~20000
ADME Parameters	FUB, intrinsic clearance, Caco2 permeability	~5000
Acute Toxicity	In vivo acute oral, dermal, and inhalation toxicity	~10000
Cancer	In vivo and in vitro Cancer, and Weight of Evidence	3042
DART	In 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



Example R code to query ICE REST API

```r
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)
```

```python
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

1. Perform a search
   - Search
2. Expand inventory: Identify similar chemicals
   - Chemical Quest
3. Characterize chemical inventory
   - Chemical characterization
4. Review in vitro data details
   - Curve Surfer
5. Generate chemical concentration predictions
   - PBPK
6. Predict equivalent administered dose from in vitro data
   - IVIVE

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

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 httk 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

Recording at
https://pcrm.widencollective.com/portals/ieooh0ol/ICE

ICE Tools Workflow

Integrated Chemical Environment

Updates 2022
Updates to results graphics

Perform a search

Search

Expand inventory: Identify similar chemicals

Chemical Quest

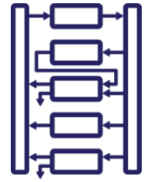
Characterize chemical inventory

Chemical characterization

Review in vitro data details

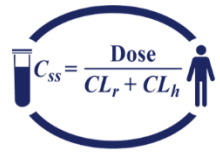
Curve Surfer

Generate chemical concentration predictions



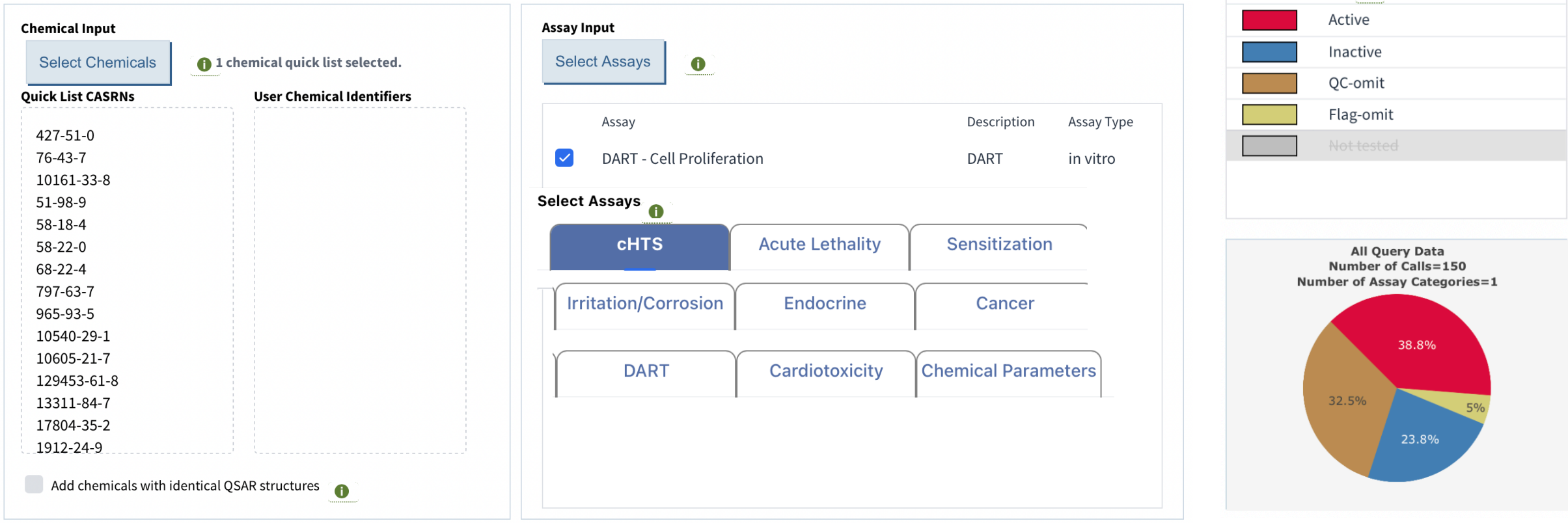
PBPK

Predict equivalent administered dose from in vitro data



IVIVE

ICE Tool: Search



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

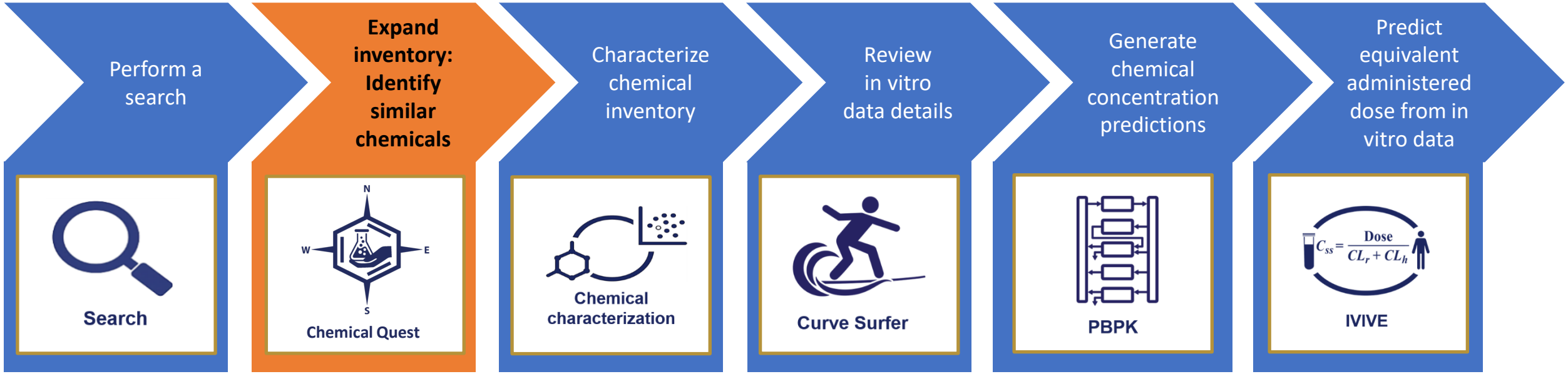
Similarity search based on custom chemical lists and targets

New filtering options

New result selection option

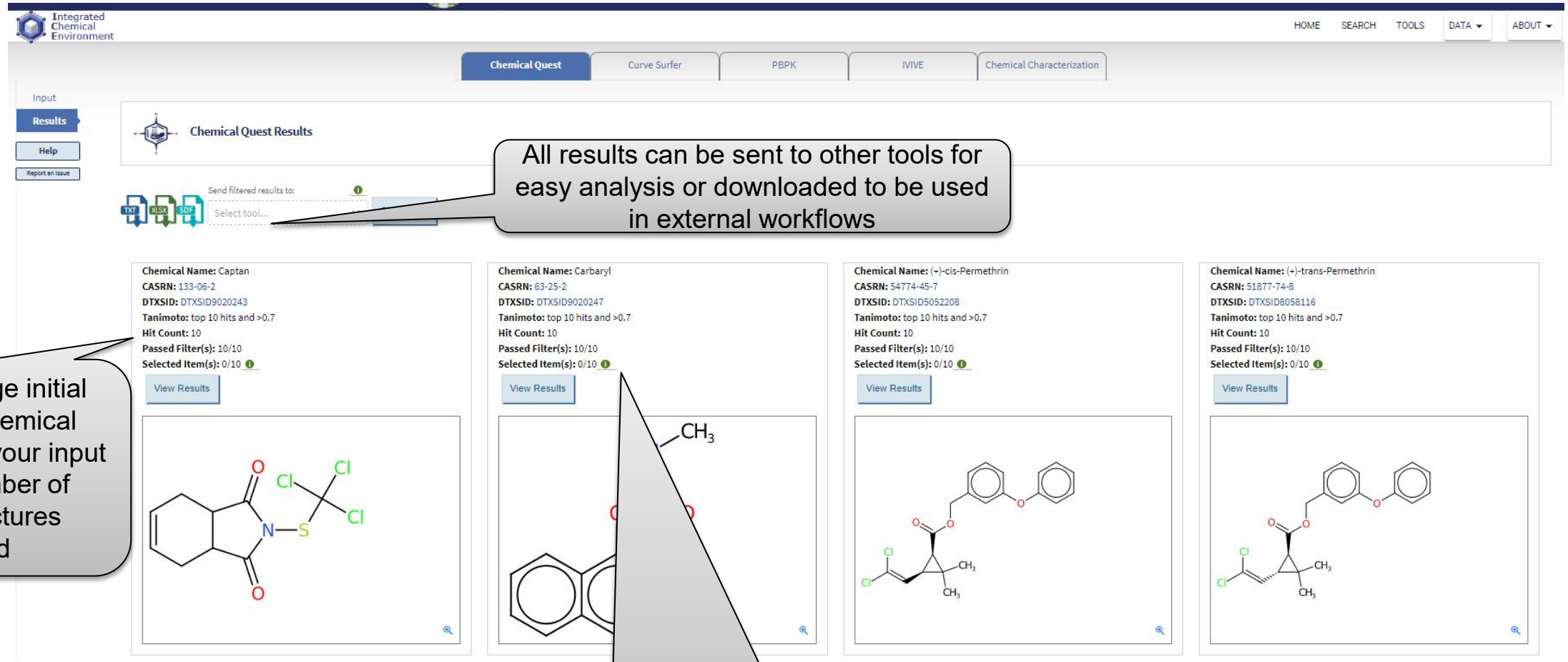
Utilizes Saggar fingerprints for structural similarity searching

Sedykh et al. 2021 Chem Res Tox



ICE Tool: Chemical Quest

Similar Structure Results



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

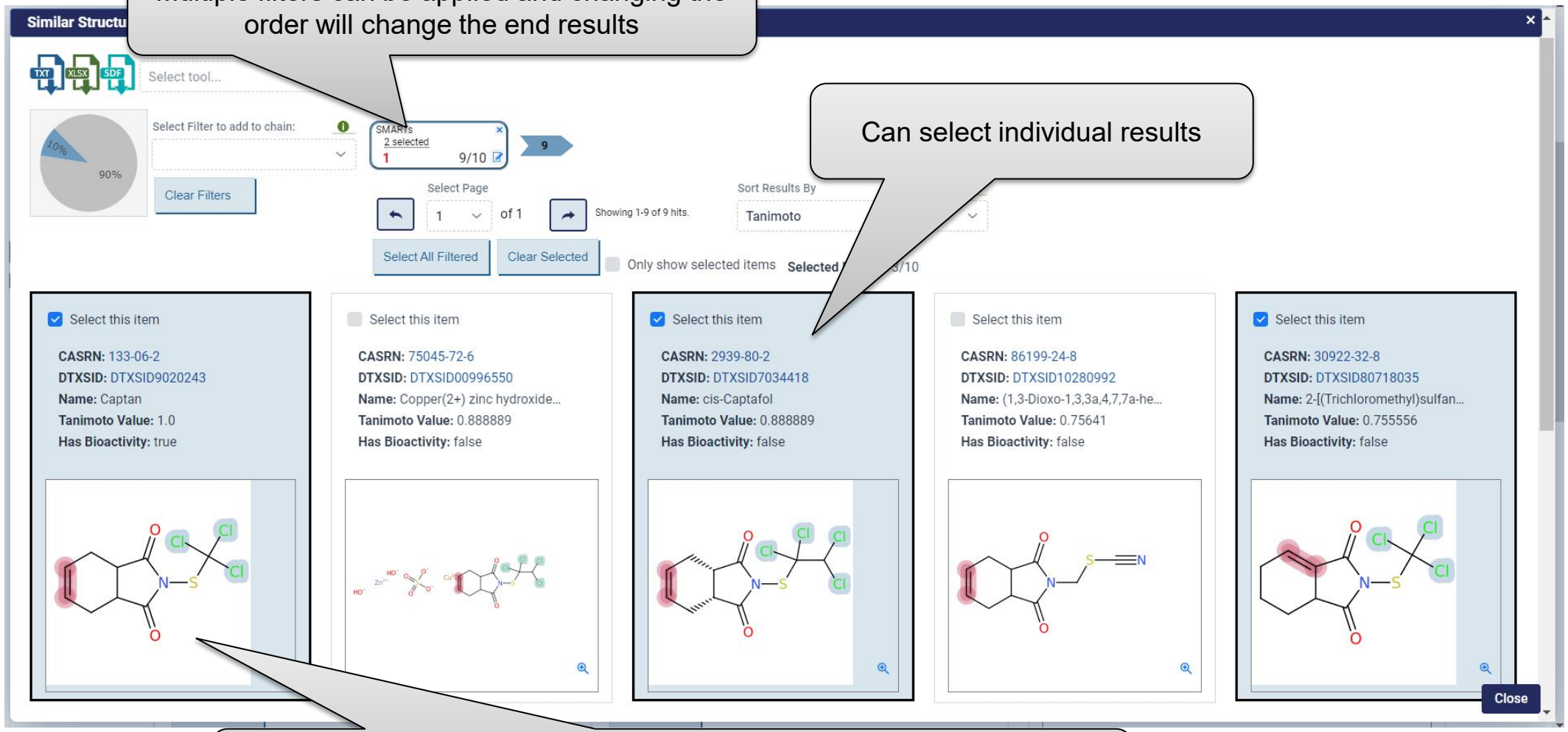
Chemicals from the input list are shown with the number of similar structures identified. This will influence the data downloads

ICE Tool: Chemical Quest

Seeing The Differences

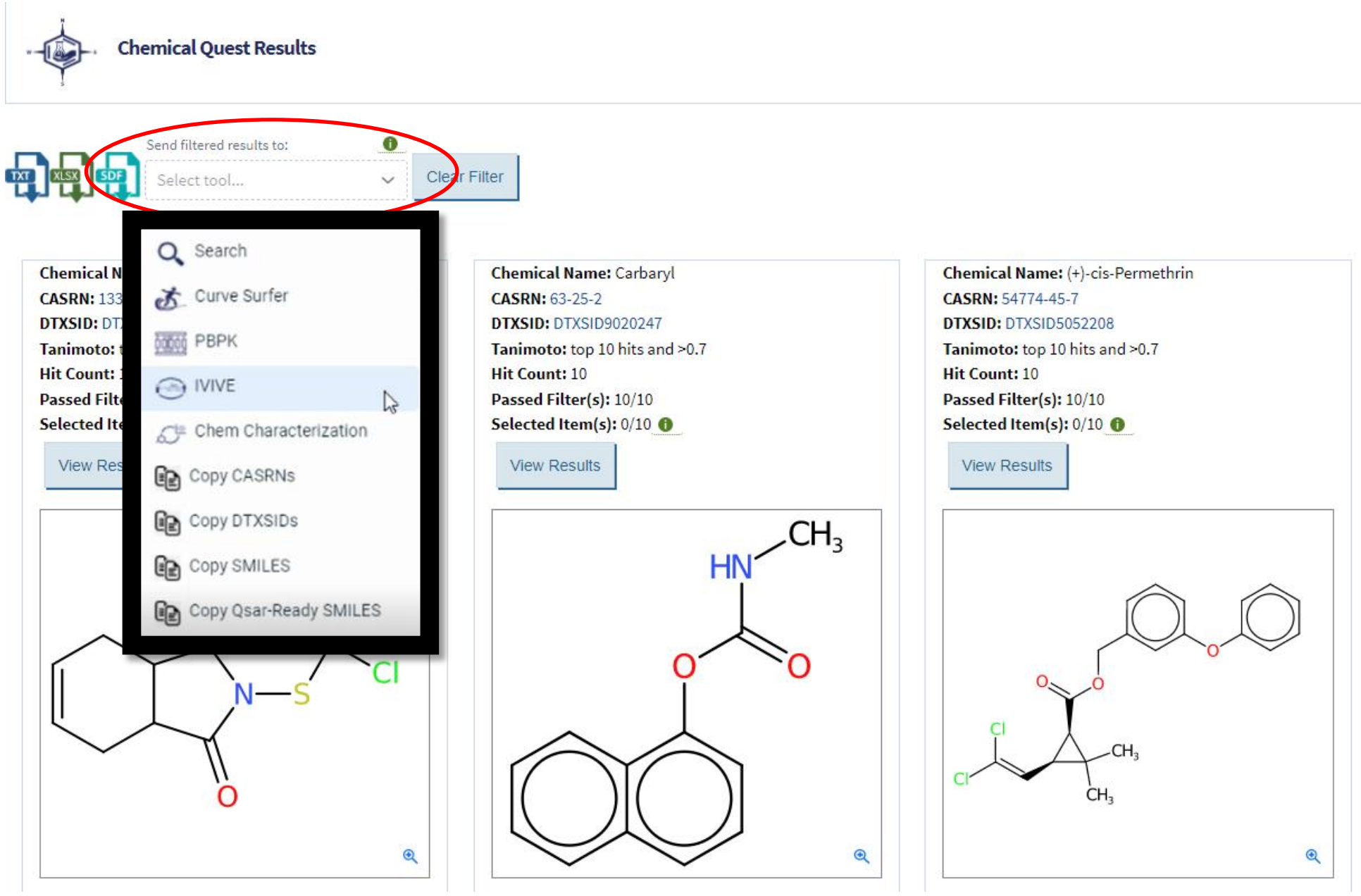
Multiple filters can be applied and changing the order will change the end results

Can select individual results



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

Send to Another Tool



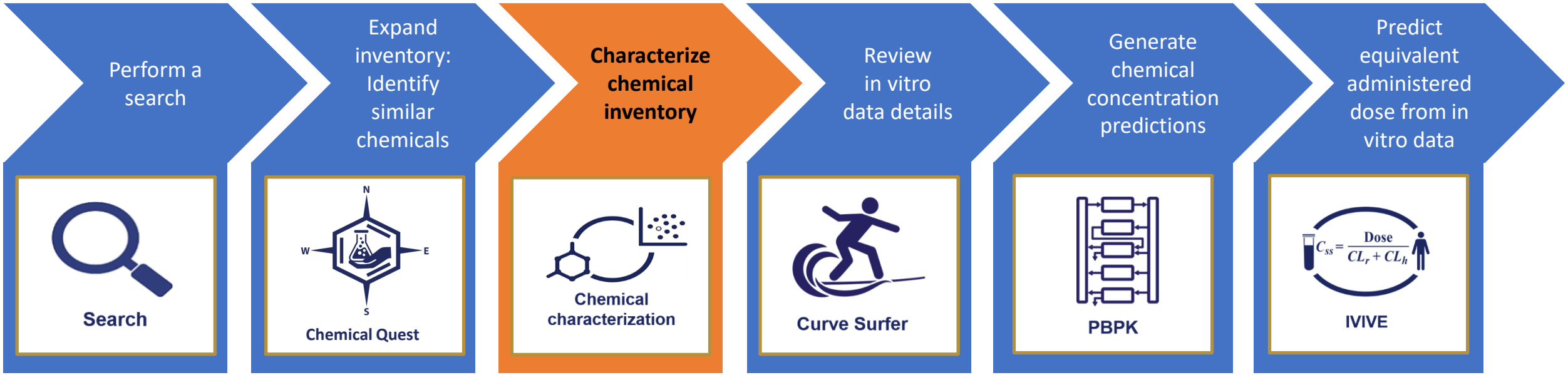
ICE Tools Workflow

Integrated Chemical Environment

Updates 2022

Improvements in Categorical characterization

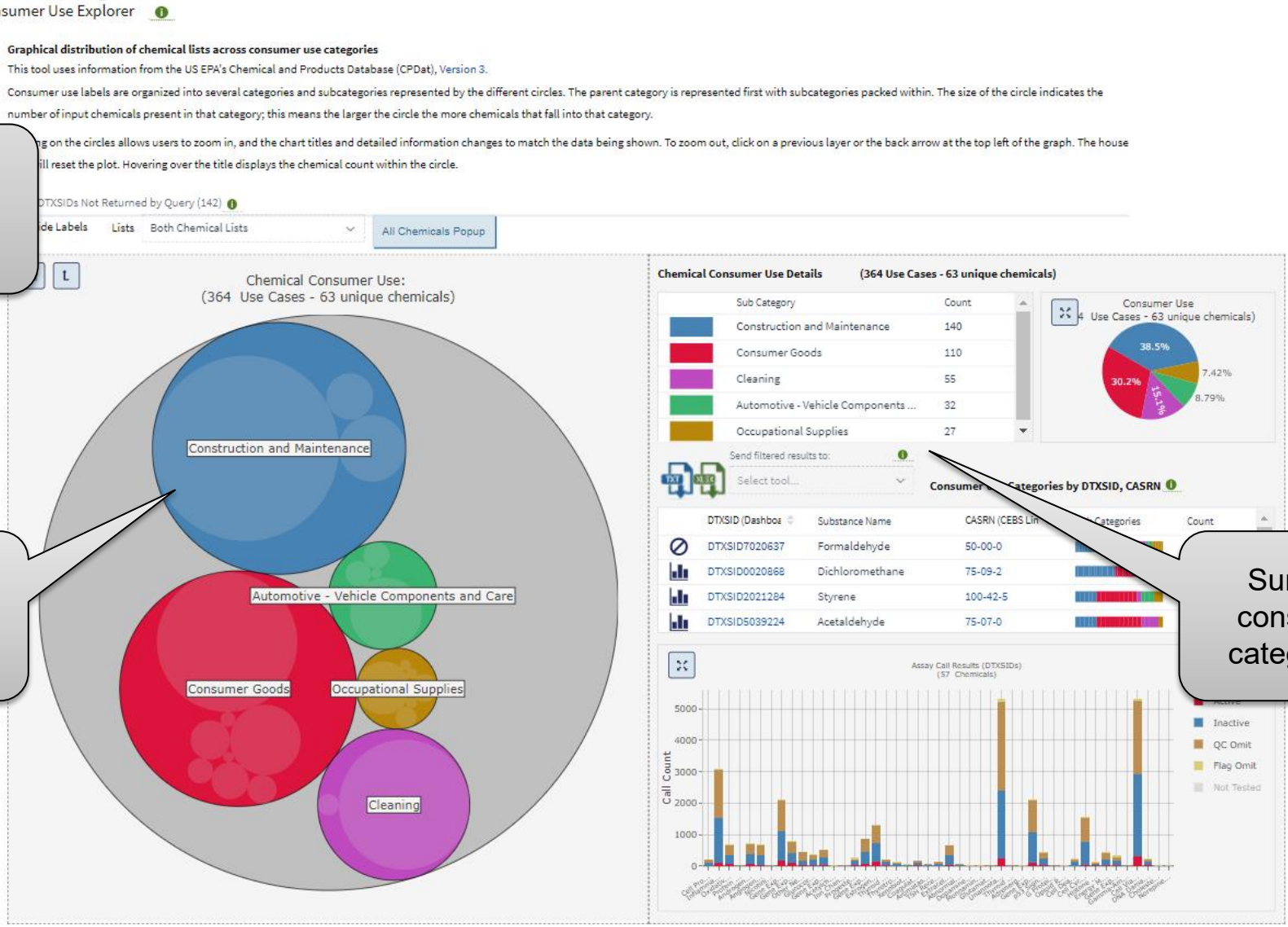
Updated documentation



ICE Tool: Chemical Characterization

Consumer Use Explorer

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



Nested bubble graphs show consumer use categories and subcategories

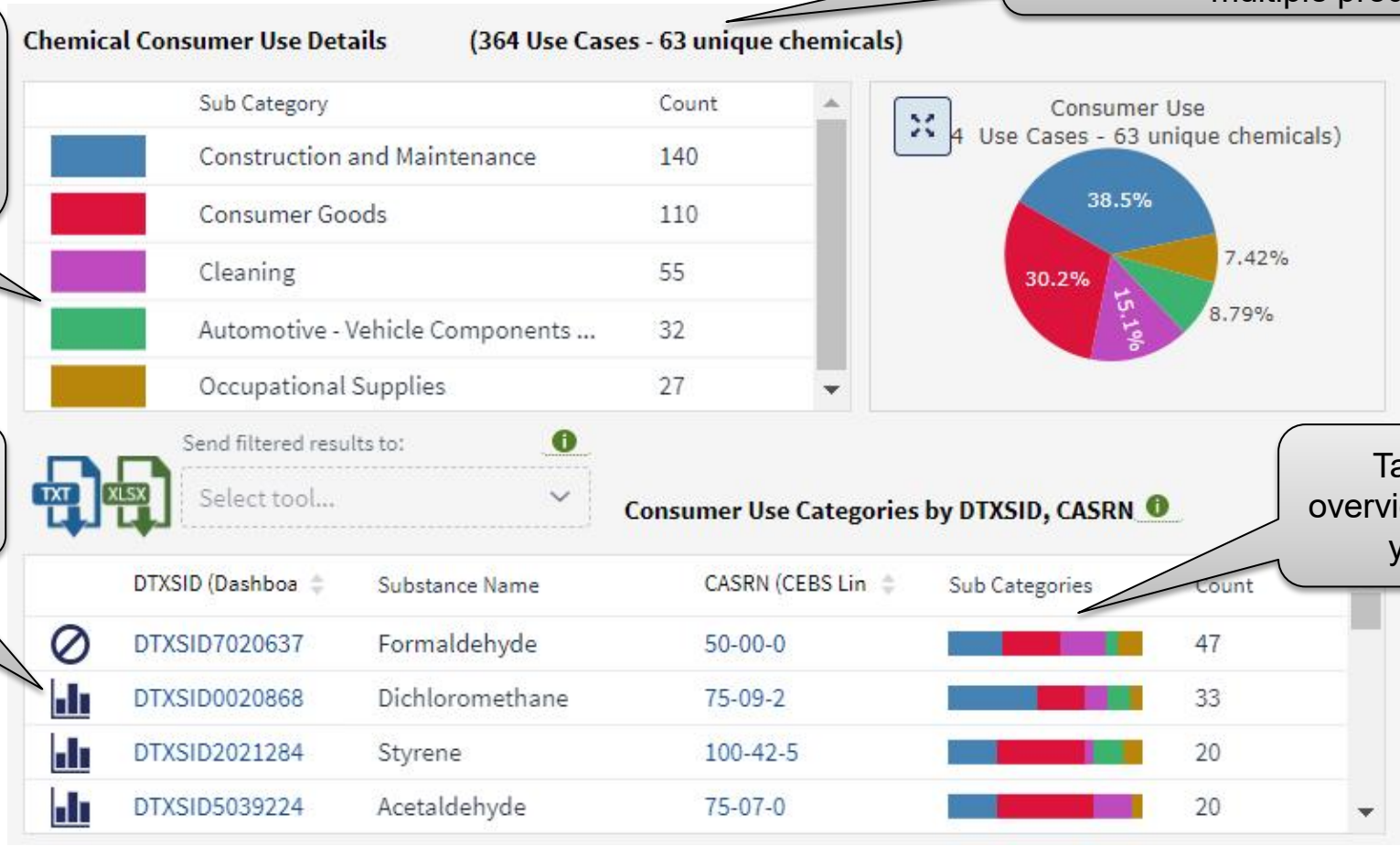
Summary details show consumer use details by category and by chemical

ICE Tool: Chemical Characterization

Breakdown Of Product Groups

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

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



Indicates if the chemical has cHTS bioactivity data

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

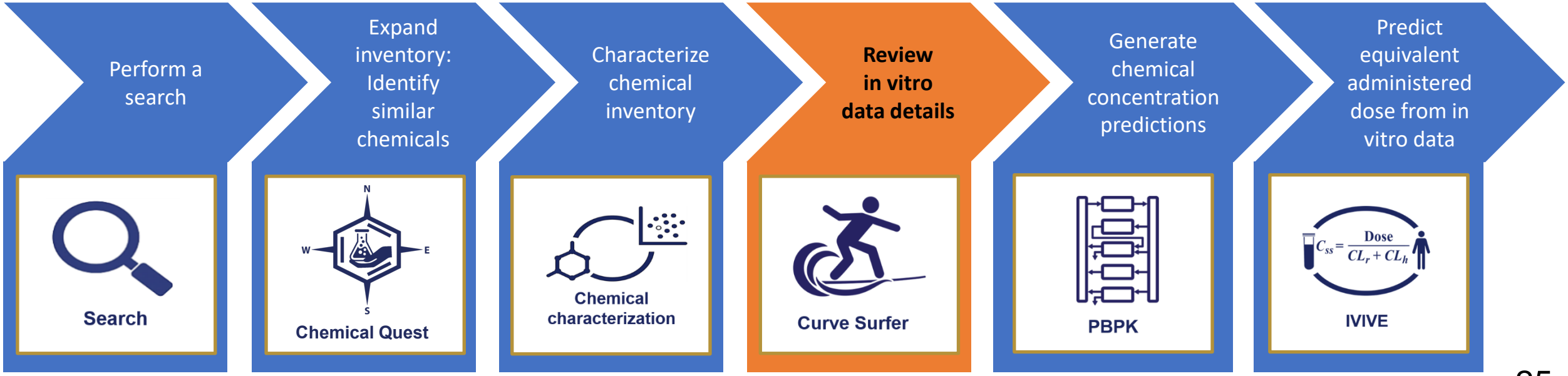
ICE Tools Workflow

Integrated Chemical Environment

Updates 2022

Overlay, 2D, and 3D curve viewing options

New filtering and selection options

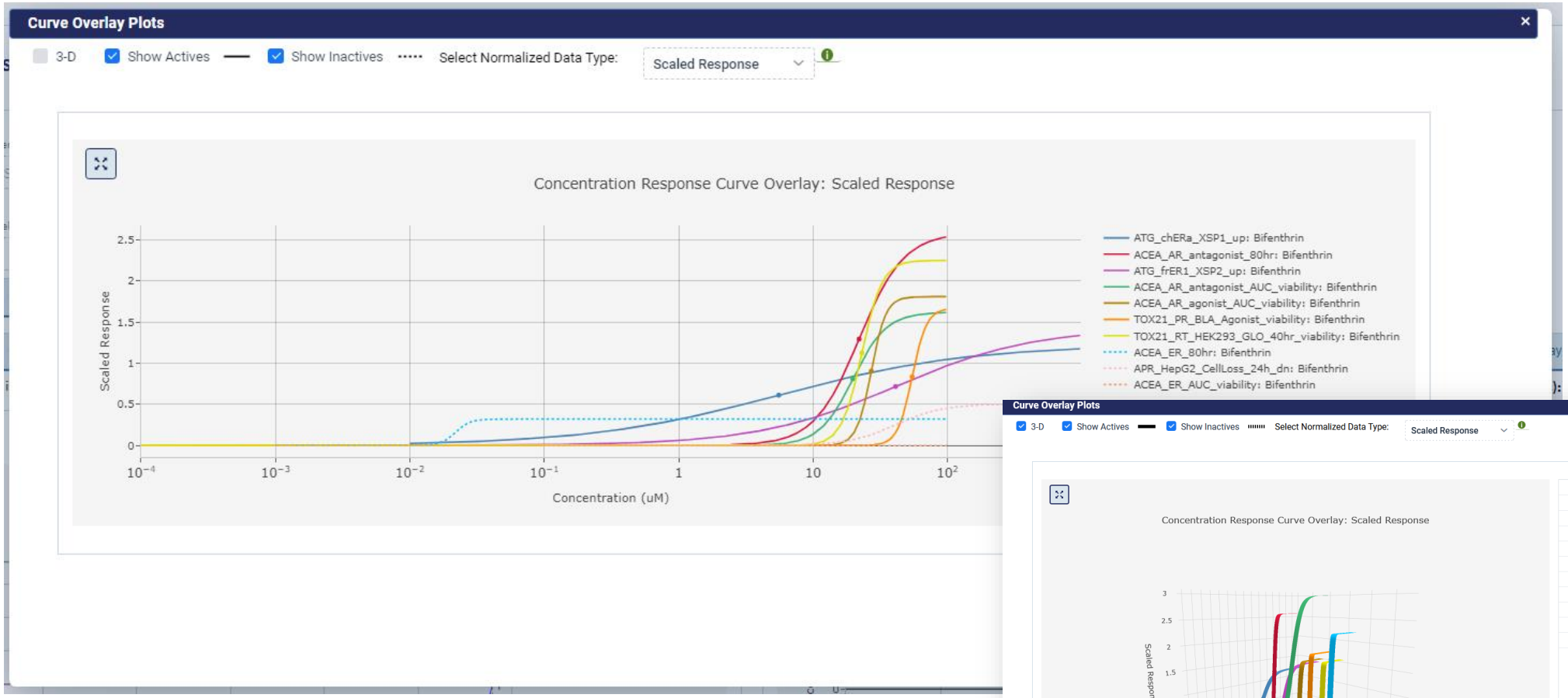


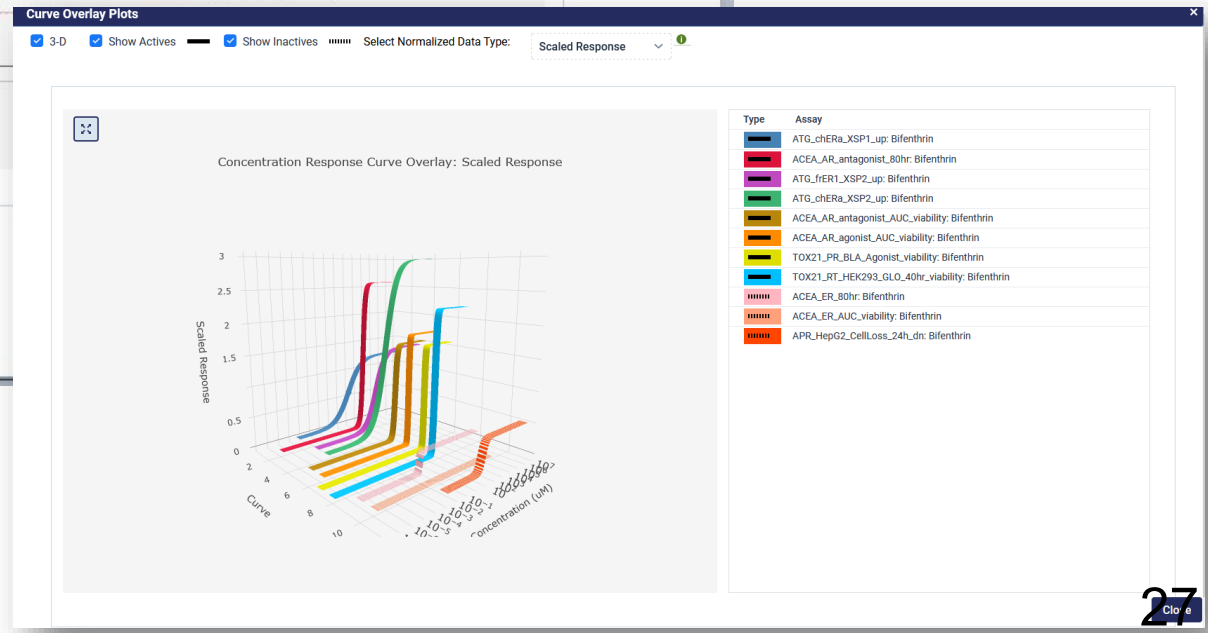
ICE Tool: Curve Surfer

View results, filter, and select for overlay

ICE Tool: Curve Surfer

Viewing overlay of multiple concentration-response curves





ICE Tools Workflow

Integrated Chemical Environment

Updates 2022
Updated httk ADME data

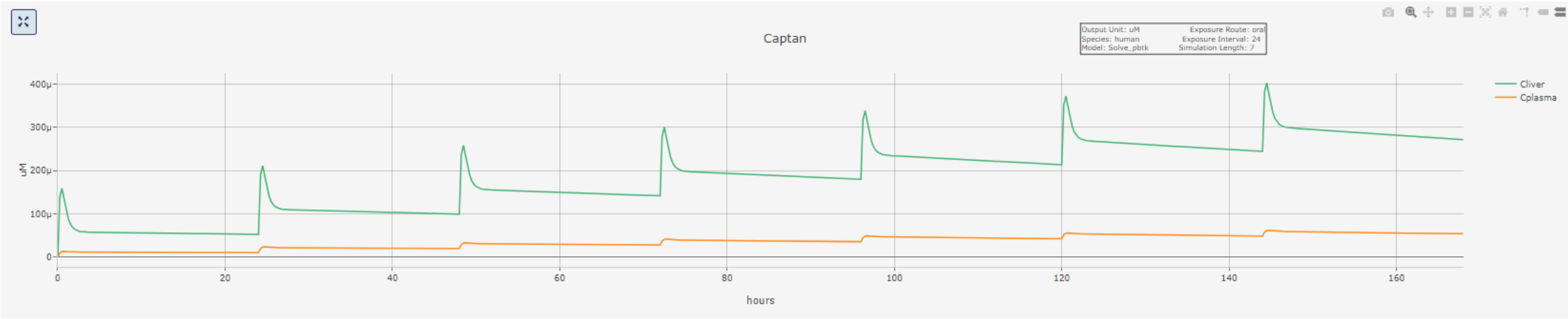
1. Perform a search
   - Search
2. Expand inventory: Identify similar chemicals
   - Chemical Quest
3. Characterize chemical inventory
   - Chemical characterization
4. Review in vitro data details
   - Curve Surfer
5. Generate chemical concentration predictions
   - PBPK
6. Predict equivalent administered dose from in vitro data
   - IVIVE

ICE Tool: PBPK

Example of predicted accumulation of chemical after oral exposure

CASRN: 133-06-2 **DTXSID:** DTXSID9020243

Chemical Name: Captan



ICE Tool: PBPK

Comparing predicted levels across tissues

Input

Results

Help

Report an Issue

PBPK workflow results

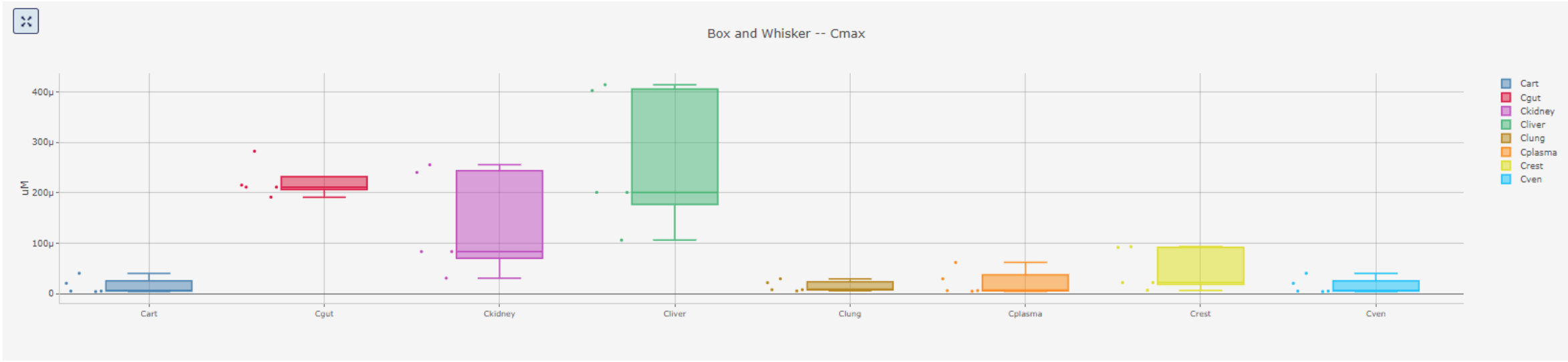
Download PBPK Files

PBPK Results

Curves

Box Plots

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



ICE Tools Workflow

Integrated Chemical Environment

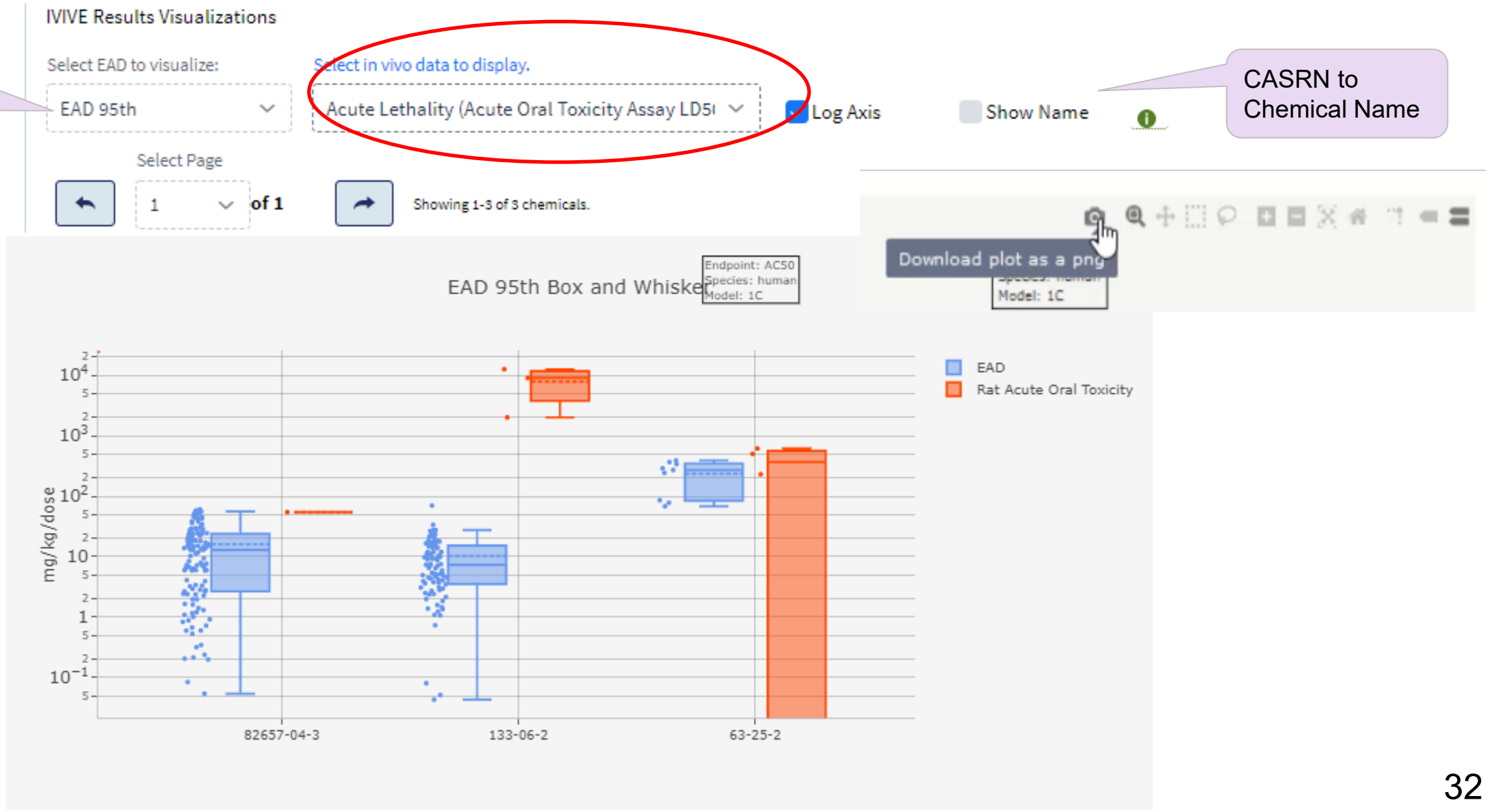
Updates 2022

Uploading custom in vivo and in vitro data

1. Perform a search
   - Search
2. Expand inventory: Identify similar chemicals
   - Chemical Quest
3. Characterize chemical inventory
   - Chemical characterization
4. Review in vitro data details
   - Curve Surfer
5. Generate chemical concentration predictions
   - PBPK
6. Predict equivalent administered dose from in vitro data
   - IVIVE

ICE Tool: IVIVE

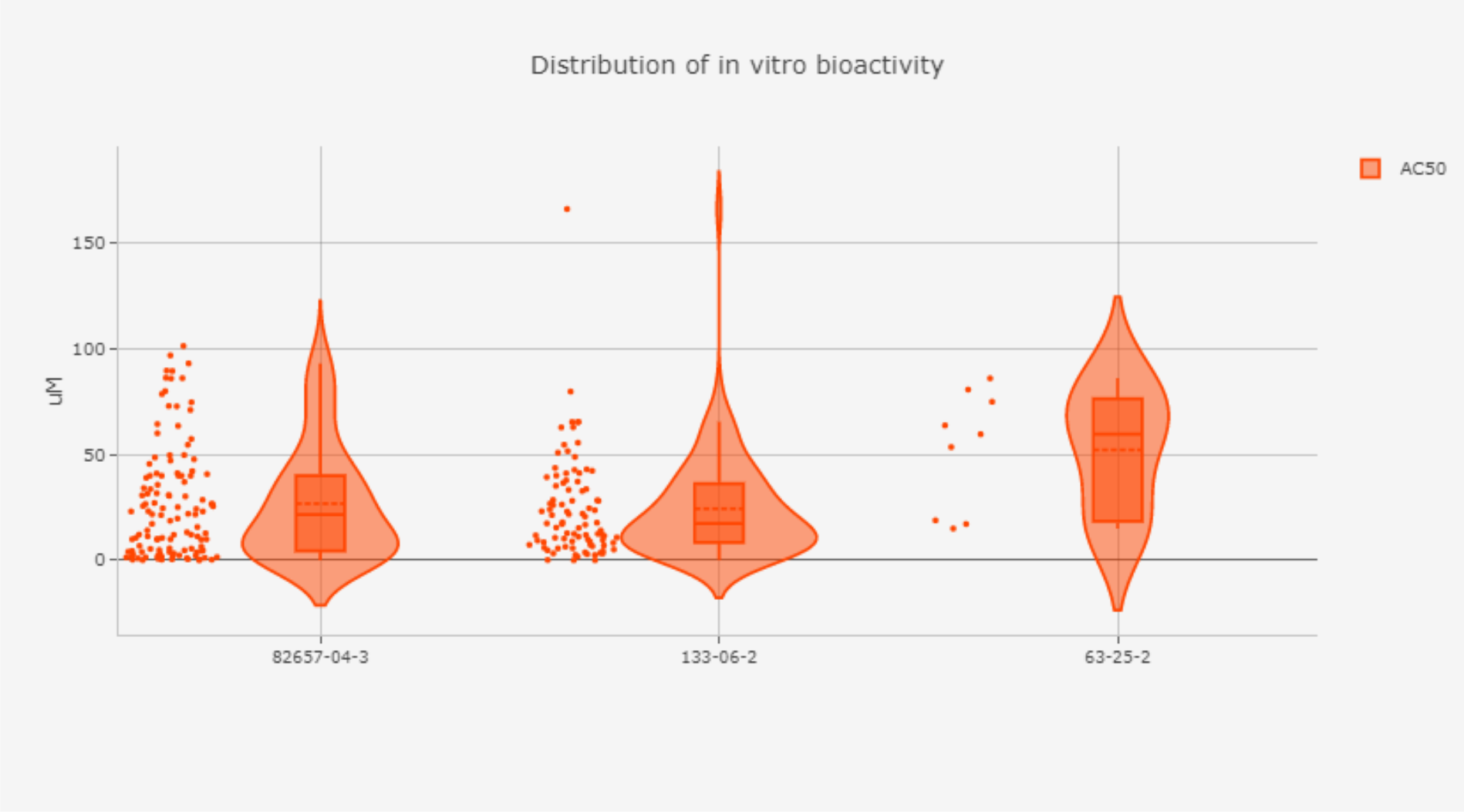
EAD 50th
EAD 95th



CASRN to Chemical Name

ICE Tool: IVIVE

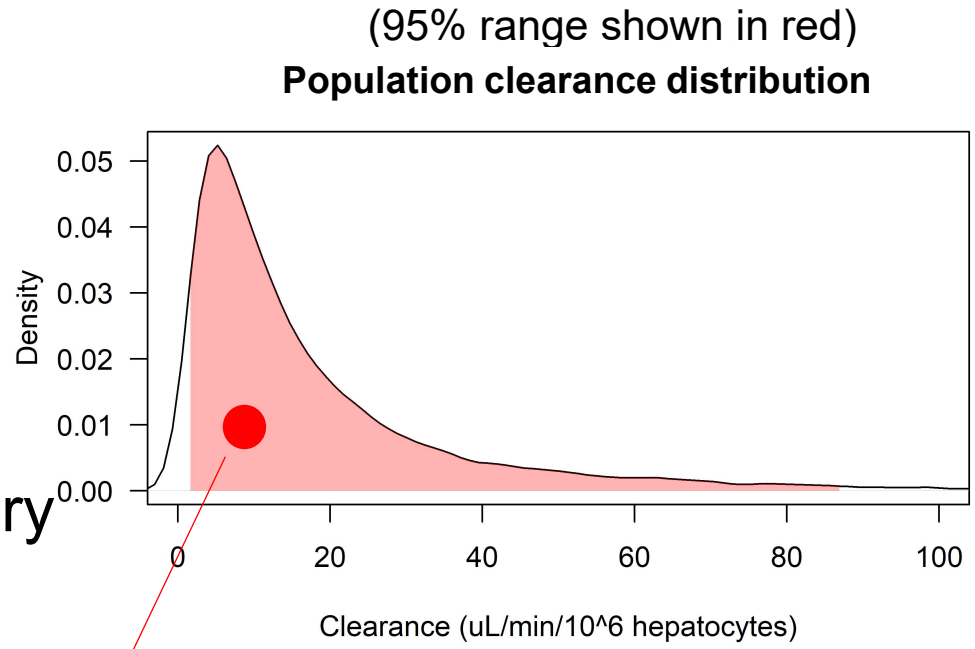
Visualizing Distributions from In Vitro Data



Incorporating Metabolism and Population Variability

Metabolism, enzyme variability, and parameter information are integrated into IVIVE models using the intrinsic clearance (CLint) parameter

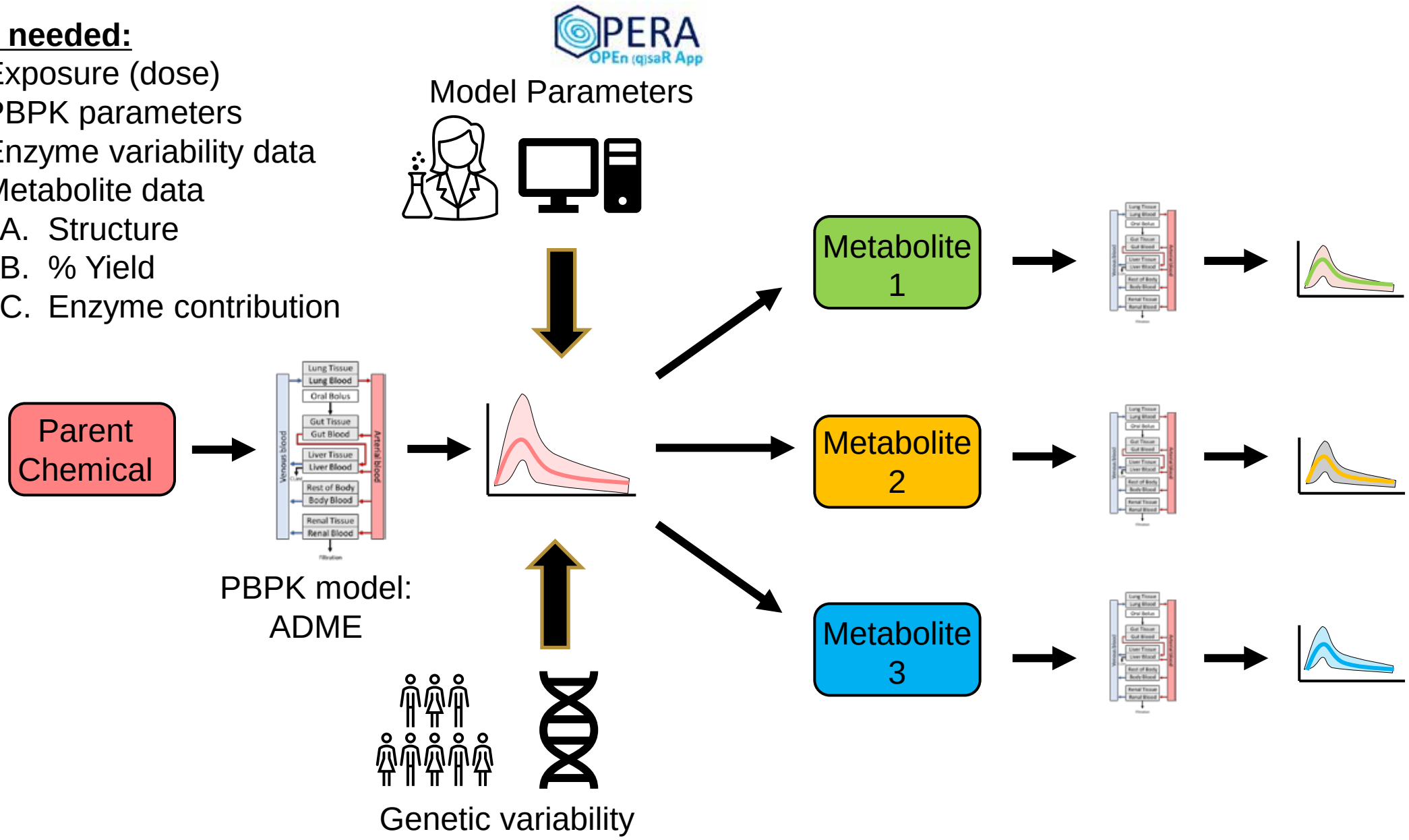
1. CLint parameter (measured or OPERA prediction) obtained
2. ADMET Predictor provides **enzymes** involved in metabolism
3. Lognormal CLint coefficient of variation (CV) for **each enzyme** obtained from EFSA summary
4. Lognormal distribution of CLint values assembled around CLint parameter using CV
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
4. Metabolite data
   A. Structure
   B. % Yield
   C. Enzyme contribution



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

NTP
National Toxicology Program

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

Integrated
Chemical
Environment

ICE

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NICEATM

ntp.niehs.nih.gov/go/niceatm