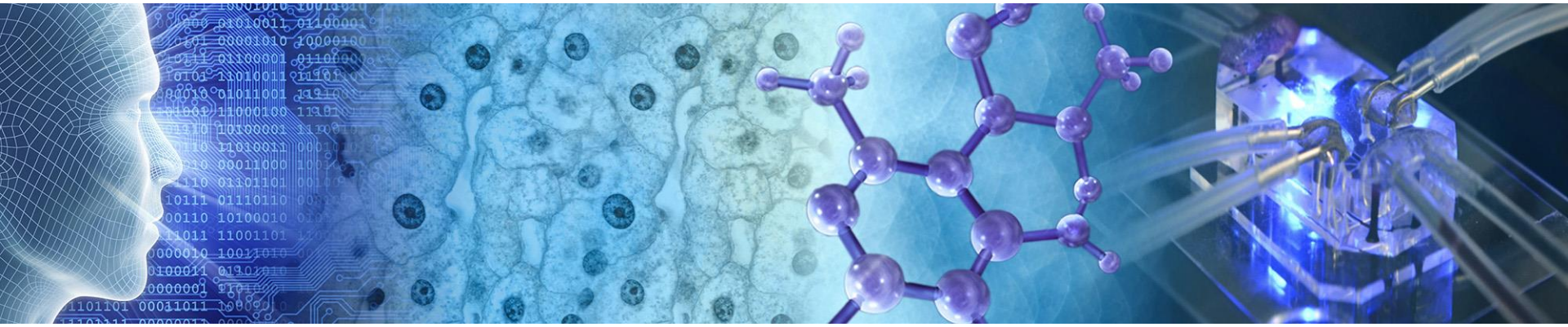
NTP
National Toxicology Program



The Integrated Chemical Environment
Tools and data to support toxicity assessments

PETA International Science Consortium
July 31, 2019

Presented by Shannon Bell, ILS
sbell@ils-inc.com
ICE-support@niehs-nih.gov

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

Acknowledgements

https://ntp.niehs.nih.gov/go/niceatm

ICE Team

Jaleh Abedini
Neal Cariello*
Patricia Ceger
Xiaoqing Chang
Farrah Hermes*
Agnes Karmaus
Kamel Mansouri
Eric McAfee **
Jason Philips**
Ruhi Rai
Catherine Sprankle
Arpit Tandon**

*Past team members
**Sciome, LLC

Integrated
Chemical
Environment

https://ice.ntp.niehs.nih.gov/ ICE-support@niehs.nih.gov

What does NICEATM do?

- Evaluate alternatives to animal use for toxicity testing
  - Alternative methods are those that Replace, Reduce, and/or Refine existing methods
- Supports the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)
- Conducts and publishes analyses/evaluations of data using new testing approaches
- Provides information to test method developers, regulators and the regulated community

Integrated Chemical Environment

- Resource access point designed for NICEATM stakeholders
  - Risk assessors, chemical producers and method developers
- User-friendly access to high confidence data and reference chemical lists
- Easy to use resources supporting prioritization and exploration
  - Search
    - Designed for ease of use; assays organized on regulatory endpoints
  - Tools
    - Web-based for easy use and exploration

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

Why use ICE?

Find bulk assay data on a list of chemicals

- Test method developer looking to find chemicals
  - To serve as controls
  - That test the method's domain of applicability
- Modeler looking for
  - Data that can be used in model development
  - Chemical parameters for existing models
- Regulatory scientist looking to
  - Understand potential risks of target compounds
  - Gather existing data for comparison

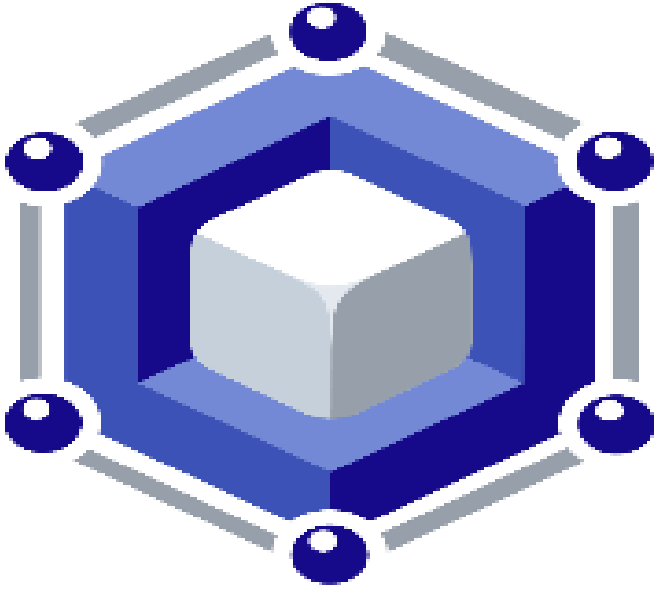
ICE features

- Bulk query mindset
- Integrate across multiple data types
- FAIR data
  - Findable, Accessible, Interoperable, and Reusable
    - By the appropriate people, at the appropriate times, in the appropriate format
  - Cleaned, curated, ready to use
- Tools to support data exploration
- Continued development based on stakeholder feedback

What goes into ICE?

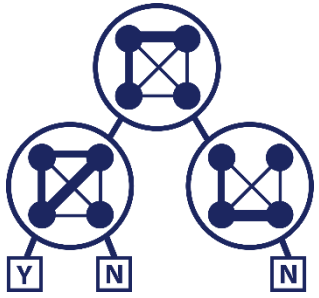
Validation Studies

Published Data



Databases

Computational Models



What data are currently in ICE?

Toxicity endpoint/ Data source	Assays	# of chemicals
Acute Oral Toxicity	In vivo acute oral toxicity	10,348
Skin Sensitization	DPRA, hCLAT, KeratinoSens, LLNA, human potency, etc	578
Skin Irritation	In vivo acute skin irritation/corrosion, 4h HPT	120
Eye Irritation	In vivo acute eye irritation/corrosion (e.g, Draize eye), Vitrigel	183
Endocrine	AR/ER Pathway Models, Uterotrophic, AR/ER binding	1903
Tox21	Curated ToxCast and Tox21 assays	9076
OPERA predictions	BP, HLC, KOA, BCF, LogP, MP, MW, VP, WS, *COMPARA*, *CERAPP*	705,666
Formulation data	six-pack	298 (747 formulations)

https://github.com/NIEHS/OPERA

Call for Data

Currently of interest:

- In vivo data
  - Collections of data generated using regulatory guideline-like requirements
  - Acute inhalation, skin and eye irritation/corrosion
  - Maternal/fetal measures
- Toxicokinetic data
  - Collections of in vivo measures
  - Data from in vitro assays aimed at informing modeling of materials within the body

ICE-support@niehs.nih.gov

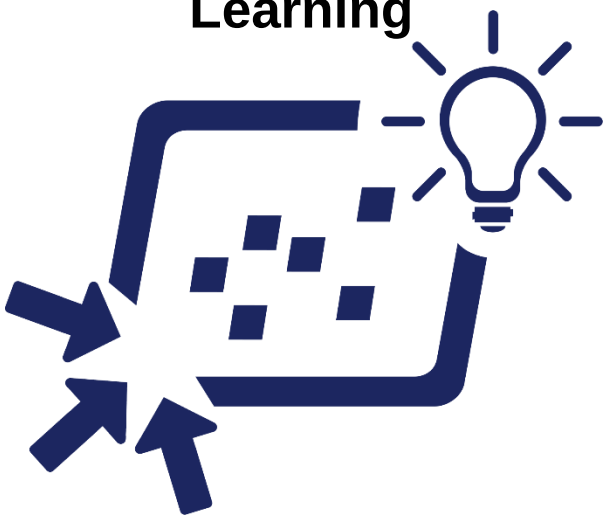
ICE tools

- Designed to support the use of ICE data
- Focus is on data exploration and providing access to computational approaches
- Ongoing area of development

IVIVE

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

Machine Learning

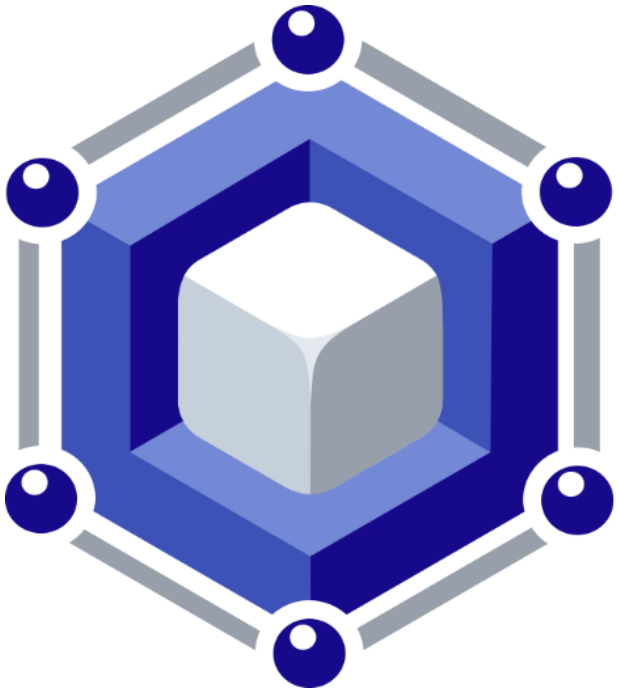


Chemical Space Characterization

NTP
National Toxicology Program

Live Demo

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



Integrated
Chemical
Environment

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

Search the NTP Website SEARCH

Integrated Chemical Environment

HOME SEARCH TOOLS DATA ABOUT HELP

News & Events

ICE 2.0 is here!

- The updated ICE release includes expanded tools, new predictions from OPERA and improved search.

Learn about ICE updates

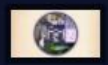
UPDATES

ICE provides data to support development of new approaches for chemical safety testing.

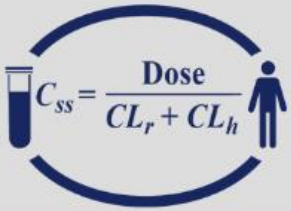
Click here to learn more about ICE!

PAUSE





Search ▸



IVIVE ▸

Machine Learning ▸

Chemical Characterization ▸

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

Search the NTP Website SEARCH

Integrated Chemical Environment

HOME SEARCH TOOLS DATA ABOUT HELP

User Guide
FAQ
Contact ICE

News & Events

ICE 2.0 is here!

- The updated ICE release includes expanded tools, new predictions from OPERA and improved search.

Learn about ICE updates

UPDATES

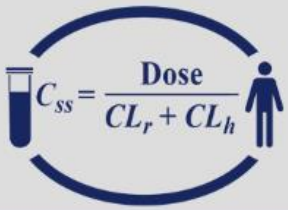
ICE provides data to suppo development of new approaches for chemical s testing.

Click here to learn more about ICE!

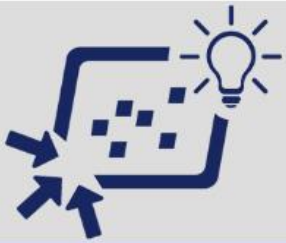
PAUSE



Search ▸



IVIVE ▸



Machine Learning ▸

Chemical Characterization ▸

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

Search the NTP Website SEARCH

Integrated Chemical Environment

HOME SEARCH TOOLS DATA ABOUT HELP

Data Sets
Chemical Quick Lists

News & Events

ICE 2.0 is here!

- The updated ICE release includes expanded tools, new predictions from OPERA and improved search.

Learn about ICE updates

UPDATES

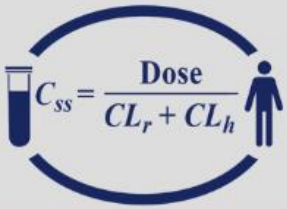
ICE pr… …upport development of new approaches for chemical safety testing.

Click here to learn more about ICE!

PAUSE



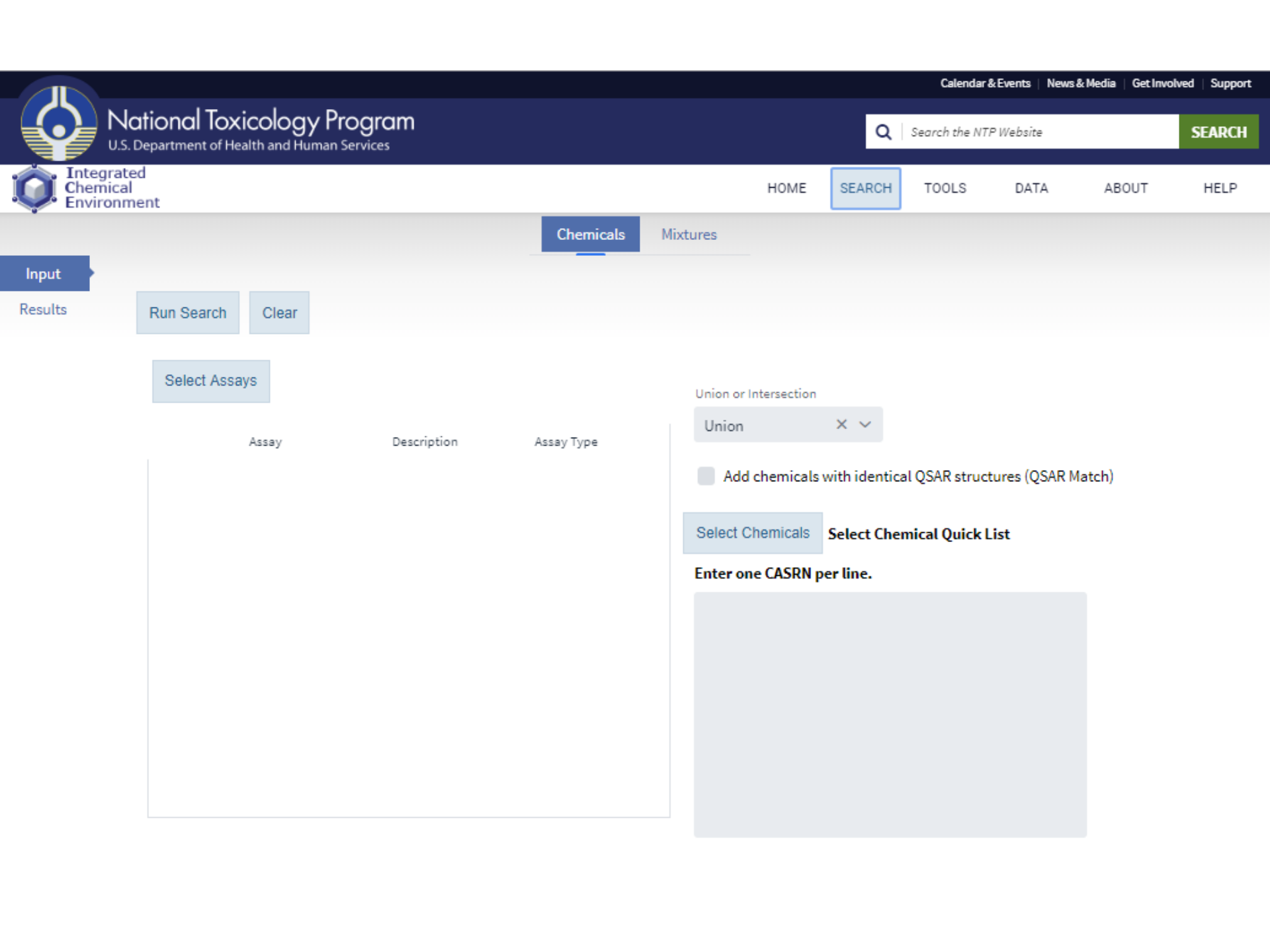
Search ▸

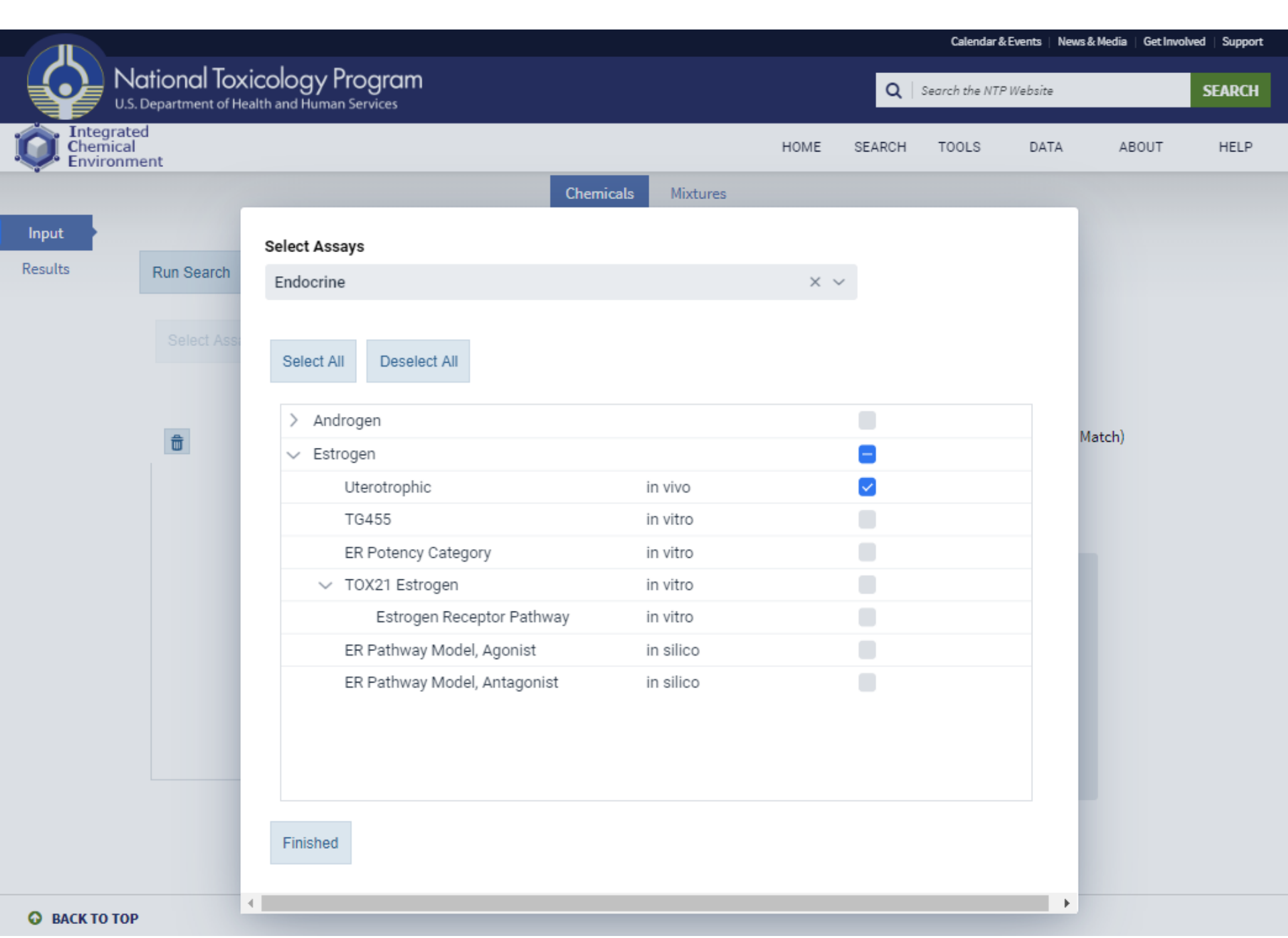


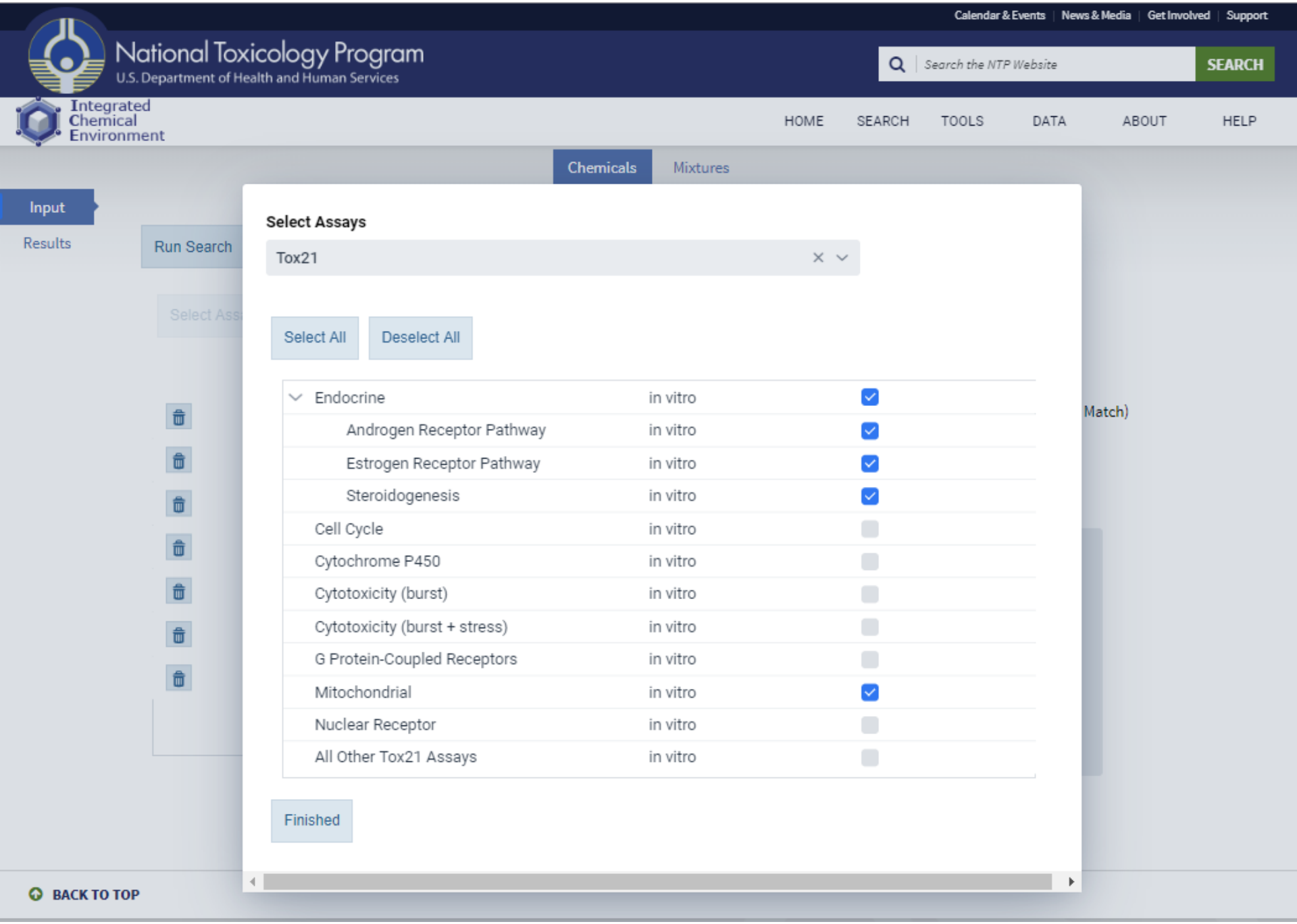
IVIVE ▸

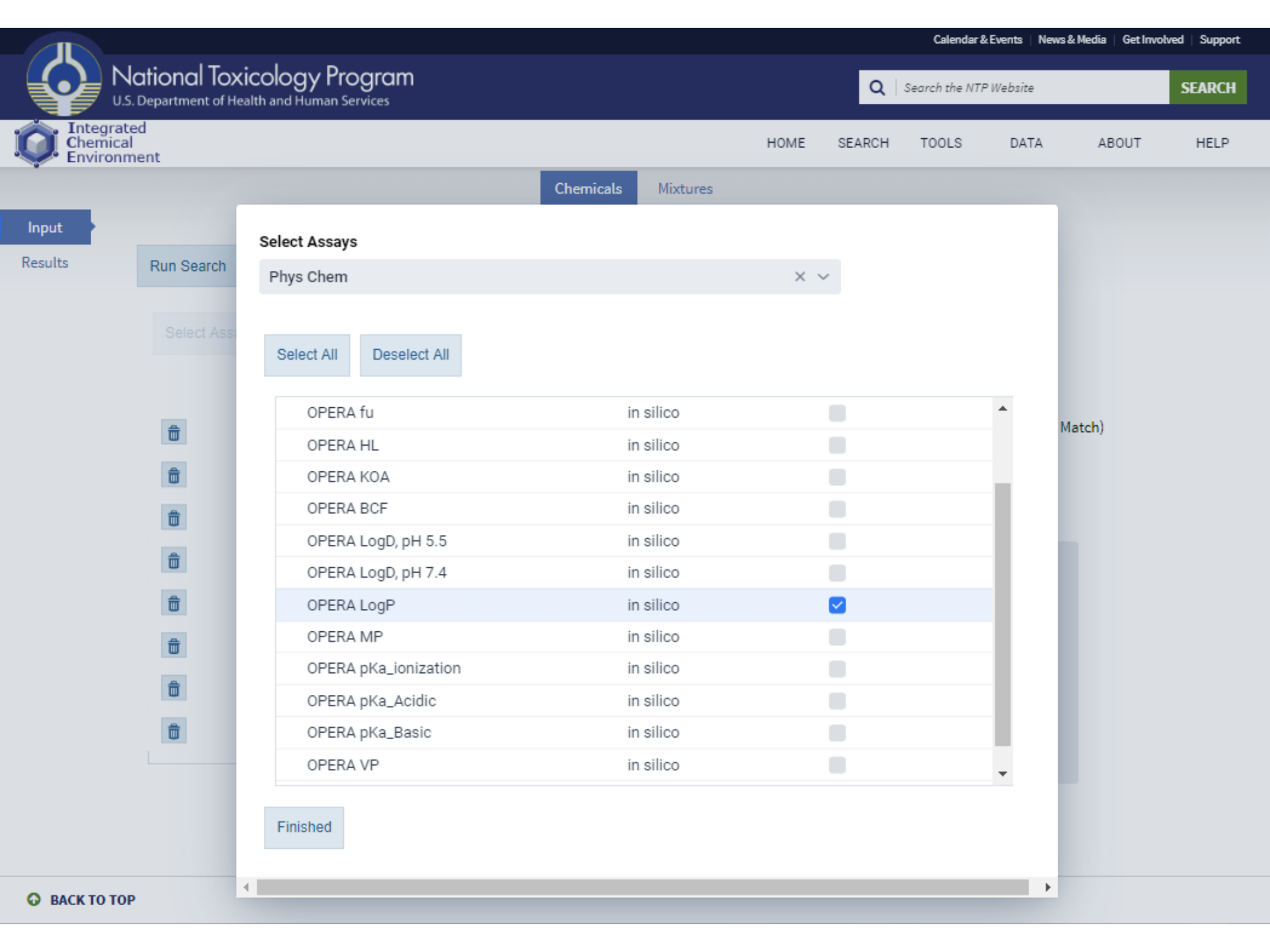
Machine Learning ▸

Chemical Characterization ▸


Calendar & Events | News & Media | Get Involved | Support
National Toxicology Program
U.S. Department of Health and Human Services
Search the NTP Website
SEARCH
Integrated Chemical Environment
HOME
SEARCH
TOOLS
DATA
ABOUT
HELP
Chemicals
Mixtures
Input
Results
Run Search
Clear
Select Assays
Assay
Description
Assay Type
Union or Intersection
Union
Add chemicals with identical QSAR structures (QSAR Match)
Select Chemicals
Select Chemical Quick List
Enter one CASRN per line.


Calendar & Events | News & Media | Get Involved | Support
National Toxicology Program
U.S. Department of Health and Human Services
Search the NTP Website
SEARCH
Integrated Chemical Environment
HOME SEARCH TOOLS DATA ABOUT HELP
Chemicals
Mixtures
Input
Results
Run Search
Select Assays
Endocrine
Select All
Deselect All
Androgen
Estrogen
Uterotrophic in vivo
TG455 in vitro
ER Potency Category in vitro
TOX21 Estrogen in vitro
Estrogen Receptor Pathway in vitro
ER Pathway Model, Agonist in silico
ER Pathway Model, Antagonist in silico
Finished
Match)
BACK TO TOP


Calendar & Events | News & Media | Get Involved | Support
National Toxicology Program
U.S. Department of Health and Human Services
Search the NTP Website
SEARCH
Integrated Chemical Environment
HOME SEARCH TOOLS DATA ABOUT HELP
Chemicals
Mixtures
Input
Results
Run Search
Select Assays
Tox21
Select All
Deselect All
Endocrine in vitro
Androgen Receptor Pathway in vitro
Estrogen Receptor Pathway in vitro
Steroidogenesis in vitro
Cell Cycle in vitro
Cytochrome P450 in vitro
Cytotoxicity (burst) in vitro
Cytotoxicity (burst + stress) in vitro
G Protein-Coupled Receptors in vitro
Mitochondrial in vitro
Nuclear Receptor in vitro
All Other Tox21 Assays in vitro
Finished
Match)
BACK TO TOP


Calendar & Events | News & Media | Get Involved | Support
National Toxicology Program
U.S. Department of Health and Human Services
Search the NTP Website
SEARCH
Integrated Chemical Environment
HOME SEARCH TOOLS DATA ABOUT HELP
Chemicals
Mixtures
Input
Results
Run Search
Select Assays
Phys Chem
Select All
Deselect All
OPERA fu in silico
OPERA HL in silico
OPERA KOA in silico
OPERA BCF in silico
OPERA LogD, pH 5.5 in silico
OPERA LogD, pH 7.4 in silico
OPERA LogP in silico
OPERA MP in silico
OPERA pKa_ionization in silico
OPERA pKa_Acidic in silico
OPERA pKa_Basic in silico
OPERA VP in silico
Finished
Match)
BACK TO TOP

Run Search Clear

Select Assays

	Assay	Description	Assay Type
	OPERA LogP	Phys Chem	in silico
	Mitochondrial	Tox21	in vitro
	Steroidogenesis	Tox21	in vitro
	Estrogen Recepto...	Tox21	in vitro
	Androgen Recept...	Tox21	in vitro
	ER Pathway Mod...	Endocrine	in silico
	ER Pathway Mod...	Endocrine	in silico
	Uterotrophic	Endocrine	in vivo

Union or Intersection

Union

Add chemicals with identical QSAR structures (QSAR Match)

Select Chemicals **Select Chemical Quick Lists.**

Enter one CASRN per line.

Select one or more chemical quick lists.

Select All | Deselect All

- [ ] AR In Vitro Agonist 2016 (R)
- [ ] AR In Vitro Antagonist 2016 (R)
- [x] AR In Vivo Agonists 2018
- [ ] AR In Vivo Antagonists 2018
- [ ] ER In Vitro Agonist 2015 (R)
- [ ] ER In Vitro Agonists and Antagonists OECD 2016 (R)
- [ ] ER In Vivo Agonist 2015 (R)
- [ ] ICCVAM Cytotox Acute Oral 2006 (R)
- [ ] ICCVAM Eye Irritation-Corrosion 2006 (R)
- [ ] ICCVAM LLNA 2009 (R)
- [ ] ICCVAM Skin Corrosion 2004 (R)
- [ ] Steroidogenesis - Androgen 2018
- [ ] Steroidogenesis - Estrogen 2018
- [x] Thyroid 2016
- [ ] Tox21
- [x] Uterotrophic Reference List (R)

Close

Chemicals Mixtures

Input

Results

Run Search Clear

Select Assays

	Assay	Description	Assay Type
	OPERA LogP	Phys Chem	in silico
	Mitochondrial	Tox21	in vitro
	Steroidogenesis	Tox21	in vitro
	Estrogen Recepto...	Tox21	in vitro
	Androgen Recept...	Tox21	in vitro
	ER Pathway Mod...	Endocrine	in silico
	ER Pathway Mod...	Endocrine	in silico
	Uterotrophic	Endocrine	in vivo

Union or Intersection

Union

Add chemicals with identical QSAR structures (QSAR Match)

Select Chemicals **3 chemical quick lists selected.**

Enter one CASRN per line.

50-00-0

Details

Selected Assays: Uterotrophic, Androgen Receptor Pathway, Estrogen Receptor Pathway, Mitochondrial, Steroidogenesis, ER Pathway Model, Agonist, ER Pathway Model, Antagonist, OPERA LogP

Selected Reference Lists: AR In Vivo Agonists 2018, Thyroid 2016, Uterotrophic Reference List (R)

Download | Query Formulations | Clear Filter

Number of chemicals = 178.

QSAR Match	Substance Name	CASRN	DTXSID	Qsar Ready ID	Uterotro... LEL mg/kg/day	Uterotro... Call	Androgen Receptor Pathway Call (# Assays=11)	Estrogen Receptor Pathway Call (# Assays=17)	Mitochon. Call (# Assays=26
YES	(Z,E)-Diethylstil...	6898-97-1	DTXSID30...	RGLYKWW... UHFFFAOY... N			Active:cou...	Active:cou...	Active:co
	Benomyl	17804-35-2	DTXSID50...	RIOXQFHN... UHFFFAOY... N		Inactive	Active:cou...	Active:cou...	Active:co
	Trifluralin	1582-09-8	DTXSID40...	ZSDSQXJS... UHFFFAOY... N			Inactive:c...	Active:cou...	Active:co

Chemicals Mixtures

Input

Results

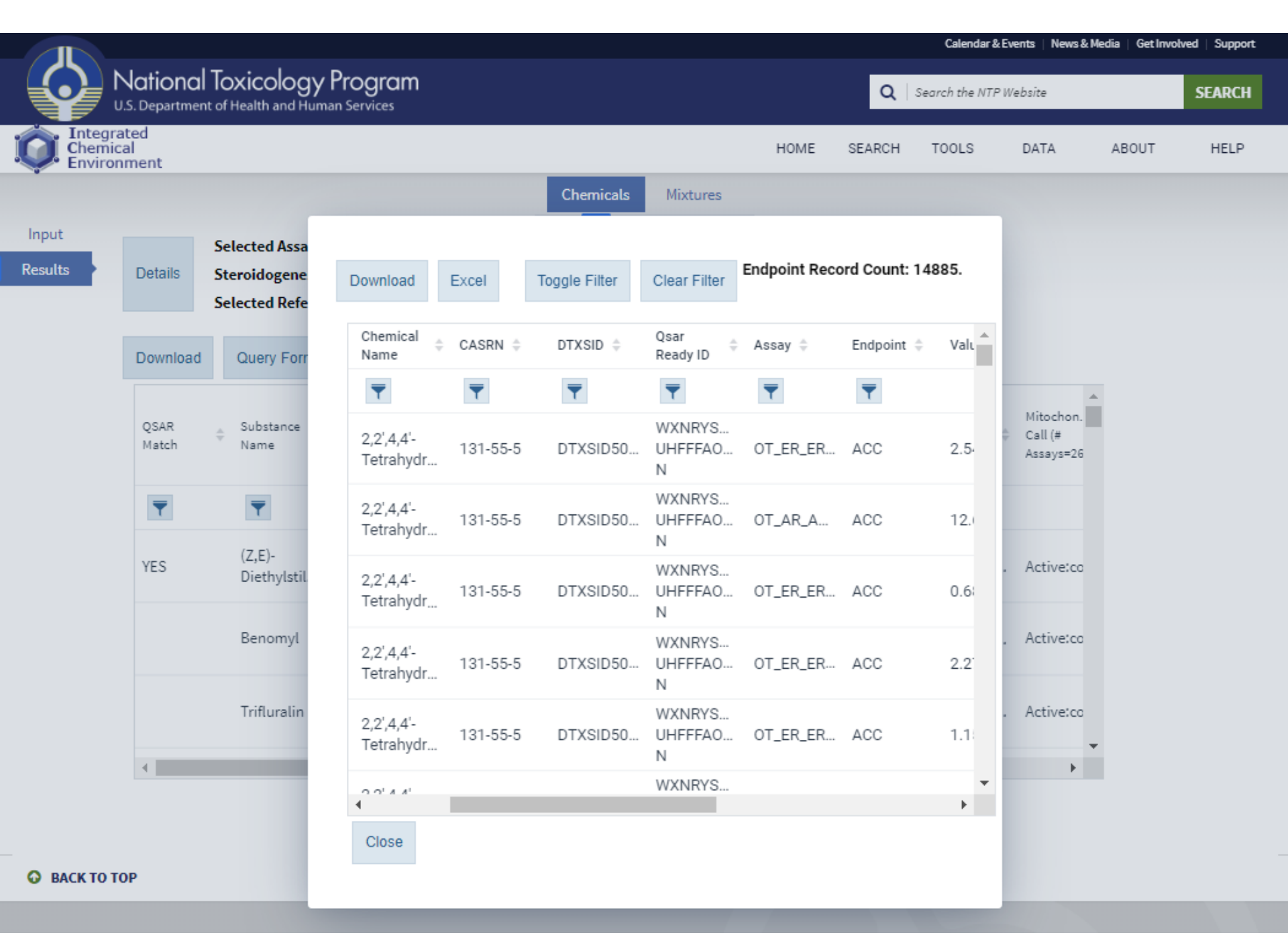
Details

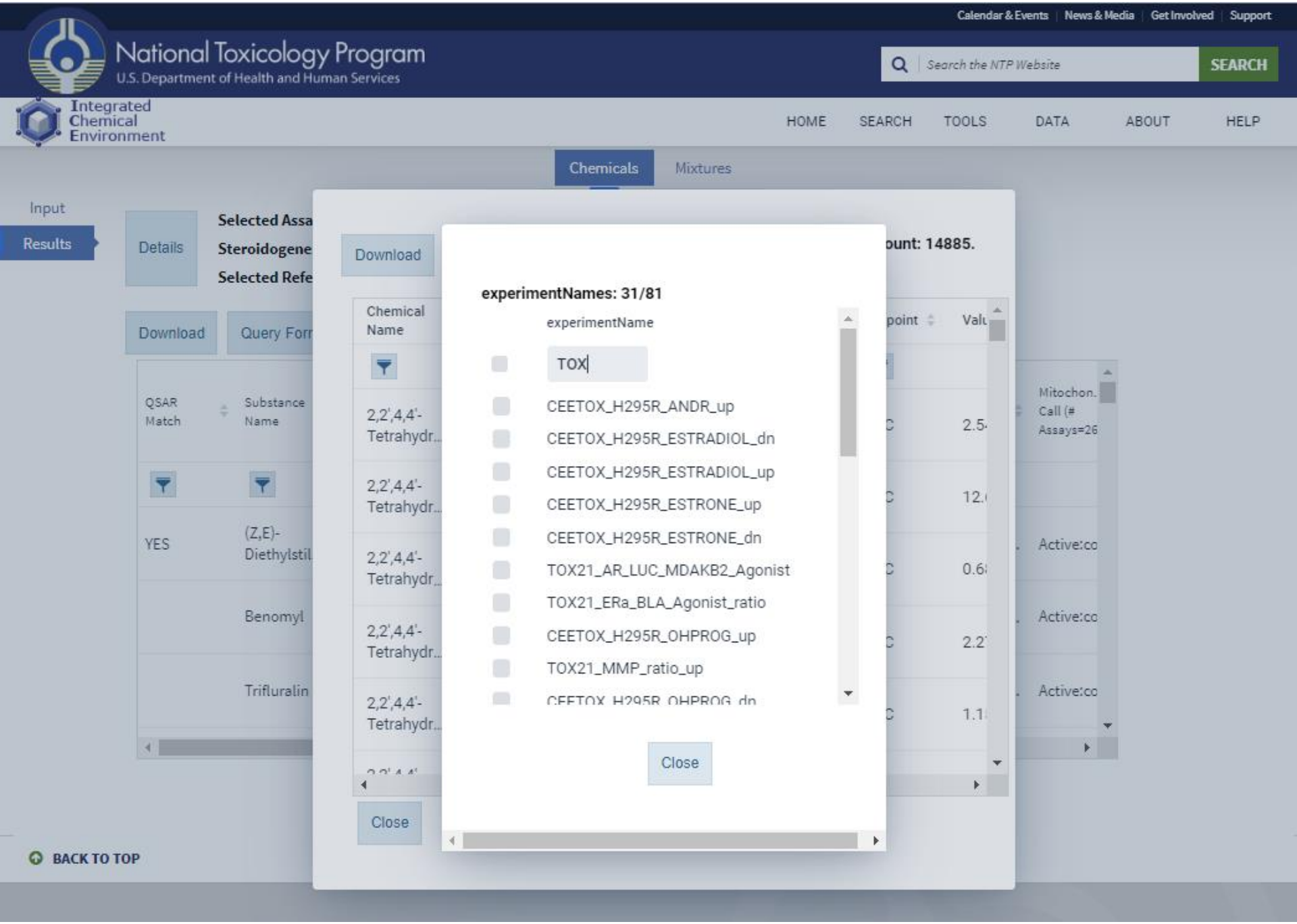
Selected Assays: Uterotrophic, Androgen Receptor Pathway, Estrogen Receptor Pathway, Mitochondrial, Steroidogenesis, ER Pathway Model, Agonist, ER Pathway Model, Antagonist, OPERA LogP

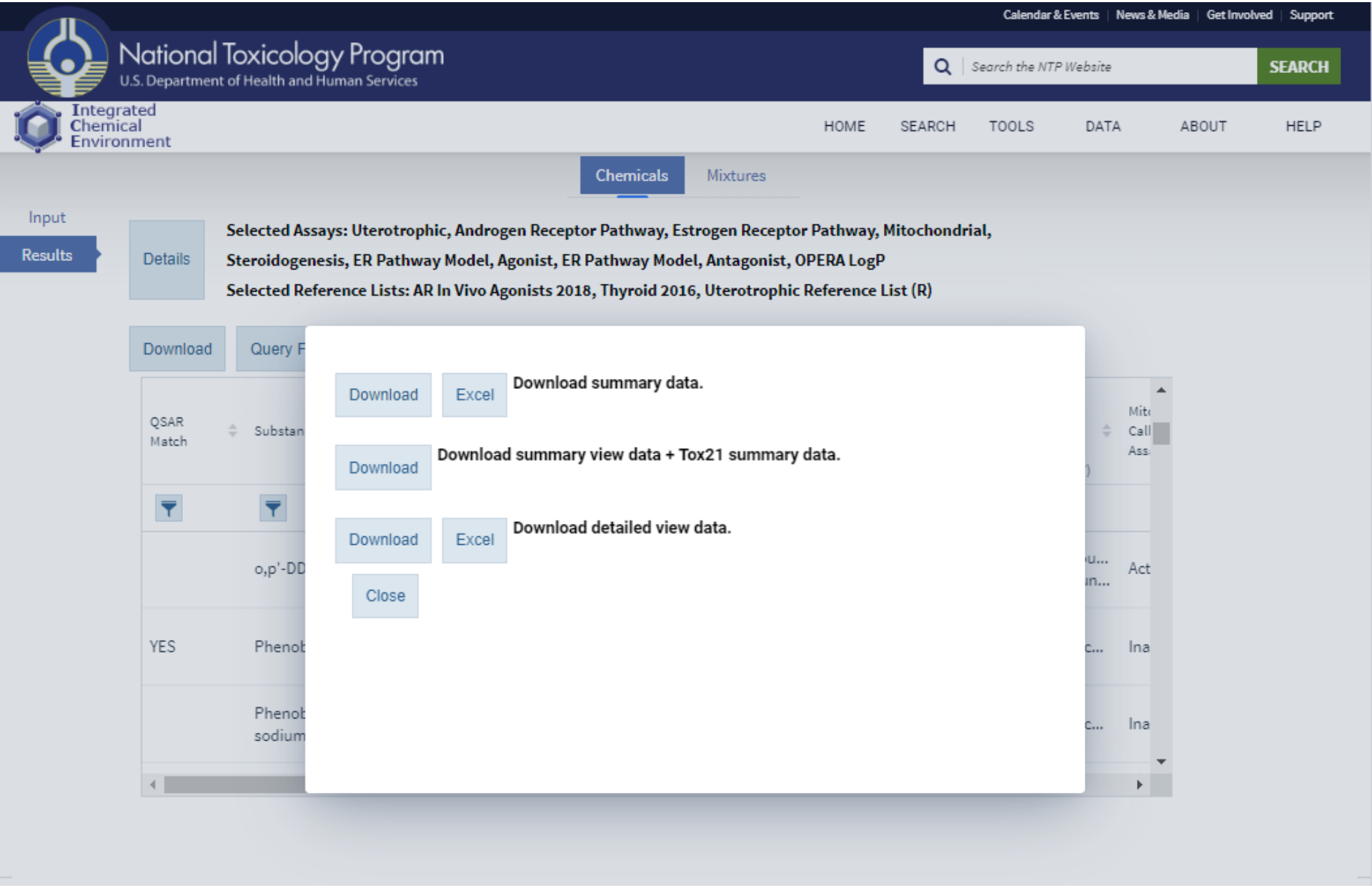
Selected Reference Lists: AR In Vivo Agonists 2018, Thyroid 2016, Uterotrophic Reference List (R)

Download Query Formulations Clear Filter **Number of chemicals = 178.**

QSAR Match	Substance Name	CASRN	DTXSID	Qsar Ready ID	Uterotro... LEL mg/kg/day	Uterotro... Call	Androgen Receptor Pathway Call (# Assays=11)	Estrogen Receptor Pathway Call (# Assays=17)	Mit... Call Ass...
	o,p'-DDT	789-02-6	DTXSID60...	CVUGPAFC... UHFFFAOY... N	[1-200], n=15, median=50	Active:cou...	Active:cou...	Active:cou... Omit:coun...	Act
YES	Phenobarbital	50-06-6	DTXSID50...	DDBREPK... UHFFFAOY... N			Inactive:c...	Inactive:c...	Ina
	Phenobarbital sodium	57-30-7	DTXSID00...	DDBREPK... UHFFFAOY... N			Inactive:c...	Inactive:c...	Ina


Calendar & Events | News & Media | Get Involved | Support
National Toxicology Program
U.S. Department of Health and Human Services
Search the NTP Website
SEARCH
Integrated Chemical Environment
HOME SEARCH TOOLS DATA ABOUT HELP
Chemicals Mixtures
Input
Results
Details
Selected Assa
Steroidogene
Selected Refe
Download
Query Forr
QSAR Match
Substance Name
YES
(Z,E)-Diethylstil
Benomyl
Trifluralin
Mitochon. Call (# Assays=26
Active:co
Active:co
Active:co
Download
Excel
Toggle Filter
Clear Filter
Endpoint Record Count: 14885.
Chemical Name
CASRN
DTXSID
Qsar Ready ID
Assay
Endpoint
Valu
2,2',4,4'-Tetrahydr...
131-55-5
DTXSID50...
WXNRYS...UHFFFAO...N
OT_ER_ER...
ACC
2.5
2,2',4,4'-Tetrahydr...
131-55-5
DTXSID50...
WXNRYS...UHFFFAO...N
OT_AR_A...
ACC
12.
2,2',4,4'-Tetrahydr...
131-55-5
DTXSID50...
WXNRYS...UHFFFAO...N
OT_ER_ER...
ACC
0.6
2,2',4,4'-Tetrahydr...
131-55-5
DTXSID50...
WXNRYS...UHFFFAO...N
OT_ER_ER...
ACC
2.2
2,2',4,4'-Tetrahydr...
131-55-5
DTXSID50...
WXNRYS...UHFFFAO...N
OT_ER_ER...
ACC
1.1
WXNRYS...
Close
BACK TO TOP


Calendar & Events | News & Media | Get Involved | Support
National Toxicology Program
U.S. Department of Health and Human Services
Search the NTP Website
SEARCH
Integrated Chemical Environment
HOME SEARCH TOOLS DATA ABOUT HELP
Chemicals
Mixtures
Input
Results
Details
Selected Assa
Steroidogene
Selected Refe
Download
Query Forr
ount: 14885.
Chemical Name
QSAR Match
Substance Name
YES
(Z,E)-Diethylstil
Benomyl
Trifluralin
2,2',4,4'-Tetrahydr...
point
Valu
Mitochon. Call (# Assays=26
Active:co
Download
experimentNames: 31/81
experimentName
TOX
CEETOX_H295R_ANDR_up
CEETOX_H295R_ESTRADIOL_dn
CEETOX_H295R_ESTRADIOL_up
CEETOX_H295R_ESTRONE_up
CEETOX_H295R_ESTRONE_dn
TOX21_AR_LUC_MDAKB2_Agonist
TOX21_ERa_BLA_Agonist_ratio
CEETOX_H295R_OHPROG_up
TOX21_MMP_ratio_up
Close
Close
BACK TO TOP


Calendar & Events | News & Media | Get Involved | Support
National Toxicology Program
U.S. Department of Health and Human Services
Search the NTP Website
SEARCH
Integrated Chemical Environment
HOME SEARCH TOOLS DATA ABOUT HELP
Chemicals
Mixtures
Input
Results
Details
Selected Assays: Uterotrophic, Androgen Receptor Pathway, Estrogen Receptor Pathway, Mitochondrial, Steroidogenesis, ER Pathway Model, Agonist, ER Pathway Model, Antagonist, OPERA LogP
Selected Reference Lists: AR In Vivo Agonists 2018, Thyroid 2016, Uterotrophic Reference List (R)
Download
Query F
QSAR Match
Substan
o,p'-DD
YES
Phenob
Phenob sodium
Download
Excel
Download summary data.
Download
Download summary view data + Tox21 summary data.
Download
Excel
Download detailed view data.
Close

Details

Selected Assay Categories: Acute Dermal Toxicity, Acute Oral Toxicity, Acute Inhalation Toxicity, Primary Skin Irritation, Primary Eye Irritation, Dermal Sensitization

Download Excel Query Integrator Clear Filter

Number of chemicals = 497.

Formulat... ID	Active Ingredient	CASRN	Percent AI	Acute Dermal Toxicity curatedE...	Acute Dermal Toxicity curatedG...	Acute Dermal Toxicity curatedL... mg/kg	Acute Oral Toxicity curatedE...	Acute Oral Toxicity curatedG...
Rancona Xxtra		ICE_41749...		4	5	>5000.0	4	5
Rancona Xxtra	Ipconazole	125225-28-7	1.029					
Rancona Xxtra	Metalaxyl	57837-19-1	1.647					
Raid Ant & Roach Killer with Germ		ICE_41056...		4	5	>5000.0	4	5

IVIVE Workflow Input

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

Run Workflow

Select Chemicals **Select Chemical Quick List**

Enter one CASRN per line.

Select Assays

- Androgen Receptor Pathway
- Cell Cycle
- Cytochrome P450
- Cytotoxicity (burst)
- Cytotoxicity (burst + stress)
- Estrogen Receptor Pathway
- G Protein-Coupled Receptors
- Mitochondrial
- Nuclear Receptor
- Steroidogenesis
- All Other Tox21 Assays

Select in vitro endpoint: AC50

Select Route: iv

Select species: human

Dosing Intervals, hours: 24

Select model: 1C

Days of exposure, days: 3

ICE tool: Chemical Characterization

- Comparison tool that allows user to look at the property distribution between one or 2 lists of chemicals
- Chemical characterization tool is aimed at:
  - Allowing users to explore property distributions relationships
  - Look at what properties may be driving differences in performance of chemicals in assays
  - Characterize the differences between lists to identify possible redundancy or define the range of property coverage in preparation for testing

Chemical List Characterization

Characterize the physicochemical and ADME properties of up to two chemical lists and compare between lists

Run Tool

Chemical Input List 1 (required)

Select Chemicals **Select Chemical Quick List**

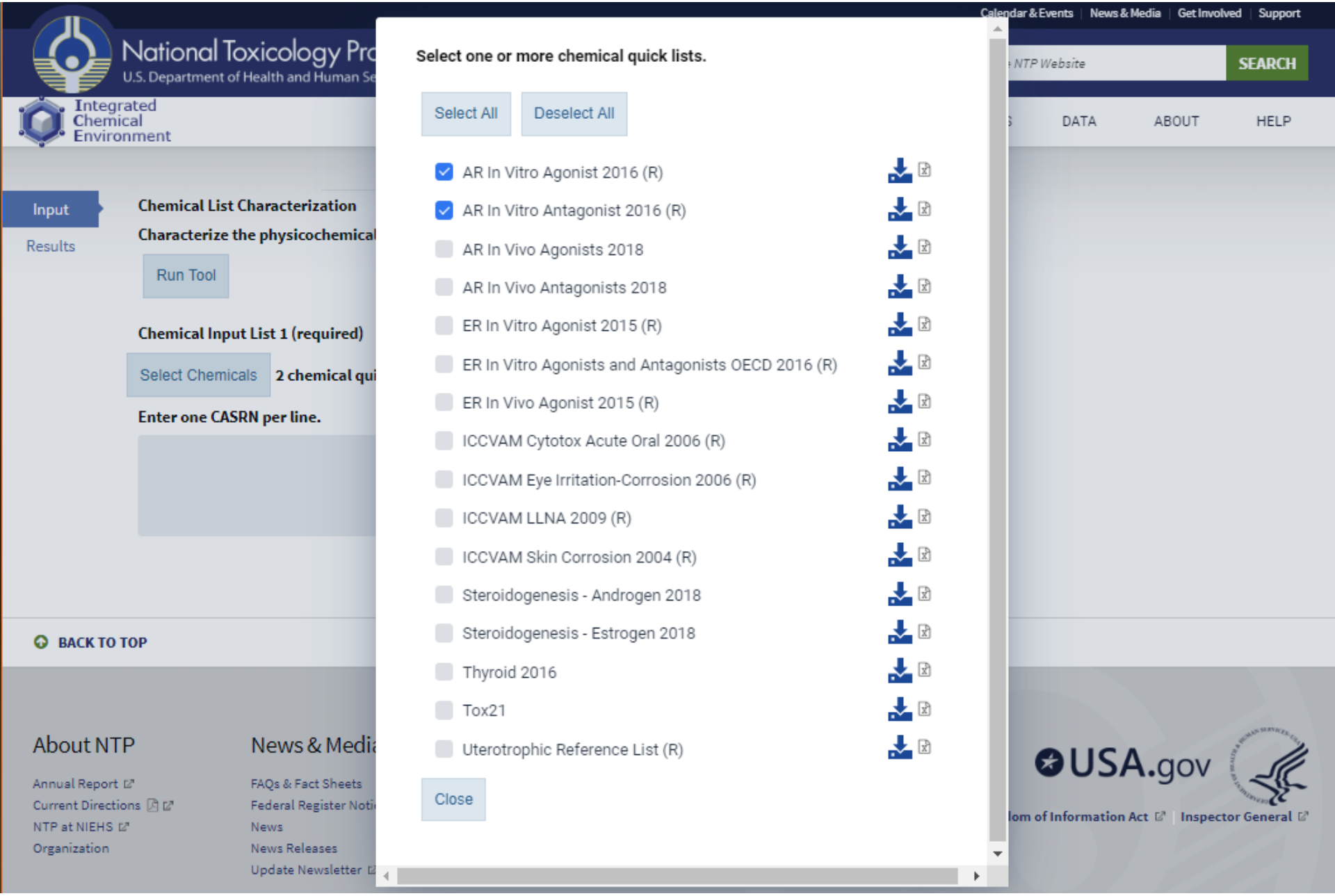
Enter one CASRN per line.

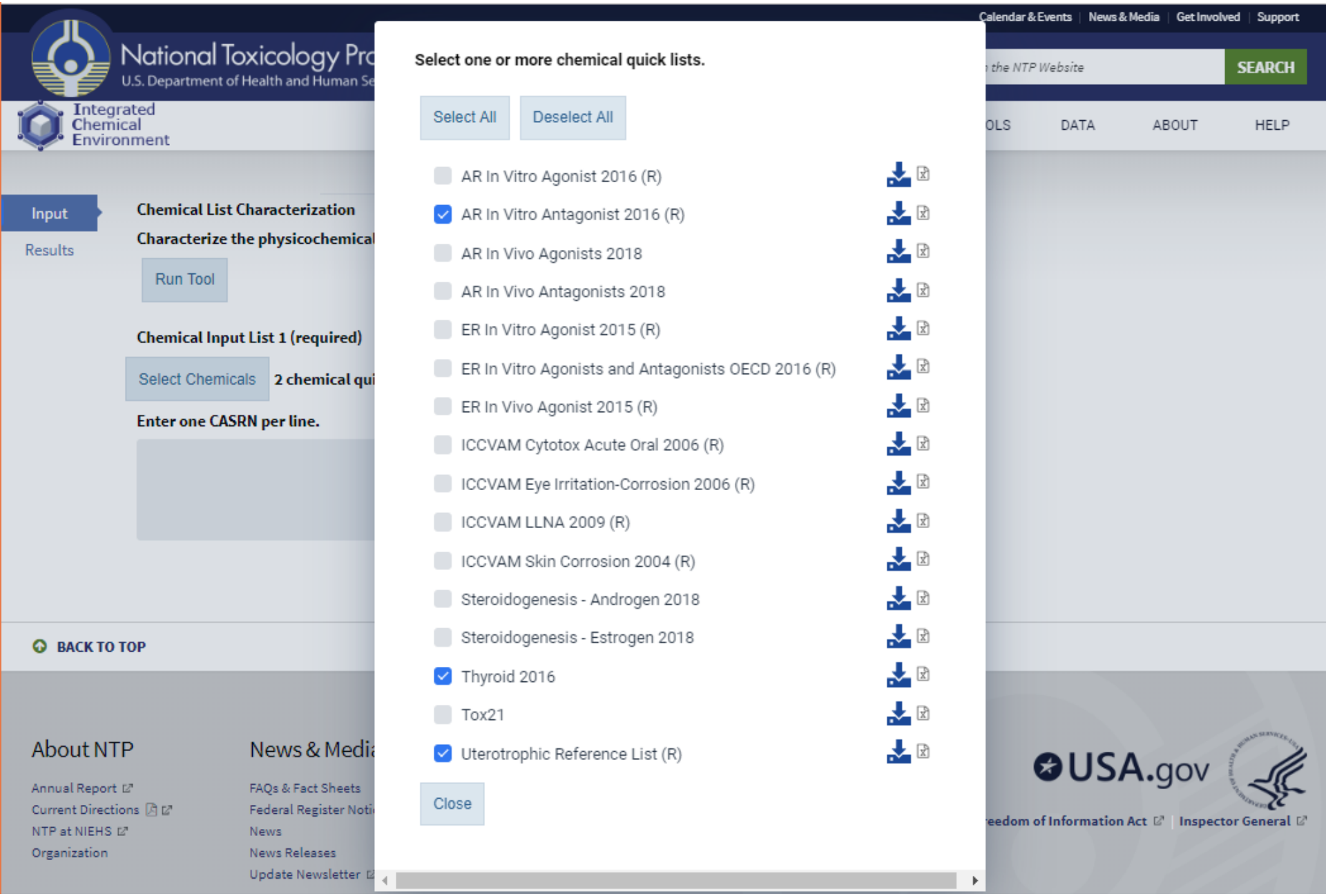
Chemical Input List 2 (optional)

Select Chemicals **Select Chemical Quick List**

Enter one CASRN per line.

BACK TO TOP


Calendar & Events | News & Media | Get Involved | Support
National Toxicology Pro
U.S. Department of Health and Human Se
NTP Website
SEARCH
Integrated Chemical Environment
DATA
ABOUT
HELP
Input
Results
Chemical List Characterization
Characterize the physicochemical
Run Tool
Chemical Input List 1 (required)
Select Chemicals
2 chemical qui
Enter one CASRN per line.
BACK TO TOP
Select one or more chemical quick lists.
Select All
Deselect All
AR In Vitro Agonist 2016 (R)
AR In Vitro Antagonist 2016 (R)
AR In Vivo Agonists 2018
AR In Vivo Antagonists 2018
ER In Vitro Agonist 2015 (R)
ER In Vitro Agonists and Antagonists OECD 2016 (R)
ER In Vivo Agonist 2015 (R)
ICCVAM Cytotox Acute Oral 2006 (R)
ICCVAM Eye Irritation-Corrosion 2006 (R)
ICCVAM LLNA 2009 (R)
ICCVAM Skin Corrosion 2004 (R)
Steroidogenesis - Androgen 2018
Steroidogenesis - Estrogen 2018
Thyroid 2016
Tox21
Uterotrophic Reference List (R)
Close
About NTP
Annual Report
Current Directions
NTP at NIEHS
Organization
News & Media
FAQs & Fact Sheets
Federal Register Noti
News
News Releases
Update Newsletter
USA.gov
lom of Information Act
Inspector General


Calendar & Events | News & Media | Get Involved | Support
National Toxicology Pro
U.S. Department of Health and Human Se
the NTP Website
SEARCH
Integrated Chemical Environment
OLS
DATA
ABOUT
HELP
Input
Results
Chemical List Characterization
Characterize the physicochemical
Run Tool
Chemical Input List 1 (required)
Select Chemicals
2 chemical qui
Enter one CASRN per line.
BACK TO TOP
Select one or more chemical quick lists.
Select All
Deselect All
AR In Vitro Agonist 2016 (R)
AR In Vitro Antagonist 2016 (R)
AR In Vivo Agonists 2018
AR In Vivo Antagonists 2018
ER In Vitro Agonist 2015 (R)
ER In Vitro Agonists and Antagonists OECD 2016 (R)
ER In Vivo Agonist 2015 (R)
ICCVAM Cytotox Acute Oral 2006 (R)
ICCVAM Eye Irritation-Corrosion 2006 (R)
ICCVAM LLNA 2009 (R)
ICCVAM Skin Corrosion 2004 (R)
Steroidogenesis - Androgen 2018
Steroidogenesis - Estrogen 2018
Thyroid 2016
Tox21
Uterotrophic Reference List (R)
Close
About NTP
Annual Report
Current Directions
NTP at NIEHS
Organization
News & Media
FAQs & Fact Sheets
Federal Register Noti
News
News Releases
Update Newsletter
USA.gov
eedom of Information Act
Inspector General

Chemical Characterization Results

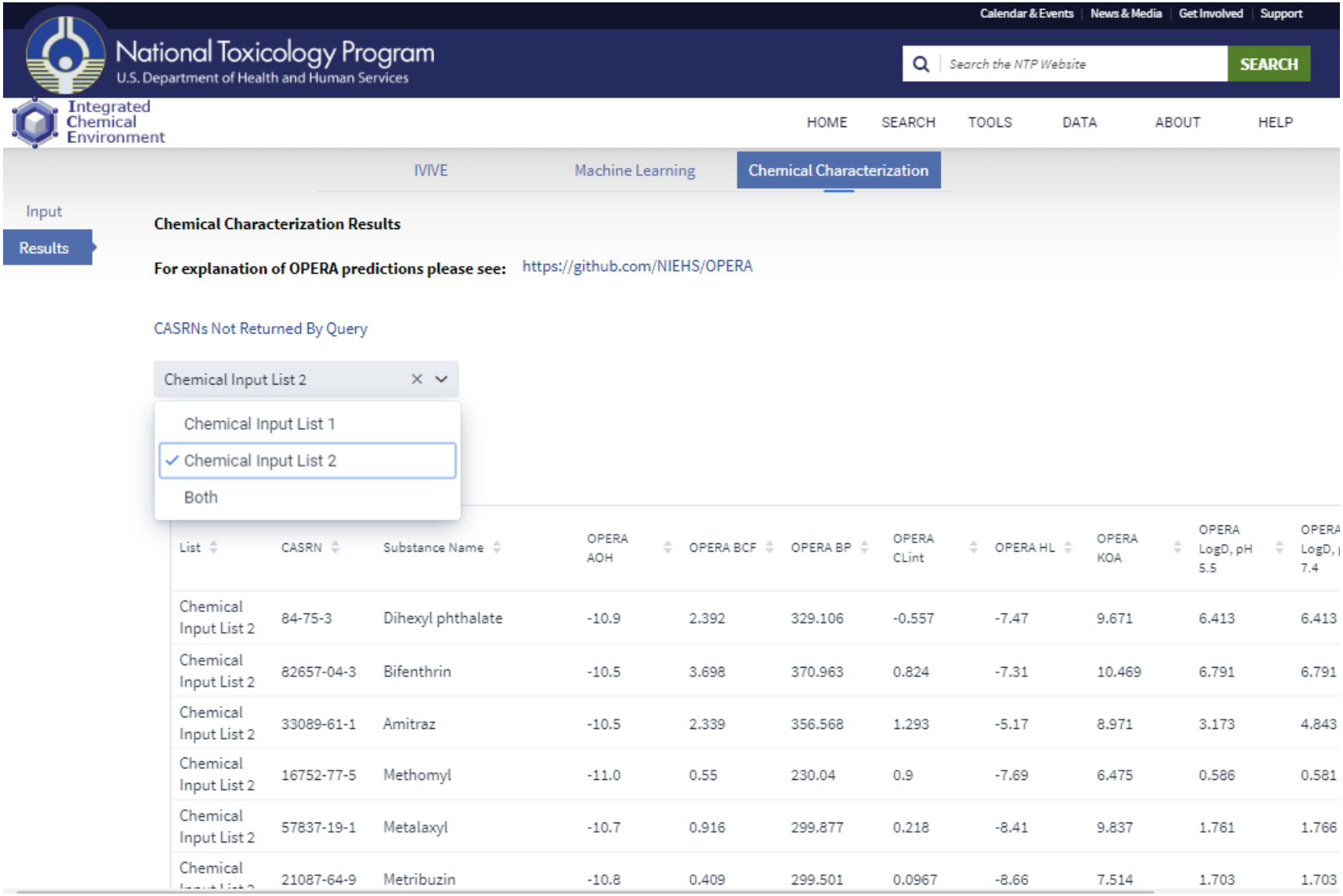
For explanation of OPERA predictions please see: https://github.com/NIEHS/OPERA

CASRNs Not Returned By Query

Both

Text Excel

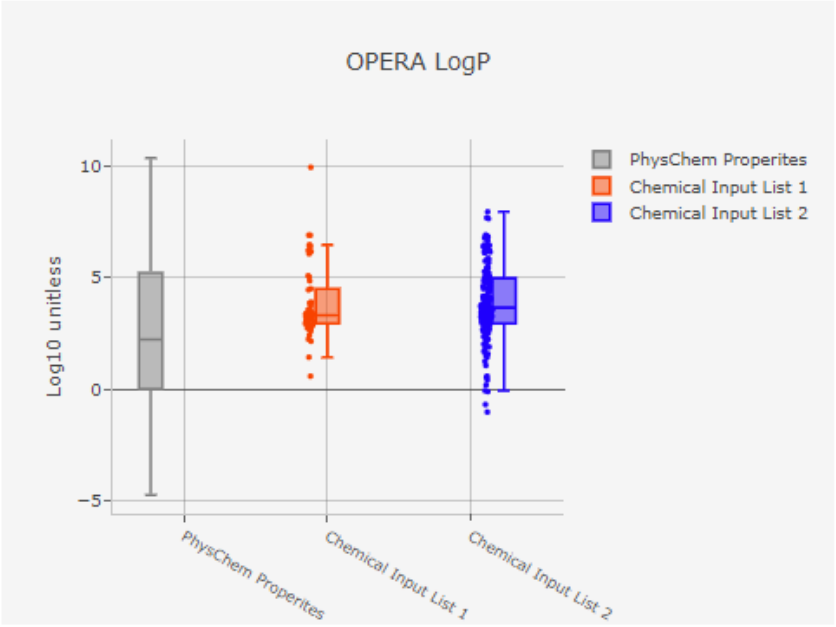
List	CASRN	Substance Name	OPERA AOH	OPERA BCF	OPERA BP	OPERA CLint	OPERA HL	OPERA KOA	OPERA LogD, pH 5.5	OPERA LogD, p 7.4
Chemical Input List 1	17804-35-2	Benomyl	-10.9	0.809	275.812	1.723	-11.3	9.432	0.919	1.557
Chemical Input List 1	16752-77-5	Methomyl	-11.0	0.55	230.04	0.9	-7.69	6.475	0.586	0.581
Chemical Input List 1	51-98-9	Norethindrone acetate	-9.85	1.594	352.481	0.926	-7.31	9.869	3.579	3.579
Chemical Input List 1	122-14-5	Fenitrothion	-10.8	1.923	353.148	1.016	-6.22	8.866	3.375	3.318
Chemical Input List 1	789-02-6	o,p'-DDT	-12.2	4.174	350.378	1.194	-4.84	9.321	6.914	6.914
Chemical Input List 1	68-22-4	Norethindrone	-10.1	1.776	310.374	1.47	-7.53	11.009	2.947	2.947



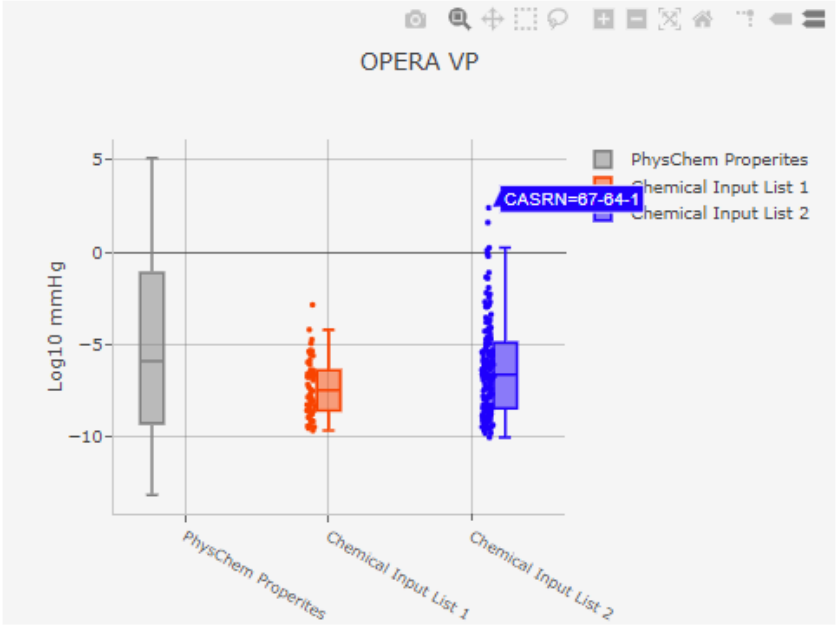
List	CASRN	Substance Name	OPERA AOH	OPERA BCF	OPERA BP	OPERA CLint	OPERA HL	OPERA KOA	OPERA LogD, pH 5.5	OPERA LogD, pH 7.4
Chemical Input List 2	84-75-3	Dihexyl phthalate	-10.9	2.392	329.106	-0.557	-7.47	9.671	6.413	6.413
Chemical Input List 2	82657-04-3	Bifenthrin	-10.5	3.698	370.963	0.824	-7.31	10.469	6.791	6.791
Chemical Input List 2	33089-61-1	Amitraz	-10.5	2.339	356.568	1.293	-5.17	8.971	3.173	4.843
Chemical Input List 2	16752-77-5	Methomyl	-11.0	0.55	230.04	0.9	-7.69	6.475	0.586	0.581
Chemical Input List 2	57837-19-1	Metalaxyl	-10.7	0.916	299.877	0.218	-8.41	9.837	1.761	1.766
Chemical Input List 2	21087-64-9	Metribuzin	-10.8	0.409	299.501	0.0967	-8.66	7.514	1.703	1.703

Box and Whiskers Charts

OPERA LogP



OPERA VP



ICE tool: Machine Learning

- In silico approach where the machine (algorithm) “learns” how to predict an outcome from a set of features based on training data
- Machine learning tool is aimed at:
  - Allowing users to explore data relationships
  - Look at what assays appear predictive of an endpoint of interest
  - See how different algorithms might sway results

Machine Learning Tool Input

The Machine Learning tool allows user to build simple predictive models for data exploration using ICE data.

Run Tool

Prediction Type:

Classification

LLNA Call Human Potency Call Uterotrophic Call

Select Machine Learning Methods

rpart knn
svmRadial rf
pls

Select Endpoints for Model Building

Assay	Endpoint

Chemicals to use

Select Chemicals **Select Chemical Quick List**

Enter one CASRN per line.

Input
Results

Machine Learning Tool Input

The Machine Learning tool allows user to build simple predictive models for data exploration using ICE data.

Run Tool

Prediction Type:

Classification

- ✓ Classification
- Regression

Potency Call Uterotrophic Call

Select Endpoints for Model Building

Assay	Endpoint

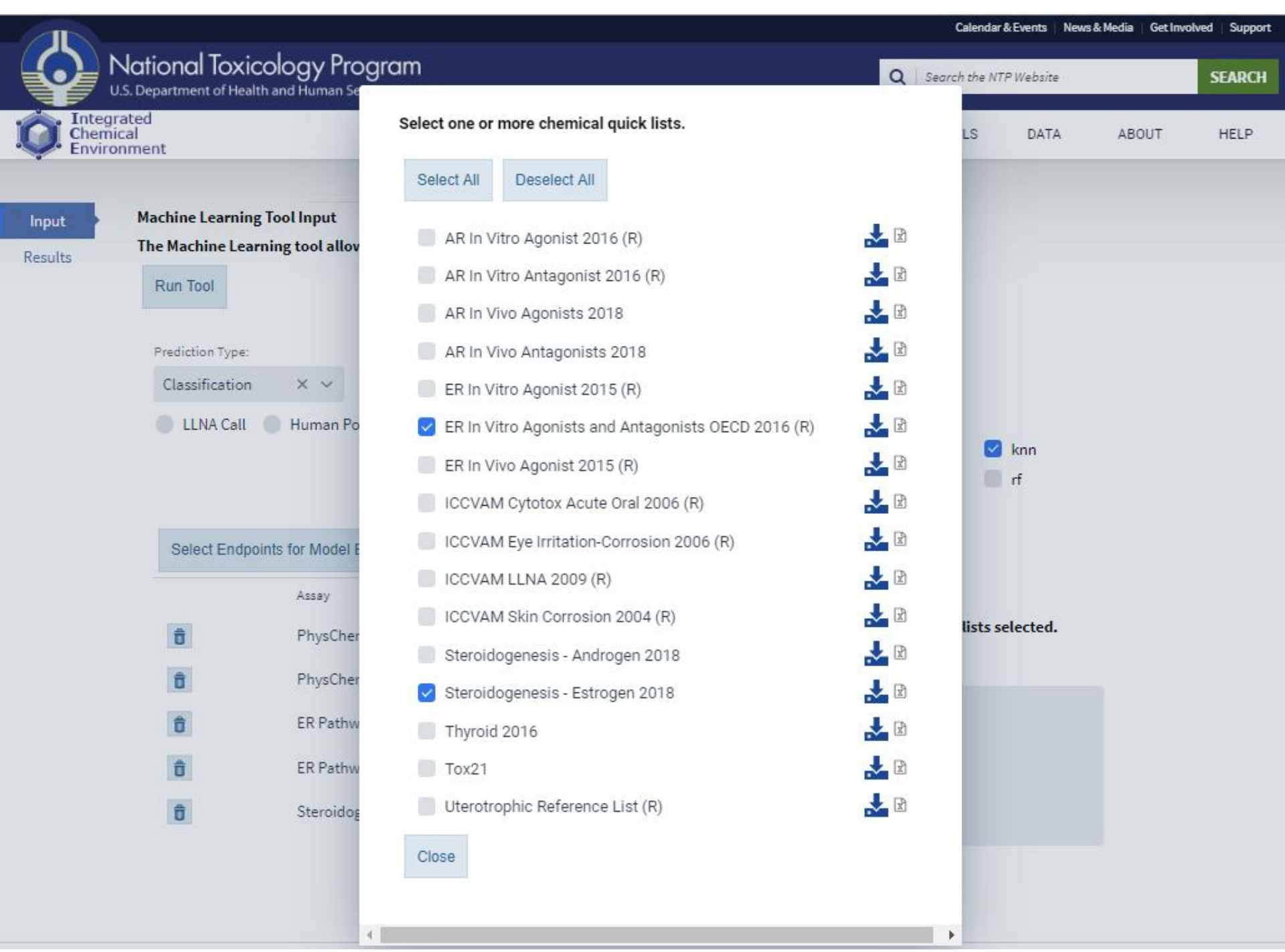
Select Machine Learning Methods

- rpart
- knn
- svmRadial
- rf
- pls

Chemicals to use

Select Chemicals **Select Chemical Quick List**

Enter one CASRN per line.


Calendar & Events | News & Media | Get Involved | Support
National Toxicology Program
U.S. Department of Health and Human Se
Search the NTP Website
SEARCH
Integrated Chemical Environment
LS
DATA
ABOUT
HELP
Input
Results
Machine Learning Tool Input
The Machine Learning tool allov
Run Tool
Prediction Type:
Classification
LLNA Call
Human Po
knn
rf
Select Endpoints for Model E
Assay
PhysCher
PhysCher
ER Pathw
ER Pathw
Steroidog
lists selected.
Select one or more chemical quick lists.
Select All
Deselect All
AR In Vitro Agonist 2016 (R)
AR In Vitro Antagonist 2016 (R)
AR In Vivo Agonists 2018
AR In Vivo Antagonists 2018
ER In Vitro Agonist 2015 (R)
ER In Vitro Agonists and Antagonists OECD 2016 (R)
ER In Vivo Agonist 2015 (R)
ICCVAM Cytotox Acute Oral 2006 (R)
ICCVAM Eye Irritation-Corrosion 2006 (R)
ICCVAM LLNA 2009 (R)
ICCVAM Skin Corrosion 2004 (R)
Steroidogenesis - Androgen 2018
Steroidogenesis - Estrogen 2018
Thyroid 2016
Tox21
Uterotrophic Reference List (R)
Close

Machine Learning Tool Input

The Machine Learning tool allows user to build simple predictive models for data exploration using ICE data.

Run Tool

Prediction Type:

Classification

LLNA Call Human Potency Call Uterotrophic Call

Select Machine Learning Methods

- [ ] rpart
- [x] knn
- [x] svmRadial
- [ ] rf
- [ ] pls

Select Endpoints for Model Building

Assay	Endpoint
PhysChem Properties	CLint
PhysChem Properties	LogP
ER Pathway Model, Ant...	Model Score
ER Pathway Model, Ago...	Model Score
Steroidogenesis	Call

Chemicals to use

Select Chemicals **2 chemical quick lists selected.**

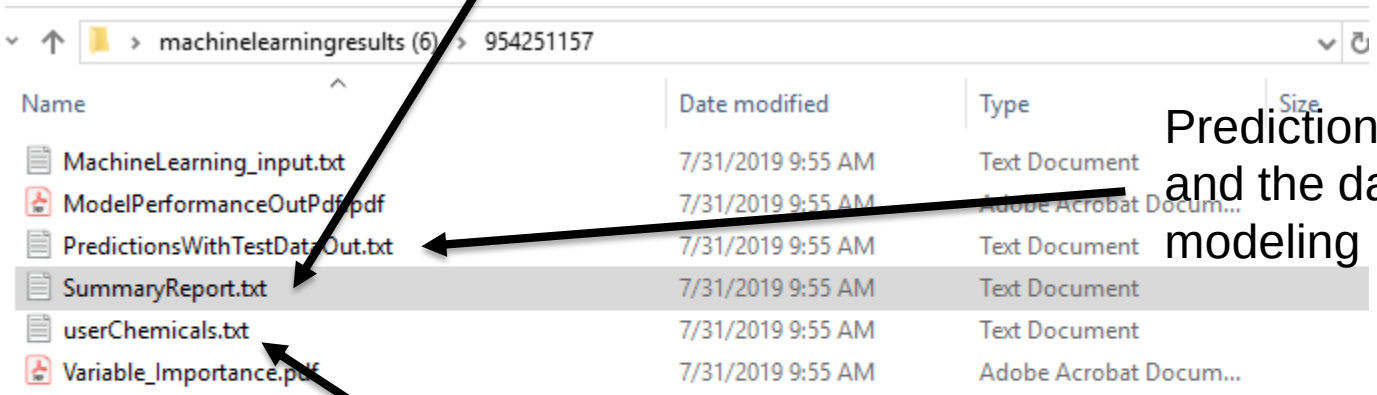
Enter one CASRN per line.

Machine Learning workflow results

Machine Learning Results Zip File

BACK TO TOP

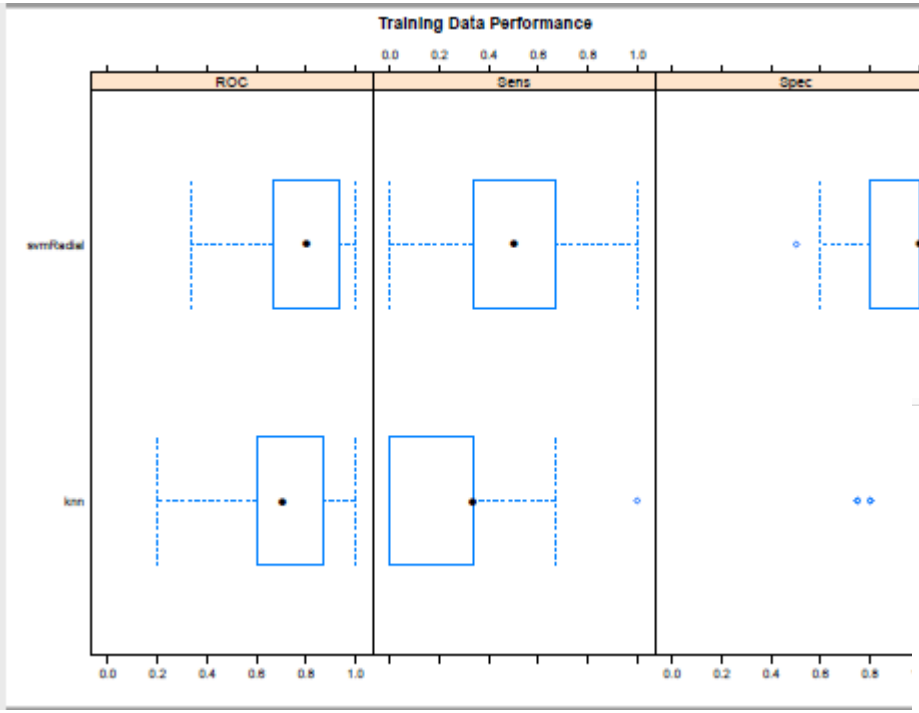
Summary of data processing and model performance statistics

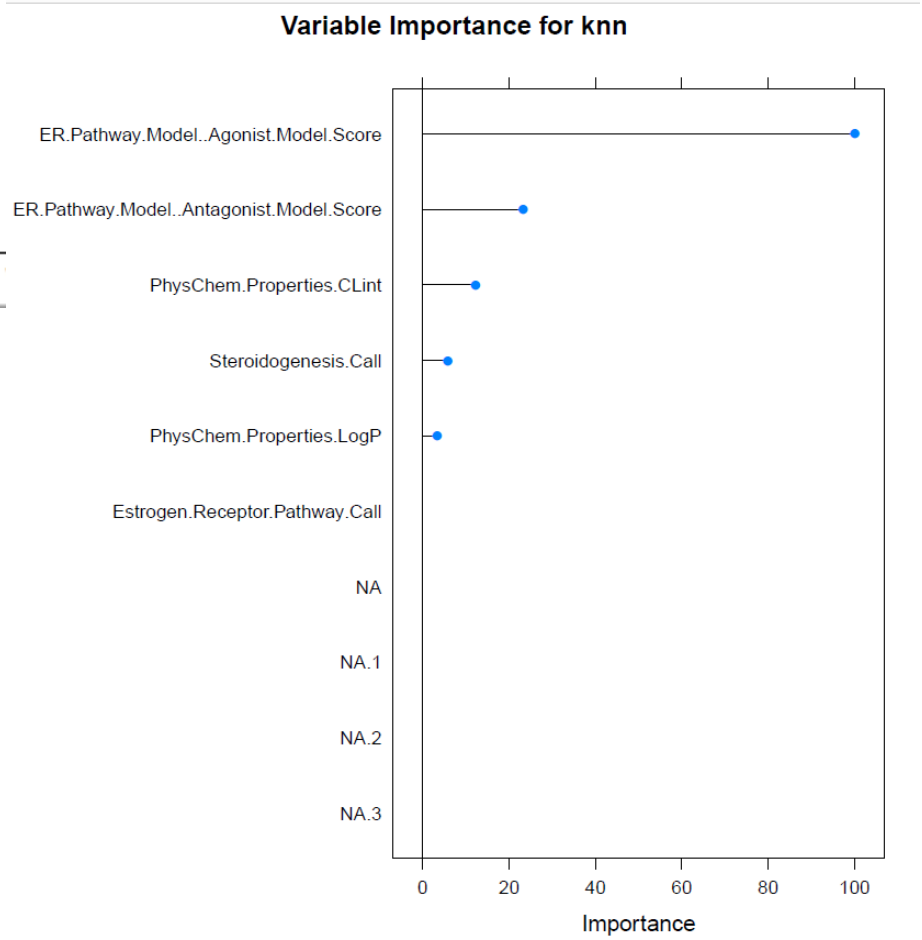


Predictions (results) and the data used for modeling

User provided chemicals

Note: if there is an error, an error file will be written instead


Training Data Performance
ROC
Sens
Spec
svmRadial
knn
0.0
0.2
0.4
0.6
0.8
1.0


Variable Importance for knn
ER.Pathway.Model..Agonist.Model.Score
ER.Pathway.Model..Antagonist.Model.Score
PhysChem.Properties.CLint
Steroidogenesis.Call
PhysChem.Properties.LogP
Estrogen.Receptor.Pathway.Call
NA
NA.1
NA.2
NA.3
0
20
40
60
80
100
Importance

ICE tool: IVIVE

- In vitro to in vivo extrapolation is a computational approach that calculates an equivilant in vivo administered dose based on the in vitro response concentration
- IVIVE tool is aimed at:
  - Allowing users to calculate the equivalent administered dose (EAD) that would be needed to achieve the concentration that yielded the in vitro response (example: AC50)
  - Compare relationships between EADs resulting from different in vitro assays and different in vivo endpoints
    - Informs on the predictability of the in vitro assay for the given endpoint
  - Characterize the probability of a biological effect given the likely in vivo exposure

IVIVE Workflow Input

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

Run Workflow

Select Chemicals **1 chemical quick list selected.**

Enter one CASRN per line.

Select Assays

- [ ] Androgen Receptor Pathway
- [ ] Cell Cycle
- [ ] Cytochrome P450
- [ ] Cytotoxicity (burst)
- [ ] Cytotoxicity (burst + stress)
- [x] Estrogen Receptor Pathway
- [ ] G Protein-Coupled Receptors
- [x] Mitochondrial
- [ ] Nuclear Receptor
- [x] Steroidogenesis
- [ ] All Other Tox21 Assays

Select in vitro endpoint:

AC50

- ✓ 1C
- Glu PBPK
- Solve_3comp

Select Route

iv

Dosing Intervals, hours

24

Select model:

1C

Days of exposure, days

3

IVIVE workflow results

CASRNs Not Returned By Query

Download PhysChem Input

Download Chemical/Metric Input

Download Results

Text Excel Clear Filter **Number of rows = 1241.**

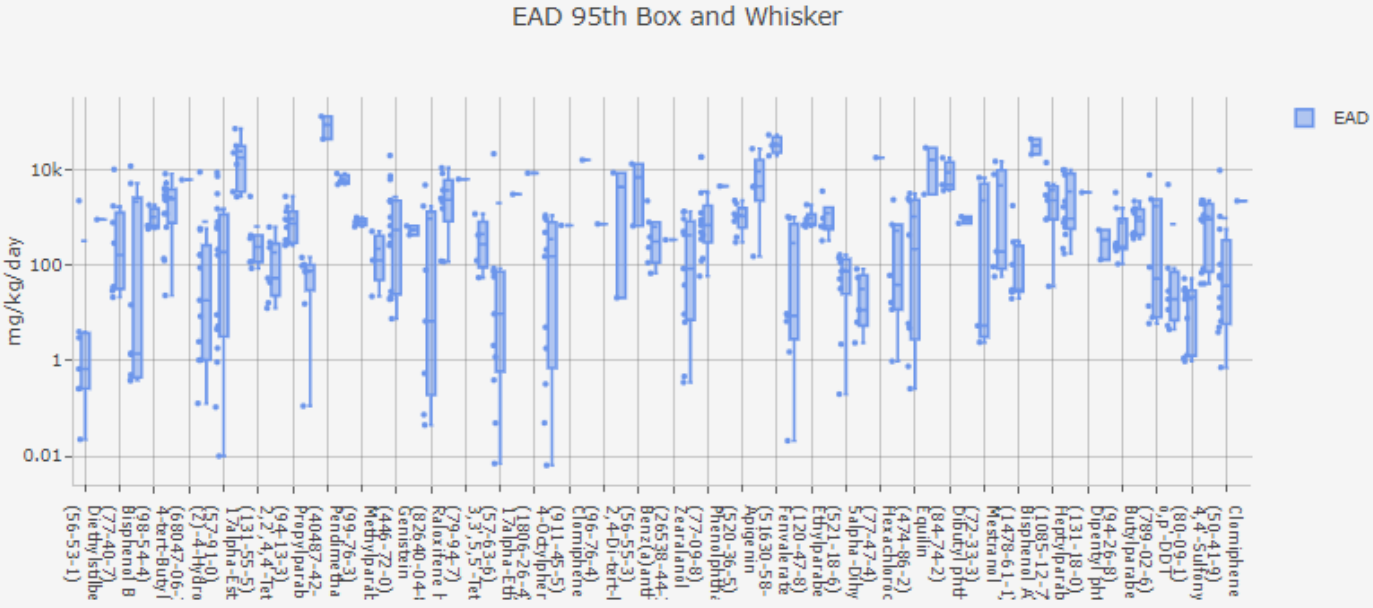
Chemical	CASRN	DTXSID	Assay	AC50 uM	EAD 50th Percentile (mg/kg/d...	EAD 95th Percentile (mg/kg/d...	LogP	Clint	Fraction Unbound	PK
Bis(2-ethylhexyl...	103-23-1	DTXSID00...	TOX21_ER...	10.895	NA	2391.688	6.851	1.177	0.038	NA
Testostero...	58-22-0	DTXSID80...	TOX21_ER...	13.28	NA	245.816	3.25	1.341	0.356	9.7
Testostero...	58-22-0	DTXSID80...	TOX21_ER...	0.0165	NA	0.305	3.25	1.341	0.356	9.7
2-Mercaptob...	149-30-4	DTXSID10...	ATG_ERa_...	134.749	NA	14309.439	2.659	1.26	0.016	6.2

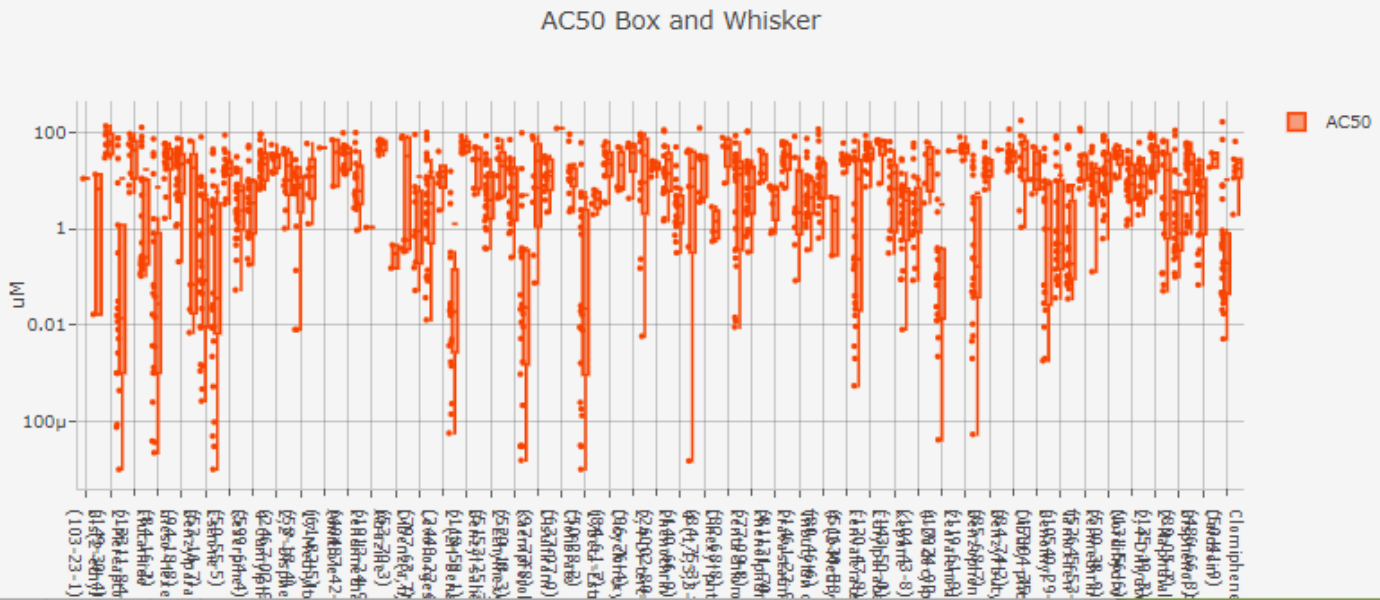
Select EAD to visualize:

EAD 95th

Select in vivo data to display.

Log Axis





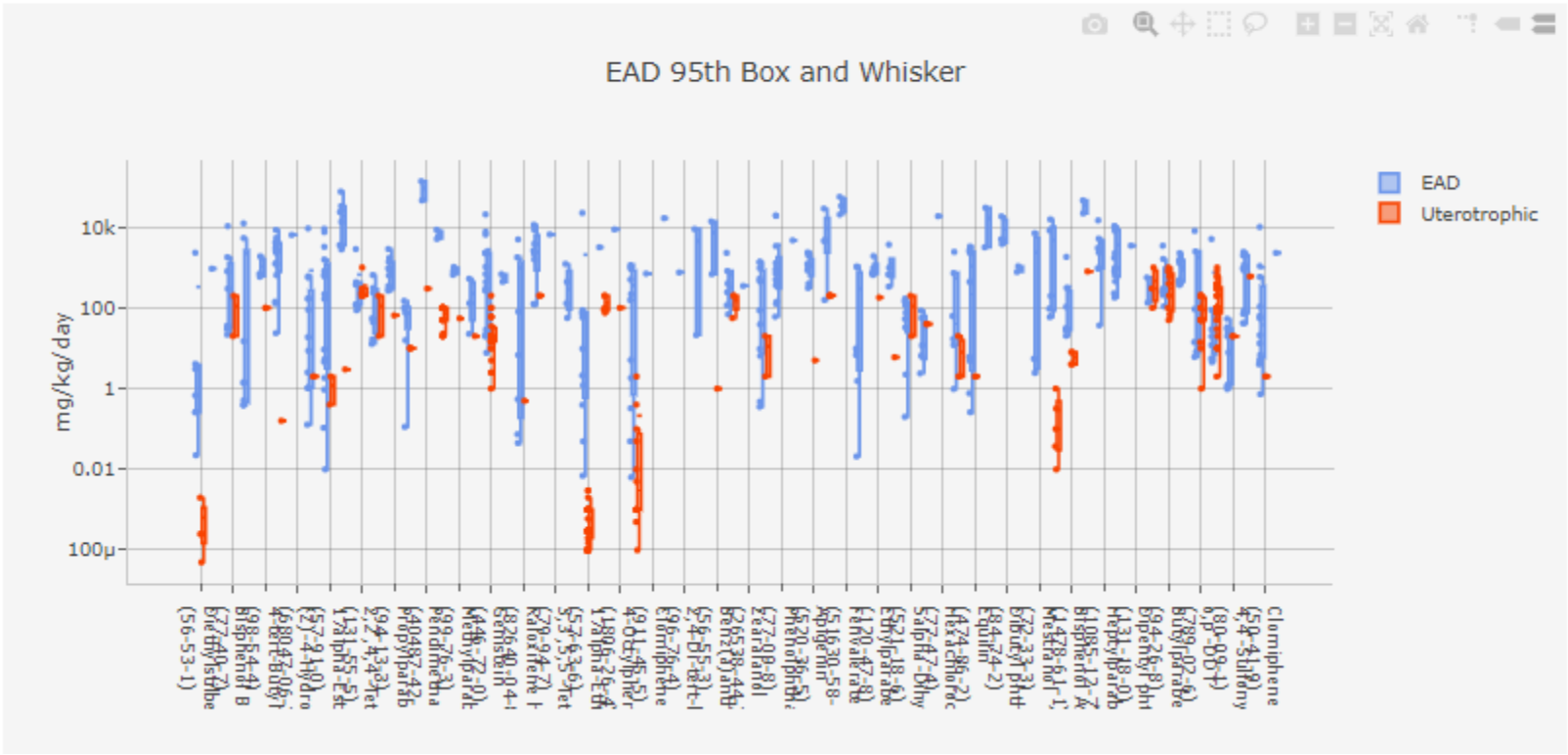
Select EAD to visualize:

EAD 95th

Select in vivo data to display.

Uterotrophic

Log Axis



Chemical	CASRN	DTXSID	Assay	AC50 uM	EAD 50th Percentile (mg/kg/d...	EAD 95th Percentile (mg/kg/d...	LogP	Clint	Fraction Unbound	PK
Bis(2-ethylhexyl...	103-23-1	DTXSID0					.851	1.177	0.038	NA
Testostero...	58-22-0	DTXSID8					.25	1.341	0.356	9.7
Testostero...	58-22-0	DTXSID8					.25	1.341	0.356	9.7
2-Mercaptob...	149-30-4	DTXSID1					.659	1.26	0.016	6.2

assays: 17/54

assay

ER

- TOX21_ERa_LUC_BG1_Antagonist
- TOX21_ERa_BLA_Agonist_ratio
- OT_ER_ERaERb_0480
- OT_ERa_EREGFP_0480
- NVS_NR_mERa
- OT_ER_ERbERb_1440
- TOX21_ERa_BLA_Antagonist_ratio
- OT_ER_ERaERa_0480
- ATG_ERa_TRANS_up
- NVS_NR_hER

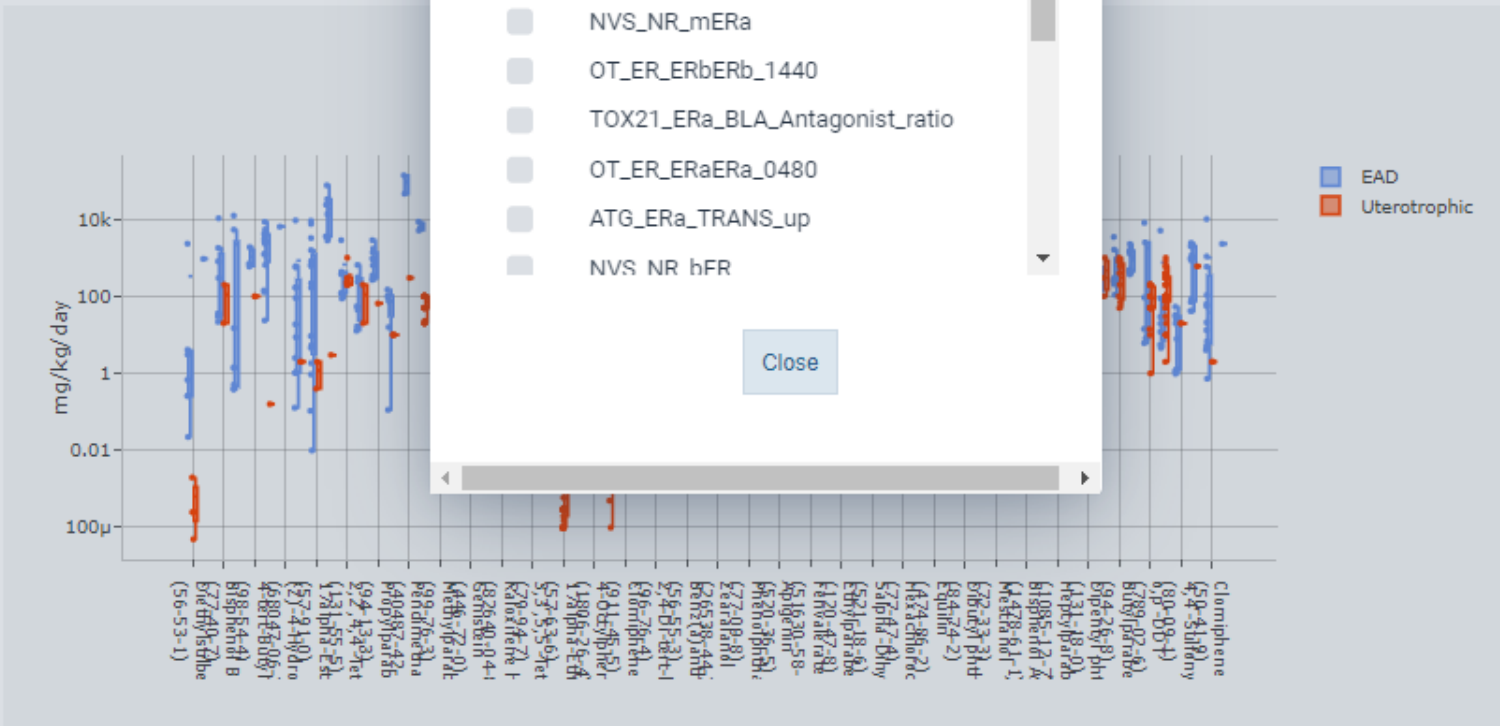
Close

Select EAD to visualize:

EAD 95th

Select in vivo

Uterotrop



Select EAD to visualize:

EAD 95th

Select in vivo data to display.

Uterotrophic

Log Axis