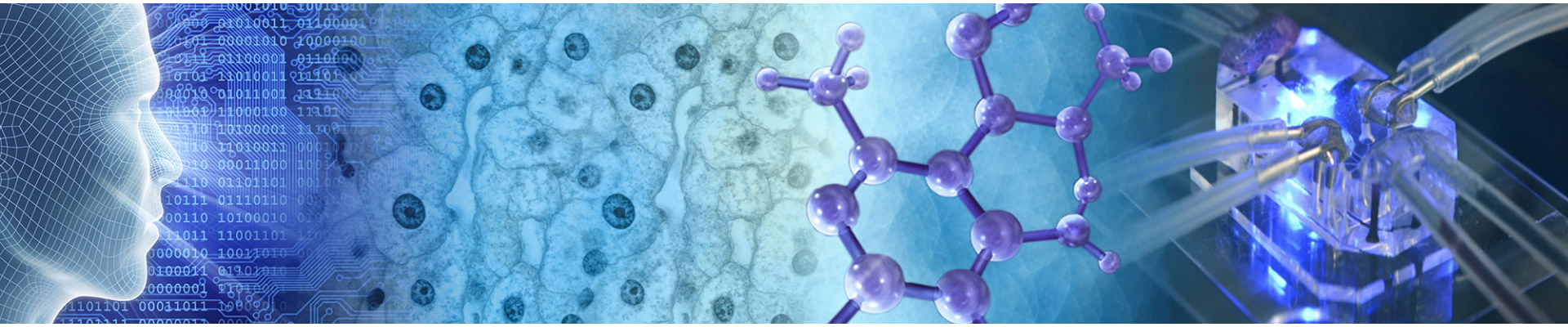
NTP
National Toxicology Program



The Integrated Chemical Environment

Tools and data to support toxicity assessments

Presented by Shannon Bell, ILS

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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.

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Arpit Tandon

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

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

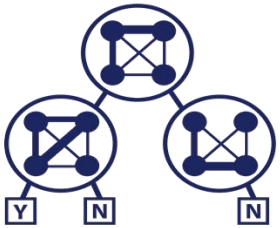
To contact us:
ICE-support@niehs.nih.gov

Integrated Chemical Environment

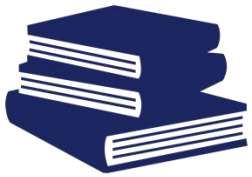
- Resource access point designed for NICEATM stakeholders
  - U.S. Federal agencies and agencies within government that use or generate toxicological data
  - Researchers and Institutional Animal Care and Use Committee (IACUC) members in companies or research institutions that perform toxicological testing
  - Companies that develop toxicological tests
  - Animal welfare organizations
  - Consumer protection organizations
  - The public
- 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

What is ICE?

Computational models



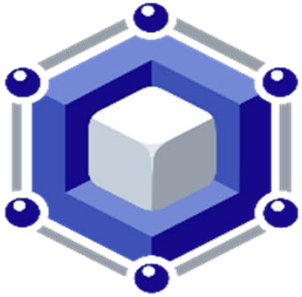
Published data



Databases

Validation studies

Download reference lists

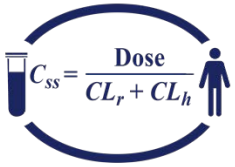


Export queries and results

Search

Data

IVIVE



Chemical characterization

Data in ICE

Toxicity endpoint	Assays	# of chemicals*
Acute Oral Toxicity	*In vivo* acute oral toxicity	10,335**
Skin Sensitization	DPRA, hCLAT, KeratinoSens, LLNA, human potency, etc.	578
Skin Irritation	*In vivo* acute skin irritation/corrosion, 4h HPT; *In vitro* irritation/corrosion (e.g.,EpiSkin, TER)	819
Eye Irritation	*In vivo* acute eye irritation/corrosion (e.g., Draize eye), Vitrigel	796
Endocrine	AR/ER Pathway Models, Uterotrophic, Hershberger, AR/ER transactivation	280**
cHTS	Curated ToxCast and Tox21 assays	9,213
OPERA predictions	BP, HLC, KOA, BCF, LogP, MP, MW, VP, WS, COMPARA, CERAPP, CATMoS, intrinsic clearance, fraction unbound	838,911
Formulation data	Six-pack	297 (747 formulations)
Experimental ADME	Intrinsic clearance and fraction unbound data generated from experimental studies	1,603

*Values from July 2020

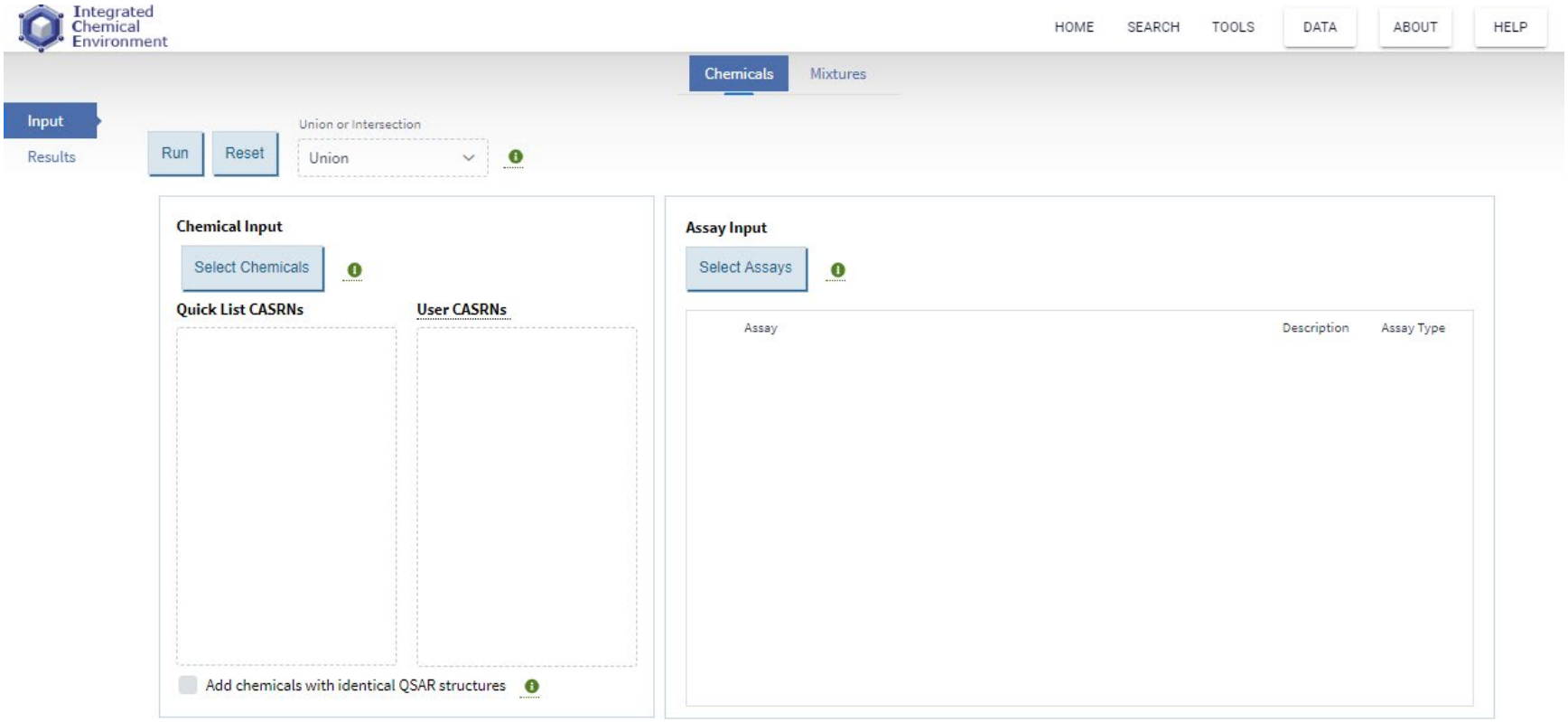
**Does not include in silico predictions from OPERA or MOA-linked assays

New Developments and Future Plans

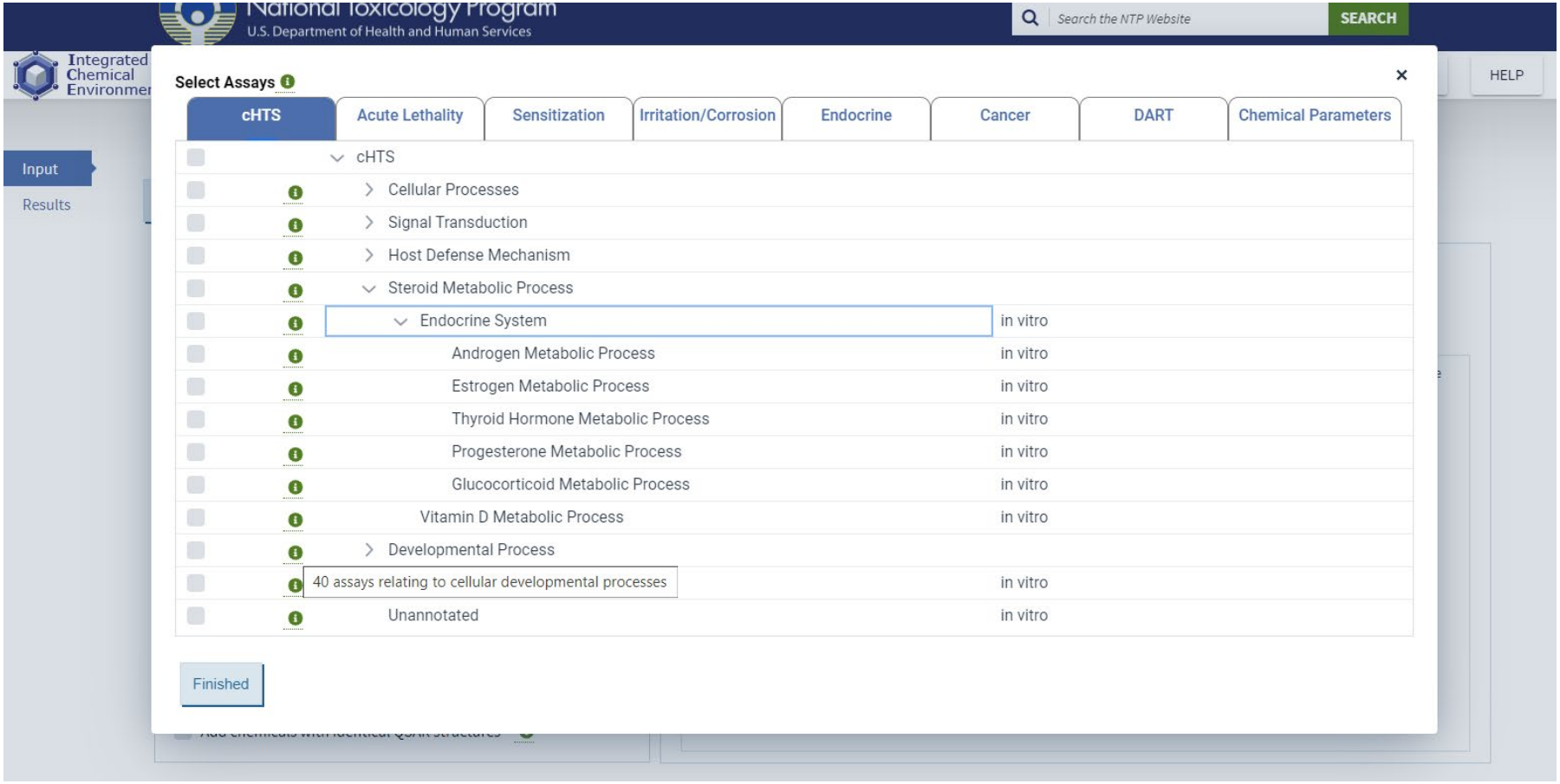
- An NTP advisory group formed
  - Providing additional guidance on tool development
  - Leveraging domain expertise as ICE expands its increased curation and toxicological context of assays
- Integration with other resources
  - Send chemical list to bulk query on EPA's Chemical Dashboard
  - Links to NTP's Chemical Effects in Biological Systems (CEBS) planned for fall
- Increased visualizations and interactions under development

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

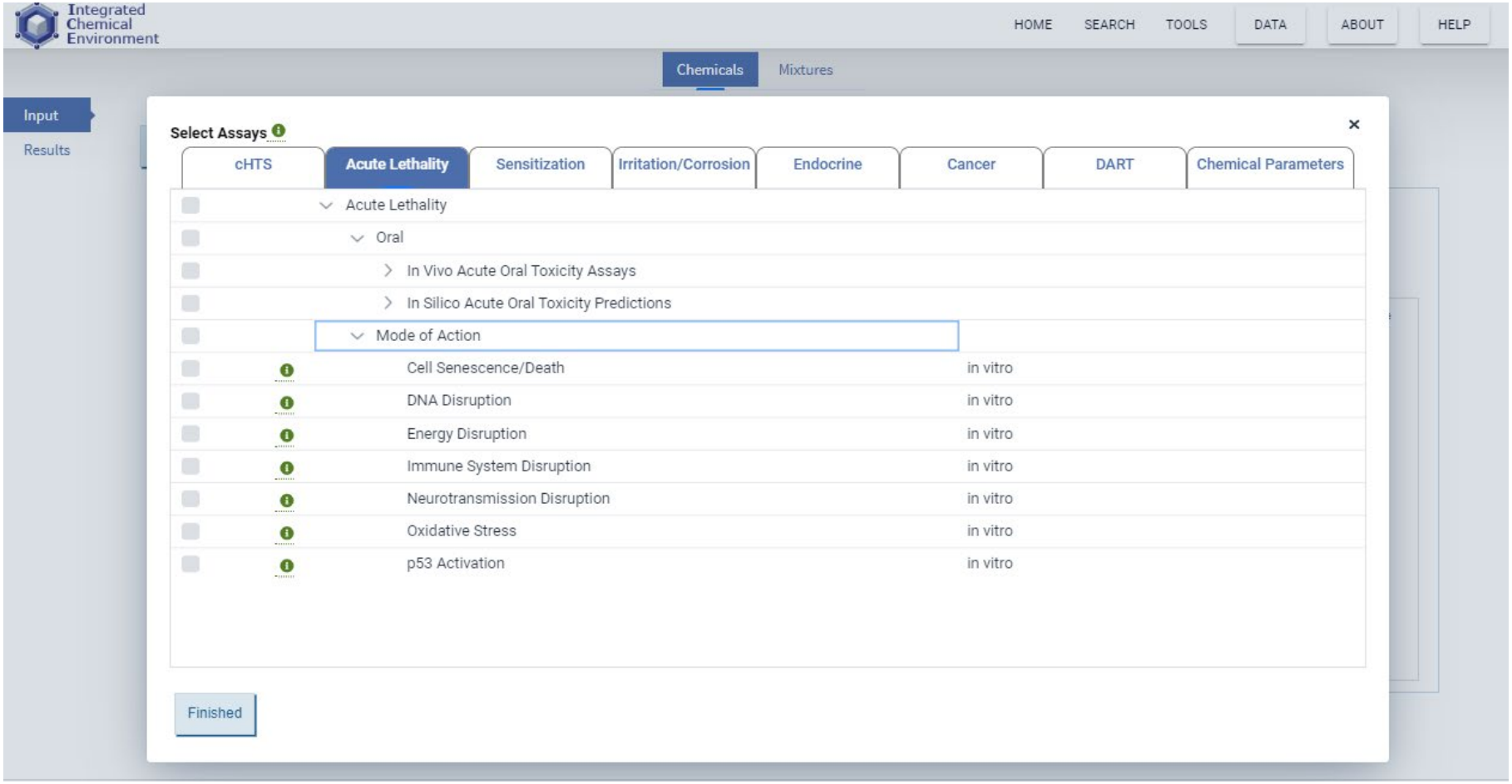
ICE Search


Integrated Chemical Environment
HOME
SEARCH
TOOLS
DATA
ABOUT
HELP
Chemicals
Mixtures
Input
Results
Run
Reset
Union or Intersection
Union
Chemical Input
Select Chemicals
Quick List CASRNs
User CASRNs
Add chemicals with identical QSAR structures
Assay Input
Select Assays
Assay
Description
Assay Type

ICE Search


National Toxicology Program
U.S. Department of Health and Human Services
Search the NTP Website
SEARCH
Integrated Chemical Environment
HELP
Input
Results
Select Assays
cHTS
Acute Lethality
Sensitization
Irritation/Corrosion
Endocrine
Cancer
DART
Chemical Parameters
cHTS
Cellular Processes
Signal Transduction
Host Defense Mechanism
Steroid Metabolic Process
Endocrine System
in vitro
Androgen Metabolic Process
in vitro
Estrogen Metabolic Process
in vitro
Thyroid Hormone Metabolic Process
in vitro
Progesterone Metabolic Process
in vitro
Glucocorticoid Metabolic Process
in vitro
Vitamin D Metabolic Process
in vitro
Developmental Process
40 assays relating to cellular developmental processes
in vitro
Unannotated
in vitro
Finished

ICE Search


Integrated Chemical Environment
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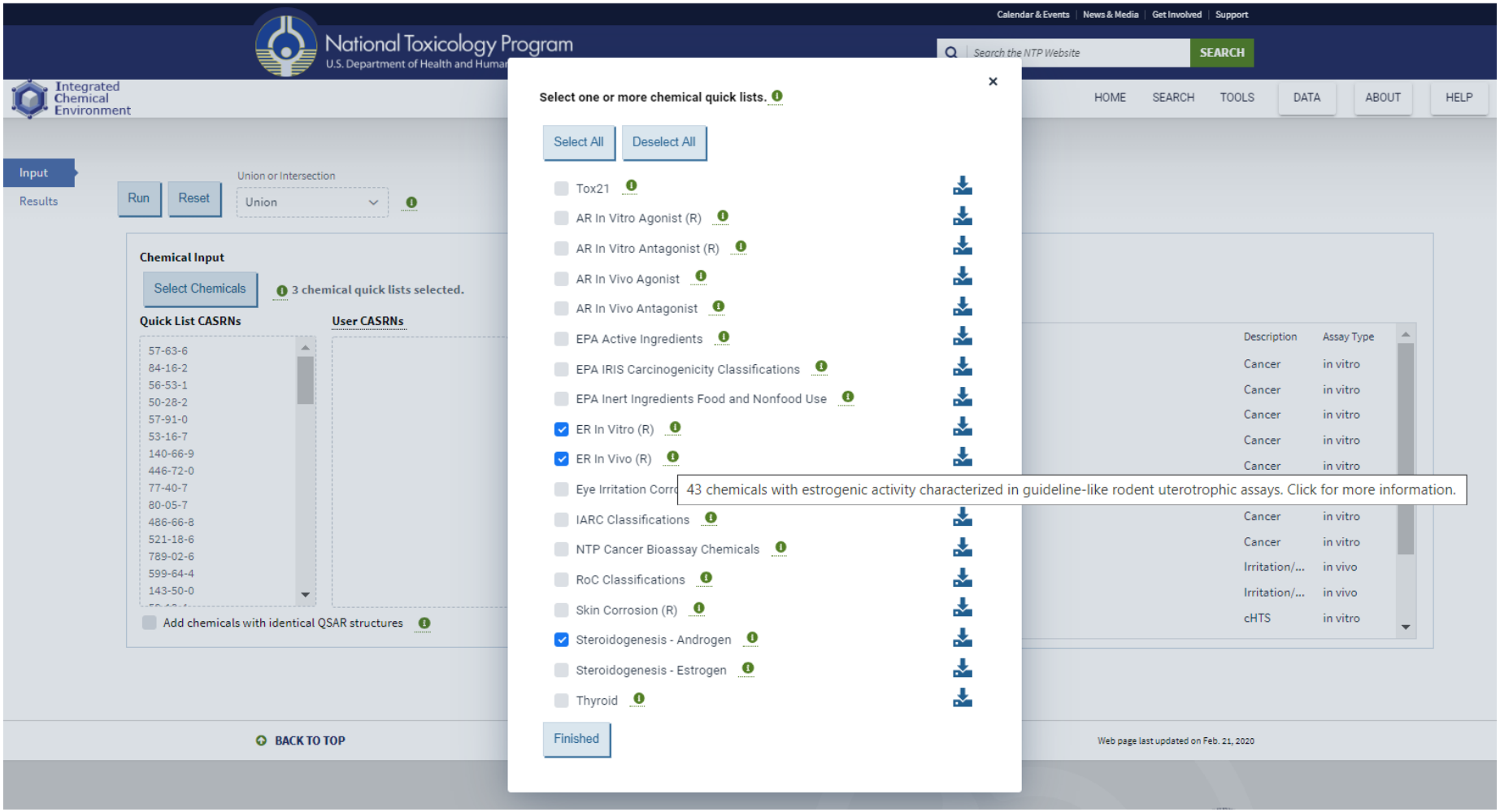
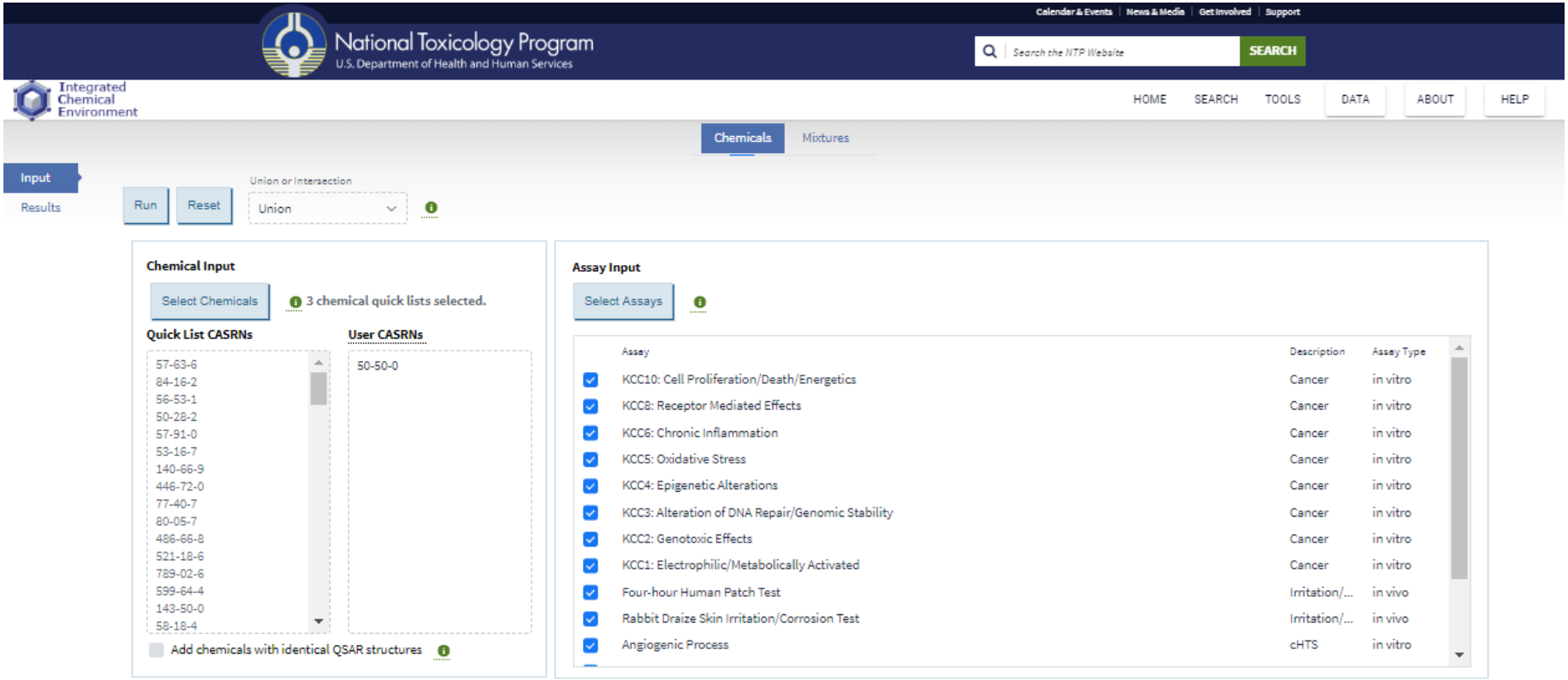
ABOUT
HELP
Chemicals
Mixtures
Input
Results
Select Assays
cHTS
Acute Lethality
Sensitization
Irritation/Corrosion
Endocrine
Cancer
DART
Chemical Parameters
Acute Lethality
Oral
In Vivo Acute Oral Toxicity Assays
In Silico Acute Oral Toxicity Predictions
Mode of Action
Cell Senescence/Death
in vitro
DNA Disruption
in vitro
Energy Disruption
in vitro
Immune System Disruption
in vitro
Neurotransmission Disruption
in vitro
Oxidative Stress
in vitro
p53 Activation
in vitro
Finished

ICE Search


Calendar & Events | News & Media | Get Involved | Support
National Toxicology Program
U.S. Department of Health and Human
Search the NTP Website
SEARCH
Integrated Chemical Environment
HOME SEARCH TOOLS DATA ABOUT HELP
Input
Results
Union or Intersection
Run
Reset
Union
Chemical Input
Select Chemicals
3 chemical quick lists selected.
Quick List CASRNs
User CASRNs
57-63-6
84-16-2
56-53-1
50-28-2
57-91-0
53-16-7
140-66-9
446-72-0
77-40-7
80-05-7
486-66-8
521-18-6
789-02-6
599-64-4
143-50-0
Add chemicals with identical QSAR structures
Select one or more chemical quick lists.
Select All
Deselect All
Tox21
AR In Vitro Agonist (R)
AR In Vitro Antagonist (R)
AR In Vivo Agonist
AR In Vivo Antagonist
EPA Active Ingredients
EPA IRIS Carcinogenicity Classifications
EPA Inert Ingredients Food and Nonfood Use
ER In Vitro (R)
ER In Vivo (R)
Eye Irritation Corro
IARC Classifications
NTP Cancer Bioassay Chemicals
RoC Classifications
Skin Corrosion (R)
Steroidogenesis - Androgen
Steroidogenesis - Estrogen
Thyroid
Finished
43 chemicals with estrogenic activity characterized in guideline-like rodent uterotrophic assays. Click for more information.
Description
Assay Type
Cancer in vitro
Cancer in vitro
Cancer in vitro
Cancer in vitro
Cancer in vitro
Cancer in vitro
Cancer in vitro
Irritation/... in vivo
Irritation/... in vivo
cHTS in vitro
BACK TO TOP
Web page last updated on Feb. 21, 2020

ICE Search


Calendar & Events | News & Media | Get Involved | Support
National Toxicology Program
U.S. Department of Health and Human Services
Search the NTP Website
SEARCH
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Reset
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Union
Chemical Input
Select Chemicals
3 chemical quick lists selected.
Quick List CASRNs
57-63-6
84-16-2
56-53-1
50-28-2
57-91-0
53-16-7
140-66-9
446-72-0
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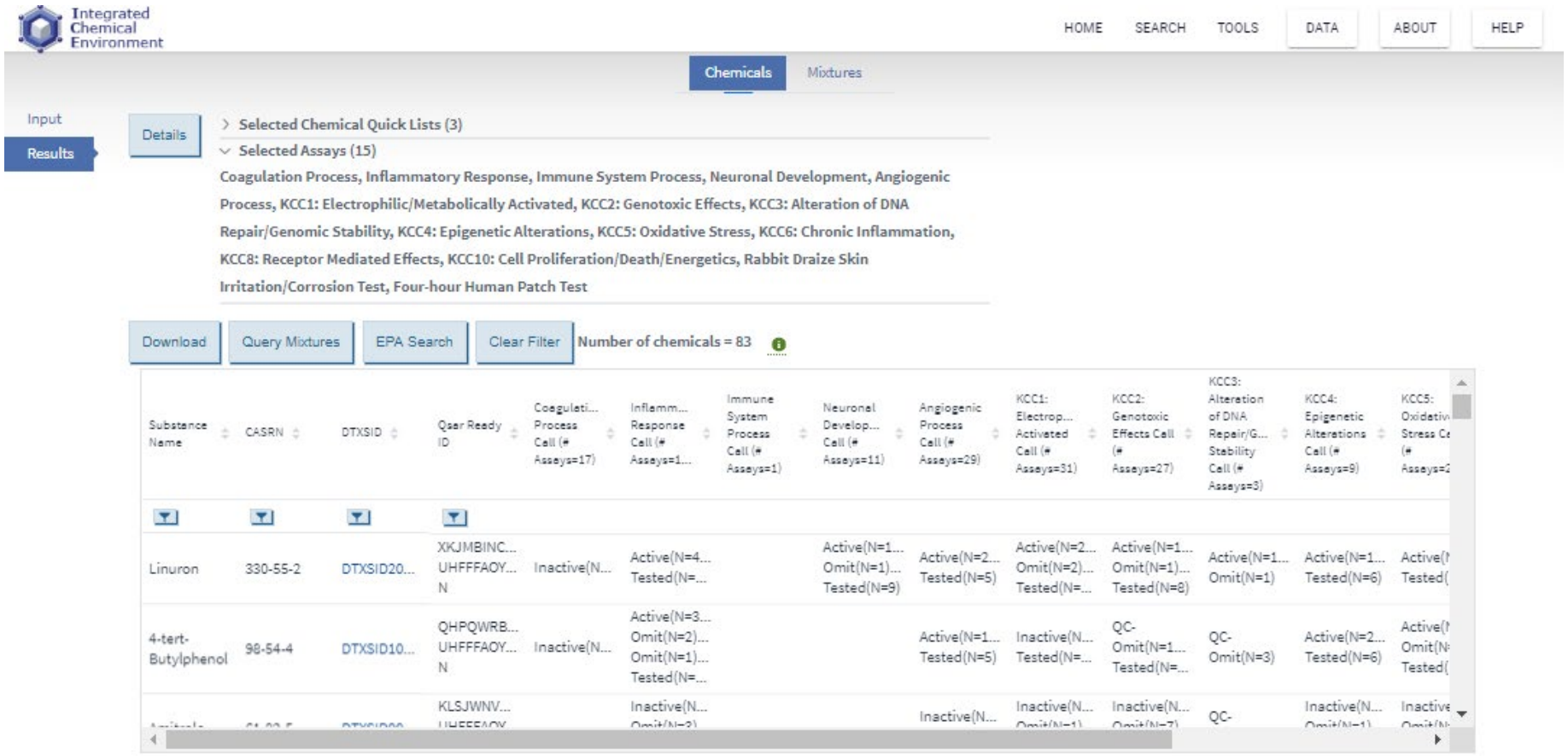
80-05-7
486-66-8
521-18-6
789-02-6
599-64-4
143-50-0
58-18-4
User CASRNs
50-50-0
Add chemicals with identical QSAR structures
Assay Input
Select Assays
Assay
Description
Assay Type
KCC10: Cell Proliferation/Death/Energetics
Cancer
in vitro
KCC8: Receptor Mediated Effects
Cancer
in vitro
KCC6: Chronic Inflammation
Cancer
in vitro
KCC5: Oxidative Stress
Cancer
in vitro
KCC4: Epigenetic Alterations
Cancer
in vitro
KCC3: Alteration of DNA Repair/Genomic Stability
Cancer
in vitro
KCC2: Genotoxic Effects
Cancer
in vitro
KCC1: Electrophilic/Metabolically Activated
Cancer
in vitro
Four-hour Human Patch Test
Irritation/...
in vivo
Rabbit Draize Skin Irritation/Corrosion Test
Irritation/...
in vivo
Angiogenic Process
cHTS
in vitro

ICE Search


Integrated Chemical Environment
HOME
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TOOLS
DATA
ABOUT
HELP
Chemicals
Mixtures
Input
Results
Details
Selected Chemical Quick Lists (3)
Selected Assays (15)
Coagulation Process, Inflammatory Response, Immune System Process, Neuronal Development, Angiogenic Process, KCC1: Electrophilic/Metabolically Activated, KCC2: Genotoxic Effects, KCC3: Alteration of DNA Repair/Genomic Stability, KCC4: Epigenetic Alterations, KCC5: Oxidative Stress, KCC6: Chronic Inflammation, KCC8: Receptor Mediated Effects, KCC10: Cell Proliferation/Death/Energetics, Rabbit Draize Skin Irritation/Corrosion Test, Four-hour Human Patch Test
Download
Query Mixtures
EPA Search
Clear Filter
Number of chemicals = 83
Substance Name
CASRN
DTXSID
Qsar Ready ID
Coagulati... Process Call (# Assays=17)
Inflamm... Response Call (# Assays=1...
Immune System Process Call (# Assays=1)
Neuronal Develop... Call (# Assays=11)
Angiogenic Process Call (# Assays=29)
KCC1: Electrop... Activated Call (# Assays=31)
KCC2: Genotoxic Effects Call (# Assays=27)
KCC3: Alteration of DNA Repair/G... Stability Call (# Assays=3)
KCC4: Epigenetic Alterations Call (# Assays=9)
KCC5: Oxidativ... Stress Ce... (# Assays=2...
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330-55-2
DTXSID20...
XKJMBINC... UHFFFAOY... N
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4-tert-Butylphenol
98-54-4
DTXSID10...
QHPQWRB... UHFFFAOY... N
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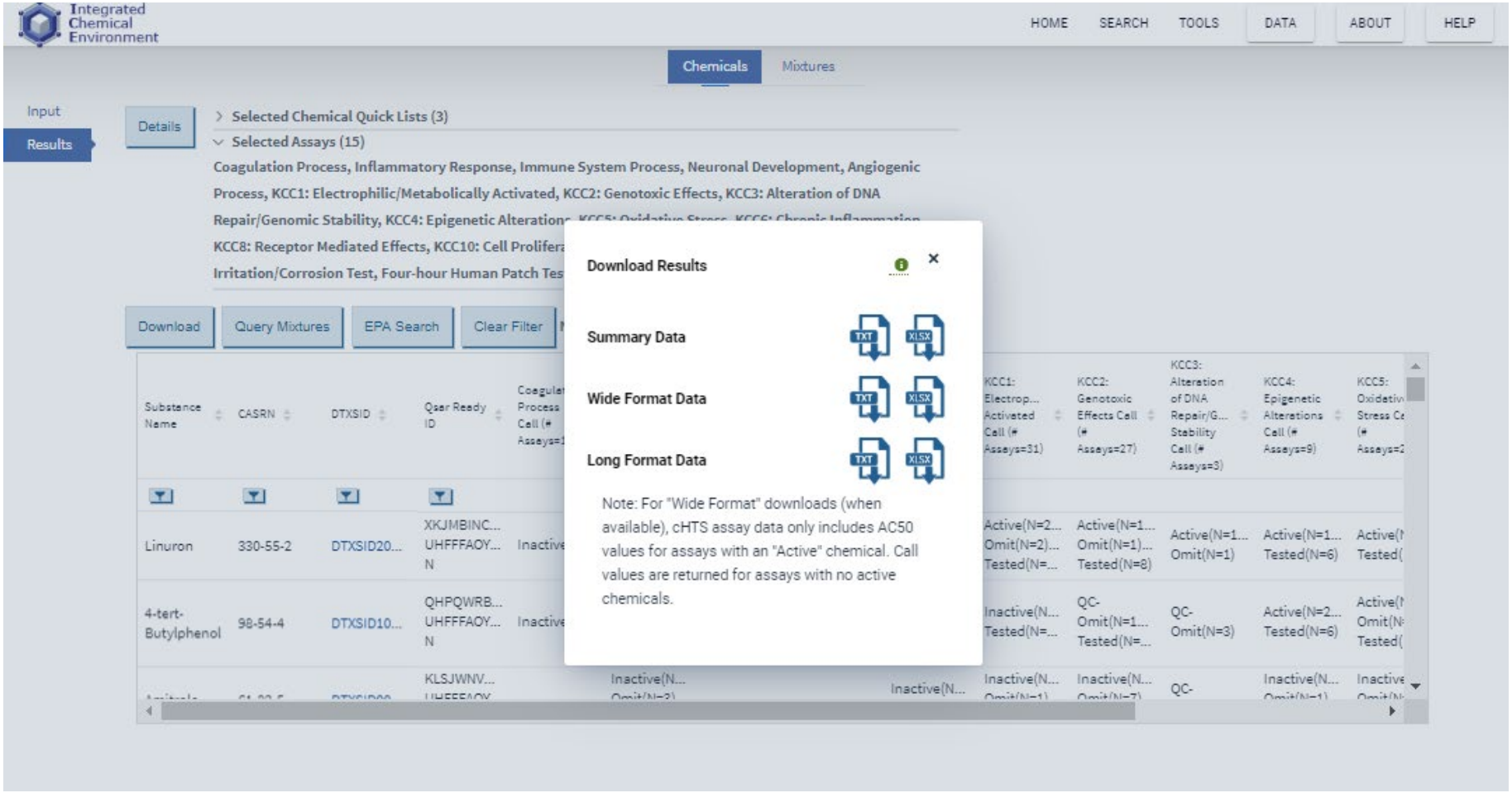
ICE Search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Details
Selected Chemical Quick Lists (3)
Selected Assays (15)
Coagulation Process, Inflammatory Response, Immune System Process, Neuronal Development, Angiogenic Process, KCC1: Electrophilic/Metabolically Activated, KCC2: Genotoxic Effects, KCC3: Alteration of DNA Repair/Genomic Stability, KCC4: Epigenetic Alterations
KCC8: Receptor Mediated Effects, KCC10: Cell Prolifera
Irritation/Corrosion Test, Four-hour Human Patch Tes
Download
Query Mixtures
EPA Search
Clear Filter
Download Results
Summary Data
Wide Format Data
Long Format Data
TXT
XLSX
Note: For "Wide Format" downloads (when available), cHTS assay data only includes AC50 values for assays with an "Active" chemical. Call values are returned for assays with no active chemicals.
Substance Name
CASRN
DTXSID
Qsar Ready ID
KCC1: Electrop... Activated Call (# Assays=31)
KCC2: Genotoxic Effects Call (# Assays=27)
KCC3: Alteration of DNA Repair/G... Stability Call (# Assays=3)
KCC4: Epigenetic Alterations Call (# Assays=9)
KCC5: Oxidativ Stress Ca (# Assays=2
Linuron
330-55-2
DTXSID20...
XKJMBINC... UHFFFAOY... N
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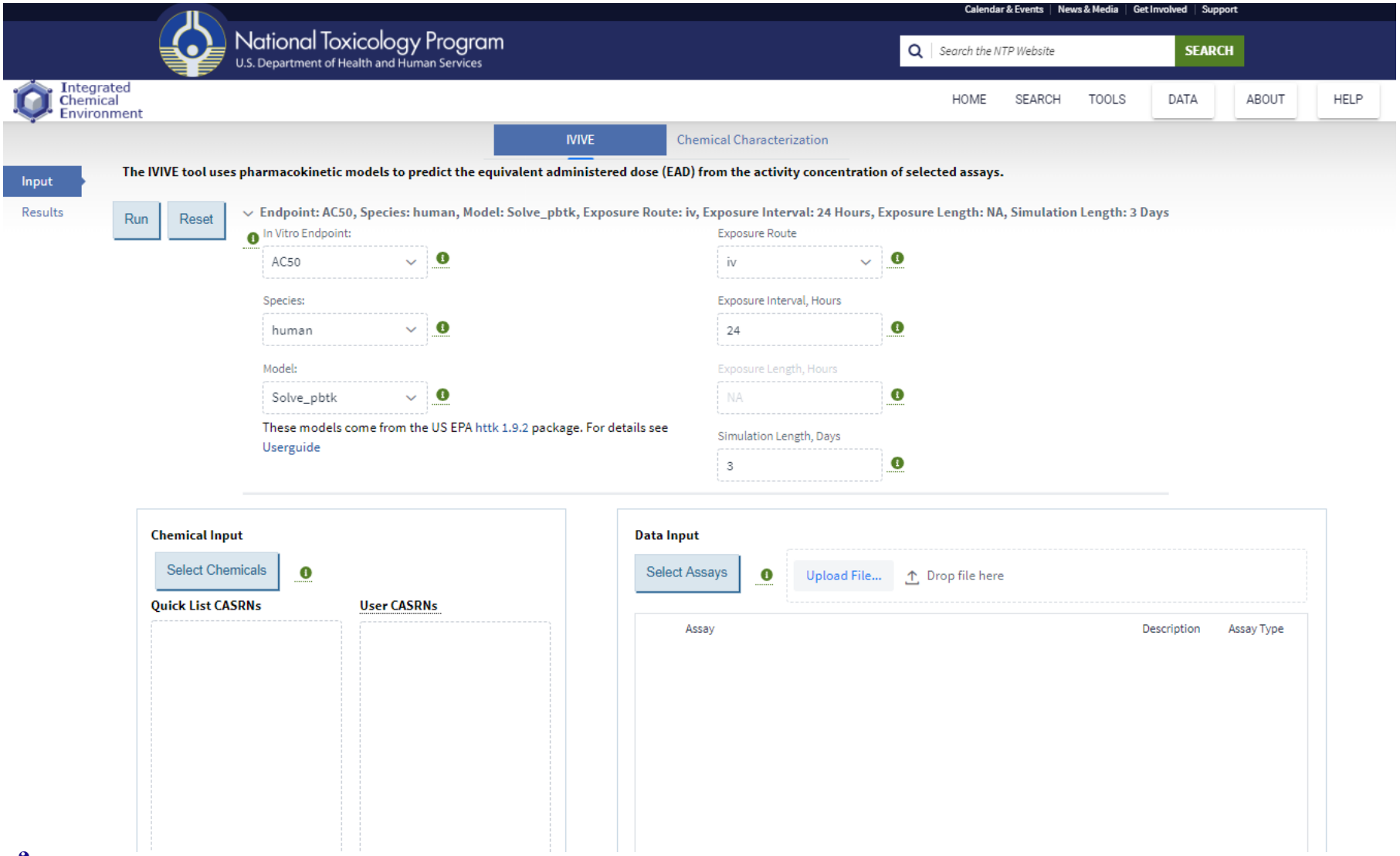
ICE Tool: IVIVE

- Calculates the **equivalent administered dose (EAD**) that would be needed to achieve the concentration that yielded the in vitro response
- Compares relationships between EADs resulting from different in vitro assays
- Overlays different in vivo endpoints on to EAD plot
- Informs on the predictability of the in vitro assay for the given endpoint
- Characterizes the probability of a biological effect given the likely in vivo exposure
  - https://github.com/NIEHS/ICE_IVIVEpipeline

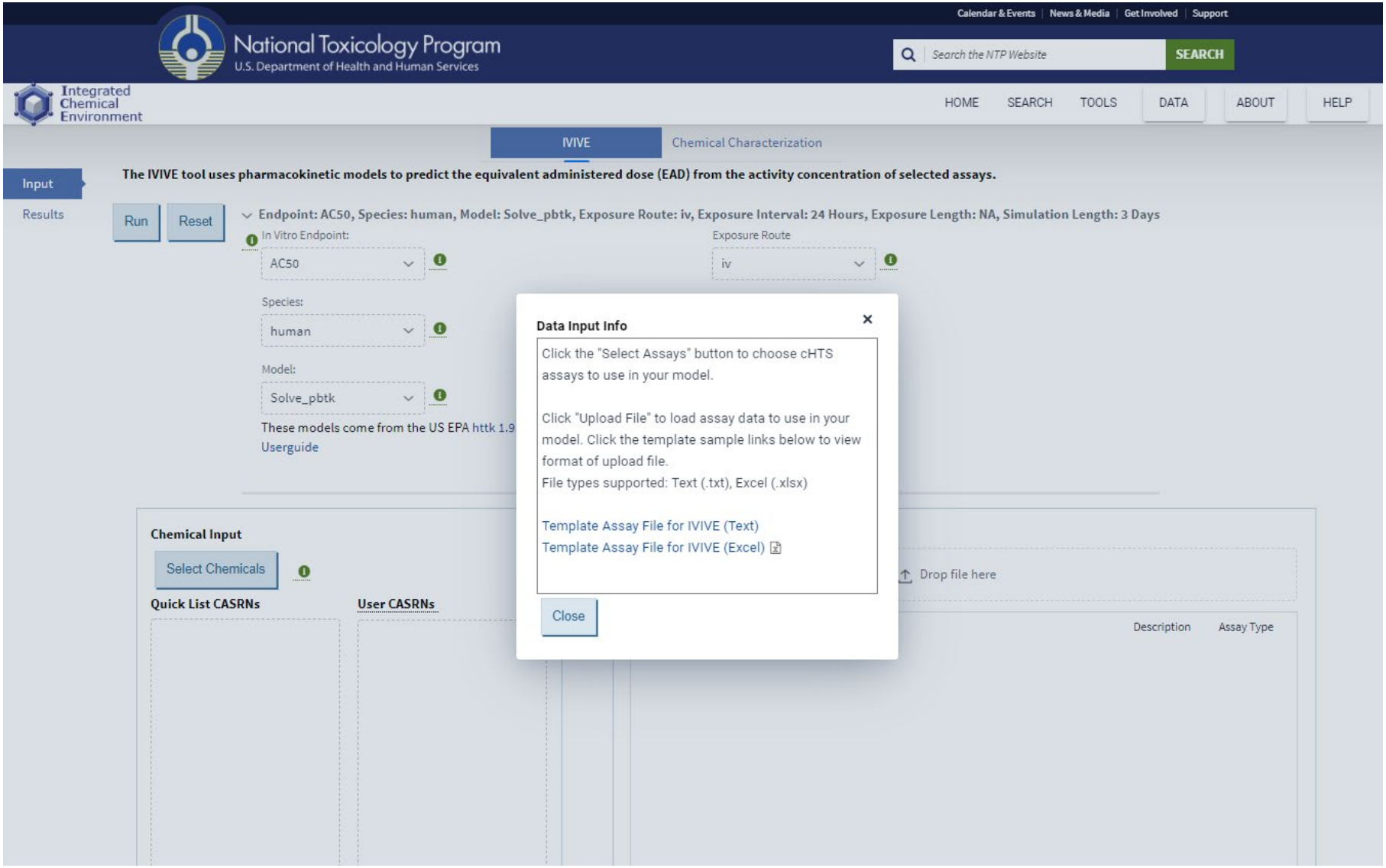
ICE TOOL: IVIVE

- Choose from:
  - **1C**: One-compartment pharmacokinetic (1C PK) model including population simulation
  - **Solve_3comp**: Three-compartment physiologically based pharmacokinetic (PBPK) models using EPA's httk package (Version 1.9.2)
  - **Solve_pbtk**: Multi-compartment physiologically based pharmacokinetic (PBPK) models using EPA's httk package (Version 1.9.2)
- New for 2020:
  - Uploading of user-supplied in vitro data for use in modeling
  - Improved assay selection using the cHTS mechanistic target mapping
  - Selection from Mode of Action is assay selection

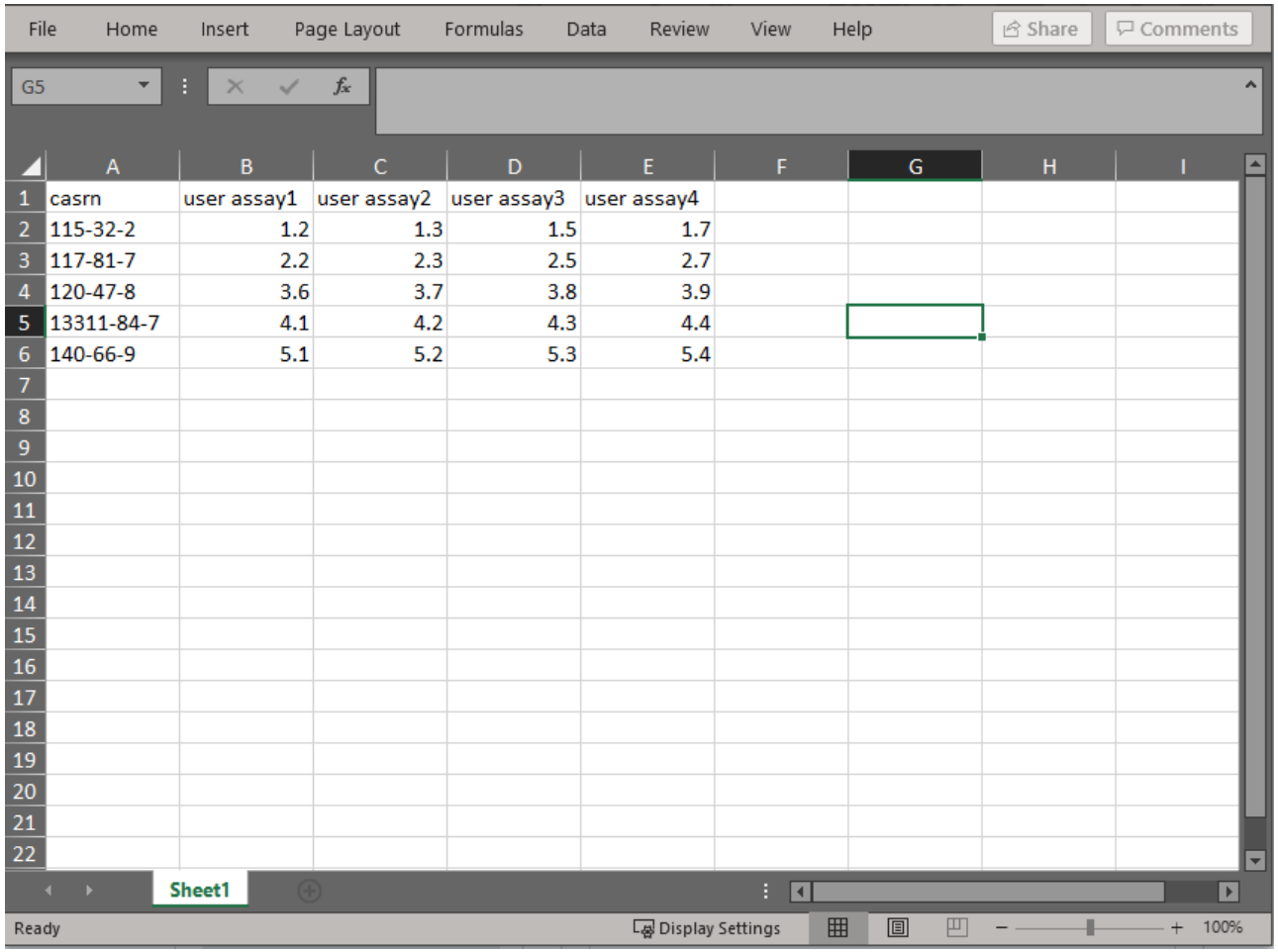
ICE Tool: IVIVE



ICE Tool: IVIVE

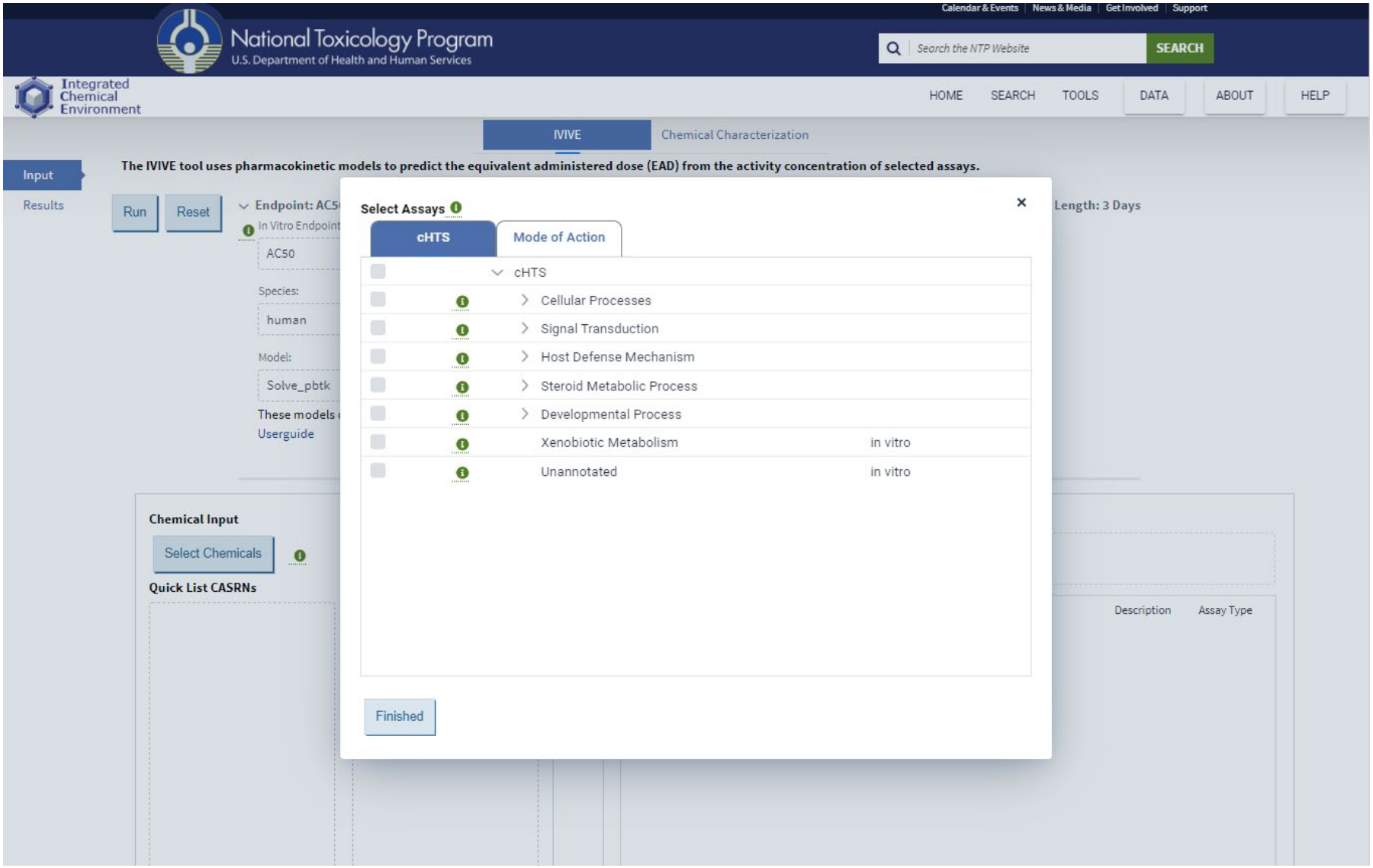


ICE Tool: IVIVE



	A	B	C	D	E
1	casrn	user assay1	user assay2	user assay3	user assay4
2	115-32-2	1.2	1.3	1.5	1.7
3	117-81-7	2.2	2.3	2.5	2.7
4	120-47-8	3.6	3.7	3.8	3.9
5	13311-84-7	4.1	4.2	4.3	4.4
6	140-66-9	5.1	5.2	5.3	5.4

ICE Tool: IVIVE



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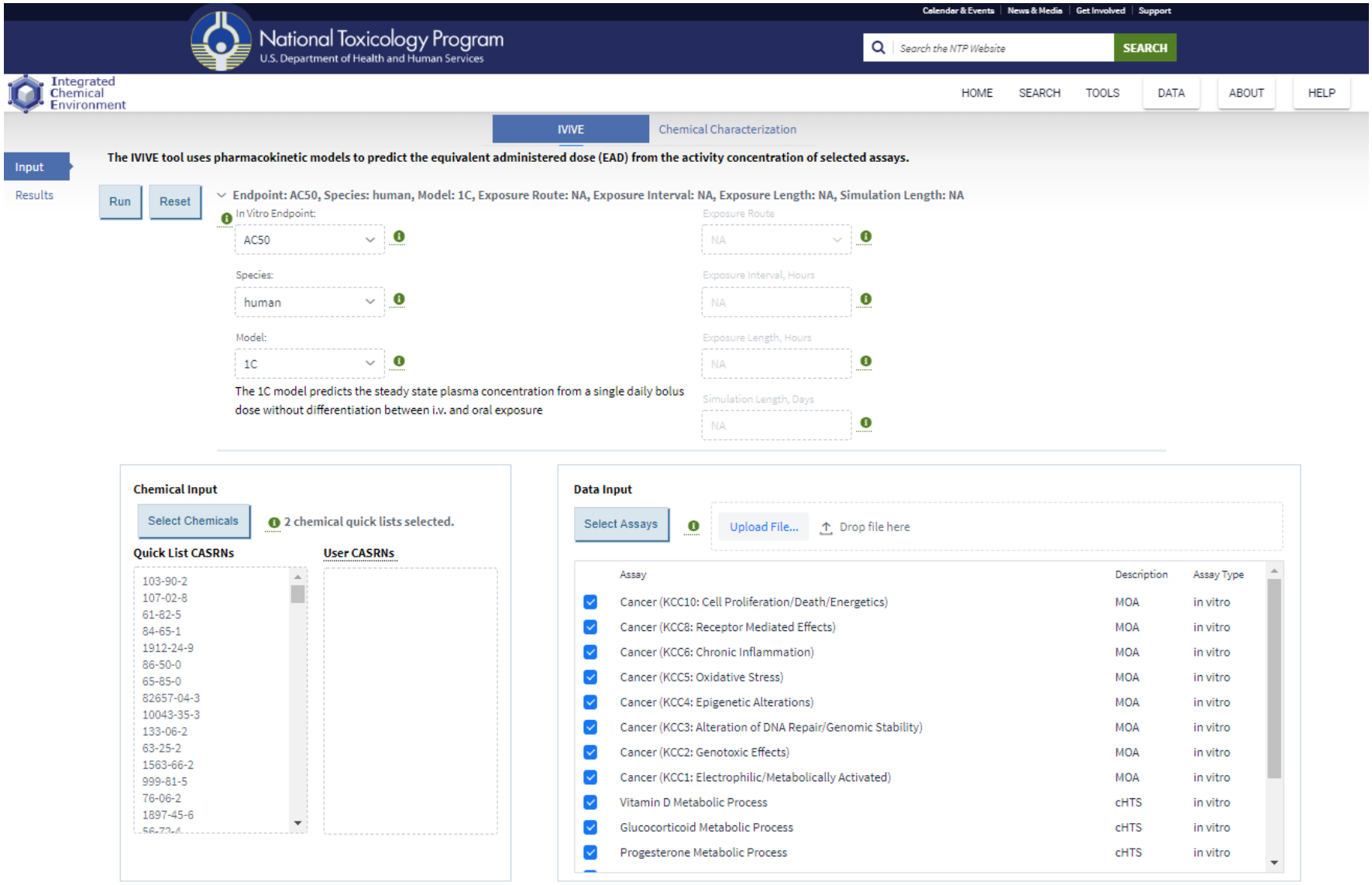

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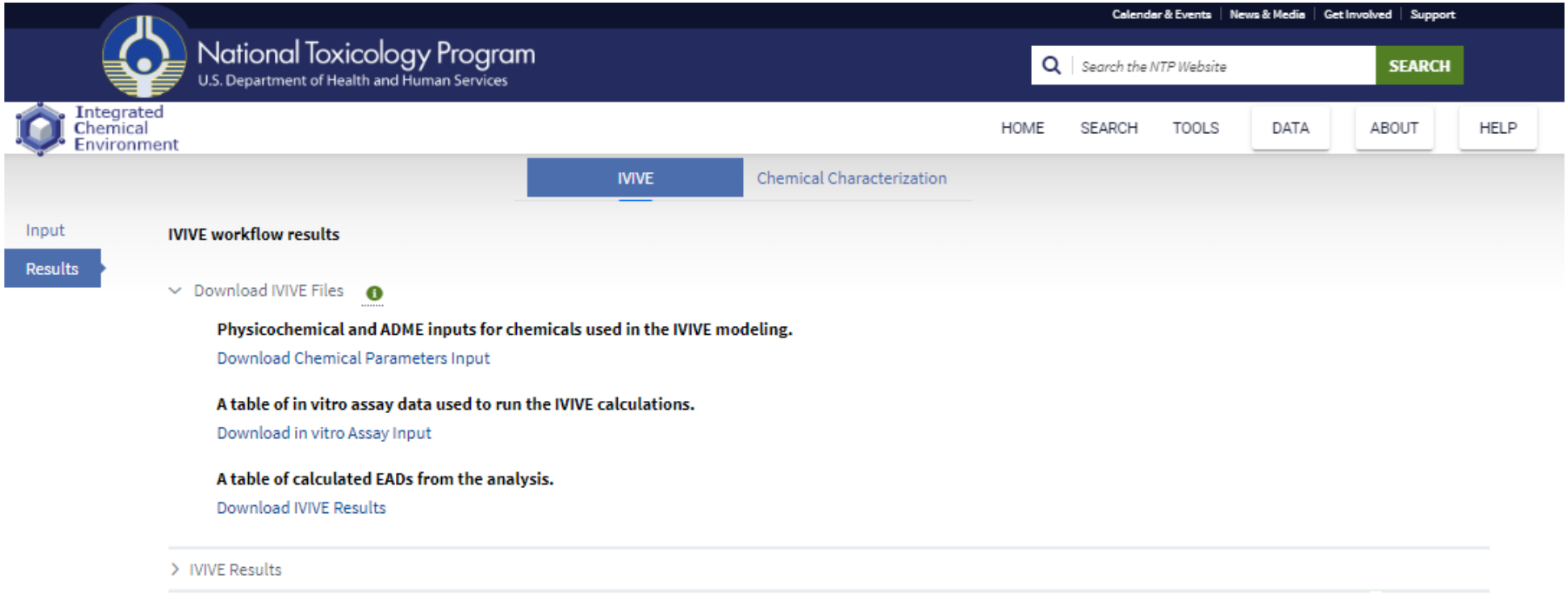

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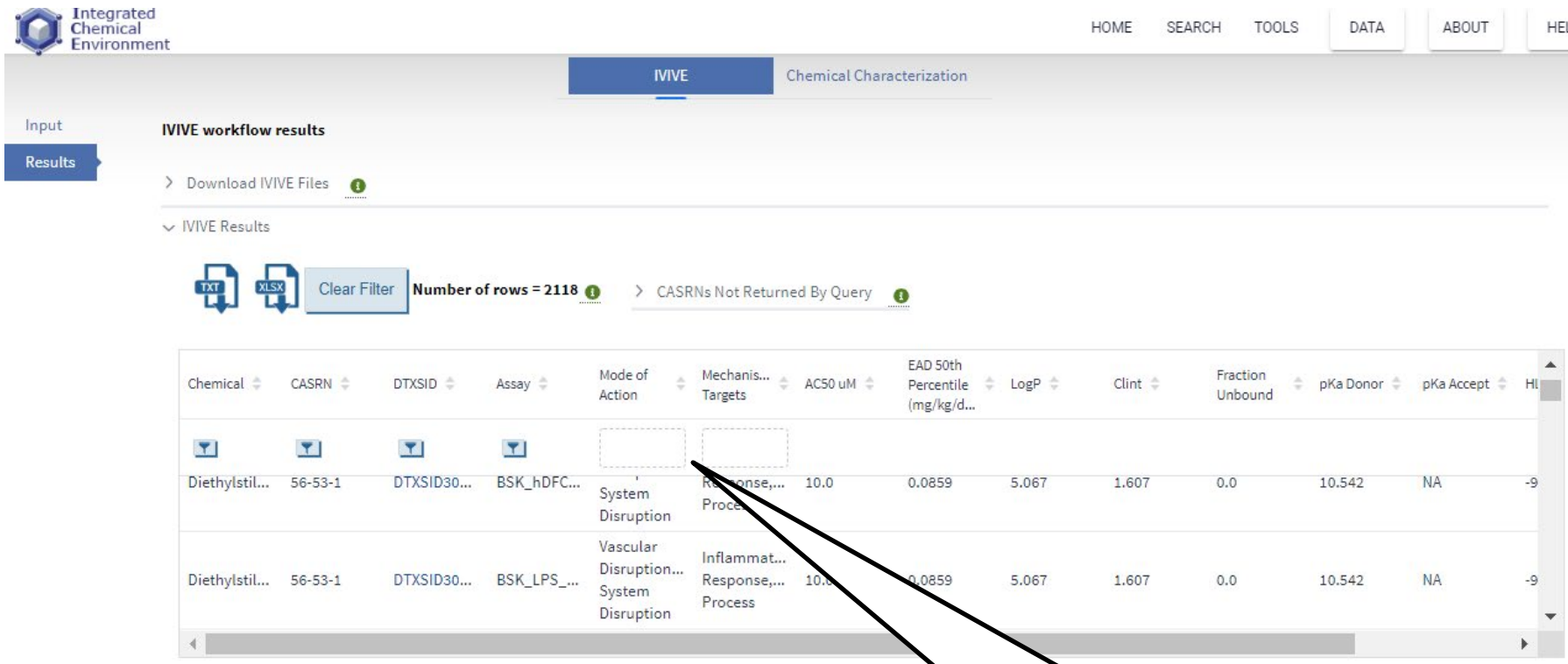
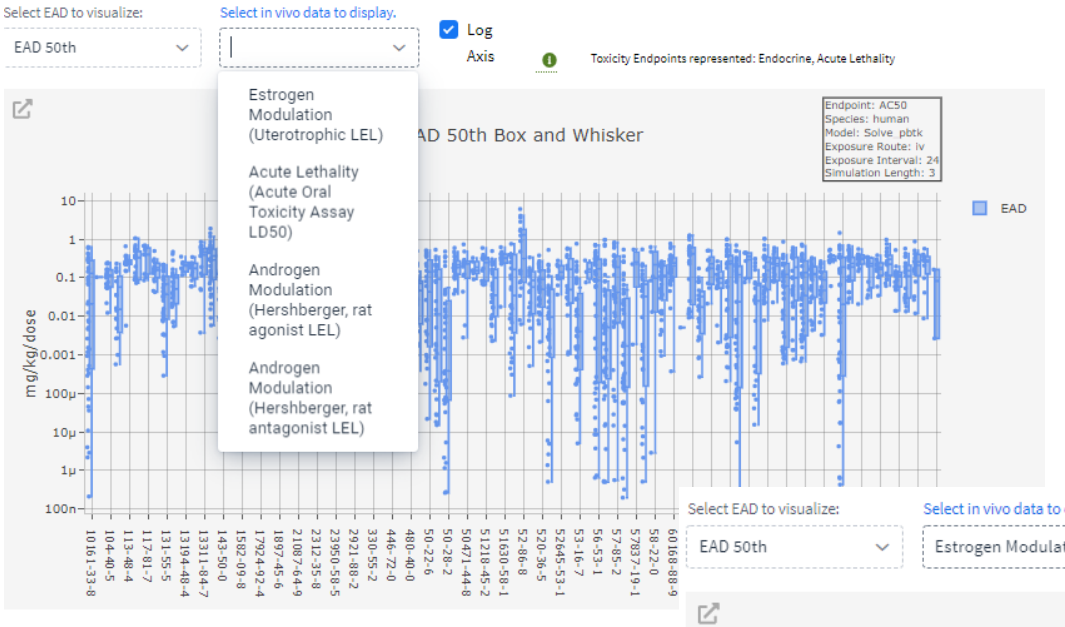


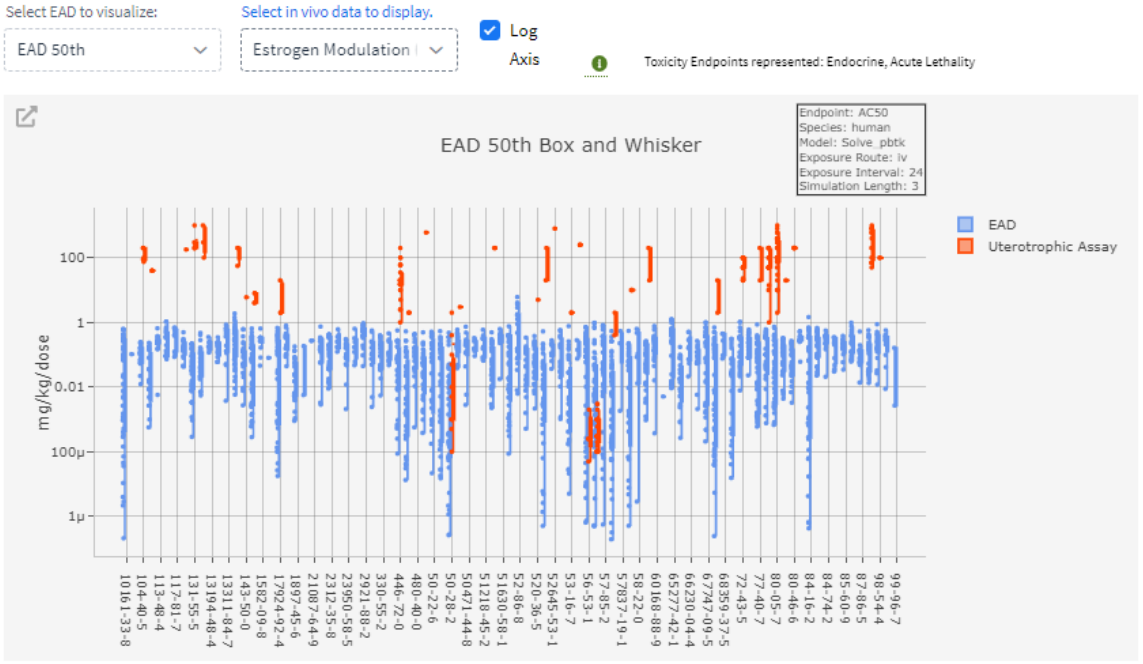
Users can filter using the annotations for in vitro mode of action or mechanistic target

ICE Tool: IVIVE

- The graphs are rescaled
- The x-axis only shows the CASRN

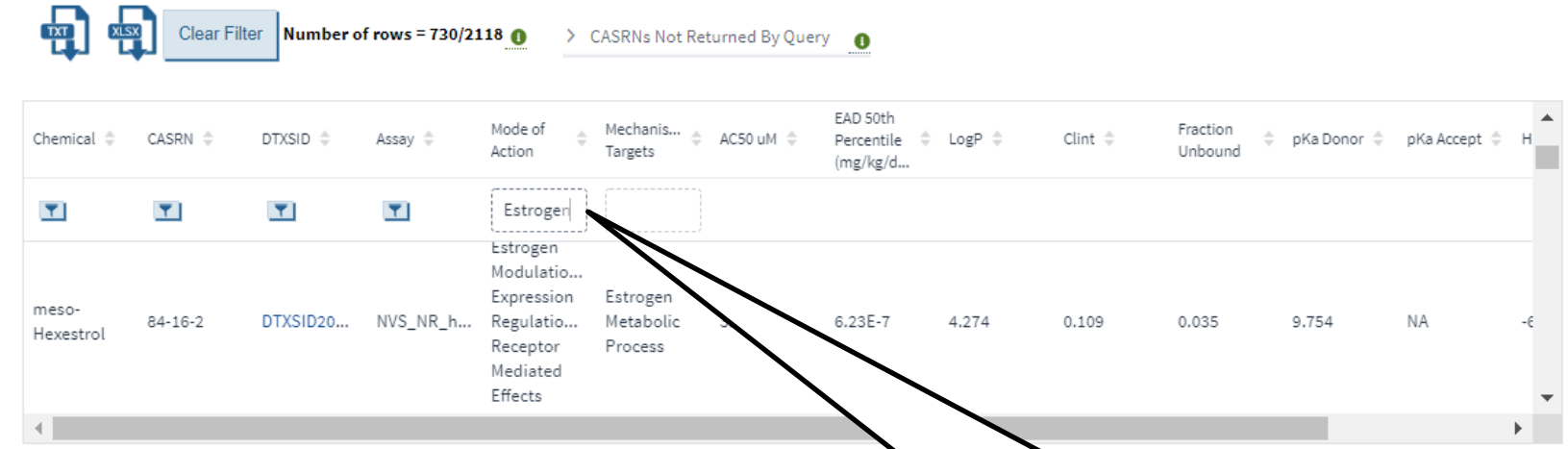
ICE Tool: IVIVE





- The graphs are rescaled
- The x-axis only shows the CASRN

ICE Tool: IVIVE

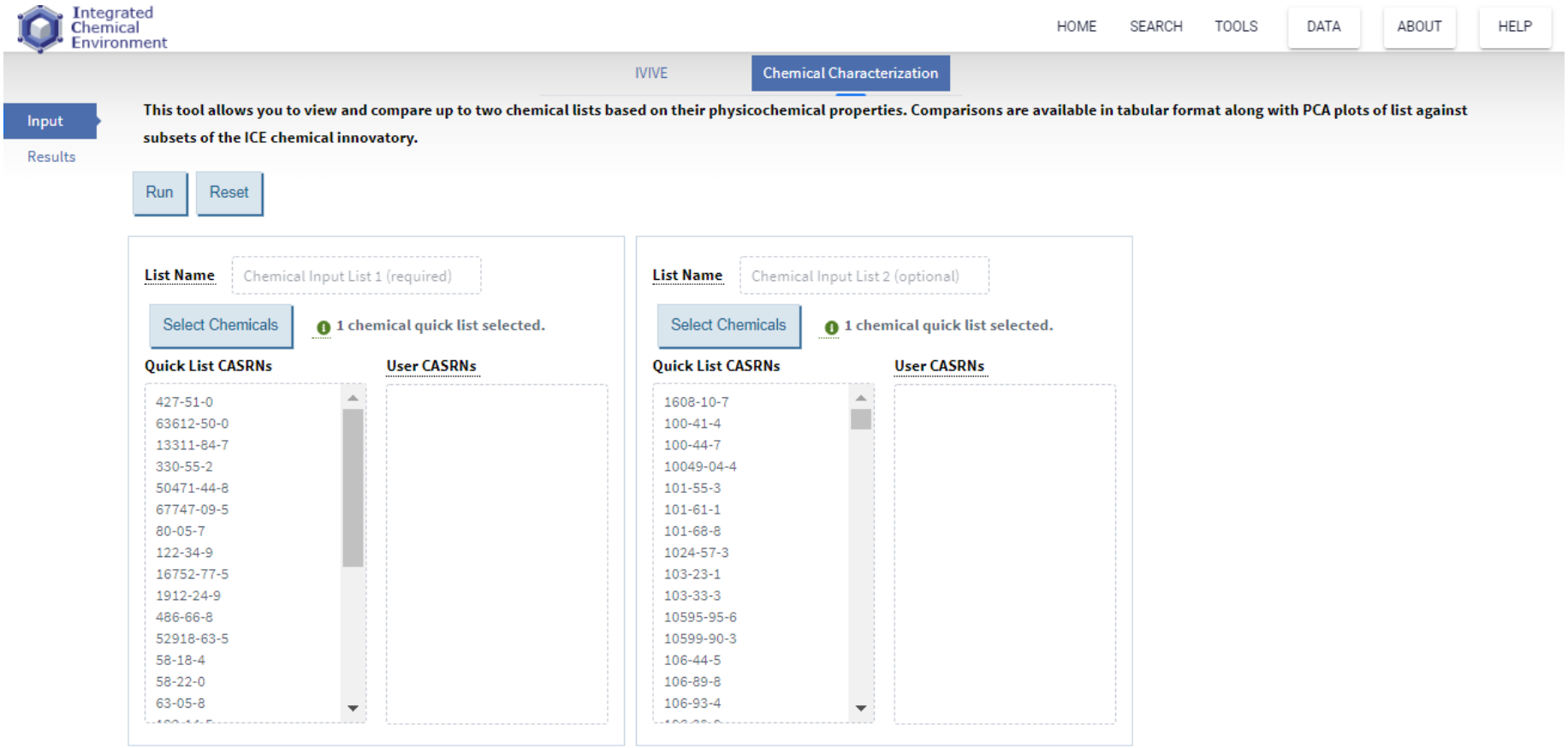


Users can filter using the annotations for in vitro mode of action and have the filter applied to the interactive plot

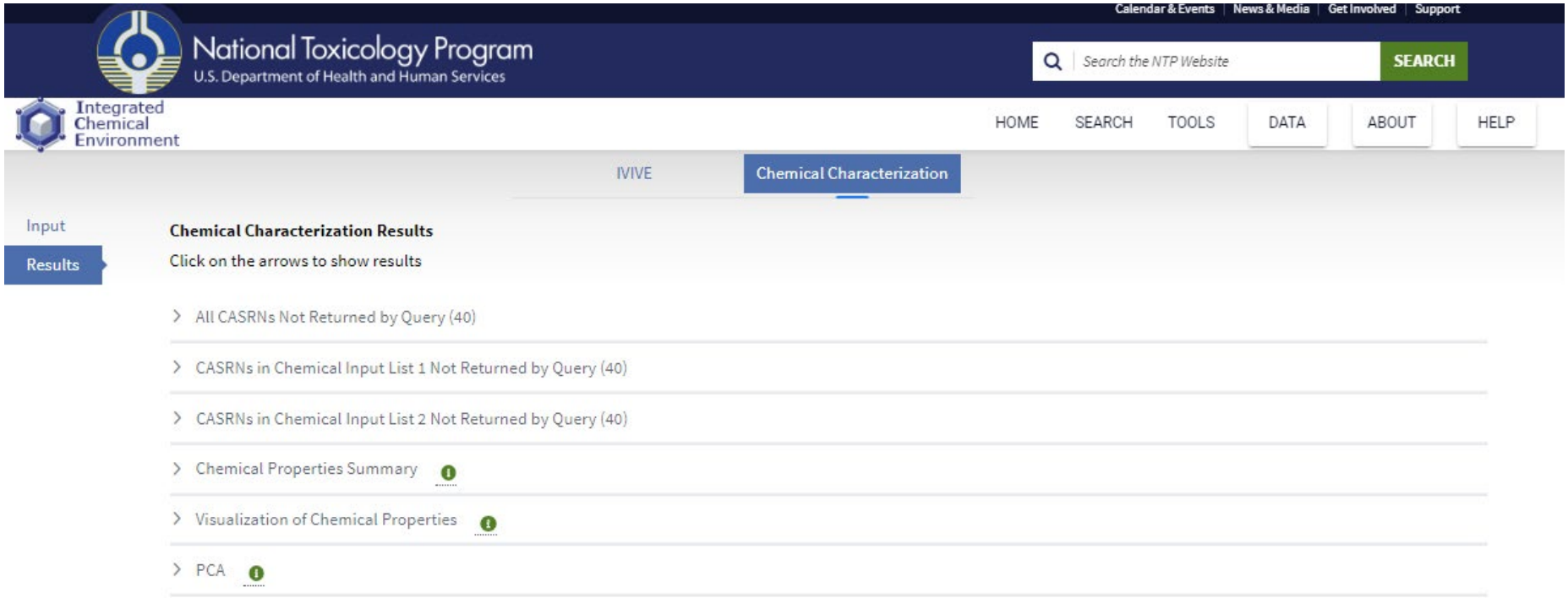
ICE Tool: Chemical Characterization

- Comparison tool that allows user to look at the property distribution between one or two 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
- New for 2020:
  - Enable the user to rename the list
  - Addition of PCA plots to enable visual comparisons of properties of user's chemical lists to Tox21 and ICE chemicals

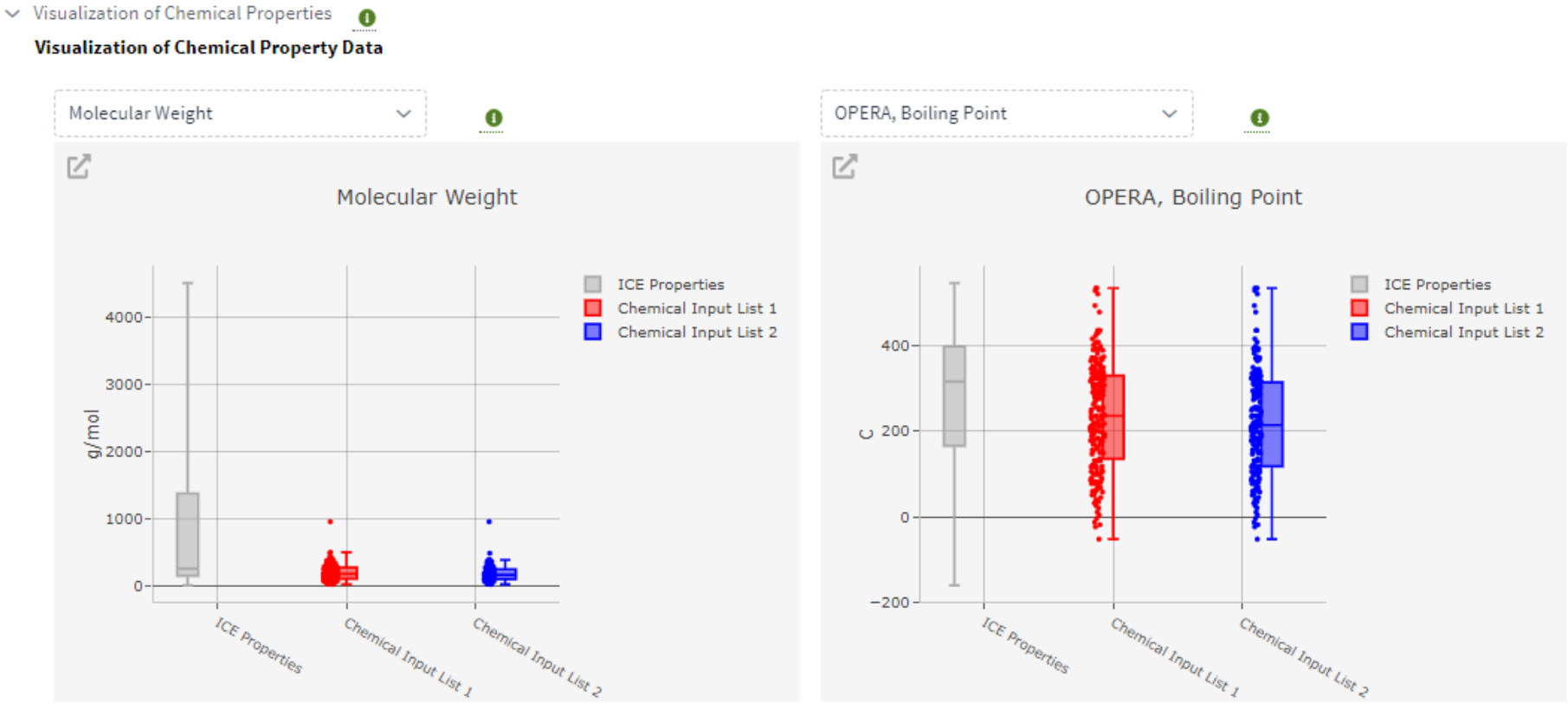
ICE Tool: Chemical Characterization



ICE Tool: Chemical Characterization



ICE Tool: Chemical Characterization



ICE Tool: Chemical Characterization

Use the drop down to choose either Tox21 or OPERA for the background

Use the drop down to choose either Chemical Properties or Molecular Descriptors for coordinate Type

PCA

Plot of returned CASRN PCA data shown with various PCA data backgrounds

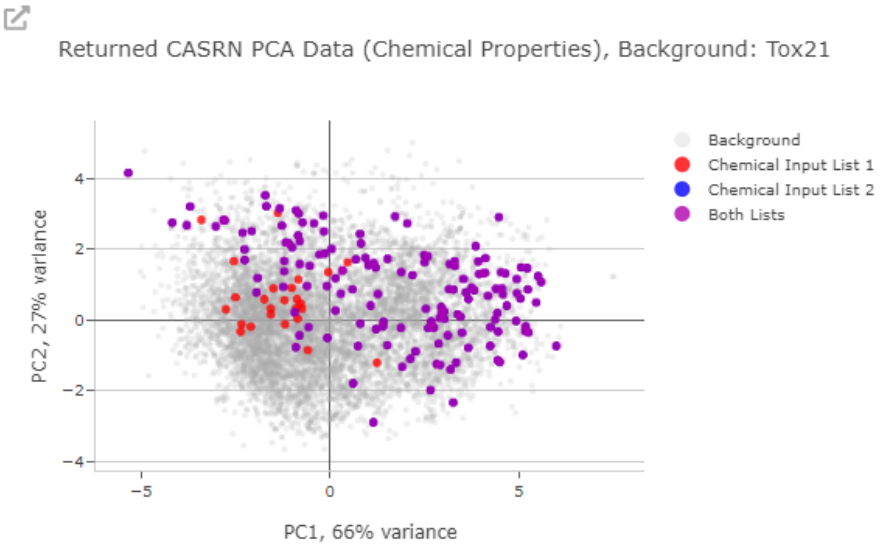
Principal Component Analysis (PCA) plots show the dimensionally reduced scatter plot rendering of chemicals based on their physicochemical predictions. Two different backgrounds (OPERA and Tox21) and two different coordinate generations (Chemical Properties and Molecular Descriptors) are available to increase the users ability to visually compare predicted properties.

Selected background: Tox21

Coordinate Type: Chemical Properties

Tox21: displays user chemical lists against the background of over 9000 chemicals tested in Tox21.

Chemical Properties: eight or more properties that describe the characteristics of the chemical substance during a reaction or a chemical change. These properties include but are not limited to boiling point, KOA, and molecular weight.



Resources

- OPERA https://github.com/NIEHS/OPERA
- QSAR ready KNIME workflow: https://github.com/kmansouri/QSAR-ready
- ICE:https://ice.ntp.niehs.nih.gov/
- ICE IVIVE workflow notebook: https://github.com/NIEHS/ICE_IVIVEpipeline
- NICEATM computational toxicology: https://ntp.niehs.nih.gov/go/niceatm-comptox