

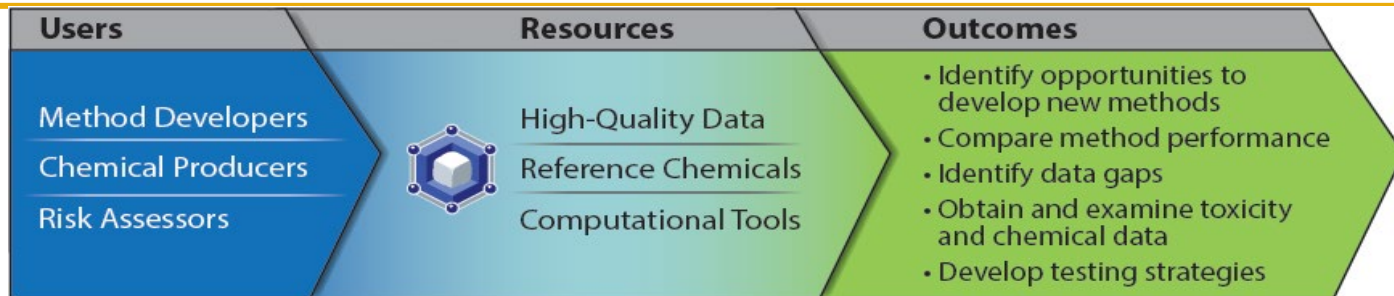
# Update on NICEATM Computational Resources

SACATM  
September 28-29, 2021

Nicole Kleinstreuer  
Acting NICEATM Director



# Integrated Chemical Environment: ICEv3.4



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

**News & Events**  
**ICE v3.4 Release**  
**ICE updates include:**  
 New tools and expanded capabilities:  
 Chemical Quest (Beta)  
 Drawing of 2D structures  
 Query by multiple chemical identifiers  
 Send Assays to other ICE tools

**Learn about ICE updates**

**ICE provides data to support development of new approaches for chemical safety testing.**  
 Click here to learn more about ICE!

Contents lists available at [ScienceDirect](#)  
**Computational Toxicology**  
 journal homepage: [www.sciencedirect.com/journal/computational-toxicology](http://www.sciencedirect.com/journal/computational-toxicology)

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

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

<sup>a</sup> Integrated Laboratory Systems LLC, P.O. Box 13501, Research Triangle Park, NC 27709, USA  
<sup>b</sup> National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods, National Institute of Environmental Health Sciences, P.O. Box 12233, MD K2-17, Research Triangle Park, NC 27709, USA  
<sup>c</sup> Scione LLC, 2 Davis Dr., Research Triangle Park, NC 27709, USA  
<sup>d</sup> Division of the National Toxicology Program, National Institute of Environmental Health Sciences, P.O. Box 12233, MD K2-16, Research Triangle Park, NC 27709, USA

**ARTICLE INFO**      **ABSTRACT**

**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.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

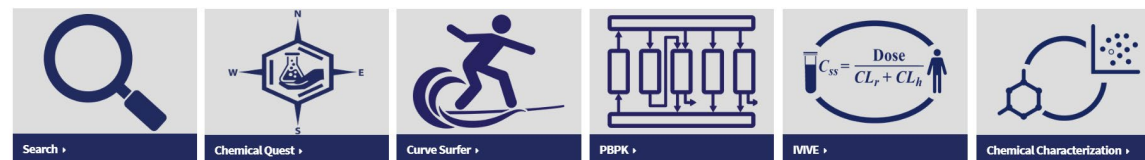
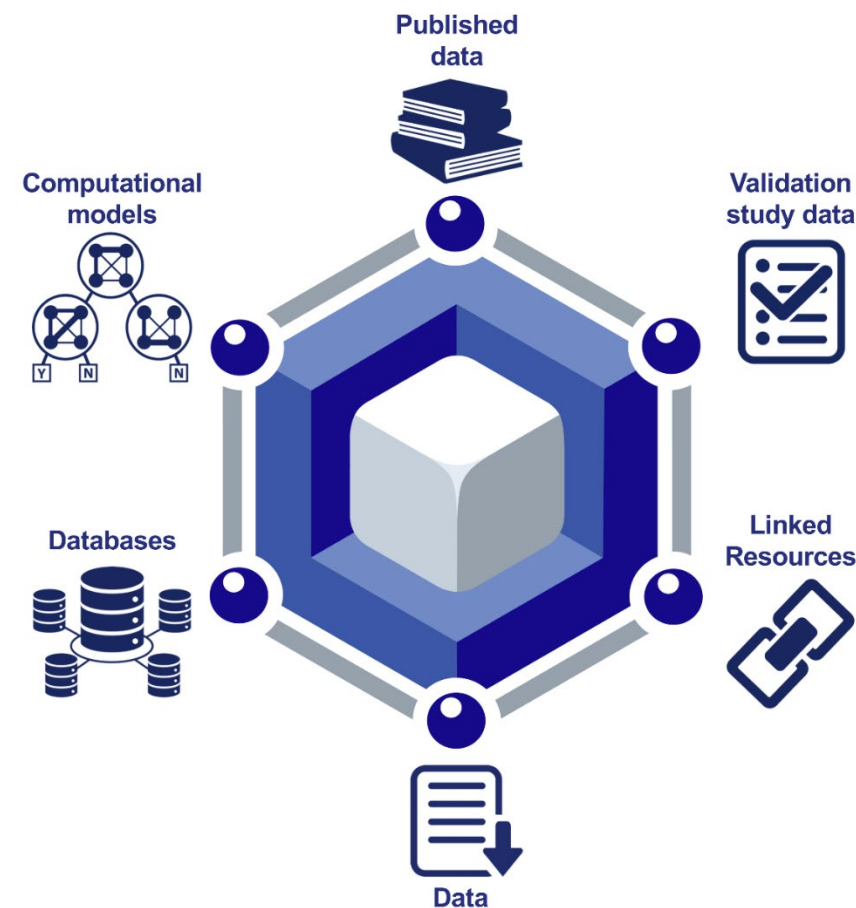
<https://ice.ntp.nih.gov/>

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





- 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

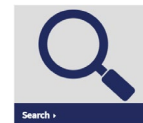




# In Silico Models in ICE

Endpoint	Model	# of chemicals*
Physicochemical Properties	OPEn (q)saR App (OPERA) <i>Mansouri et al. J Cheminform 2018</i>	800,000+
Acute Oral Toxicity	Collaborative Acute Toxicity Modeling Suite (CATMoS) - Rat acute oral toxicity. <i>Mansouri et al. EHP 2021</i>	800,000+
Endocrine	Estrogen Receptor pathway Model. <i>Browne et al. ES&amp;T 2015</i>	1812
	Androgen Receptor Pathway Model. <i>Kleinstreuer et al. Chem Res Tox 2017</i>	1855
	Collaborative Estrogen Receptor Activity Prediction Project (CERAPP). <i>Mansouri et al. EHP 2016</i>	800,000+
	Collaborative Modeling Project for Androgen Receptor Activity (COMAPRA). <i>Mansouri et al. EHP 2020</i>	800,000+





## Overview



Search ▶



### Input

Results

Help

Report an Issue



The Search tool allows you to query ICE data (chemicals and mixtures) using predefined or user-defined chemical lists and assays from dozens of categories.

Run

Reset

Scope of Search

Union

#### Chemical Input

Select Chemicals

Quick List CASRNs

User Chemical Identifiers

#### Assay Input

Select Assays

Assay

Description

Assay Type

- 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.



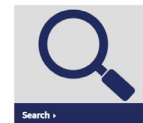


## Chemical Selection and Quick Lists

The screenshot displays the National Toxicology Program's Integrated Chemical Environment (ICE) search interface. A modal dialog box titled "Select one or more chemical quick lists" is open, allowing users to choose from a list of predefined chemical sets. The list includes various toxicity endpoints and classifications, with "AR In Vivo Antagonist" and "Genotoxicity (R)" currently selected. The background interface shows the "Chemical Input" section with options for "Quick List CASRNs" and "User CASRNs".

- 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.





# Curation to assist meaningful assay selection and model building

Select Assays 1 x

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

Assay	Biological Process	Assay Type
<input type="checkbox"/> <span>1</span> cHTS		
<input type="checkbox"/> <span>1</span>	Abnormal Growth and Differentiation	in vitro
<input type="checkbox"/> <span>1</span>	Angiogenic Process	in vitro
<input type="checkbox"/> <span>1</span>	> Cellular Processes	
<input type="checkbox"/> <span>1</span>	> Cellular Stress Response	
<input type="checkbox"/> <span>1</span>	> Endocrine-Related Processes	in vitro
<input type="checkbox"/> <span>1</span>	Energy Metabolism Process	in vitro
<input type="checkbox"/> <span>1</span>	> Epigenetic Process	in vitro
<input type="checkbox"/> <span>1</span>	> Gene Expression	in vitro
<input type="checkbox"/> <span>1</span>	> Immune and Inflammatory Response	in vitro
<input type="checkbox"/> <span>1</span>	> Neuronal Transmission	
<input type="checkbox"/> <span>1</span>	Xenobiotic Metabolism	in vitro
<input type="checkbox"/> <span>1</span>	Unannotated	in vitro

Finished

- 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.







**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

The screenshot displays the ICE Search interface. At the top, it shows the 'Integrated Chemical Environment' logo and the 'U.S. Department of Health and Human Services' header. The main section is titled 'Search Results' and includes a search bar, a 'Results' tab, and a 'Help' button. Below this, there are filters for 'Selected Chemical Quick Lists (2)', 'Selected Assays (28)', and 'Chemical Identifiers Not Returned By Query (228)'. A 'Download' button and a 'Send filtered results to:' dropdown are also present. The 'Number of chemicals = 773' is displayed. The main table shows columns for 'Substance Name', 'Substance Type', 'CASRN (CEBS Link)', 'DTXSID (Dashboard Link)', and various assay categories like 'QAR Ready ID', 'DNA Damage Cell Assay', 'Oxidative Stress Cell Assay', etc. Two rows are visible, showing chemical details and assay results.

The 'Summary Data' section includes a 'Hover over graphic for interactive tools. View interactive tools user guide.' link. It features a 'Plot Type' selector with 'Stacked Bar' selected and 'Pie' as an option. A 'Select Assay Type(s)' dropdown is set to 'In Vitro'. A legend identifies the categories: Active (red), Inactive (blue), QC-omit (orange), Flag-omit (yellow), and Not tested (grey). A pie chart shows the distribution of all query data: 74% Inactive, 14.5% Active, 9.6% QC-omit, and 1.88% Flag-omit. The total number of calls is 227,963 and the number of assay categories is 25.

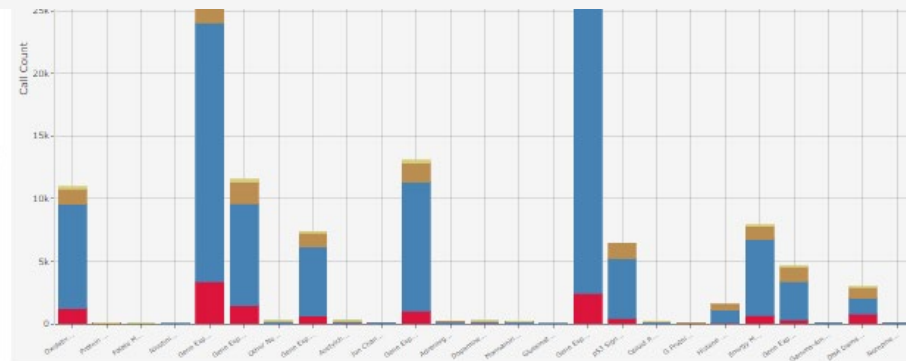
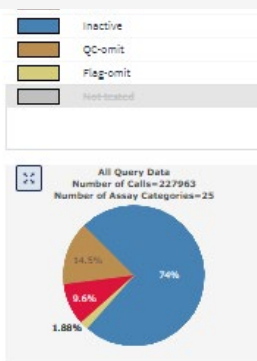
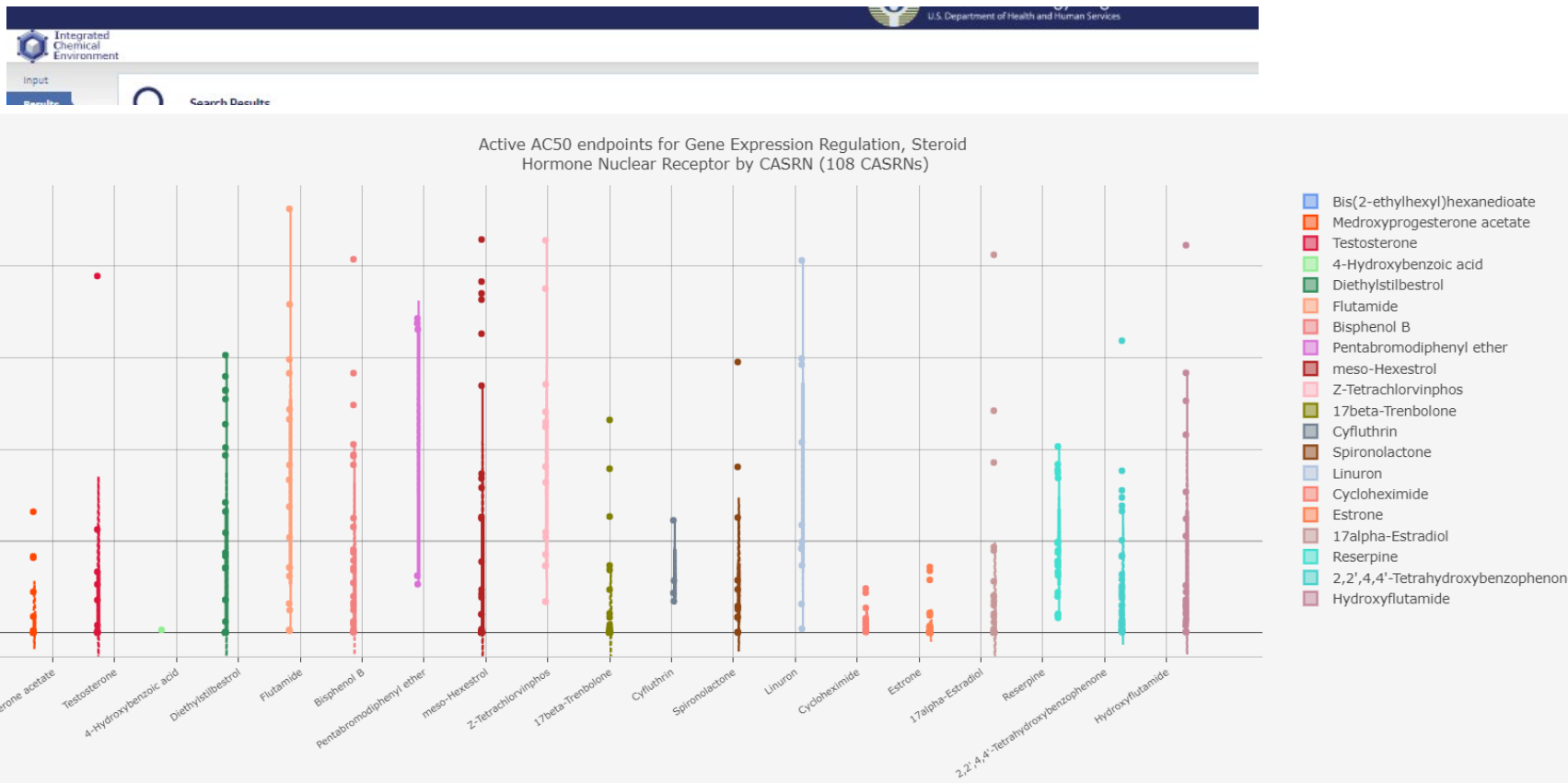
The 'Assay Results (All CASRN)' bar chart shows the call count for various assays. The y-axis is 'Call Count' ranging from 0 to 40k. The x-axis lists assays such as 'Oxidative Stress Cell Assay', 'DNA Damage Cell Assay', 'Oxidative Stress Cell Assay', 'p38 Signaling Pathway Cell Assay', 'Energy Metabolism Process Cell Assay', 'Histone Modification Cell Assay', 'Protein Disassembly Cell Assay', and 'Folate Metabolism Cell Assay'. The 'Oxidative Stress Cell Assay' shows the highest call count, exceeding 35k.





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

- Interactive visualization provides graphic overview of summary level bioactivity data.
- **Upcoming:** Detail of AC50s of active chemicals in each category available by clicking bars in plot





## 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 Metabolism Process Call (# Assays=23)	Histone Modification Call (# Assays=4)	Protein Deacetylation 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)	





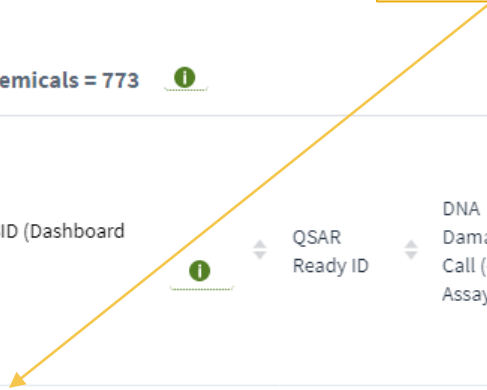
## Results Table

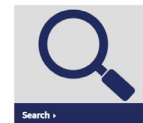
- > Selected Chemical Quick Lists (2)
- > Selected Assays (28)
- > Chemical Identifiers Not Returned By Query (228)

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)	

Filterable Results





## Results Table

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

Filtered results can be sent to other ICE TOOLS

Filterable Results

Send filtered results to:     **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

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

Filtered results can be sent to other ICE TOOLS

Filterable Results

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)	





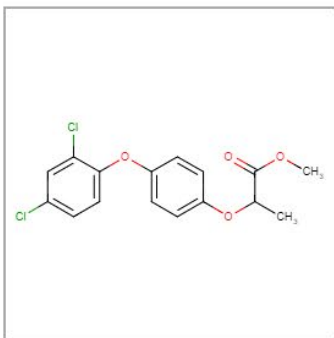
## Results Table

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

- > Select
- > Select
- > Chemi

Downlo

View  
Details



PhysChem Property	(+)-Diclofop-methyl
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

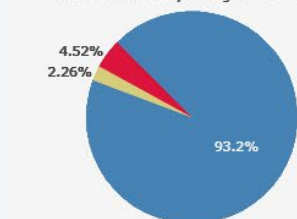
Select Assay Type(s)

In Vitro x + x v

Legend

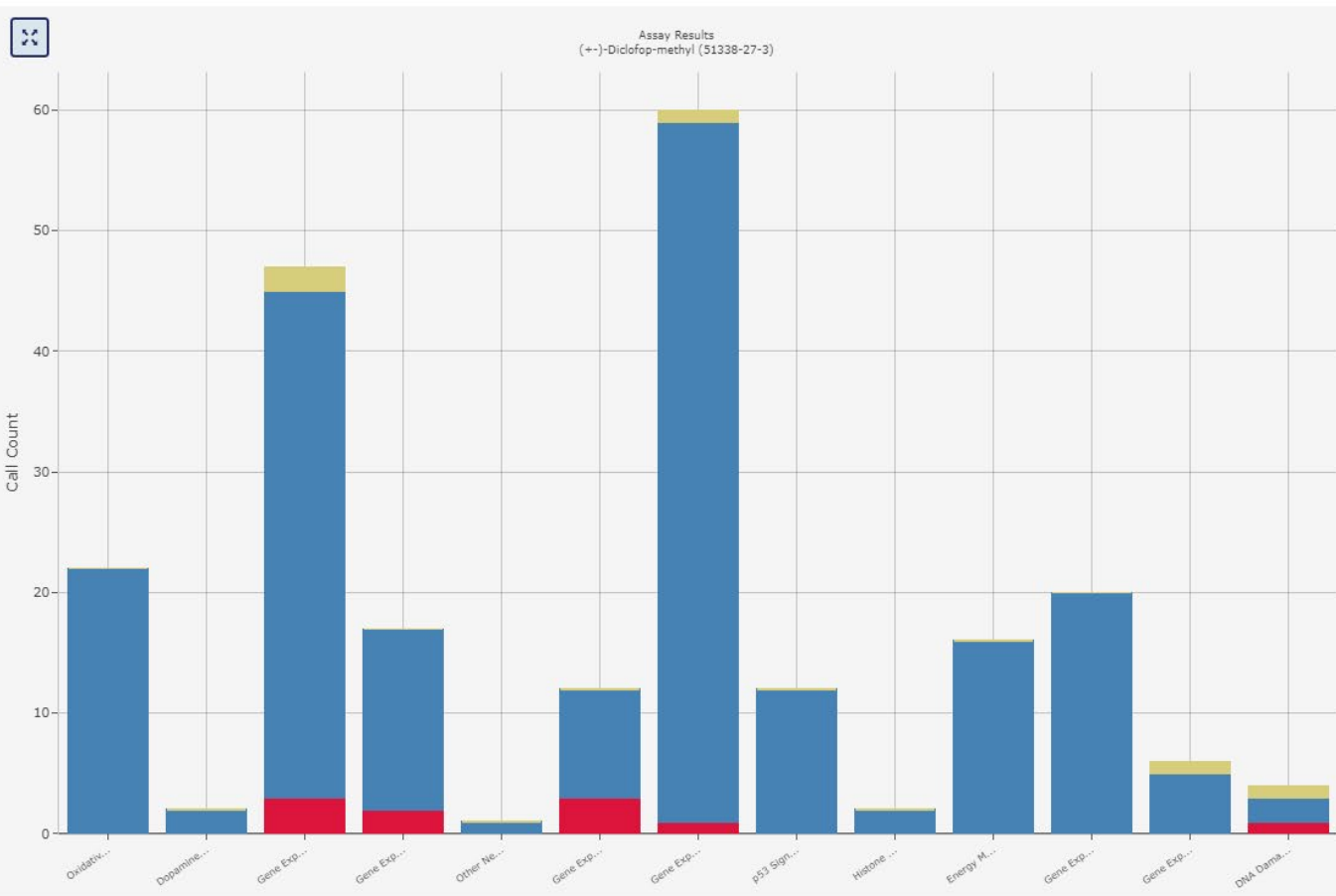
- Active
- Inactive
- QC-omit
- Flag-omit
- Not-tested

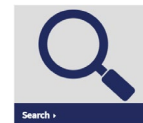
(+)-Diclofop-methyl (51338-27-3)  
Number of Assays=305  
Number of Assay Categories=13/25



Substance Details

Curve Surfer





## Search Results - Mixtures Detail

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

Integrated Chemical Environment

Search the NTP Website

### Gordon's Horse & Pony Spray (ICE\_475386645)

Mixture Details

Active Ingredient	CASRN	Percent AI
Butoxypolypropylene glycol	9003-13-8	10.0
Permethrin	52645-53-1	0.5
Piperonyl butoxide	51-03-6	0.5
Pyrethrins	8003-34-7	0.05
Other ingredients		88.95

Active Ingredient composition for Gordon's Horse & Pony Spray (ICE\_475386645)

Active Ingredient Box and Whisker

Active ingredient AC50 endpoints for Gordon's Horse & Pony Spray (ICE\_475386645)

Property	Butoxypolypropylene glycol (9003-13-8)	Permethrin (52645-53-1)	Piperonyl butoxide (51-03-6)	Pyrethrins (8003-34-7)
BP C	NA	401.45	324.41	NA
HL log10, atm-m3/mole	NA	-7.62	-5.65	NA
KOA log10	NA	11.68	10.91	NA
LogD, pH 5.5 log10	NA	6.50	4.75	NA
LogD, pH 7.4 log10	NA	6.50	4.75	NA
LogP log10	NA	6.50	4.75	NA
MP C	NA	34.28	34.35	NA
MW g/mol	NA	391.29	338.44	NA
pKa, Ionizations	NA	0.00	0.00	NA
pKa, Acidic	NA	NA	NA	NA
pKa, Basic	NA	NA	NA	NA
VP log10, mmHg	NA	-7.66	-7.06	NA
WS log10, moles/L	NA	-6.67	-4.37	NA

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





**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.

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

Select Page: 1 of 21

Order By: Chemical Name, Asc

Only showing curves for 200 chemicals. Please reduce your query to view all chemicals.

Select Mechanistic Target To View Curves: All

Assay Text Fil...:

Select Assay(s): 0 values

Select CASRN(s): 0 values

Select Call(s): Active

**Assay: ACEA\_AR\_agonist\_80hr**  
Mechanistic Target: Androgen Metabolic Process  
CASRN: 58-18-4  
DTXSID: DTXSID1033664  
Chemical Name: 17-Methyltestosterone  
Winning Curve-Fit Model: Hill  
AC50: 5.7E-4  
ACC: 2.0E-4  
Top of Curve: 110.66  
Call: Active  
View EPA curve (testing purposes only)

**Assay: ACEA\_ER\_80hr**  
Mechanistic Target: Estrogen Metabolic Process  
CASRN: 58-18-4  
DTXSID: DTXSID1033664  
Chemical Name: 17-Methyltestosterone  
Winning Curve-Fit Model: Hill  
AC50: 0.048  
ACC: 0.016  
Top of Curve: 89.94  
Call: Active  
View EPA curve (testing purposes only)

ACEA\_AR\_agonist\_80hr  
58-18-4

percent\_activity

Concentration (uM)

ACEA\_ER\_80hr  
58-18-4

percent\_activity

Concentration (uM)





Curve Surfer

**PBPK**

IVIVE

Chemical Characterization

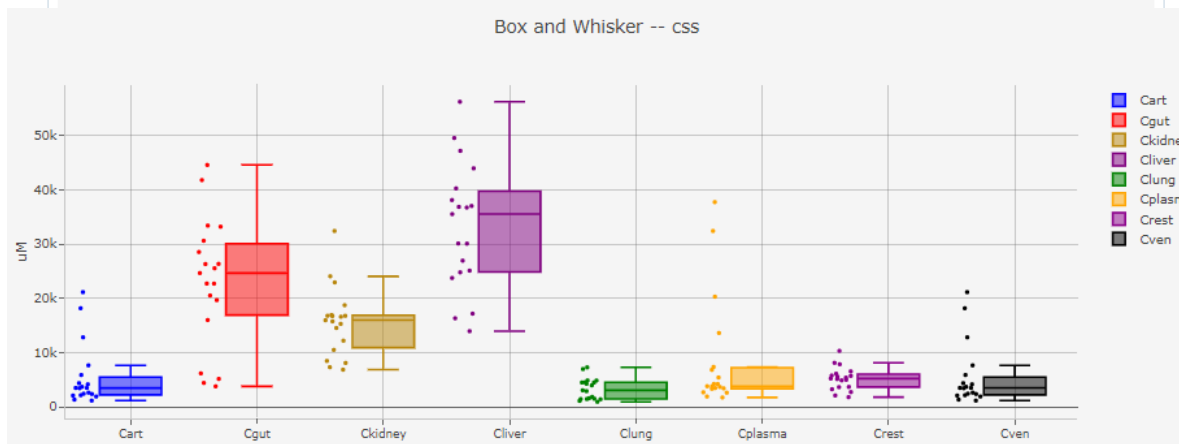
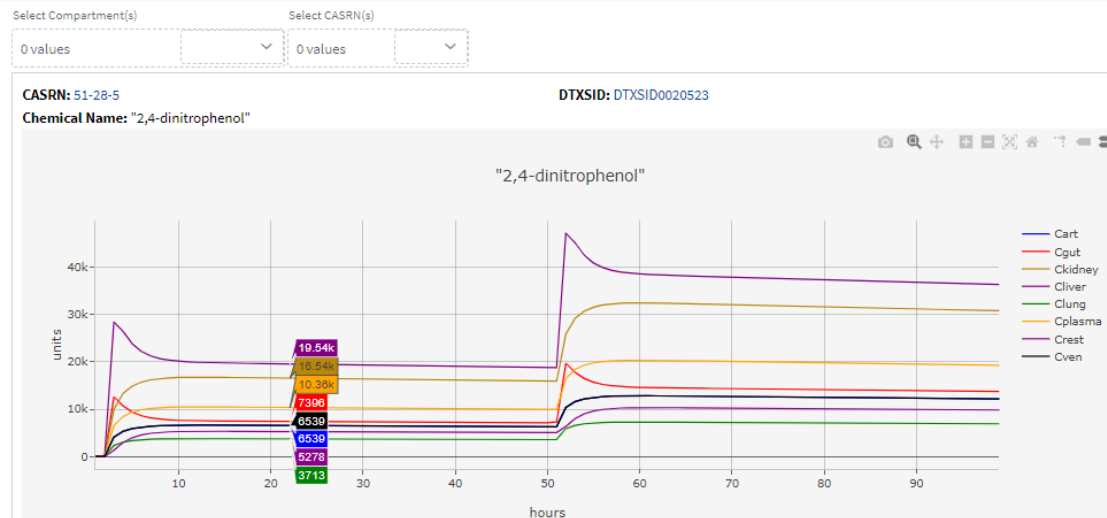
Chemical Quest



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

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

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



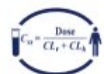
\* <https://www.epa.gov/chemical-research/htk-epas-tool-high-throughput-toxicokinetics>







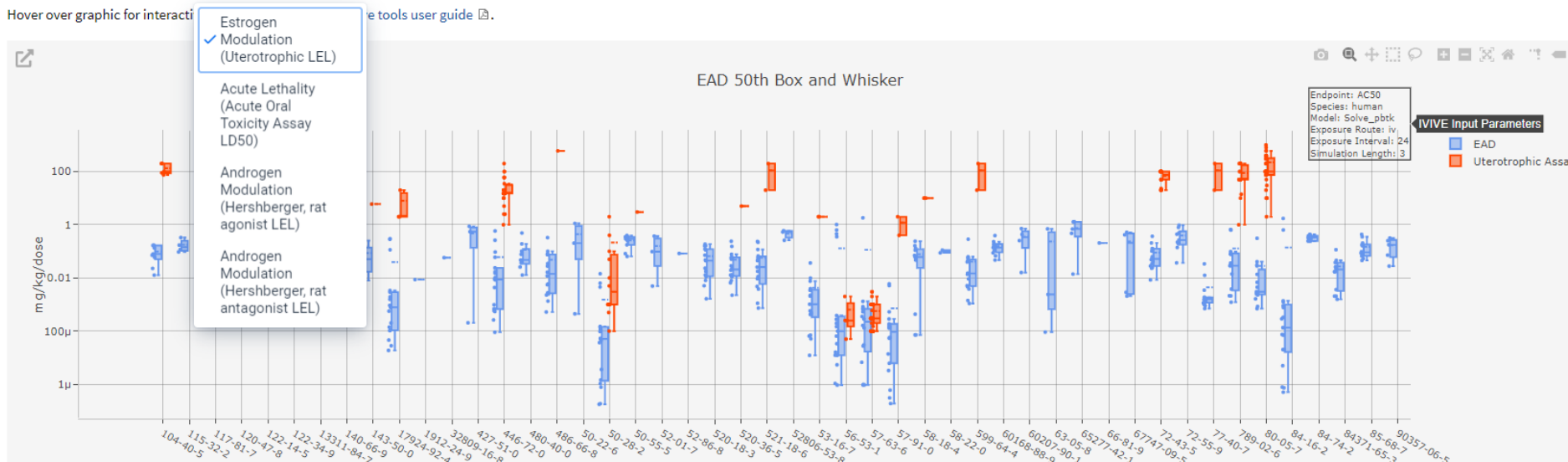
Curve Surfer    PBPk    **IVIVE**    Chemical Characterization    Chemical Quest



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

Chemical	CASRN	DTXSID	Flag	Assay	Mode of Action	Mechanistic Targets	AC50 $\mu$ M	EAD 50th Percentile (mg/kg/day)	Clint	Fraction Unbound
Testosterone	58-22-0	DTXSID8022371		TOX21_ERa_BLA_Agon...	estrog Receptor Mediated Effects	Estrogen Modulation, Gene Expression Regulation, KCC8: Receptor Mediated Effects	13.28	0.111	1.46	0.39952

Select EAD to visualize: EAD 50th  
Select in vivo data to display: ion (Uterotrophic LEL)  
 Log Axis     Show Name    Toxicity Endpoints represented: Endocrine

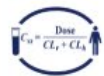


## Transparency and annotation to help guide use and interpretation





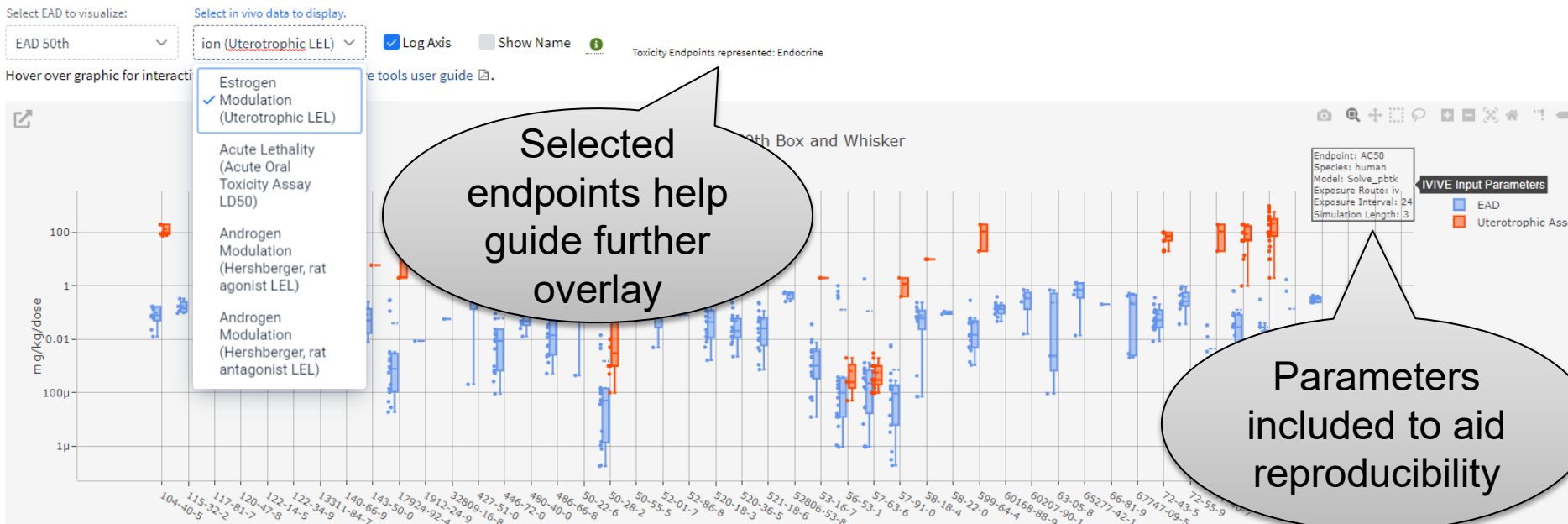
Curve Surfer    PBPK    **IVIVE**    Chemical Characterization    Chemical Quest



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

Chemical	CASRN	DTXSID	Flag	Assay	Mode of Action	Mechanistic Targets	AC50 $\mu$ M	EAD 50th Percentile (mg/kg/day)	Clint	Fraction Unbound
Testosterone	58-22-0	DTXSID8022371		TOX21_ERa_BLA_Agon...	estrog Receptor Mediated Effects	Estrogen Modulation, Gene Expression Regulation, KCC8: Receptor Mediated Effects Estrogen Metabolic Process	13...			0.39952

Annotation provided for filtering



Selected endpoints help guide further overlay

Parameters included to aid reproducibility

## Transparency and annotation to help guide use and interpretation





# ICE Tools: Chemical Characterization



Curve Surfer

PBPK

IVIVE

**Chemical Characterization**

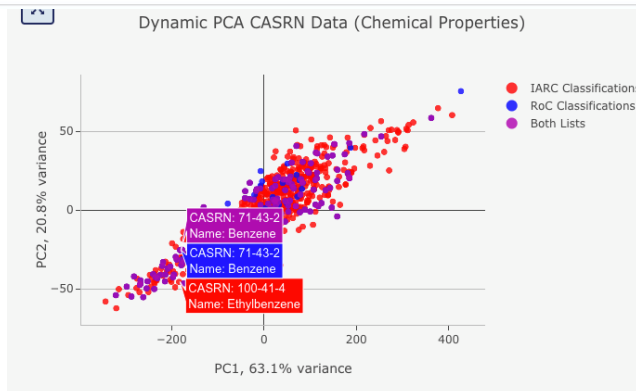
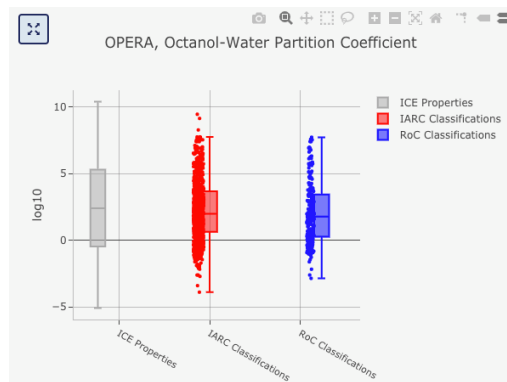
Chemical Quest



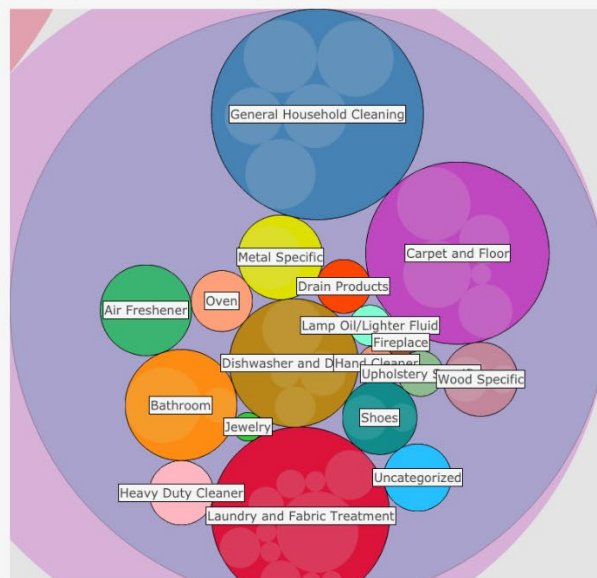
The Chemical Characterization tool allows you to view and compare one or two chemical lists based on their physicochemical properties. Comparisons are available in tabular format along with principal component analysis plots of list against subsets of the ICE chemical inventory.

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

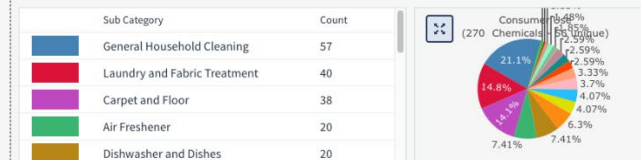
- Physicochemical property distributions
- Interactive PCA plots of chemical space coverage
- Presence in consumer products (EPA CPDat\*)



Chemical Consumer Use  
(1875 Chemicals - 203 unique): Cleaning Products and Household Care



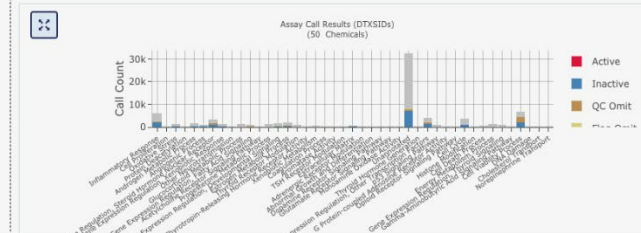
Chemical Consumer Use Details: Cleaning Products and Household Care (270 Chemicals - 56 unique)



Send filtered results to:

Select tool...

DTXSID (Dashboard)	Substance Name	CASRN (CEBS Link)	Sub Categories	Count
DTXSID7020762	Isopropanol	67-63-0		27
DTXSID9020584	Ethanol	64-17-5		27
DTXSID1024097	2-Butoxyethanol	111-76-2		24
DTXSID1020778	D-Limonene	5989-27-5		21



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





## Structure based Similarity Search

Curve Surfer

PBPK

IVIVE

Chemical Characterization

**Chemical Quest**

Input

Results

Help

Report an Issue



The Chemical Quest tool uses fingerprints to predict structure similarity. (Beta)

Run

Reset

Max hits per input:



Tanimoto Coefficient:  or greater



Chemical ID input (one per line)

10161-33-8  
57-85-2  
58-18-4  
58-22-0  
65-04-3  
1071-83-6

Smiles Structures for similarity search

Draw

Enter

Chemical Structure

**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





## Structure based Similarity Search

Input

Results

Help

Report an Issue

Run

Reset

Max hits per input: 10

Tanimoto Coefficient

Chemical ID input (one per line)

10161-33-8  
57-85-2  
58-18-4  
58-22-0  
65-04-3  
1071-83-6

close

**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





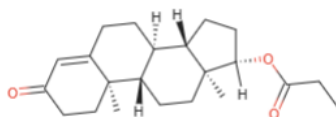
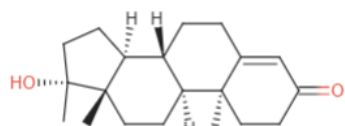
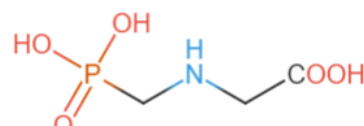
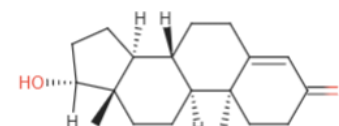
[Curve Surfer](#)[PBPK](#)[IVIVE](#)[Chemical Characterization](#)[Chemical Quest](#)

## 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](#)



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

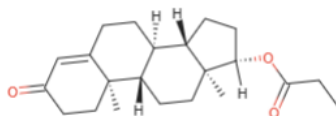
**DTXSID:** DTXSID9036515

**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

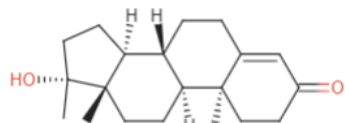
**DTXSID:** DTXSID1033664

**Tanimoto:** top 10 hits and >0.7

**Hit Count:** 10

**Passed Filter(s):** 10/10

[View Results](#)



**Chemical Name:** Glyphosate

**CASRN:** 1071-83-6

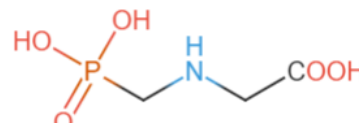
**DTXSID:** DTXSID1024122

**Tanimoto:** top 10 hits and >0.7

**Hit Count:** 10

**Passed Filter(s):** 10/10

[View Results](#)



**Chemical Name:** Testosterone

**CASRN:** 58-22-0

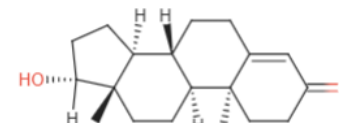
**DTXSID:** DTXSID8022371

**Tanimoto:** top 10 hits and >0.7

**Hit Count:** 10

**Passed Filter(s):** 10/10

[View Results](#)





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

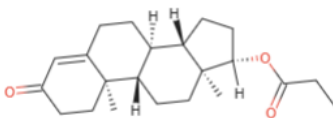
**DTXSID:** DTXSID9036515

**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

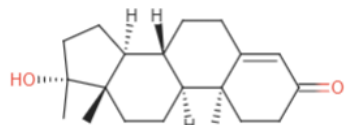
**DTXSID:** DTXSID1033664

**Tanimoto:** top 10 hits and >0.7

**Hit Count:** 10

**Passed Filter(s):** 10/10

[View Results](#)



**Chemical Name:** Glyphosate

**CASRN:** 1071-83-6

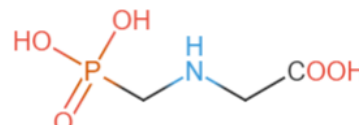
**DTXSID:** DTXSID1024122

**Tanimoto:** top 10 hits and >0.7

**Hit Count:** 10

**Passed Filter(s):** 10/10

[View Results](#)



**Chemical Name:** Testosterone

**CASRN:** 58-22-0

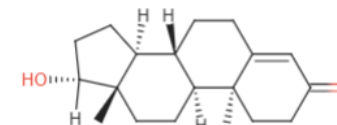
**DTXSID:** DTXSID8022371

**Tanimoto:** top 10 hits and >0.7

**Hit Count:** 10

**Passed Filter(s):** 10/10

[View Results](#)





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

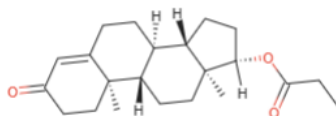
**DTXSID:** DTXSID9036515

**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

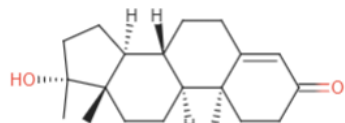
**DTXSID:** DTXSID1033664

**Tanimoto:** top 10 hits and >0.7

**Hit Count:** 10

**Passed Filter(s):** 10/10

View Results



**Chemical Name:** Glyphosate

**CASRN:** 1071-83-6

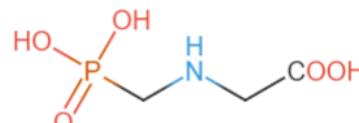
**DTXSID:** DTXSID1024122

**Tanimoto:** top 10 hits and >0.7

**Hit Count:** 10

**Passed Filter(s):** 10/10

View Results



**Chemical Name:** Testosterone

**CASRN:** 58-22-0

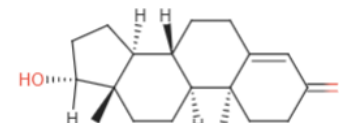
**DTXSID:** DTXSID8022371

**Tanimoto:** top 10 hits and >0.7

**Hit Count:** 10

**Passed Filter(s):** 10/10

View Results



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





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

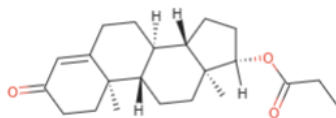
**DTXSID:** DTXSID9036515

**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

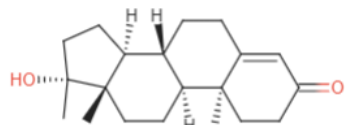
**DTXSID:** DTXSID1033664

**Tanimoto:** top 10 hits and >0.7

**Hit Count:** 10

**Passed Filter(s):** 10/10

View Results



**Chemical Name:** Glyphosate

**CASRN:** 1071-83-6

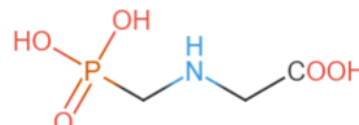
**DTXSID:** DTXSID1024122

**Tanimoto:** top 10 hits and >0.7

**Hit Count:** 10

**Passed Filter(s):** 10/10

View Results



**Chemical Name:** Testosterone

**CASRN:** 58-22-0

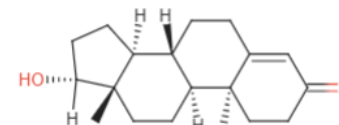
**DTXSID:** DTXSID8022371

**Tanimoto:** top 10 hits and >0.7

**Hit Count:** 10

**Passed Filter(s):** 10/10

View Results



View results button opens new window displaying similar chemicals





Curve Surfer

PBPK

IVIVE

Chemical Characterization

Chemical Quest

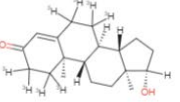
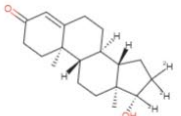
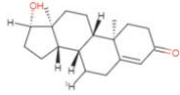

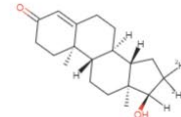
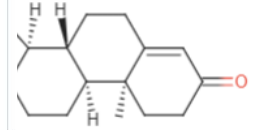


## Chemical Quest Results

Similar Structures to: C[C@]12CC[C@H]3[C@@H](CCC4=CC(=O)CC[C@]43C)[C@@H]1CC[C@@H]2O

Select Page: 1 of 1 Showing 1-10 of 10 hits. Sort Results By: Tanimoto Direction: Desc

Select CASRN(s): 0 values Tanimoto Filter: SMARTS Filter:

<p>CASRN: 67308-98-9 DTXSID: DTXSID30745538 Chemical Name: (17beta)-17-Hydroxy(1,1,2,2,6,6,7,7-~3~H_8_)androst-4-en-3-one Tanimoto Value: 1.0</p> 	<p>CASRN: 77546-39-5 DTXSID: DTXSID40662202 Chemical Name: (17beta)-17-Hydroxy(16,16,17-~2~H_3_)androst-4-en-3-one Tanimoto Value: 1.0</p> 	<p>CASRN: 52844-06-1 DTXSID: DTXSID90967315 Chemical Name: 17-Hydroxy(7-~3~H_1_)androst-4-en-3-one Tanimoto Value: 1.0</p> 	<p>CASRN: 481-30-1 DTXSID: DTXSID8022329 Chemical Name: Epitestosterone Tanimoto Value: 1.0</p> 	<p>CASRN: 117338-89-3 DTXSID: DTXSID601016404 Chemical Name: Epitestosterone-16,16-d2 Tanimoto Value: 1.0</p> 	<p>Testosterone</p> <p>022371 Hits and &gt;0.7</p> <p>10/10</p> 
---	--	---	---	---	---

View results button opens new window displaying similar chemicals







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.

Similar Structures to: C[C@]12CC[C@H]3[C@@H](CCC4=CC(=O)CC[C@@]43C)[C@@H]1CC[C@@H]2O

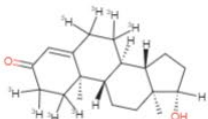
Select Page: 1 of 1 Showing 1-10 of 10 hits.

Sort Results By: Tanimoto Direction: Desc

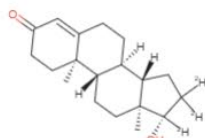
Select CASRN(s): 0 values

Tanimoto Filter: [ ] SMARTS Filter: [ ]

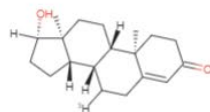
CASRN: 67308-98-9  
DTXSID: DTXSID30745538  
Chemical Name: (17beta)-17-Hydroxy(1,1,2,2,6,6,7,7~3~H\_8\_)androst-4-en-3-one  
Tanimoto Value: 1.0



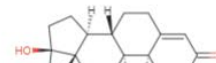
CASRN: 77546-39-5  
DTXSID: DTXSID40662202  
Chemical Name: (17beta)-17-Hydroxy(16,16,17~2~H\_3\_)androst-4-en-3-one  
Tanimoto Value: 1.0



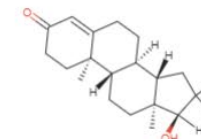
CASRN: 52844-06-1  
DTXSID: DTXSID90967315  
Chemical Name: 17-Hydroxy(7~3~H\_1\_)androst-4-en-3-one  
Tanimoto Value: 1.0



CASRN: 481-30-1  
DTXSID: DTXSID8022329  
Chemical Name: Epitestosterone  
Tanimoto Value: 1.0



CASRN: 117338-89-3  
DTXSID: DTXSID601016404  
Chemical Name: Epitestosterone-16,16-d2  
Tanimoto Value: 1.0





# 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 resources
  - 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



- 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

Toxicology Letters 312 (2019) 173-180

Contents lists available at ScienceDirect

Toxicology Letters

journal homepage: [www.elsevier.com/locate/toxlet](http://www.elsevier.com/locate/toxlet)

Metabolism of triflumuron in the human liver: Contribution of cytochrome P450 isoforms and esterases

Rim Timoumi<sup>a,b</sup>, Franca M. Buratti<sup>c,d</sup>, Salwa Abid-Essefi<sup>e</sup>, Jean-Lou C.M. Dorne<sup>f</sup>, Emanuela Testai<sup>g</sup>

Toxicology Letters

journal homepage: [www.elsevier.com/locate/toxlet](http://www.elsevier.com/locate/toxlet)

Inter-phenotypic differences in CYP2C9 and CYP2C19 metabolism: Bayesian meta-regression of human population variability in kinetics and application in chemical risk assessment

Nadia Quignot<sup>a,b,c</sup>, Witold Wiecek<sup>b,d,e</sup>, Leonie Lautz<sup>c</sup>, Jean-Lou Dorne<sup>f</sup>, Billy Amzal<sup>g</sup>

Computational Toxicology

journal homepage: [www.elsevier.com/locate/comtox](http://www.elsevier.com/locate/comtox)

Inter-ethnic differences in CYP3A4 metabolism: A Bayesian meta-analysis for the refinement of uncertainty factors in chemical risk assessment

Keyvin Darney<sup>a</sup>, Emanuela Testai<sup>b</sup>, Franca M. Buratti<sup>c</sup>, Emma Di Consiglio<sup>b</sup>, Emma E.J. Kasteel<sup>d</sup>, Nynke Kramer<sup>e</sup>, Laura Turco<sup>f</sup>, Susanna Vichi<sup>g</sup>, Alain-Claude Roudot<sup>h</sup>, Jean-Lou Dorne<sup>i</sup>, Camille Béchaux<sup>j</sup>

Environment International

journal homepage: [www.elsevier.com/locate/envint](http://www.elsevier.com/locate/envint)

Bayesian meta-analysis of inter-phenotypic differences in human serum paraoxonase-1 activity for chemical risk assessment

K. Darney<sup>a</sup>, E.E.J. Kasteel<sup>b</sup>, F.M. Buratti<sup>c</sup>, L. Turco<sup>d</sup>, S. Vichi<sup>e</sup>, C. Béchaux<sup>f</sup>, A.C. Roudot<sup>g</sup>, N.I. Kramer<sup>h</sup>, E. Testai<sup>i</sup>, J.L.C.M. Dorne<sup>j</sup>, E. Di Consiglio<sup>k</sup>, L.S. Lautz<sup>l</sup>

TOXICOKINETICS AND METABOLISM

Human variability in isoform-specific UDP-glucuronosyltransferases: markers of acute and chronic exposure, polymorphisms and uncertainty factors

E. E. J. Kasteel<sup>a</sup>, K. Darney<sup>b</sup>, N. I. Kramer<sup>c</sup>, J. L. C. M. Dorne<sup>d</sup>, L. S. Lautz<sup>e</sup>

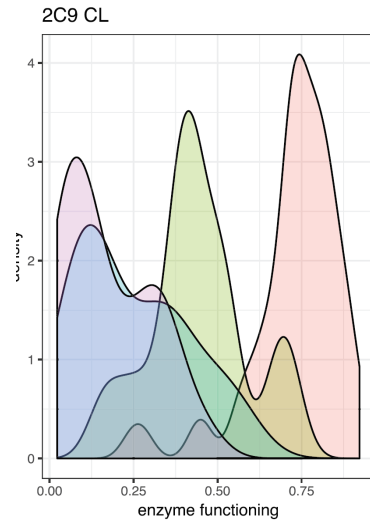
Computational Toxicology

journal homepage: [www.elsevier.com/locate/comtox](http://www.elsevier.com/locate/comtox)

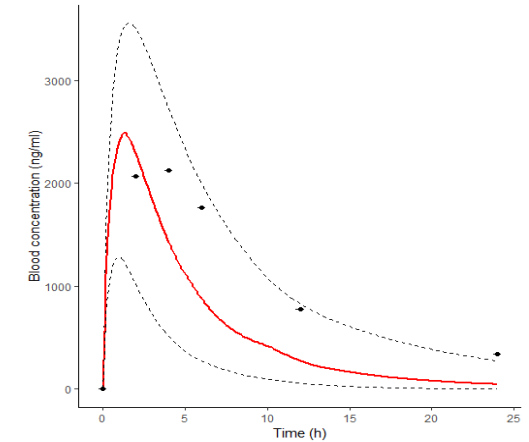
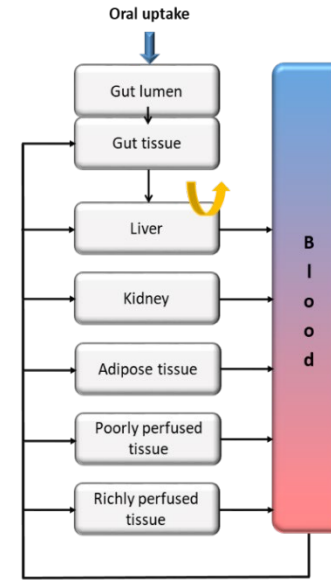
A generic Bayesian hierarchical model for the meta-analysis of human population variability in kinetics and its applications in chemical risk assessment

Witold Wiecek<sup>a,b</sup>, Jean-Lou Dorne<sup>b</sup>, Nadia Quignot<sup>c</sup>, Camille Béchaux<sup>d</sup>, Billy Amzal<sup>e</sup>

Covering Phase I  
CYP450 and Phase II  
UGTs enzymes

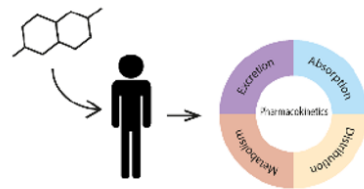


## PBPK models + virtual population

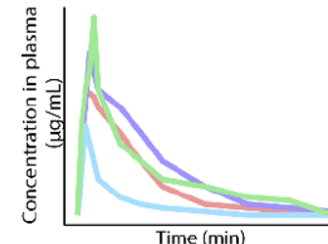


<https://ice.ntp.niehs.nih.gov/>

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



Interindividual differences in kinetics and polymorphisms



UGT-related uncertainty factors

Data on polymorphism frequencies in different populations is collected and summarised

Partnership with:







# Acknowledgments: The NICEATM Group

Speaker View Exit Full Screen

Judy Strickland Nicole Kleinstreuer Jaleh Abedini Dave Allen John Rooney

Pei-Li Yao Amber Daniel Bethany Cook Xiaoqing Chang Agnes Karmaus

Patricia Ceger Alex Borrel Jon Hamm Cathy Sprankle Lauren Browning

Arpit Tandon Eric McAfee Jason Phillips Shannon Bell Steven Morefield

David Hines Matt Stout Kamel Mansouri Ruchir Shah Neepa Choksi

Mute Stop Video Security Participants 25 Chat Share Screen Polling Record Reactions End



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