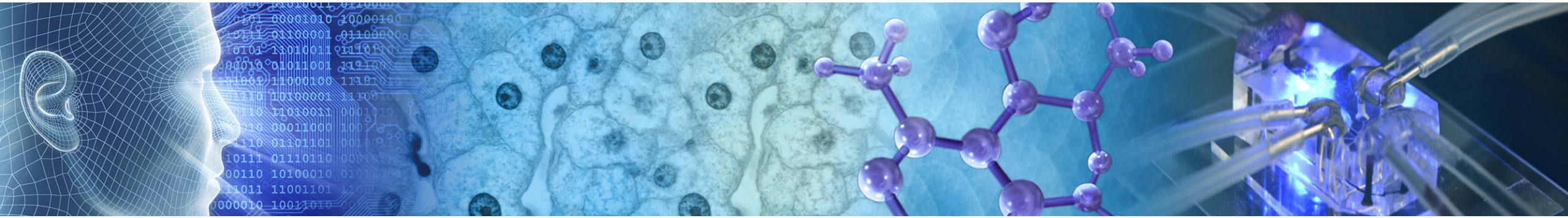
NTP
National Toxicology Program

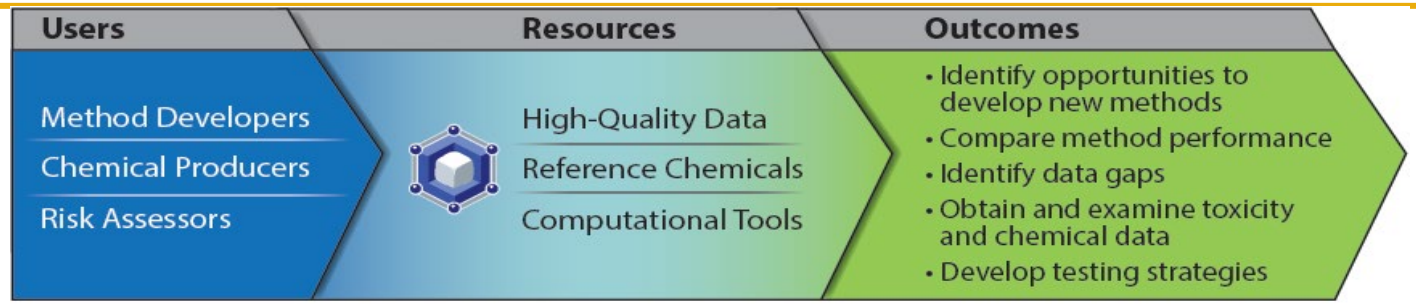


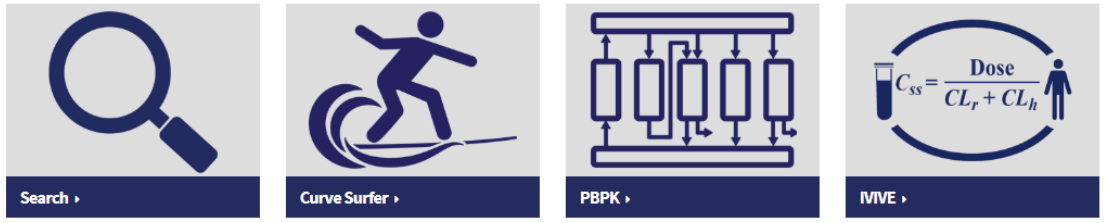
Update on NICEATM Computational Resources

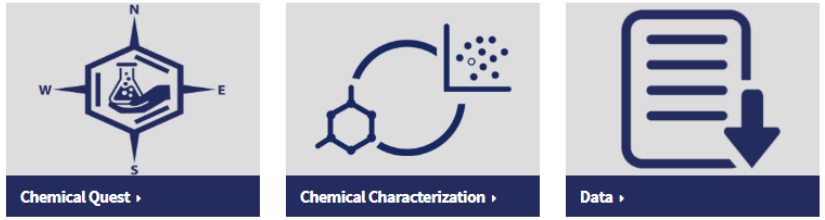
SACATM
September 28-29, 2021

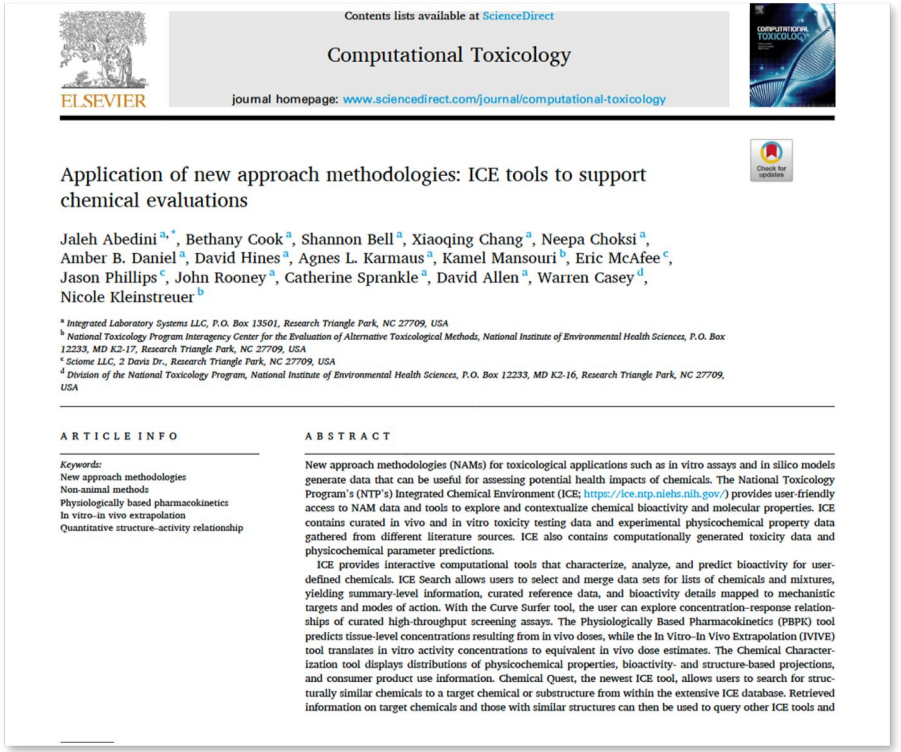
Nicole Kleinstreuer
Acting NICEATM Director

Integrated Chemical Environment: ICEv3.4









Contents lists available at ScienceDirect

Computational Toxicology

journal homepage: www.sciencedirect.com/journal/computational-toxicology

ELSEVIER

Application of new approach methodologies: ICE tools to support chemical evaluations

Jaleh Abedini [a,*], Bethany Cook [a], Shannon Bell [a], Xiaoqing Chang [a], Neepa Choksi [a], Amber B. Daniel [a], David Hines [a], Agnes L. Karmaus [a], Kamel Mansouri [b], Eric McAfee [c], Jason Phillips [c], John Rooney [a], Catherine Sprankle [a], David Allen [a], Warren Casey [d], Nicole Kleinstreuer [b]

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[c] Sciome LLC, 2 Davis Dr., Research Triangle Park, NC 27709, USA
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ARTICLE INFO

Keywords:
New approach methodologies
Non-animal methods
Physiologically based pharmacokinetics
In vitro-in vivo extrapolation
Quantitative structure-activity relationship

ABSTRACT

New approach methodologies (NAMs) for toxicological applications such as in vitro assays and in silico models generate data that can be useful for assessing potential health impacts of chemicals. The National Toxicology Program's (NTP's) Integrated Chemical Environment (ICE; https://ice.ntp.niehs.nih.gov/) provides user-friendly access to NAM data and tools to explore and contextualize chemical bioactivity and molecular properties. ICE contains curated in vivo and in vitro toxicity testing data and experimental physicochemical property data gathered from different literature sources. ICE also contains computationally generated toxicity data and physicochemical parameter predictions.

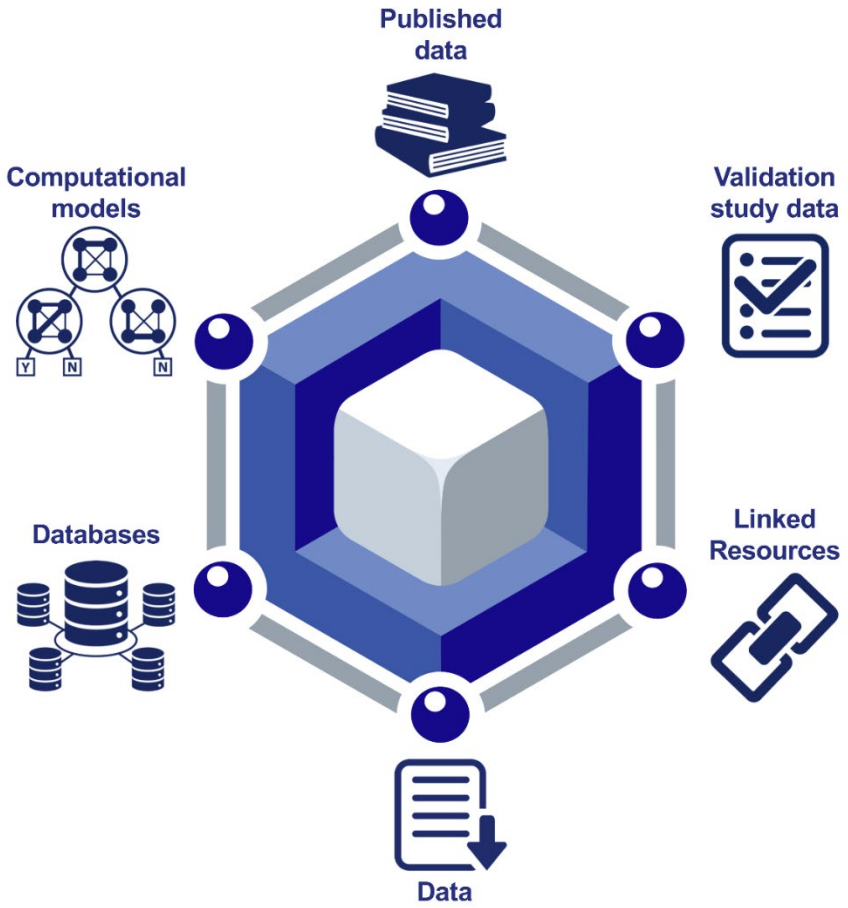
ICE provides interactive computational tools that characterize, analyze, and predict bioactivity for user-defined chemicals. ICE Search allows users to select and merge data sets for lists of chemicals and mixtures, yielding summary-level information, curated reference data, and bioactivity details mapped to mechanistic targets and modes of action. With the Curve Surfer tool, the user can explore concentration-response relationships of curated high-throughput screening assays. The Physiologically Based Pharmacokinetics (PBPK) tool predicts tissue-level concentrations resulting from in vivo doses, while the In Vitro-In Vivo Extrapolation (IVIVE) tool translates in vitro activity concentrations to equivalent in vivo dose estimates. The Chemical Characterization tool displays distributions of physicochemical properties, bioactivity- and structure-based projections, and consumer product use information. Chemical Quest, the newest ICE tool, allows users to search for structurally similar chemicals to a target chemical or substructure from within the extensive ICE database. Retrieved information on target chemicals and those with similar structures can then be used to query other ICE tools and

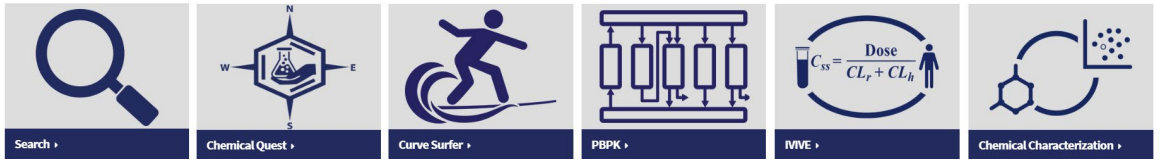
https://ice.ntp.niehs.nih.gov/

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

What is ICE?

- Curated data and search tools
  - Organized by toxicity endpoints
  - Standardized terminology, units, and formatting
- Curated chemical lists
  - Reference lists with classifications and bioactivity
  - In vitro assays linked with defined terminology
- Computational workflows
  - In vitro to in vivo extrapolation (IVIVE) and physiologically based pharmacokinetics (PBPK)
  - Quantitative structure-activity relationship (QSAR) models
  - Interfaces to explore concentration-response curves and chemical properties





In Vivo and In Vitro Data in ICE

Toxicity endpoint	Assays	# of chemicals
Chemical Parameters	Physchem, ADME, and toxicity Endpoints	~10000 *
Acute Oral Toxicity	In vivo acute oral 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 in vitro data on AR and ER agonist and antagonist activity	281
cHTS	Curated ToxCast and Tox21 assays	~9213

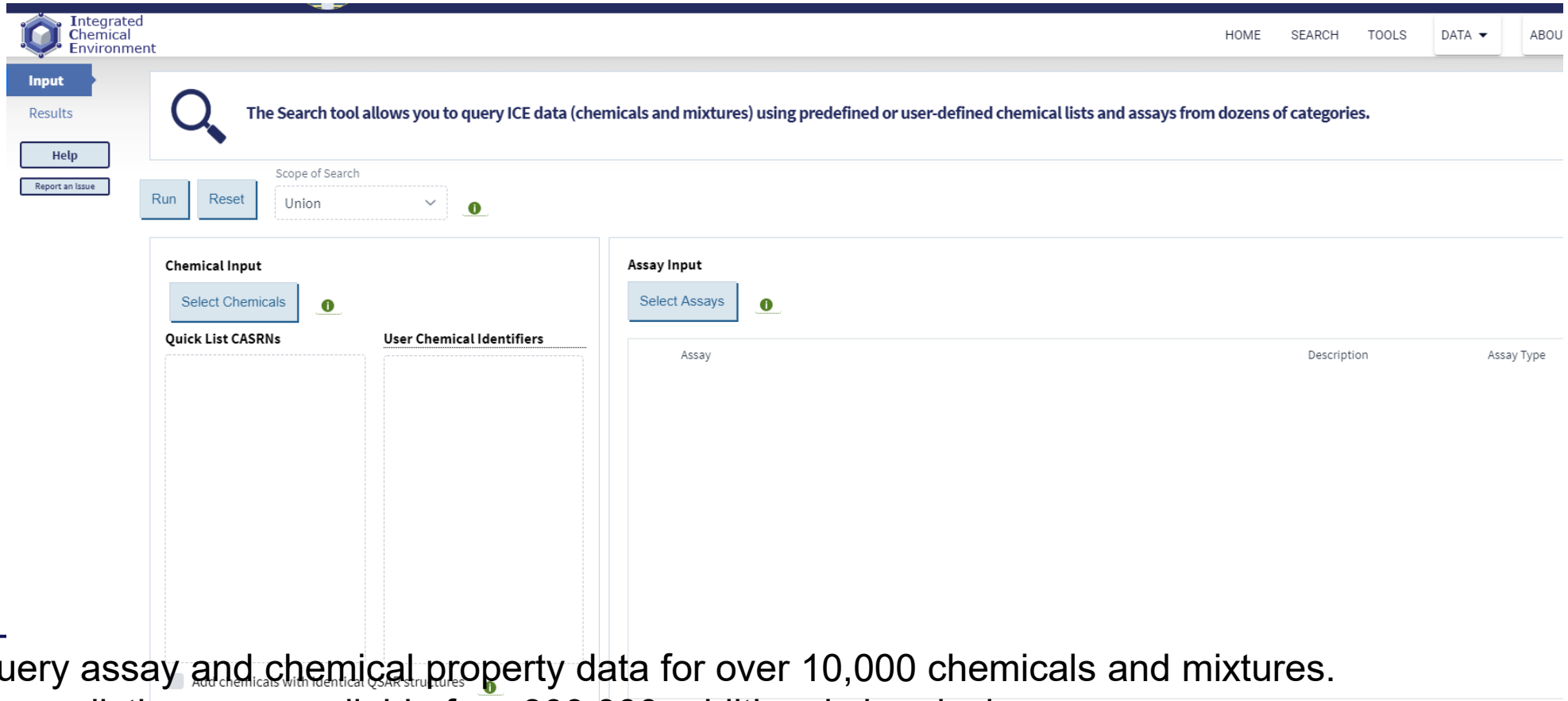
* in silico predictions are available for ~800,000 additional chemicals

In Silico Models in ICE

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+

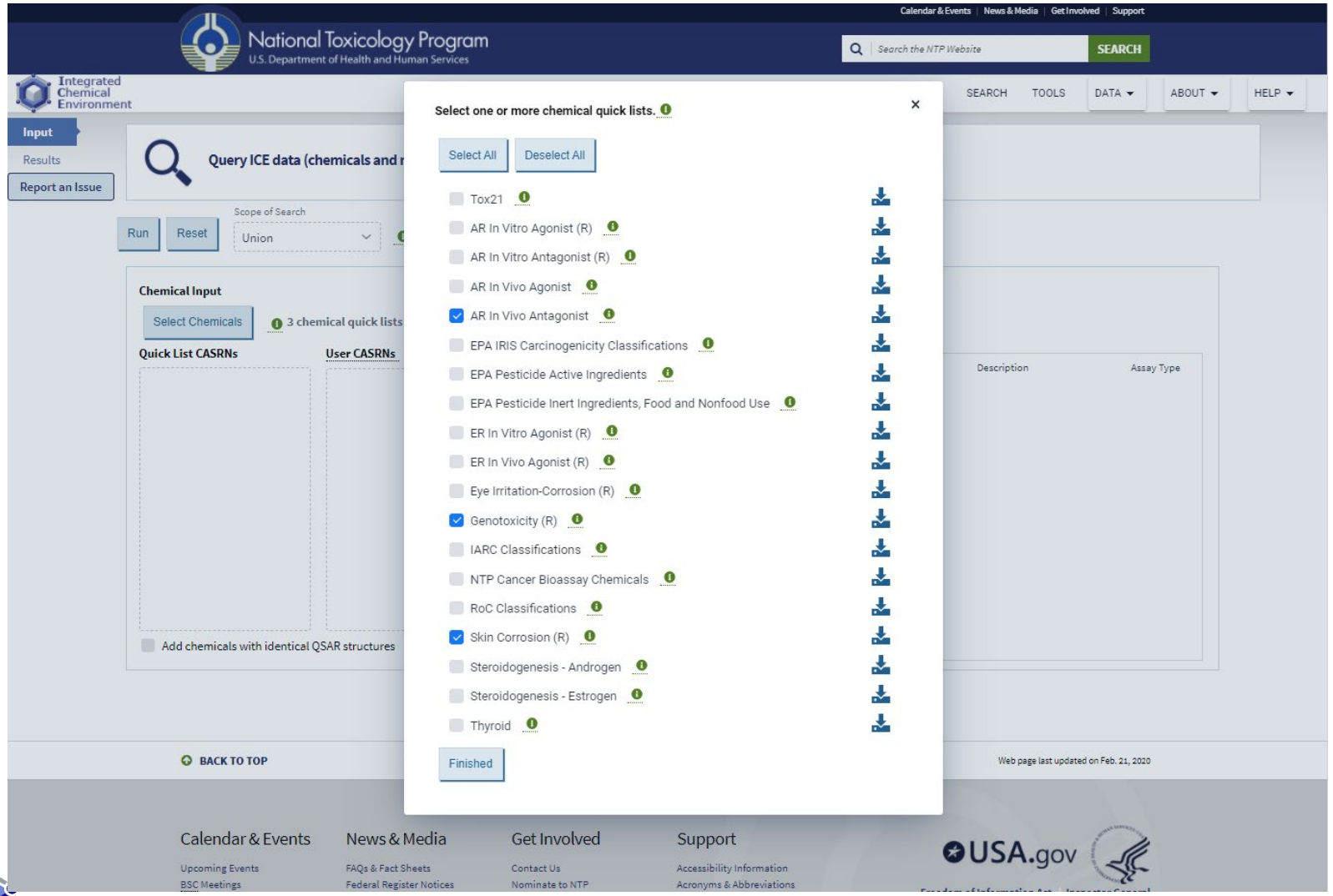
ICE Search

Overview



- User can query assay and chemical property data for over 10,000 chemicals and mixtures.
  - in silico predictions are available for ~800,000 additional chemicals
- **New for 2021**:
  - Query results now provides graphical visualizations of substance bioactivity in an assay.
  - Single chemicals and mixtures combined view.
  - **Help videos** to walk users through various parts of tools.

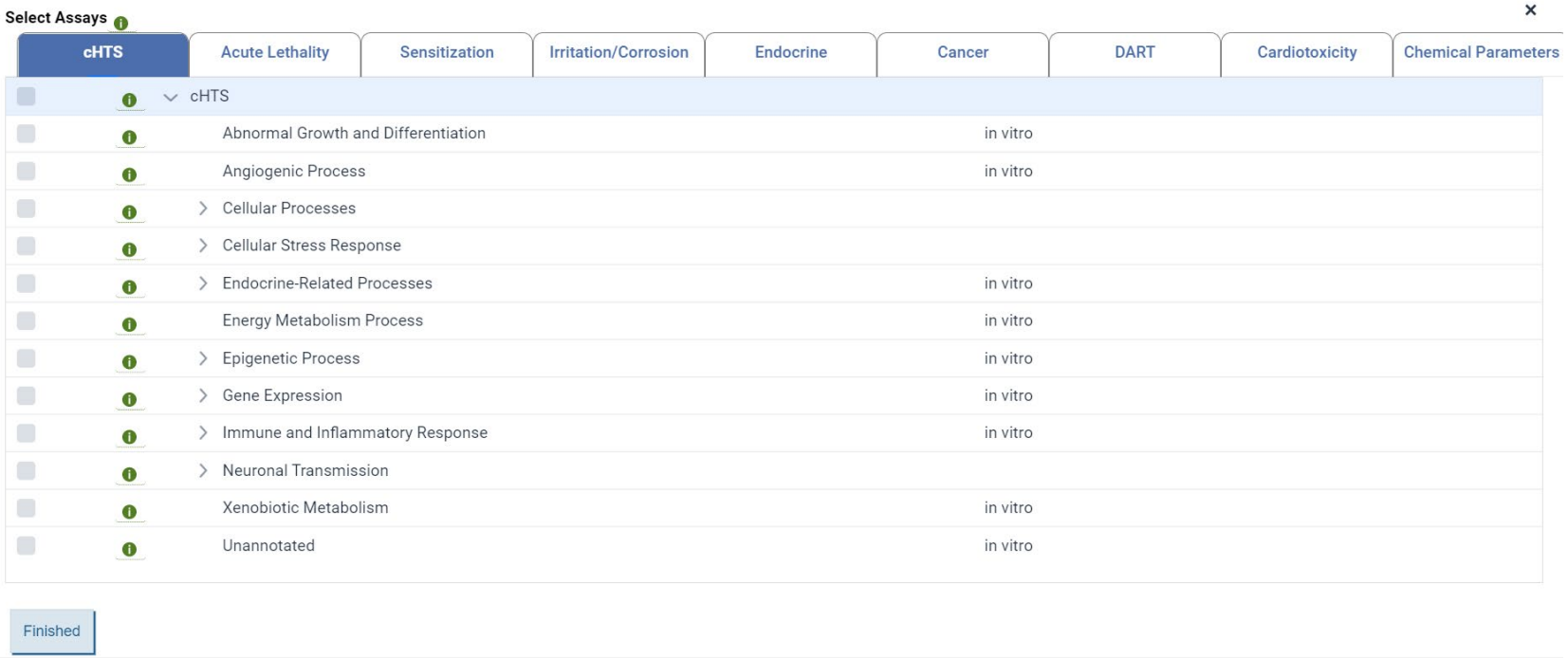
Chemical Selection and Quick Lists



- 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.
- **New for 2021**: In addition to CASRNs, DTSXIDs and Inchi Keys are accepted chemical identifiers.

ICE Search

Curation to assist meaningful assay selection and model building



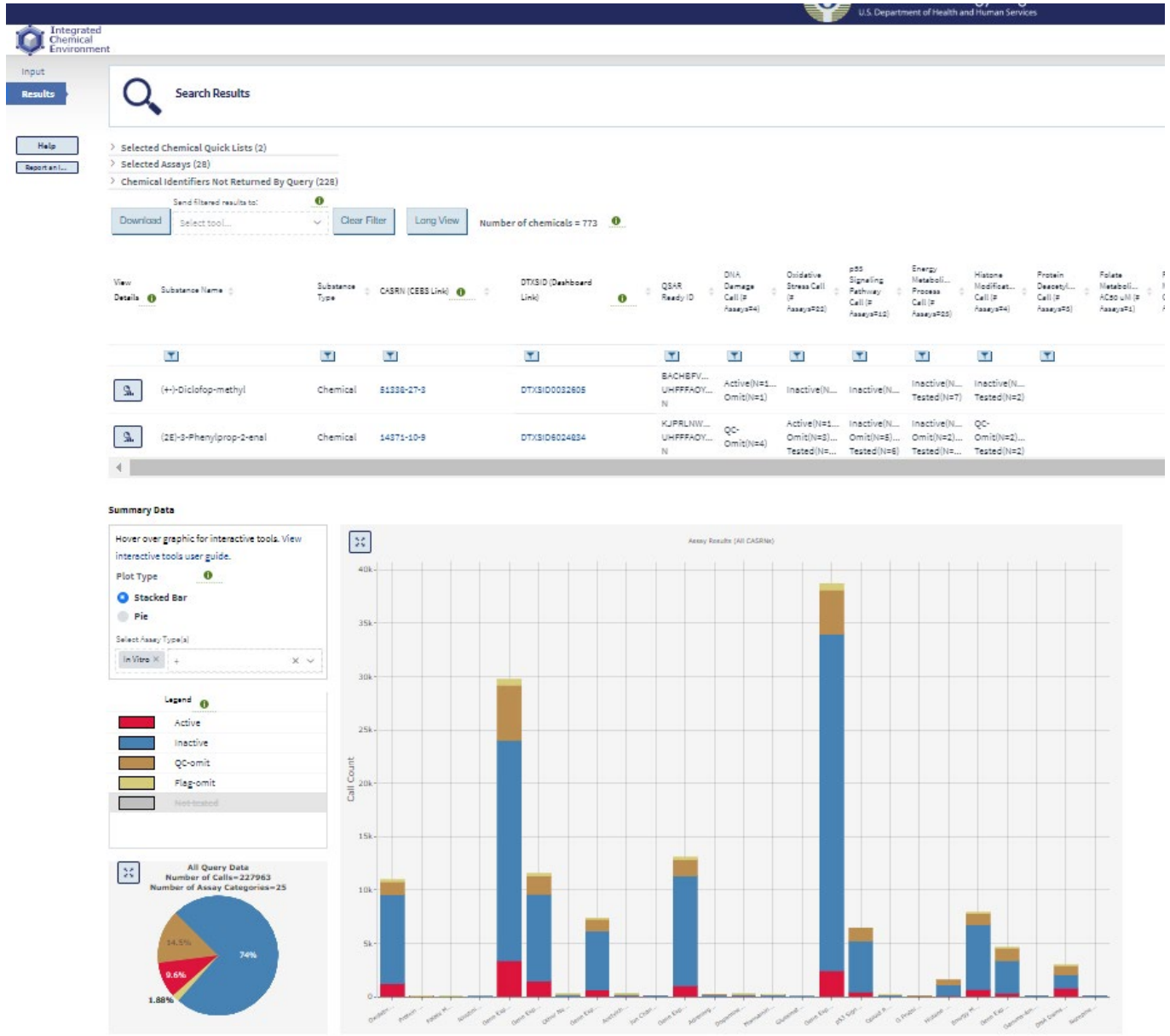
- Curated high-throughput screening data (cHTS) starts with EPA invitrodb and incorporates chemical QC information and technology-specific flags
- Assays are grouped by biological process, mechanistic target, and MoA, and linked to ontologies
- **New for 2021**:
  - Addition of Cardiotoxicity annotations to cHTS assays (*Krishna et al. 2021 Chem Res Tox*).
  - Expanded and refined Mode of Action (MOA) and Mechanistic Target (MT) annotations.

ICE Search

Search Results: Table allows users to explore summary data in tabular format and filter on column values.

- Interactive visualization provides graphical overview of summary level bioactivity data.

- **Upcoming:** Details of AC50s of active chemicals in each category available by clicking bars in plot



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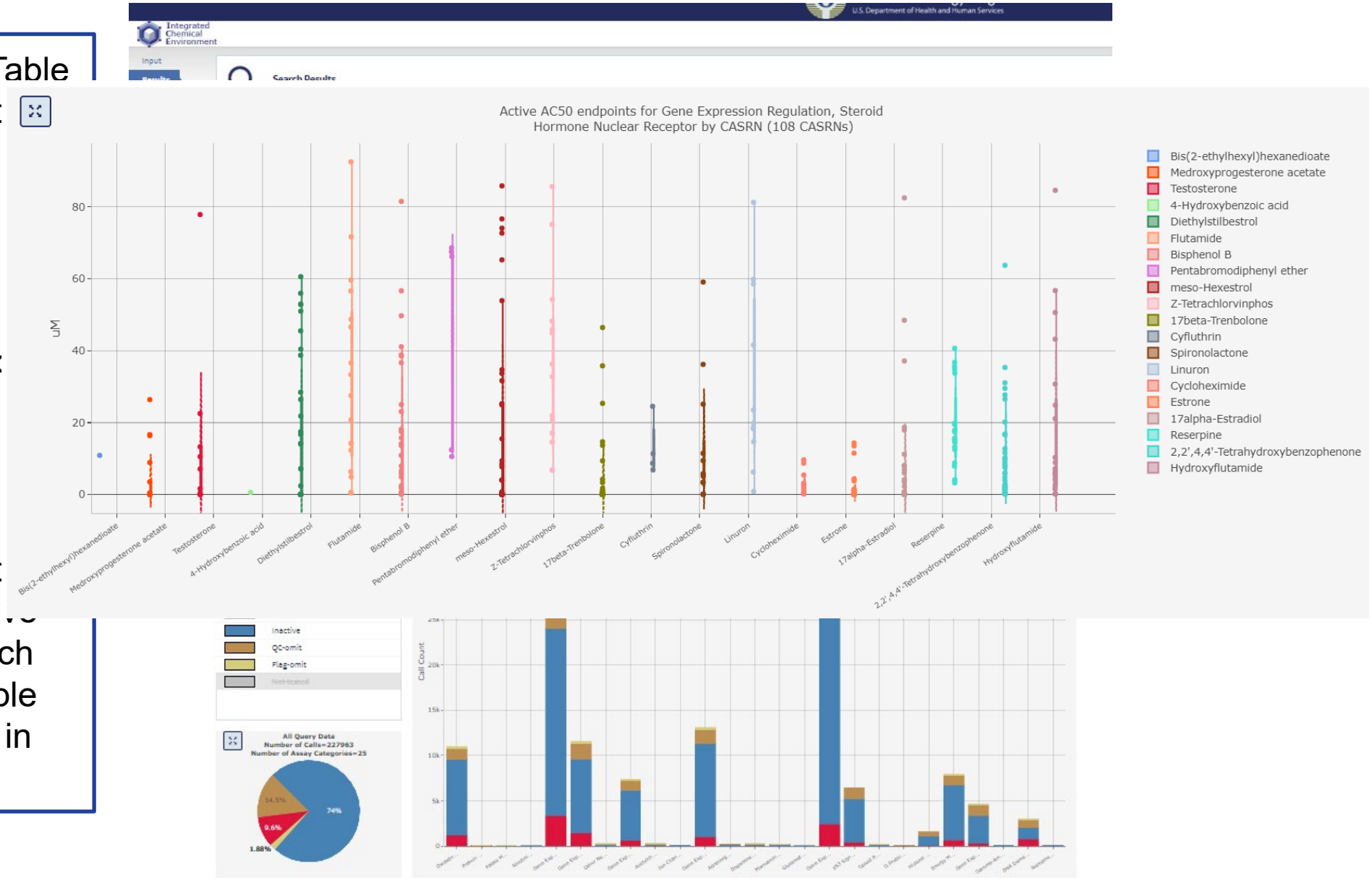


Results Table

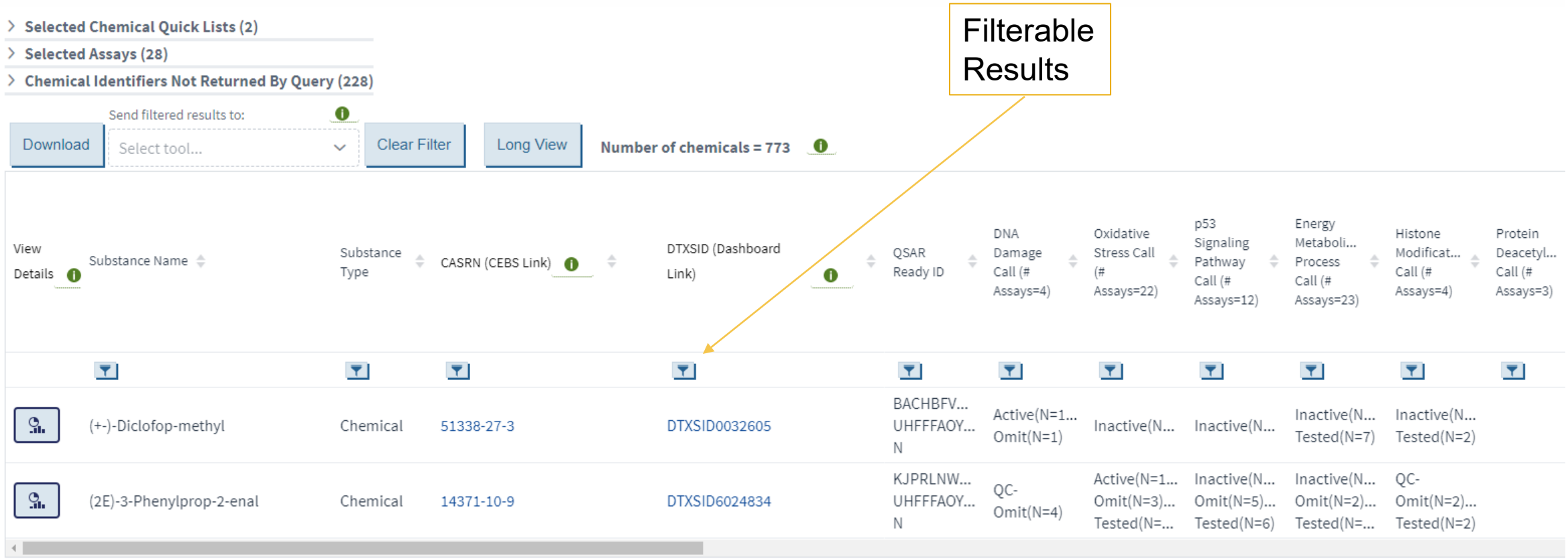
> Selected Chemical Quick Lists (2)
> Selected Assays (28)
> Chemical Identifiers Not Returned By Query (228)

Send filtered results to:

Download | Select tool... | Clear Filter | Long View | Number of chemicals = 773

View Details	Substance Name	Substance Type	CASRN (CEBS Link)	DTXSID (Dashboard Link)	QSAR Ready ID	DNA Damage Call (# Assays=4)	Oxidative Stress Call (# Assays=22)	p53 Signaling Pathway Call (# Assays=12)	Energy Metaboli... Process Call (# Assays=23)	Histone Modificat... Call (# Assays=4)	Protein Deacetyl... Call (# Assays=3)
	(+)-Diclofop-methyl	Chemical	51338-27-3	DTXSID0032605	BACHBFV... UHFFFAOY... N	Active(N=1... Omit(N=1)	Inactive(N...	Inactive(N...	Inactive(N... Tested(N=7)	Inactive(N... Tested(N=2)	
	(2E)-3-Phenylprop-2-enal	Chemical	14371-10-9	DTXSID6024834	KJPRLNW... UHFFFAOY... N	QC-Omit(N=4)	Active(N=1... Omit(N=3)... Tested(N=...	Inactive(N... Omit(N=5)... Tested(N=6)	Inactive(N... Omit(N=2)... Tested(N=...	QC-Omit(N=2)... Tested(N=2)	

Results Table



Results Table

Filtered results can be sent to other ICE TOOLS

Filterable Results

> Selected Chemical Quick Lists (2)
> Selected Assays (28)
> Chemical Identifiers Not Returned By Query (228)

Send filtered results to:

Download | Select tool... | Clear Filter | Long View | Number of chemicals = 773

View Details	Substance Name	Substance Type	CASRN (CEBS Link)	DTXSID (Dashboard Link)	QSAR Ready ID	DNA Damage Call (# Assays=4)	Oxidative Stress Call (# Assays=22)	p53 Signaling Pathway Call (# Assays=12)	Energy Metaboli... Process Call (# Assays=23)	Histone Modificat... Call (# Assays=4)	Protein Deacetyl... Call (# Assays=3)
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	(2E)-3-Phenylprop-2-enal	Chemical	14371-10-9	DTXSID6024834	KJPRLNW... UHFFFAOY... N	QC-Omit(N=4)	Active(N=1... Omit(N=3)... Tested(N=...	Inactive(N... Omit(N=5)... Tested(N=6)	Inactive(N... Omit(N=2)... Tested(N=...	QC-Omit(N=2)... Tested(N=2)	

Results Table

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Send filtered results to:

Download | Select tool... | Clear Filter | Long View | Number of chemicals = 773

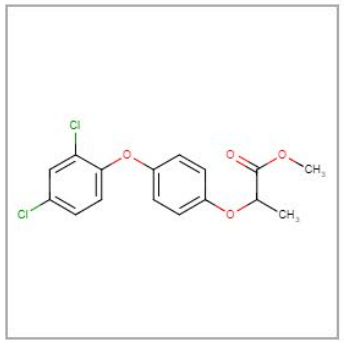
View Details	Substance Name	Substance Type	CASRN (CEBS Link)	DTXSID (Dashboard Link)	QSAR Ready ID	DNA Damage Call (# Assays=4)	Oxidative Stress Call (# Assays=22)	p53 Signaling Pathway Call (# Assays=12)	Energy Metaboli... Process Call (# Assays=23)	Histone Modificat... Call (# Assays=4)	Protein Deacetyl... Call (# Assays=3)
	(+)-Diclofop-methyl	Chemical	51338-27-3	DTXSID0032605	BACHBFV... UHFFFAOY... N	Active(N=1... Omit(N=1)	Inactive(N...	Inactive(N...	Inactive(N... Tested(N=7)	Inactive(N... Tested(N=2)	
	(2E)-3-Phenylprop-2-enal	Chemical	14371-10-9	DTXSID6024834	KJPRLNW... UHFFFAOY... N	QC-Omit(N=4)	Active(N=1... Omit(N=3)... Tested(N=...	Inactive(N... Omit(N=5)... Tested(N=6)	Inactive(N... Omit(N=2)... Tested(N=...	QC-Omit(N=2)... Tested(N=2)	

ICE Search

Results Table

(+-)-Diclofop-methyl (51338-27-3)

Substance Details | Curve Surfer



PhysChem Property	(+-)-Diclof
BP C	349.27
HL log10, atm-m3/mole	-8.04
KOA log10	9.82
LogD, pH 5.5 log10	4.71
LogD, pH 7.4 log10	4.71
LogP log10	4.71
MP C	40.10
MW g/mol	341.19
pKa, Ionizations	0.00
pKa, Acidic	NA
pKa, Basic	NA
VP log10, mmHg	-5.46
WS log10, moles/L	-5.13

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

Plot Type

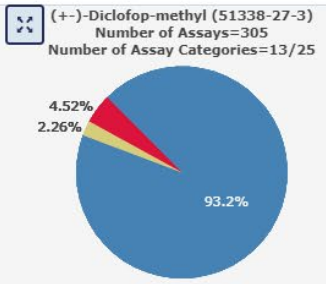
- Stacked Bar
- Pie

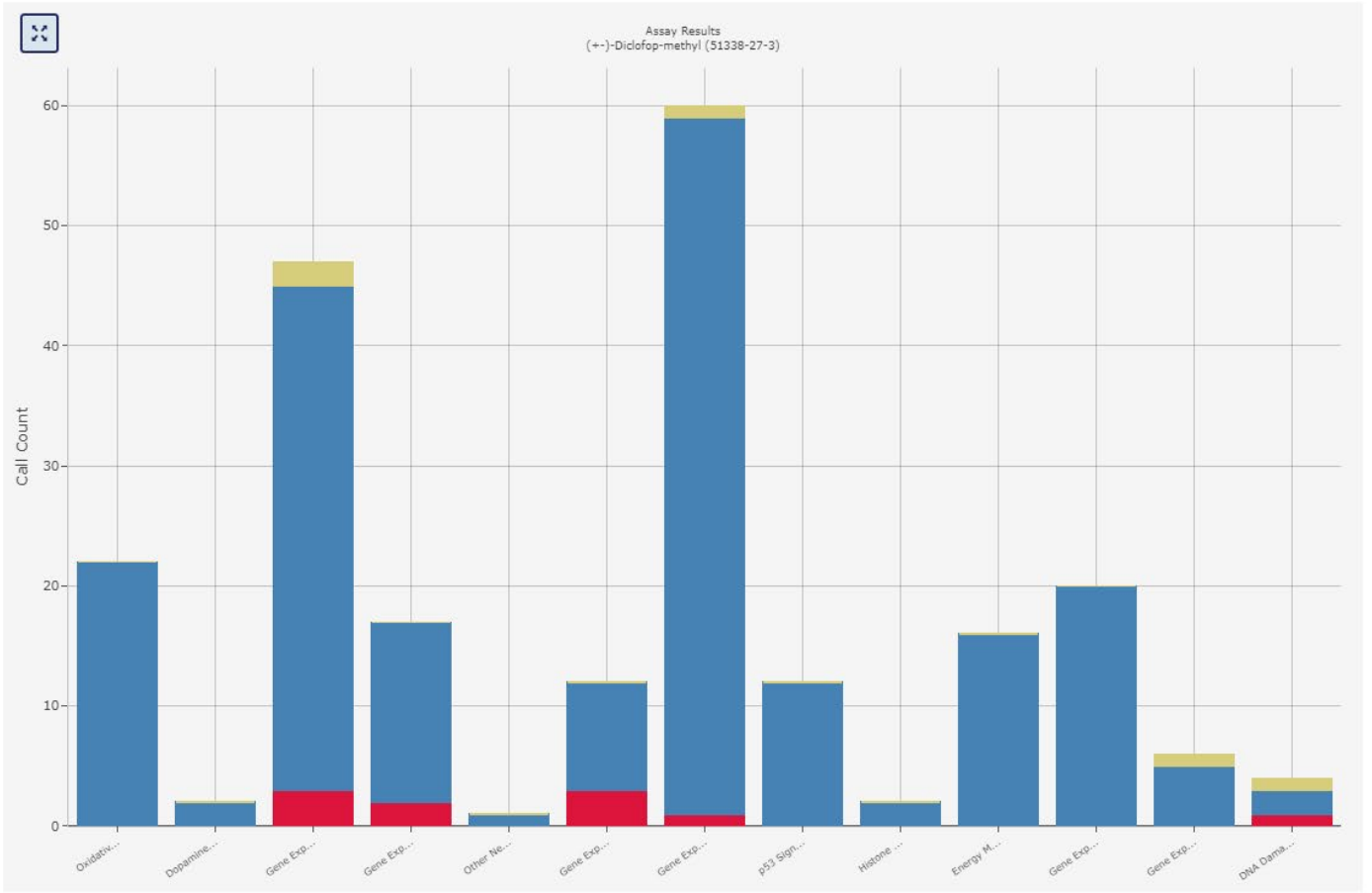
Select Assay Type(s)

In Vitro ×

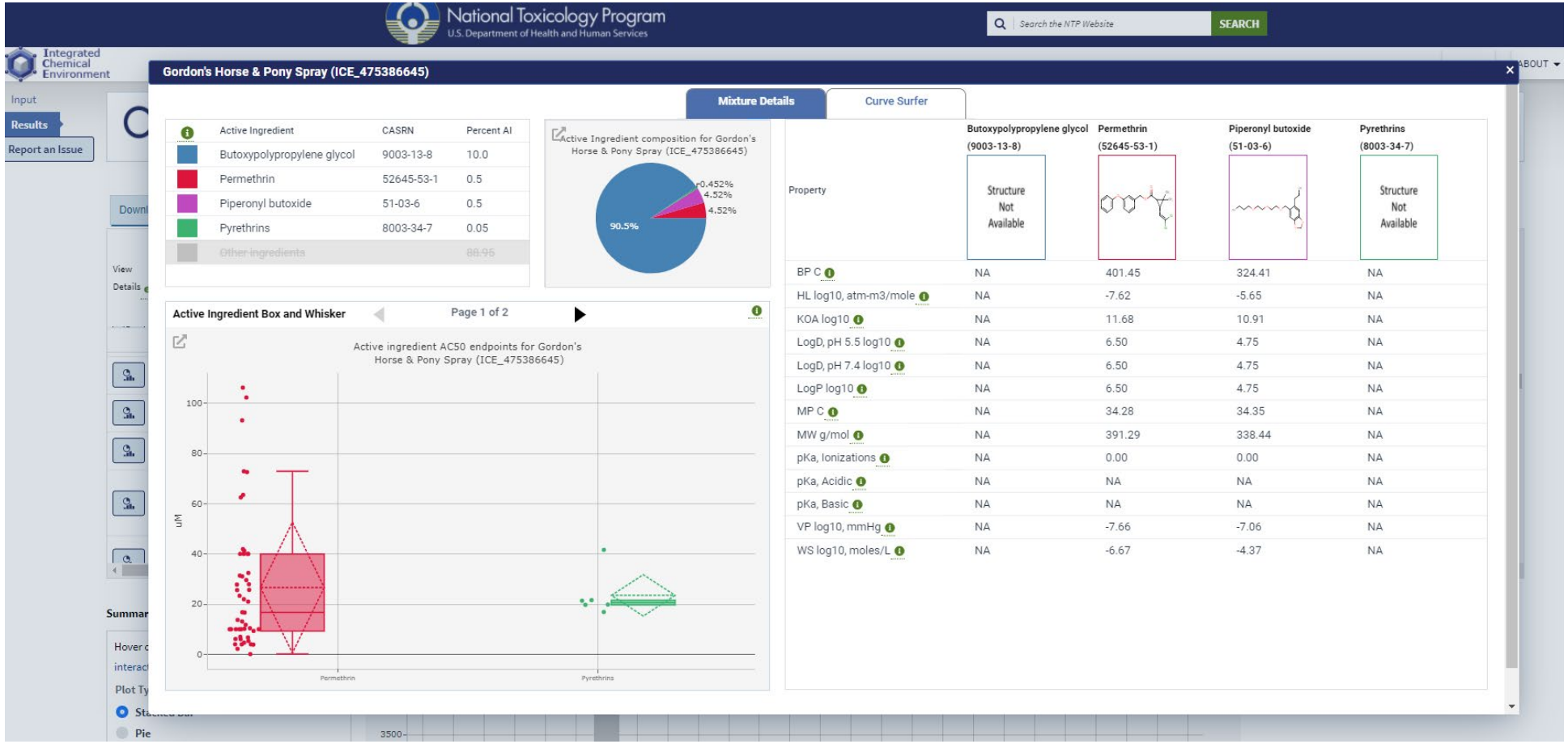
Legend

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





Search Results - Mixtures Detail



- Mixtures Detail view incorporates data from individual active ingredients including:
  - Percent composition, cHTS AC50s and phys-chem properties

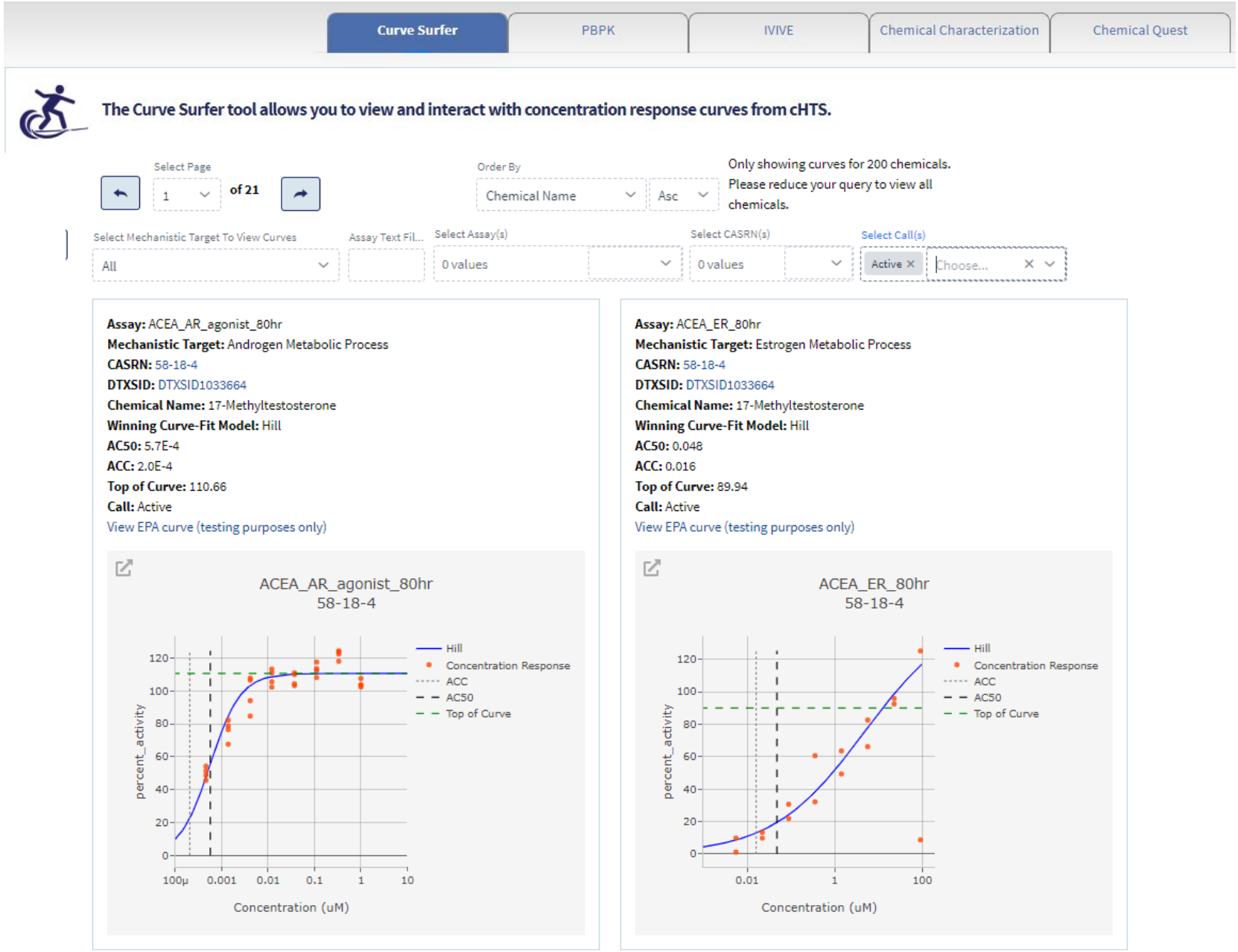
ICE Tools: Curve Surfer

Curve Surfer is an interactive concentration response visualization tool for cHTS data

- Select/filter assays based on Mechanistic Target
- View specific assays/chemicals
- Filter on activity call, AC50

- **Upcoming:** Select subset of curves to send to other tool or export to PDF.

- **In development:** Overlay multiple curves on the same plot.



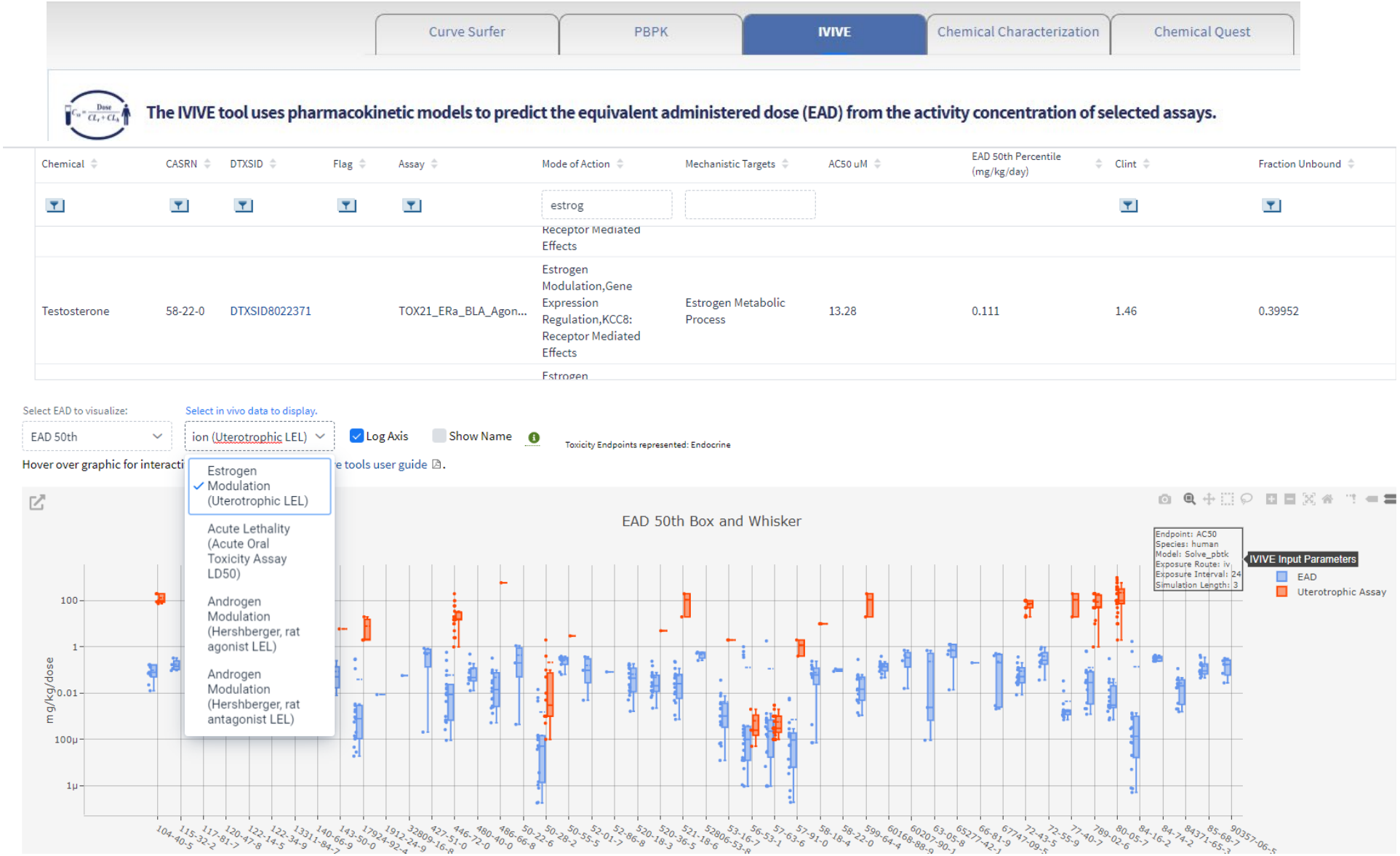
ICE Tools: PBPK

PBPK tool allows users to calculate internal chemical concentrations using PBPK models from the EPA httk R package* and in-house code

- Tissue level concentrations
- View individual chemical curves
- View overall distribution in different tissue compartments for all query chemicals

* https://www.epa.gov/chemical-research/httk-epas-tool-high-throughput-toxicokinetics

ICE Tools: IVIVE

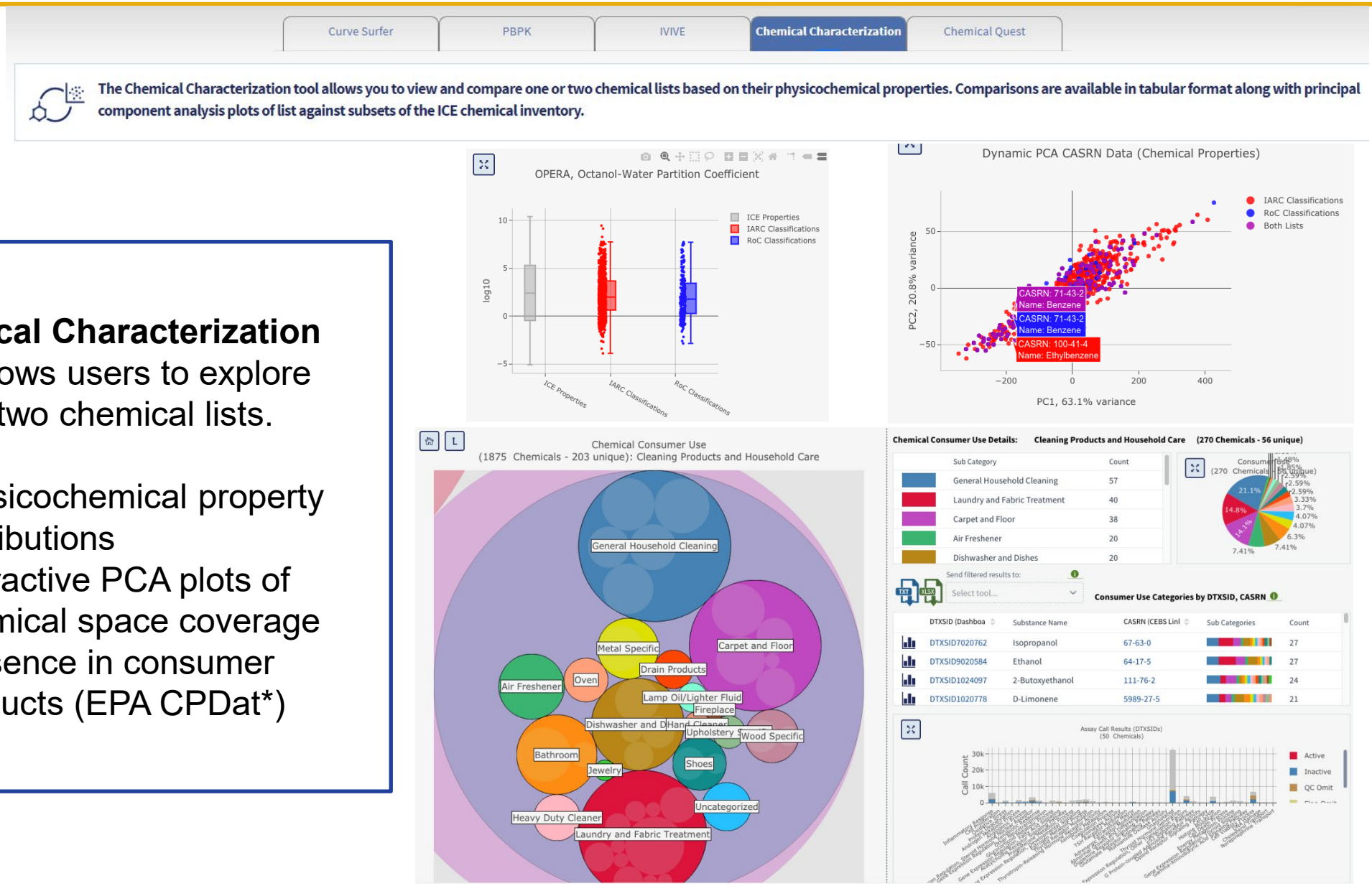


Transparency and annotation to help guide use and interpretation

ICE Tools: IVIVE

Transparency and annotation to help guide use and interpretation

ICE Tools: Chemical Characterization

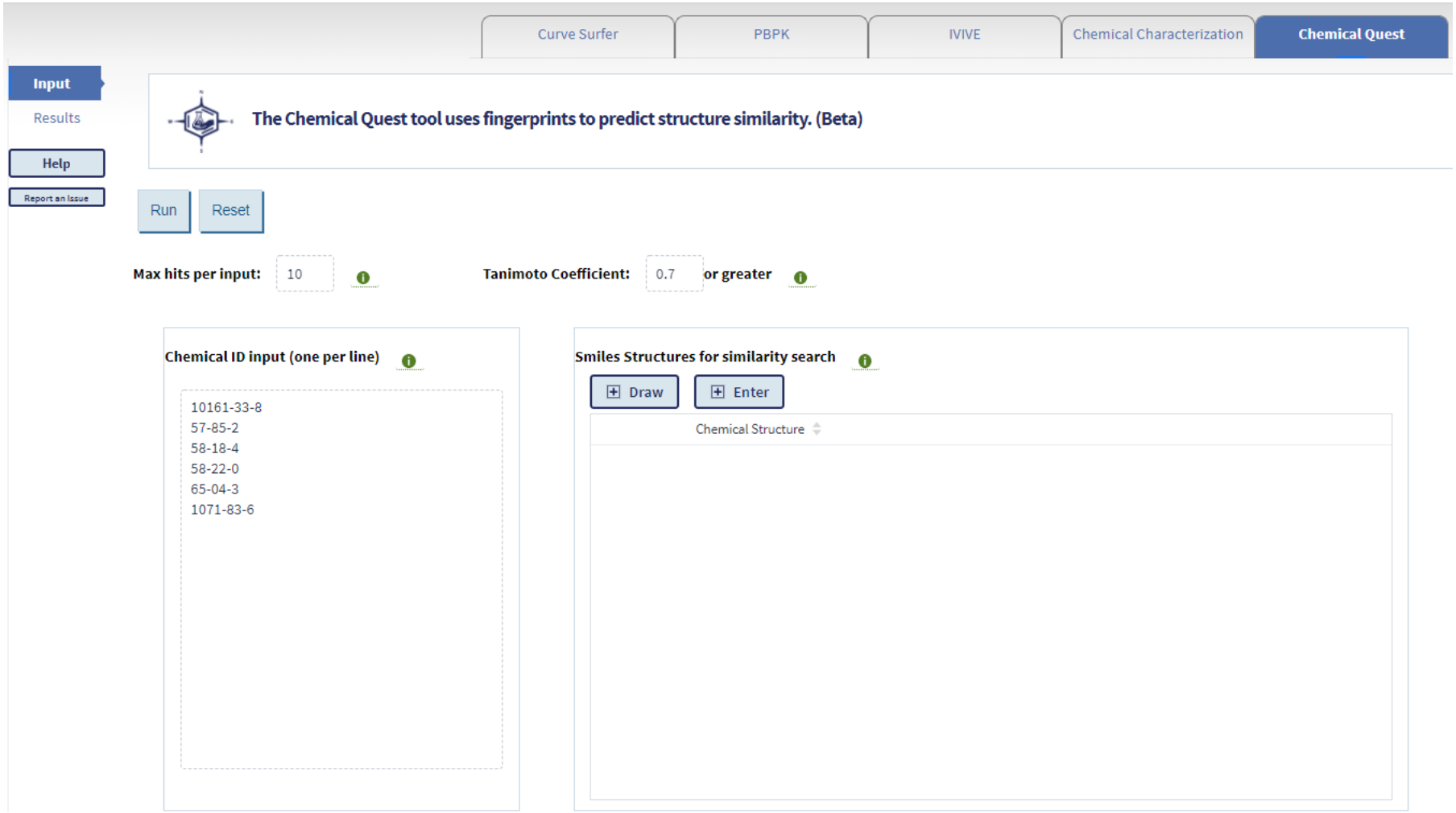


Chemical Characterization tool allows users to explore one or two chemical lists.

- Physicochemical property distributions
- Interactive PCA plots of chemical space coverage
- Presence in consumer products (EPA CPDat*)

* https://www.epa.gov/chemical-research/chemical-and-products-database-cpdat

Structure based Similarity Search

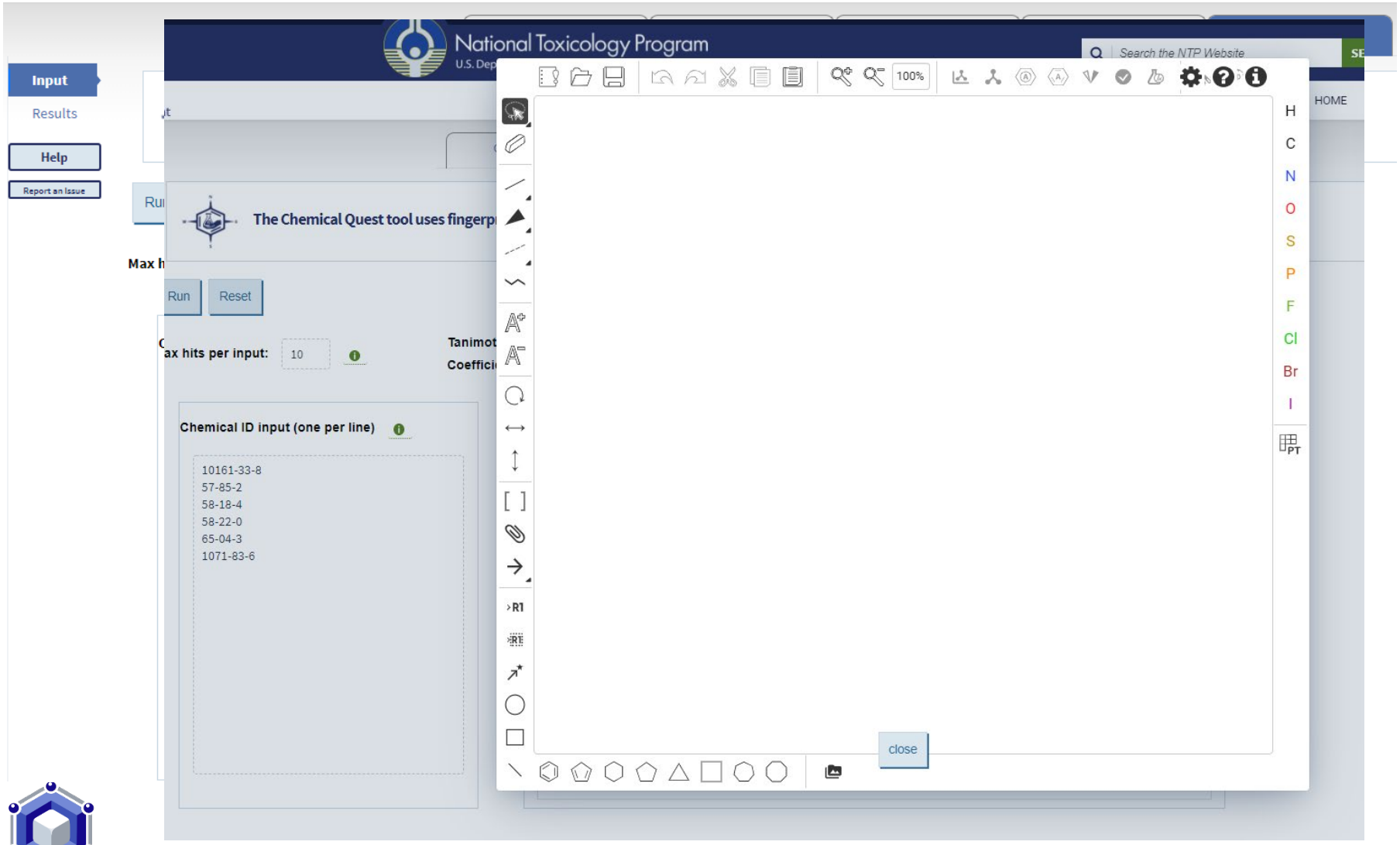


Chemical Quest tool allows users search for structurally similar chemicals.

- Users can specify CASRN, DTSXID, Inchi Key or SMILES strings as inputs
- Chemical structures can also be drawn as input

ICE Tools: Chemical Quest

Structure based Similarity Search



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- Chemical structures can also be drawn as input

ICE Tools: Chemical Quest

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

Chemical Quest Results

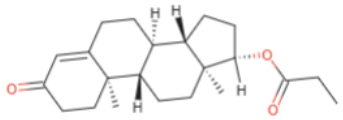
Send filtered results to:

Select tool...

Clear Filter

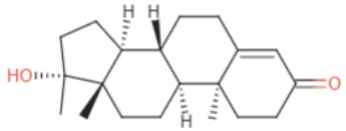
Chemical Name: Testosterone propionate
CASRN: 57-85-2
DTXSID: DTXSID9036515
Tanimoto: top 10 hits and >0.7
Hit Count: 10
Passed Filter(s): 10/10

View Results



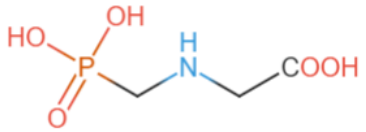
Chemical Name: 17-Methyltestosterone
CASRN: 58-18-4
DTXSID: DTXSID1033664
Tanimoto: top 10 hits and >0.7
Hit Count: 10
Passed Filter(s): 10/10

View Results



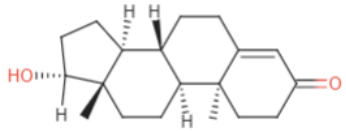
Chemical Name: Glyphosate
CASRN: 1071-83-6
DTXSID: DTXSID1024122
Tanimoto: top 10 hits and >0.7
Hit Count: 10
Passed Filter(s): 10/10

View Results



Chemical Name: Testosterone
CASRN: 58-22-0
DTXSID: DTXSID8022371
Tanimoto: top 10 hits and >0.7
Hit Count: 10
Passed Filter(s): 10/10

View Results



ICE Tools: Chemical Quest

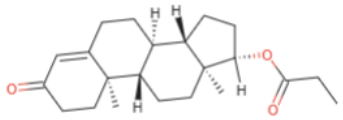
Curve Surfer | PBPK | IVIVE | Chemical Characterization | **Chemical Quest**

Chemical Quest Results

Results can be sent to other ICE tools

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

Chemical Name: Testosterone propionate
CASRN: 57-85-2
DTXSID: DTXSID9036515
Tanimoto: top 10 hits and >0.7
Hit Count: 10
Passed Filter(s): 10/10
View Results



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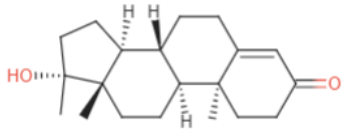

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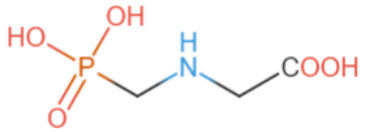
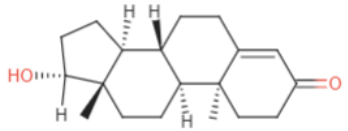
DTXSID: DTXSID1024122
Tanimoto: top 10 hits and >0.7
Hit Count: 10
Passed Filter(s): 10/10
View Results



Chemical Name: Testosterone
CASRN: 58-22-0
DTXSID: DTXSID8022371
Tanimoto: top 10 hits and >0.7
Hit Count: 10
Passed Filter(s): 10/10
View Results



ICE Tools: Chemical Quest

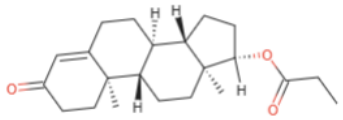
Curve Surfer | PBPK | IVIVE | Chemical Characterization | **Chemical Quest**

Chemical Quest Results

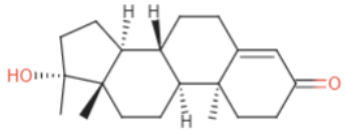
Results can be sent to other ICE tools

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

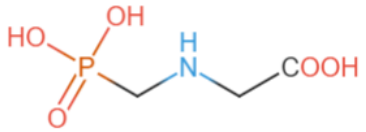
Chemical Name: Testosterone propionate
CASRN: 57-85-2
DTXSID: DTXSID9036515
Tanimoto: top 10 hits and >0.7
Hit Count: 10
Passed Filter(s): 10/10
View Results



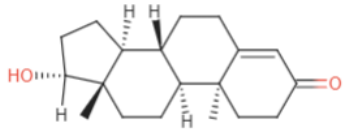
Chemical Name: 17-Methyltestosterone
CASRN: 58-18-4
DTXSID: DTXSID1033664
Tanimoto: top 10 hits and >0.7
Hit Count: 10
Passed Filter(s): 10/10
View Results



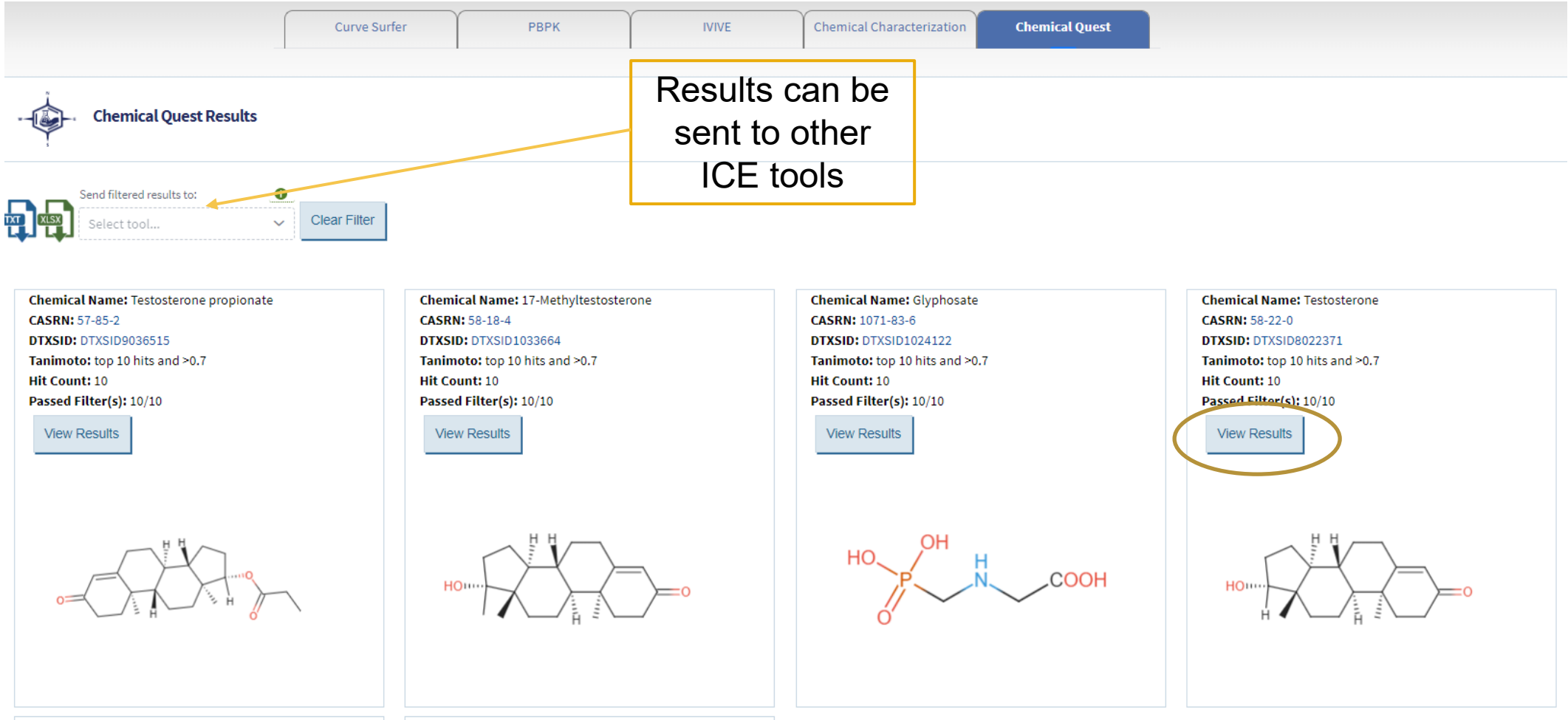
Chemical Name: Glyphosate
CASRN: 1071-83-6
DTXSID: DTXSID1024122
Tanimoto: top 10 hits and >0.7
Hit Count: 10
Passed Filter(s): 10/10
View Results



Chemical Name: Testosterone
CASRN: 58-22-0
DTXSID: DTXSID8022371
Tanimoto: top 10 hits and >0.7
Hit Count: 10
Passed Filter(s): 10/10
View Results



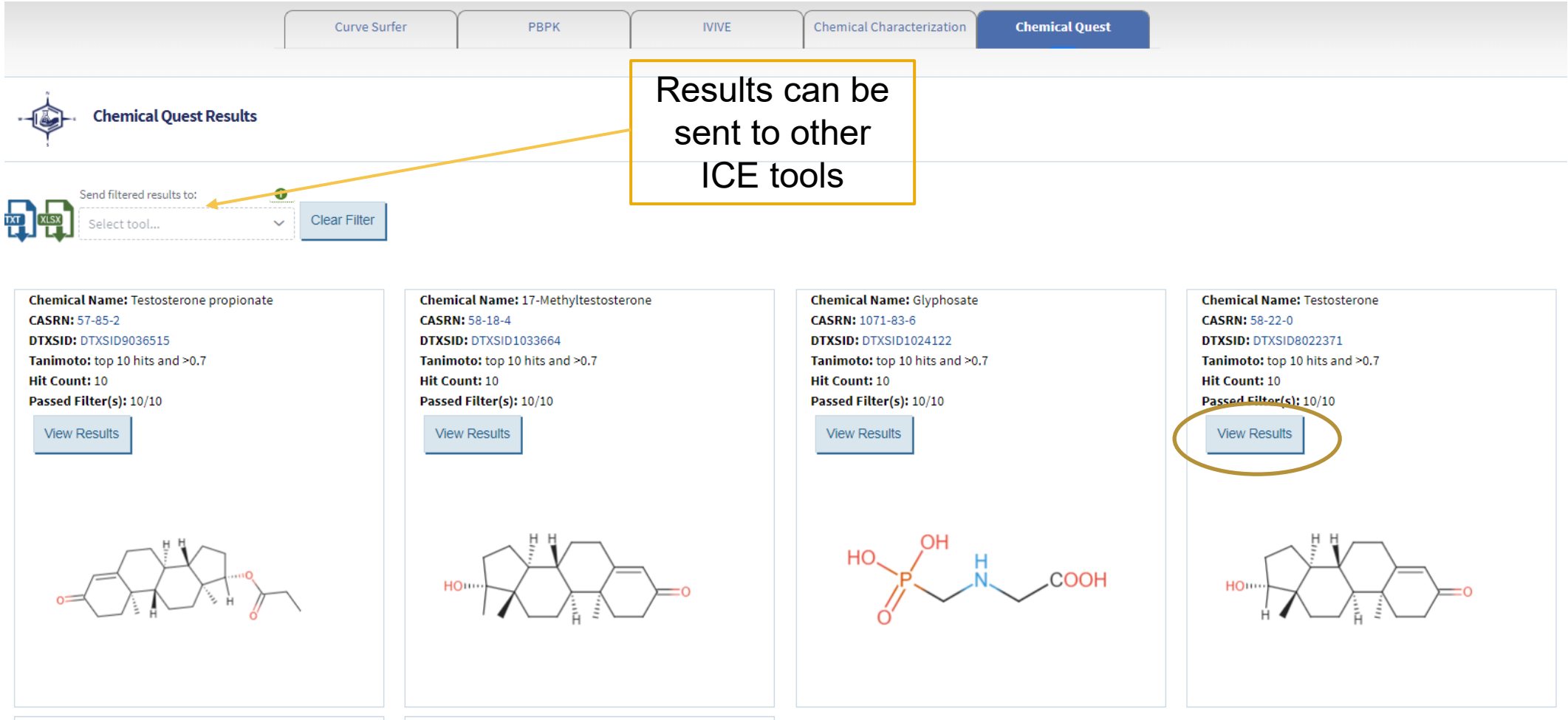
ICE Tools: Chemical Quest



Results can be sent to other ICE tools

Results page displays the chemical identification information for each source chemical input, as well as the number of hits and Tanimoto score stringency selected

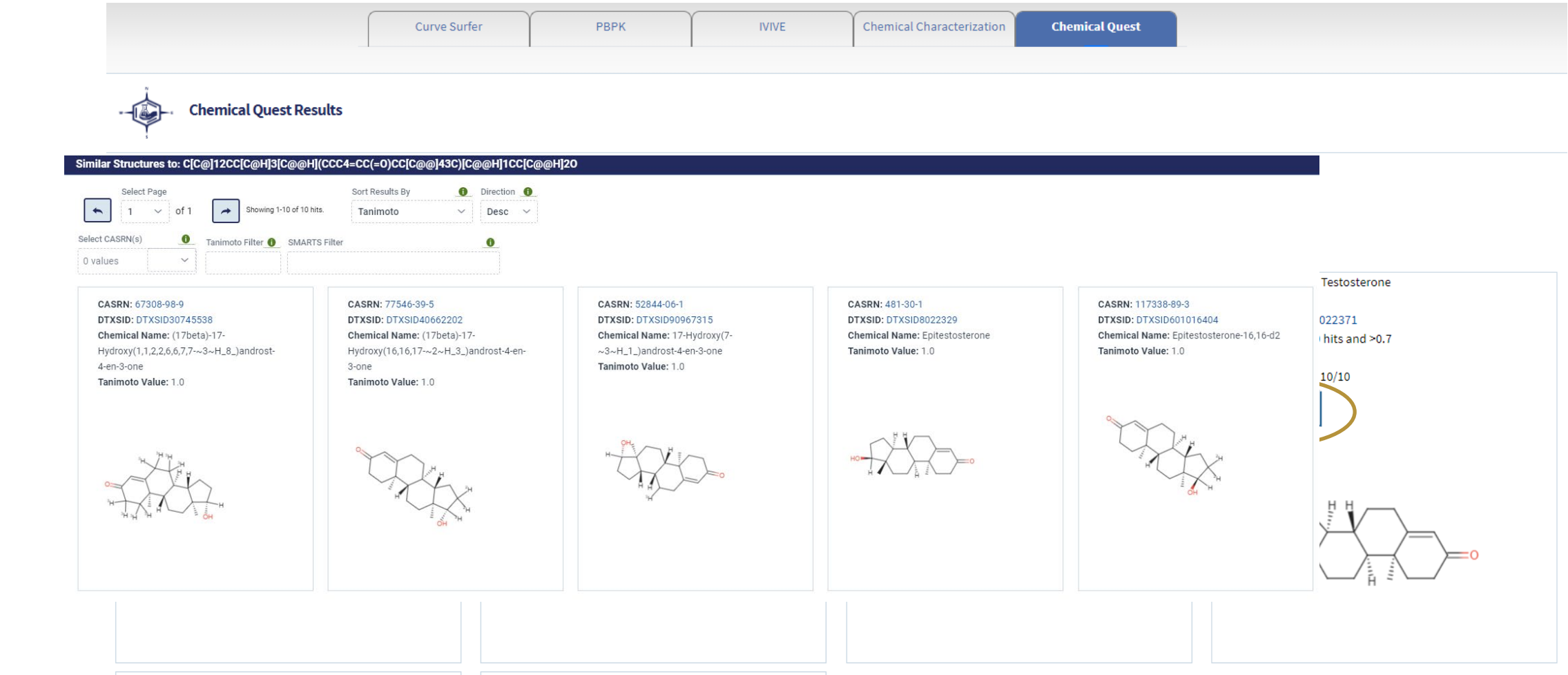
ICE Tools: Chemical Quest



Results can be sent to other ICE tools

View results button opens new window displaying similar chemicals

ICE Tools: Chemical Quest



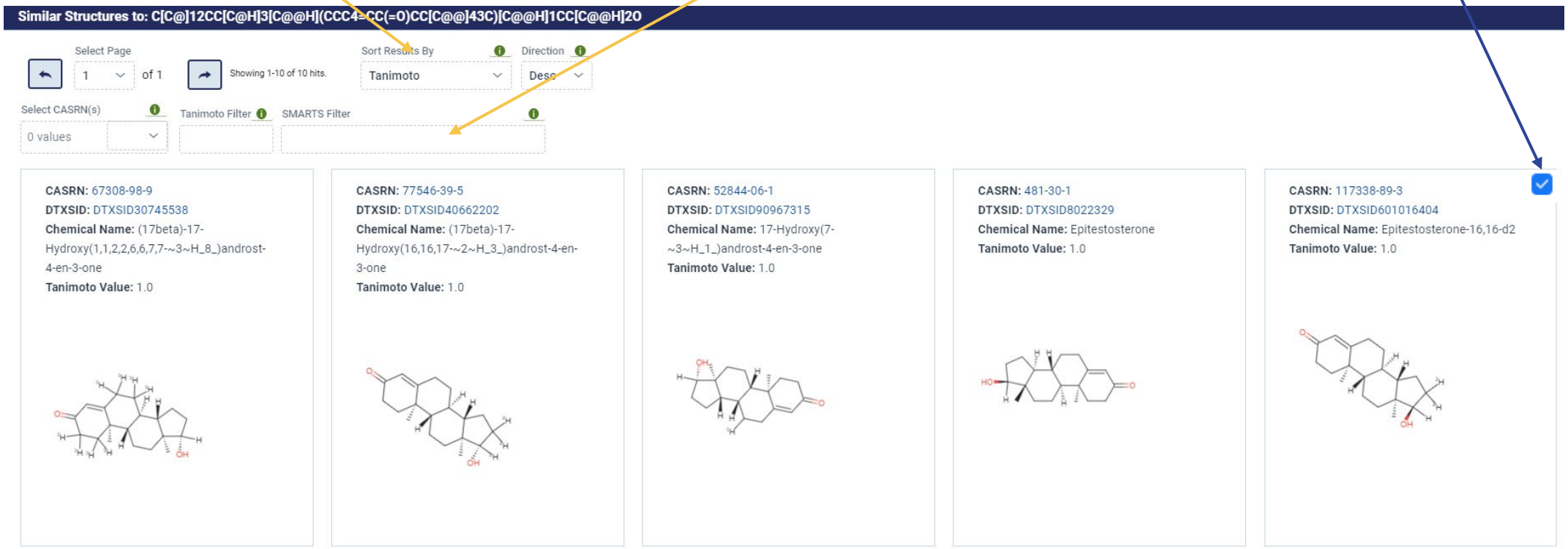
View results button opens new window displaying similar chemicals

ICE Tools: Chemical Quest

Results are sortable and filterable

SMARTS strings can be used to filter results based on chemical substructures

Upcoming: Users can select individual results to send to other tools.



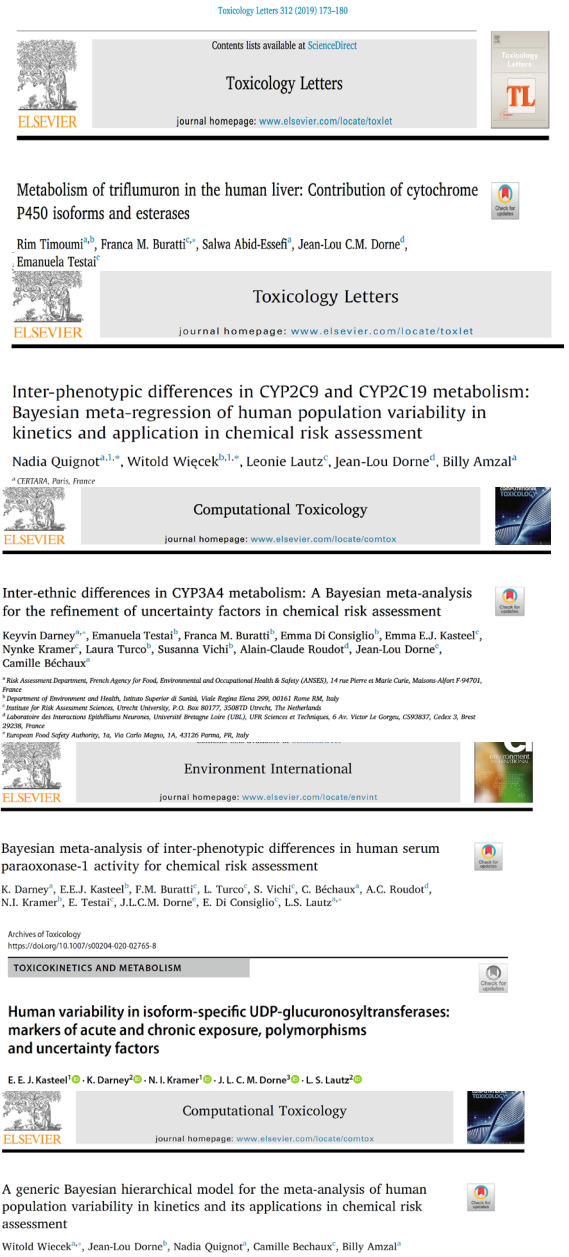
ICE Improvements motivated by SACATM Feedback

- Increased usability for non-subject matter experts
  - Ongoing: developing help videos, user guides and UI / visualization updates
- Increased technical documentation
  - Ongoing: data set harmonization, annotation and expansion of metadata
- Expanding connections with other resurces
  - Complete: DTXSID and CASRN link out to EPA Dashboard and CEBS from all pages
  - Planning: API for access to ICE data, API connection with CEBS
- Increase structure-based methods
  - Complete: Chemical Quest Tool for structure-based similarity searching
  - Ongoing: Implementing similarity searching for additional descriptor libraries

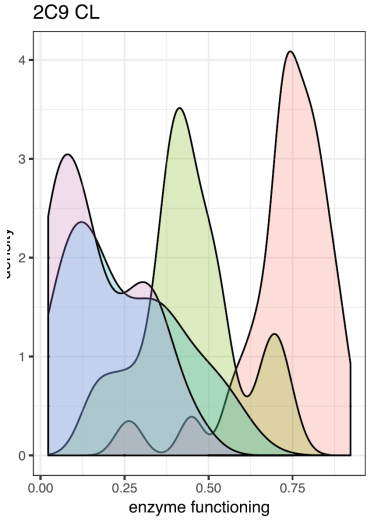
ICE: Future Plans

- Upcoming features in ICE 3.5 Release (early October 2021):
  - Inclusion of Saagar features for similarity searching in Chemical Quest Tool (*Sedykh et al. 2021 Chem Res Tox)*
  - Ability to select subsets of chemicals to send to other assays in Curve Surfer and Chemical Quest Tools
  - AC50 detail view plots on cHTS summary charts and additional data download options included on plots
  - Help videos: https://ice.ntp.niehs.nih.gov/test/Search
- In Development:
  - Further refinement of assay annotations, additional data sets
  - Inclusion of additional search and filtering capabilities, further roll out of help videos
  - Additional visualization tools and new visualizations for various data types
  - Incorporating population variability in metabolic enzymes in ICE PBPK workflows

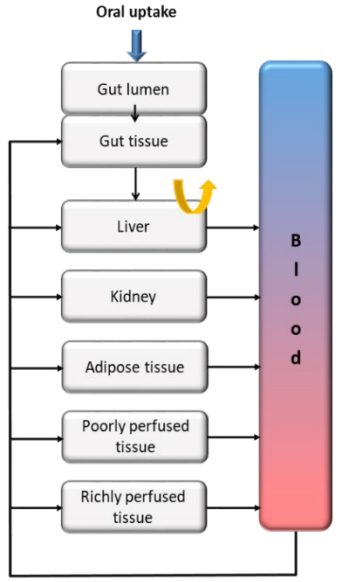
Connecting Metabolism and Variability in Humans: Toxicokinetics

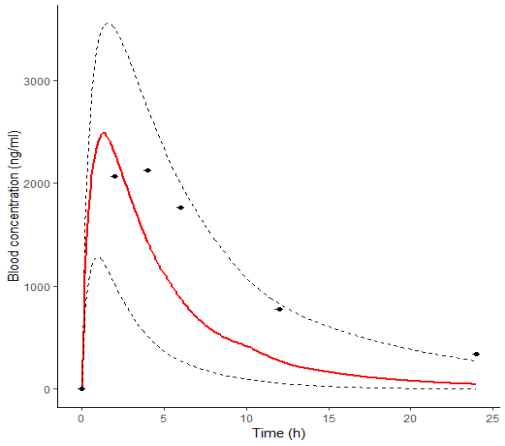


Covering Phase I CYP450 and Phase II UGTs enzymes



PBPK models + virtual population



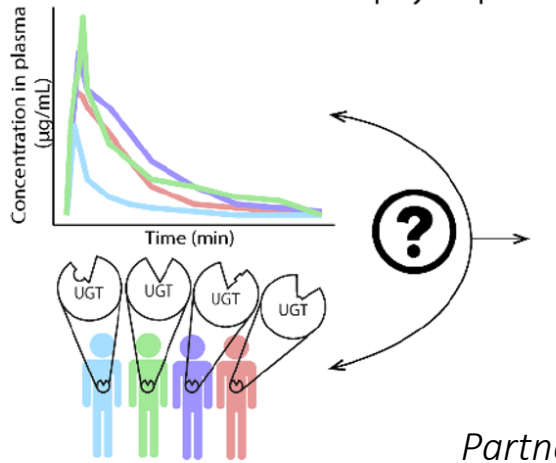


https://ice.ntp.niehs.nih.gov/

Pharmacokinetic data on compounds metabolised by UGT isoforms is collected and summarised in a database

Data on polymorphism frequencies in different populations is collected and summarised

Interindividual differences in kinetics and polymorphisms



UGT-related uncertainty factors

Partnership with:

efsa
European Food Safety Authority

Acknowledgments: The NICEATM Group

Acknowledgments: The NICEATM Group


thank you
danke
рахмат
謝謝
ngiyabonga
شكراً جزيلاً
teşekkür ederim
Баярлалаа
спасибо
faafetai lava
mersi
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welalin
tack
spas
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misaotra
matondo
gracias
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tapadh leat
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তোমাকে ধন্যবাদ
감사합니다
xièxie
merci

Questions?