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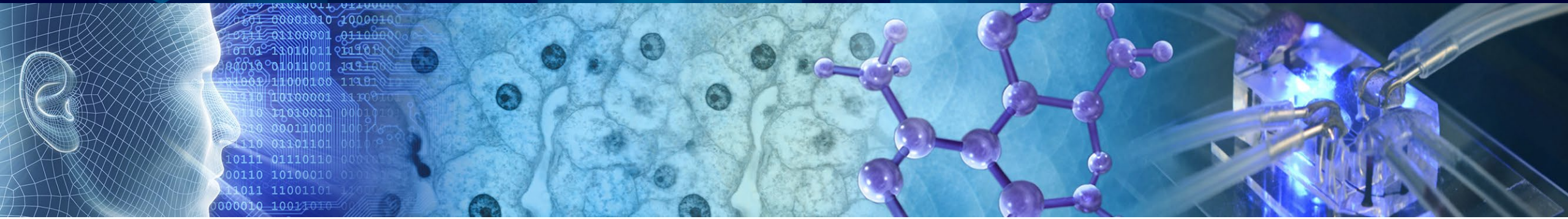


NICEATM's Integrated Chemical Environment (ICE): Updates, Enhancements, and Advances

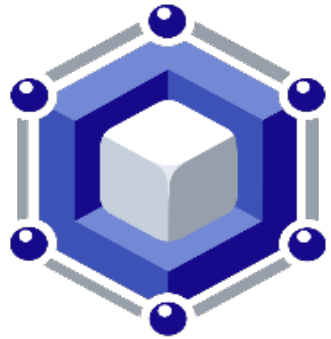
Brad Reisfeld, PhD, DABT, ATS
Inotiv, Inc., Contractor Supporting the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)

SACATM 2024

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

National Institutes of Health • U.S. Department of Health and Human Services

Topics for today



- What is the Integrated Chemical Environment (ICE)?
- Usage of the environment
- Data and updates
- Tools and updates
- Strategic activities to improve ICE
- Ongoing work and future enhancements

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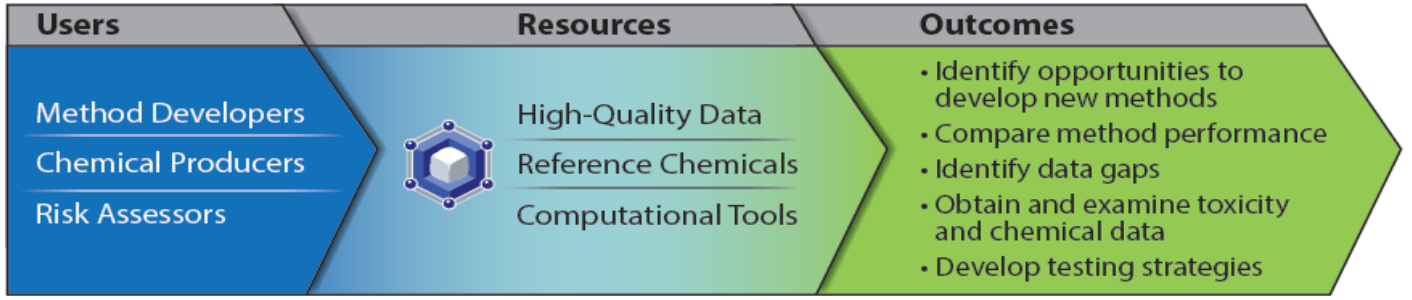
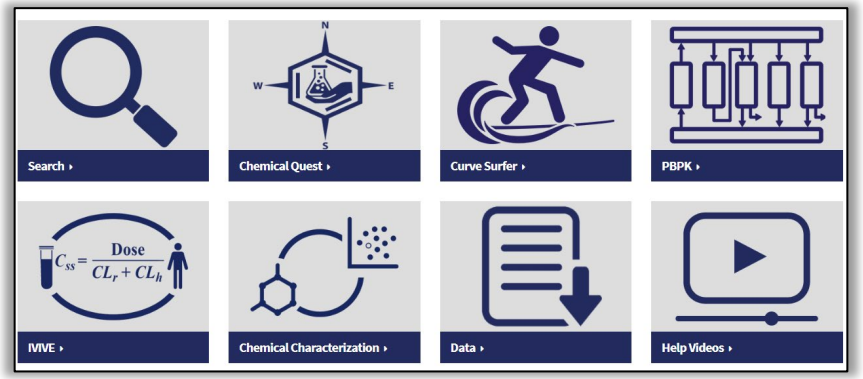
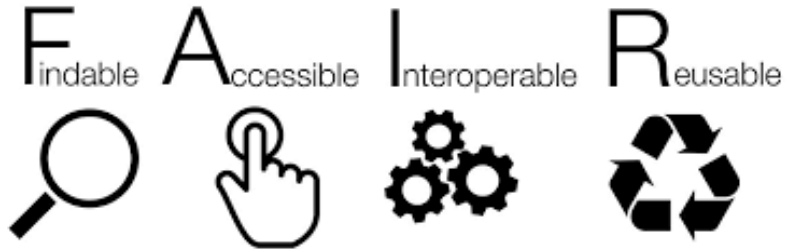
Integrated Chemical Environment



- Curated *in vivo* and *in vitro* test data
- In silico toxicity predictions and chemical property data
- Reference chemical lists
- Computational tools for chemical characterization and predicting toxicity

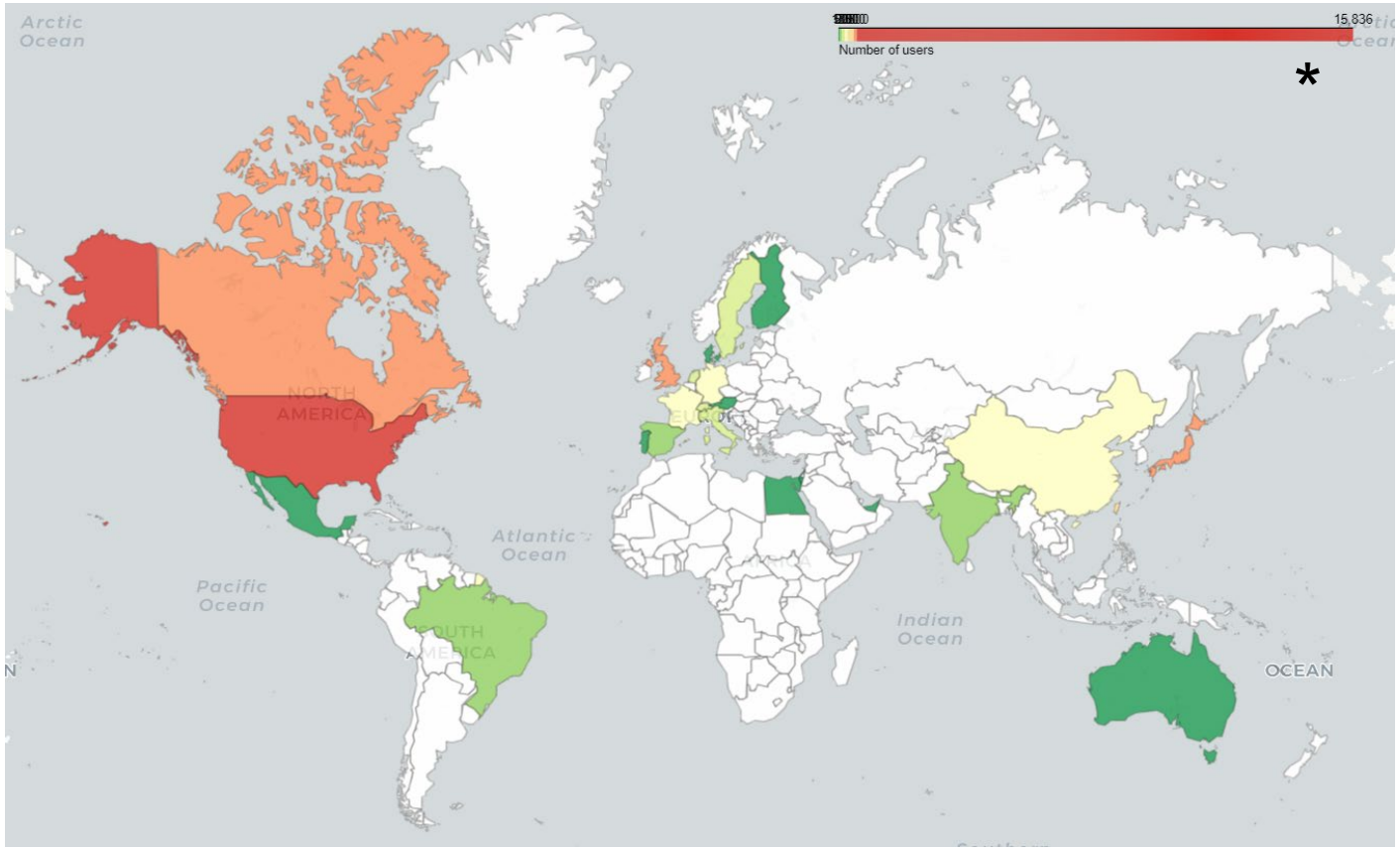




https://ice.ntp.niehs.nih.gov/

ICE: Usage of the platform

ICE user sessions based on website analytics



July 2023 - August 2024
- 27 countries
- 19,043 user sessions

*nonlinear color bar to show qualitative differences

ICE: Usage of the platform (2)

Some applications of ICE described in the recent scientific literature

Kvasnicka, et al. Two-Stage Machine Learning-Based Approach to Predict Points of Departure for Human Noncancer and Developmental/Reproductive Effects. *Environ Sci Technol*. 2024 Sep 3;58(35):15638-15649.

Luiz, et al. A novel approach to triazole fungicides risk characterization: Bridging human biomonitoring and computational toxicology, *Science of The Total Environment*, 2024, 953.

Kreutz, et al. Integrated Approach for Testing and Assessment for Developmental Neurotoxicity (DNT) to Prioritize Aromatic Organophosphorus Flame Retardants. *Toxics*. 2024 Jun 18;12(6):437.

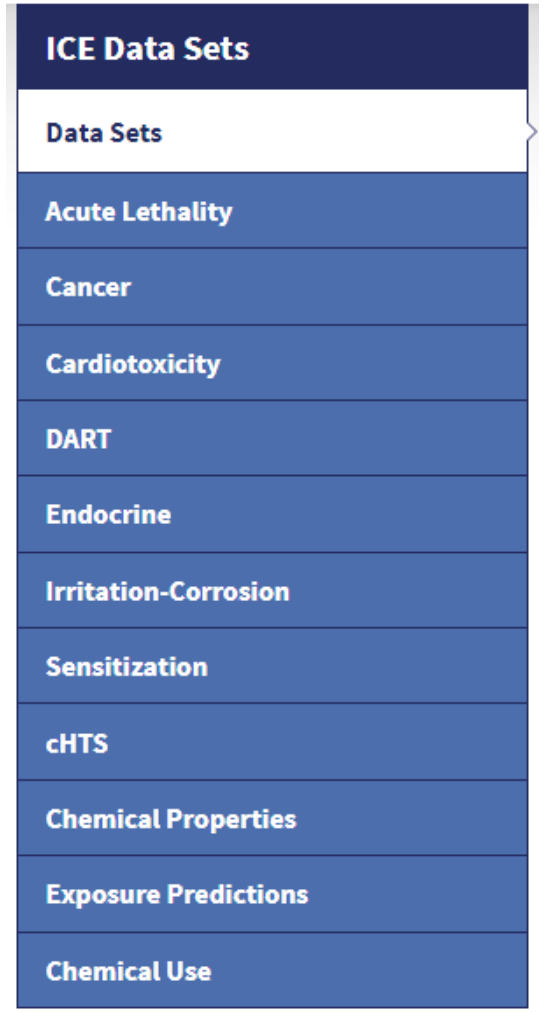
Silva. Investigating open access new approach methods (NAM) to assess biological points of departure: A case study with 4 neurotoxic pesticides. *Curr Res Toxicol*. 2024 Feb 15;6:100156.

Silva and Kwok. Use of computational toxicology models to predict toxicological points of departure: A case study with triazine herbicides. *Birth Defects Res*. 2023 Mar 15;115(5):525-544.

Chang, et al. Quantitative in vitro to in vivo extrapolation for developmental toxicity potency of valproic acid analogues. *Birth Defects Res*. 2022 Oct 1;114(16):1037-1055.

Hines et al. Application of an Accessible Interface for Pharmacokinetic Modeling and In Vitro to In Vivo Extrapolation. *Front Pharmacol*. 2022 Apr 13;13:864742. doi: 10.3389/fphar.2022.864742.

ICE Data



Size of Data Sets

Datasets	Data points
Acute Dermal	2757
Acute Inhalation	5590
Acure Oral	16839
ADME Parameters	3821
Cancer	10502
cHTS	3599802
DART	138480
Endocrine: in vitro	16629
Endocrine: in vivo	2270
Exposure Predictions	1439598
Eye Irritation	3028
Functional Use	266926
Functional Use Category	29784
Skin Irritation: in vitro	7058
Skin Irritation: in vivo	2079
Skin Sensitization: in vitro	9259
Skin Sensitization: in vivo	14997
Total	**5,569,419**

+ OPERA predictions for the DSSTox chemicals (50 M data points)

ICE Data (*in vivo* and *in vitro*)

Toxicity endpoint	Assays	# of chemicals
Chemical Parameters	Experimental physicochemical properties	~20000
ADME Parameters	Fu, intrinsic clearance, Caco2 permeability	~3000
Acute Toxicity	In vivo acute oral, dermal, and inhalation toxicity	~10000
Cancer	In vivo and in vitro cancer, and Weight of Evidence	3038
DART	In vivo and in vitro DART	628
Skin Sensitization	In vivo and in vitro skin sensitization	1771
Skin Irritation	In vivo and in vitro skin irritation/corrosion	595
Eye Irritation	In vivo and in vitro eye irritation/corrosion	455
Endocrine	In vivo and low throughput in vitro data on AR and ER agonist and antagonist activity	384
cHTS	Curated US EPA's ToxCast and Federal Tox21 assays (In vitro)	~10000

New in release v4.1:
Updated cHTS data to include annotations to OBO Foundry ontologies.

New in release v4.1:
Versioning information to data sets.
Links to the NTP CEBS database and EPA CompTox Chemicals Dashboard in data downloads.

ICE Data (In Silico Models/Integrated Approaches)

Endpoint	Model	# of chemicals
Physicochemical Properties	OPEn (q)saR App (OPERA) Mansouri et al. J Cheminform 2018	1M+
Structural Properties	OPEn (q)saR App (OPERA) Mansouri et al. J Cheminform 2018	1M+
Predicted ADME Properties	OPEn (q)saR App (OPERA) Mansouri et al. J Cheminform 2018	1M+
Environmental Fate	OPEn (q)saR App (OPERA) Mansouri et al. J Cheminform 2018	1M+
Acute Oral Toxicity	Collaborative Acute Toxicity Modeling Suite (CATMoS) - Rat acute oral toxicity. Mansouri et al. EHP 2021	1M+
Endocrine	Estrogen Receptor pathway Model. Browne et al. ES&T 2015	1812
	Androgen Receptor Pathway Model. Kleinstreuer et al. Chem Res Tox 2017	1855
	Collaborative Estrogen Receptor Activity Prediction Project (CERAPP). Mansouri et al. EHP 2016	1M+
	Collaborative Modeling Project for Androgen Receptor Activity (COMPARA). Mansouri et al. EHP 2020	1M+
Exposure Predictions	Systematic Empirical Evaluation of Models (US EPA'S SEEM3). Ring et al. Environ Sci Technol 2019	475,000+

New in release v4.1: Inclusion of applicability domain information for OPERA predictions in the ICE graphical user interface and REST API

ICE Chemical Quick Lists

Reference Chemical List
AR In Vitro Agonist
AR In Vitro Antagonist
ER In Vivo Agonist
ER In Vitro Agonist
Eye Irritation-Corrosion
Genotoxicity
OECD Defined Approach to Skin Sensitization: Human
OECD Defined Approach to Skin Sensitization: LLNA
Skin Corrosion

Non-reference Chemical List
AR In Vivo Agonists
AR In Vivo Antagonists
EPA Pesticide Active Ingredients
EPA Pesticide Inert Ingredients, Food and Nonfood Use
EPA IRIS Cancer Assessment
EPA IRIS Non-Cancer Assessment
EPA PFAS Master List
IARC Classifications
Mixtures and Formulations in ICE
NTP Cancer Bioassay Chemicals
RoC Classifications
Steroidogenesis - Androgen
Steroidogenesis - Estrogen
Thyroid
Tox21
ToxCast Phase I, Phase II, and e1k

New in release v4.1:

- New PFAS Quick List.
- Updated RoC Classifications Quick List based on the 15th Report on Carcinogens.

ICE Tools

Search	Query ICE data and visualize results
Chemical Quest	Identify similar chemicals
Chemical Characterization	Explore chemical properties and use categories
Curve Surfer	Explore concentration-response curves
PBPK	Predict tissue-specific chemical concentrations
IVIVE	Predict equivalent administered dose from in vitro data

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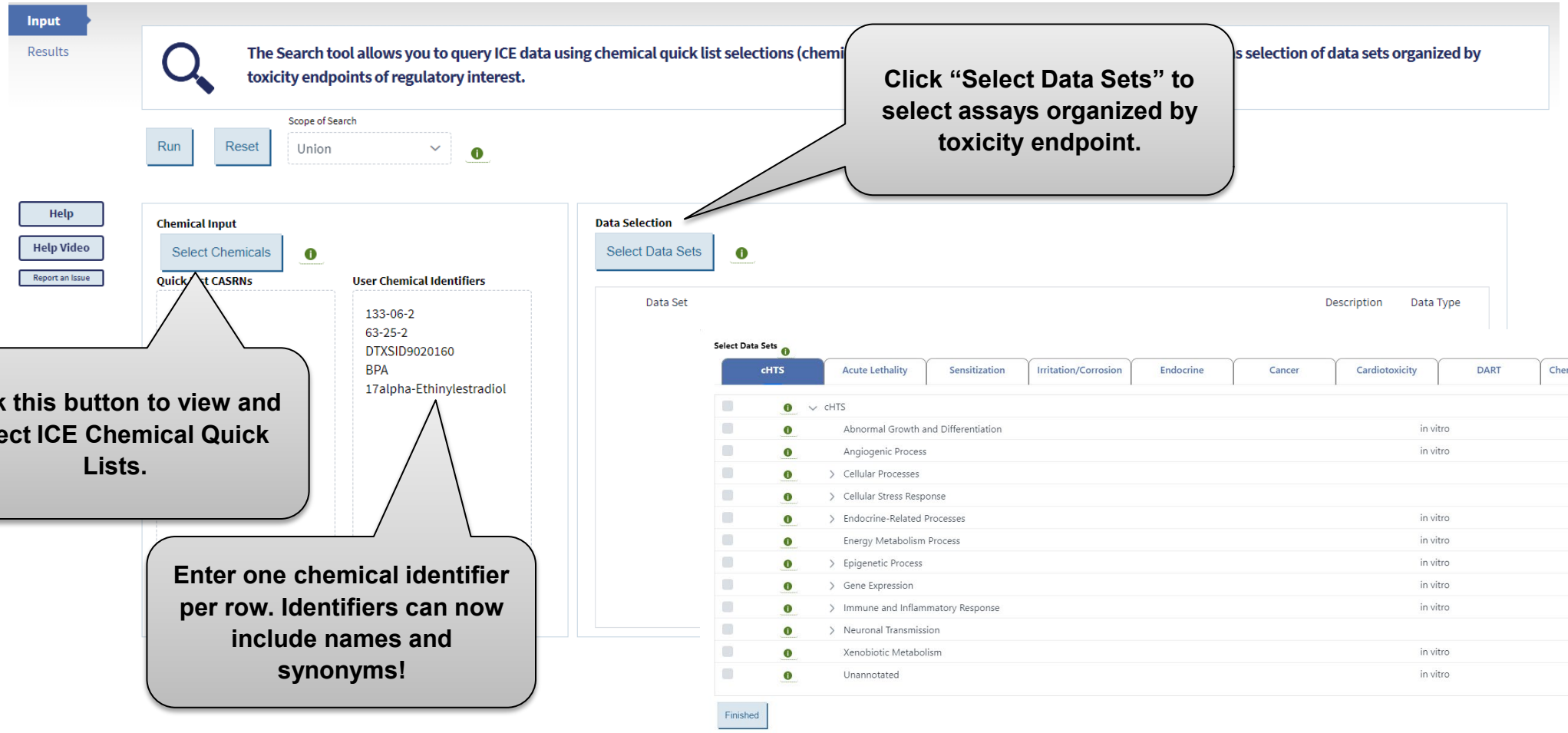
Search Tool

Search

Perform a search → Identify similar chemicals → Characterize chemical inventory → Review in vitro data details → Generate chemical concentration predictions → Predict equivalent administered dose



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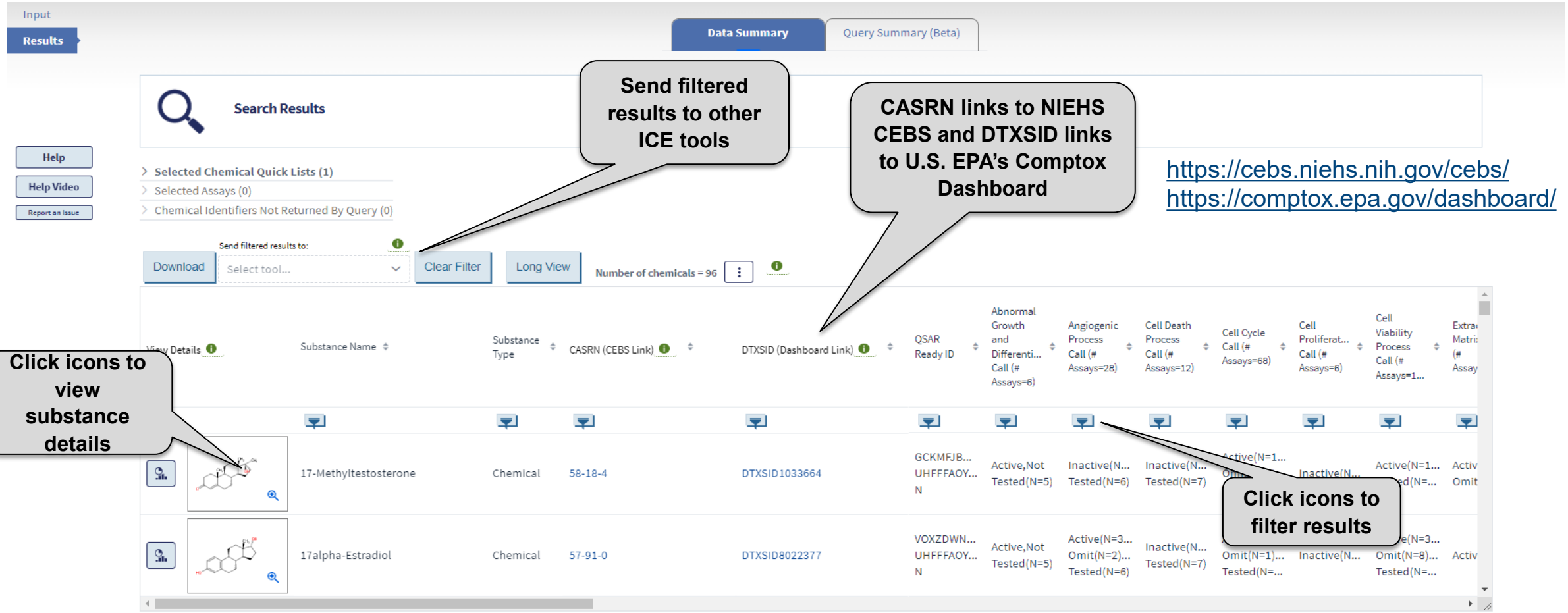

Send filtered results to other ICE tools

CASRN links to NIEHS CEBS and DTXSID links to U.S. EPA's Comptox Dashboard

https://cebs.niehs.nih.gov/cebs/
https://comptox.epa.gov/dashboard/

Click icons to view substance details

Click icons to filter results

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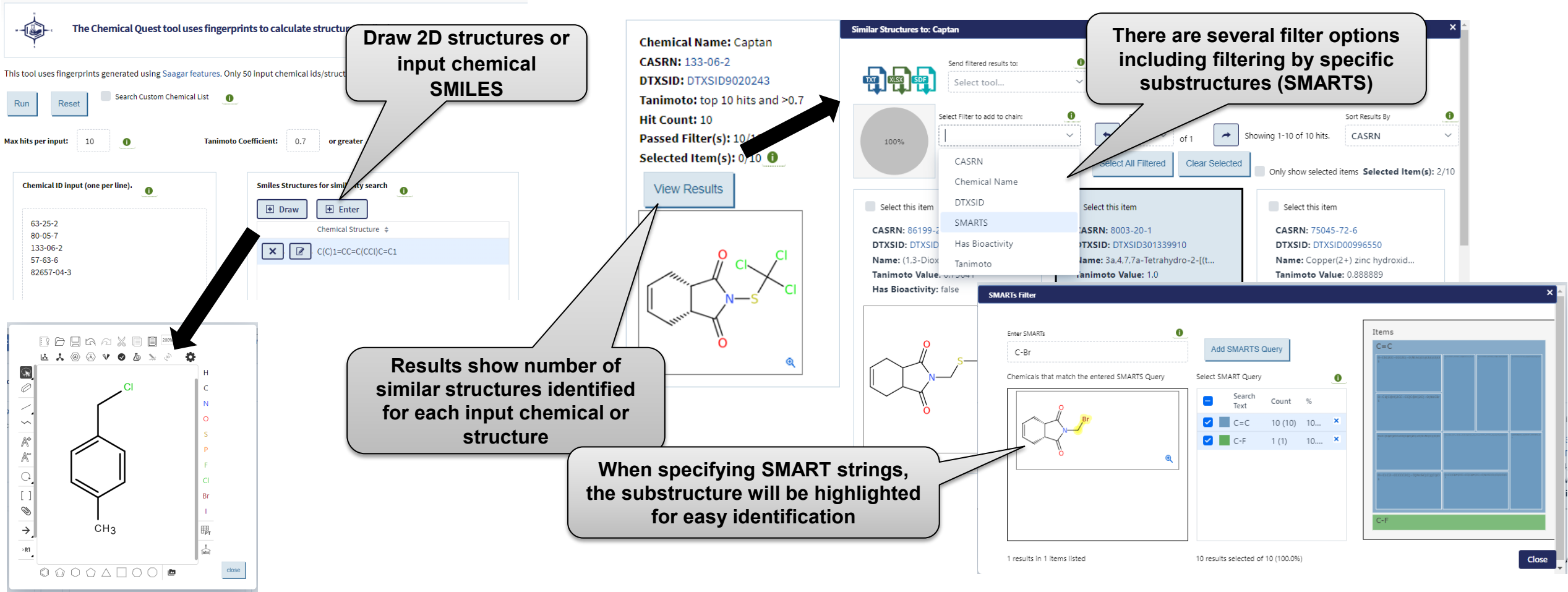
Chemical Quest

Perform a search → **Identify similar chemicals** → Characterize chemical inventory → Review in vitro data details → Generate chemical concentration predictions → Predict equivalent administered dose



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Chemical Characterization

Chemical Characterization

Perform a search → Identify similar chemicals → **Characterize chemical inventory** → Review in vitro data details → Generate chemical concentration predictions → Predict equivalent administered dose

Chemical Properties Summary

Values displayed are Open Structure-Activity/Property Relationship App (OPERA) predictions:

Lists: Both Chemical Lists

Users can input one or two lists of chemicals and toggle results to show one or both lists

Send filtered results to: Select tool...

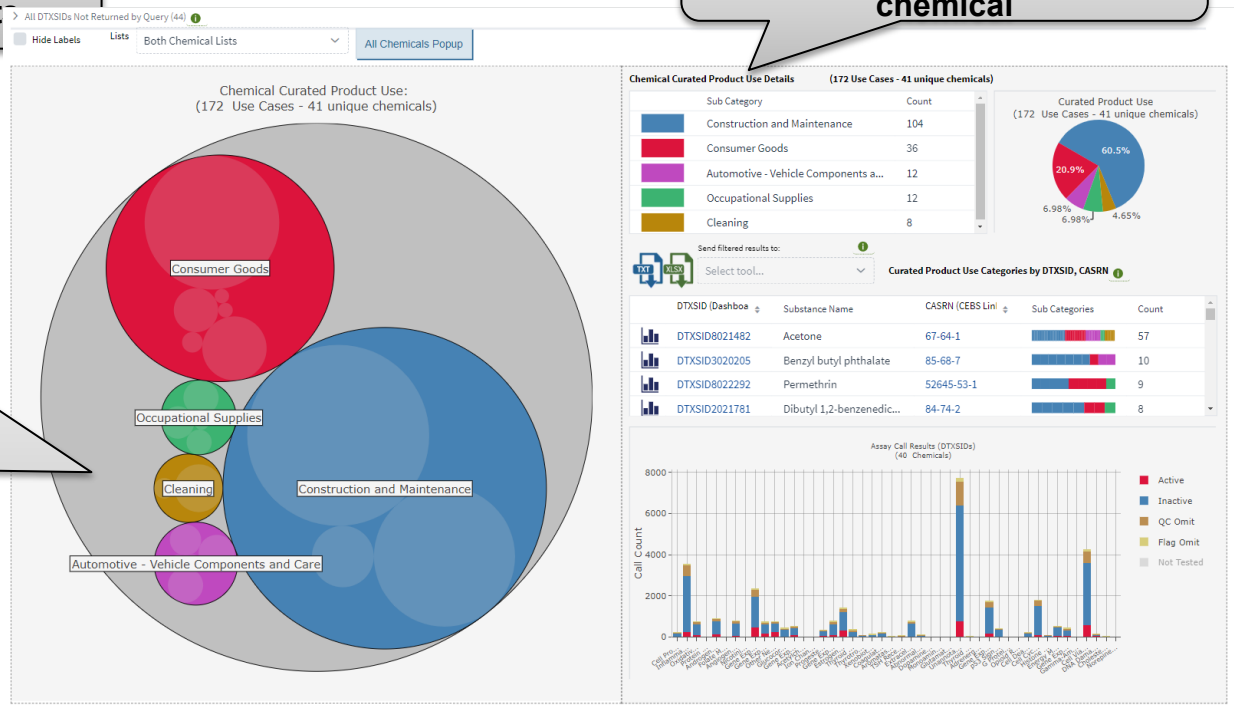
Chemical List (OPERA) Predictions by Input List, CASRN

List	Substance Name	CASRN (CEBS Link)	DTXSID (Dashboard Link)	Molecular Weight, g/mol	OPERA, Boiling Point, C	OPERA, Henry's Law Constant, atm-m3/mol
Custom Chemical List 1	Carbaryl	63-25-2	DTXSID9020247	201.221	314.943	-7.86
Custom Chemical List 1	Captan	133-06-2	DTXSID9020243	300.589	302.104	-5.43
Custom Chemical List 1	(+)-cis-Permethrin	54774-45-7	DTXSID5052208	391.288	401.446	-7.62

Chemical List Statistical Summary of (OPERA) Predictions

Endpoint	Min	25th	Median	Mean	75th	Max
OPERA, Water Solubility, log10, moles/L	-10.4	-4.35	-2.33	-2.81	-0.869	1.355
Molecular Weight, g/mol	30.026	120.17	197.446	214.652	268.352	1202.611
OPERA, Octanol-Air Partition Coefficient, KOA log10	0.969	3.854	7.843	6.883	9.383	11.757

Nested bubble graphs show curated product use categories derived from EPA's Chemicals and Products Database (CPDat)



Summary details show product use details by category and by chemical

OPERA v2.8 (Mansouri et al., 2018)

CPDat v3 (Williams, 2017)

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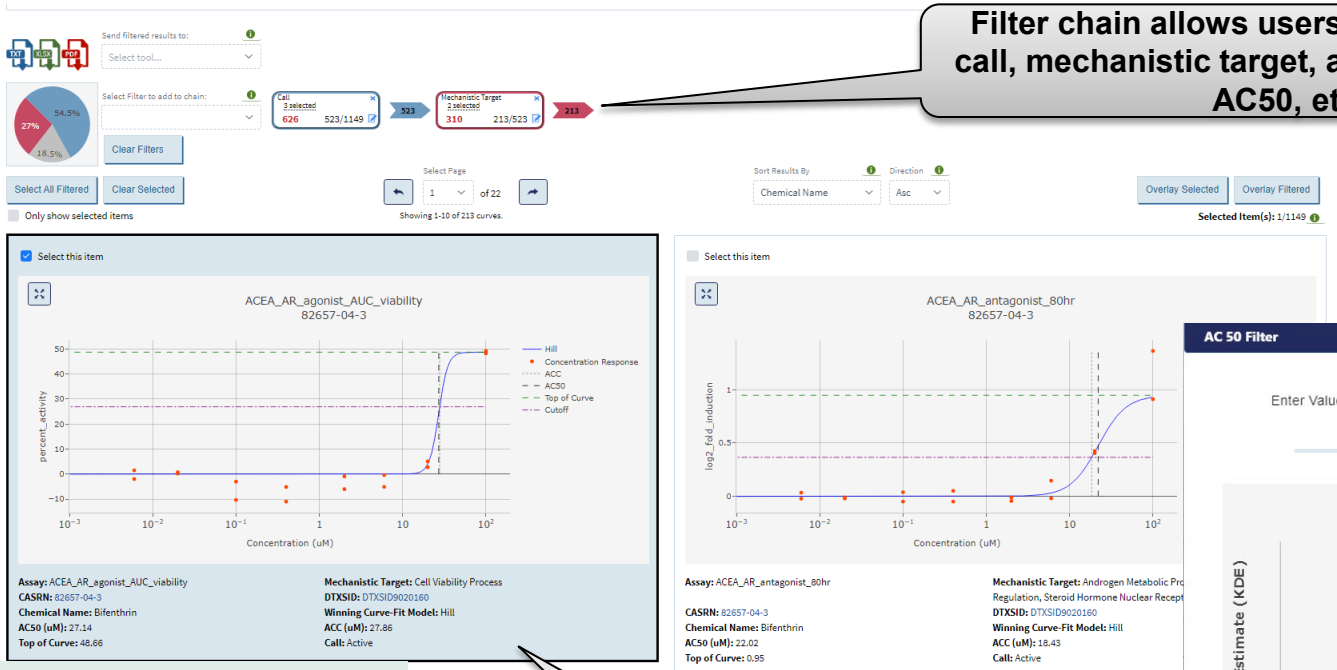
Curve Surfer

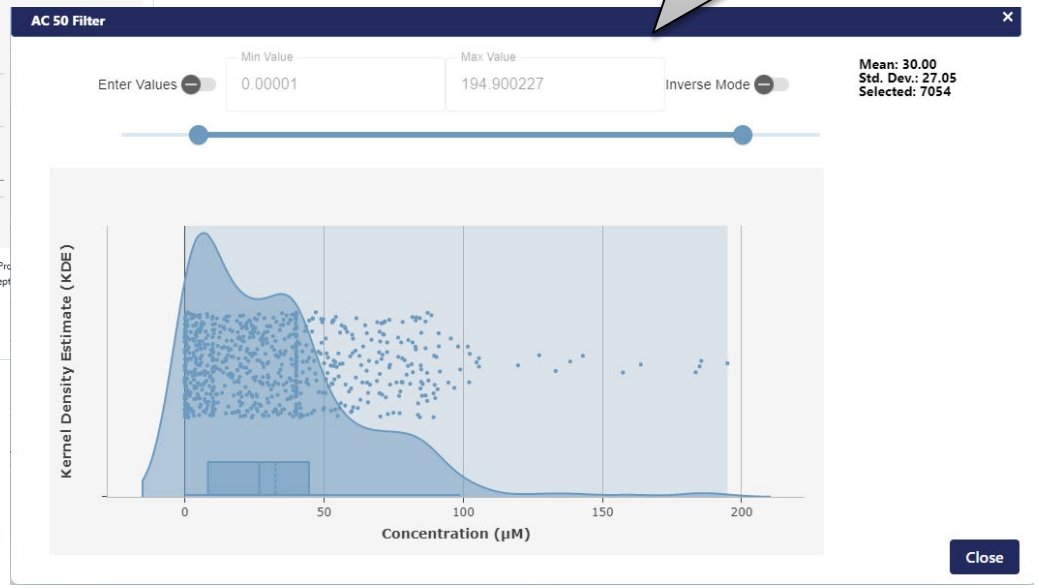
Curve Surfer

Perform a search → Identify similar chemicals → Characterize chemical inventory → **Review in vitro data details** → Generate chemical concentration predictions → Predict equivalent administered dose



Filter chain allows users to filter based on call, mechanistic target, assay, assay target, AC50, etc.

View data breakdown by filter terms and see selection highlighted



Plots have key features highlighted and details for assay and chemical information are provided below plots

New in release v4.1: Additional information regarding data flags on results cards.

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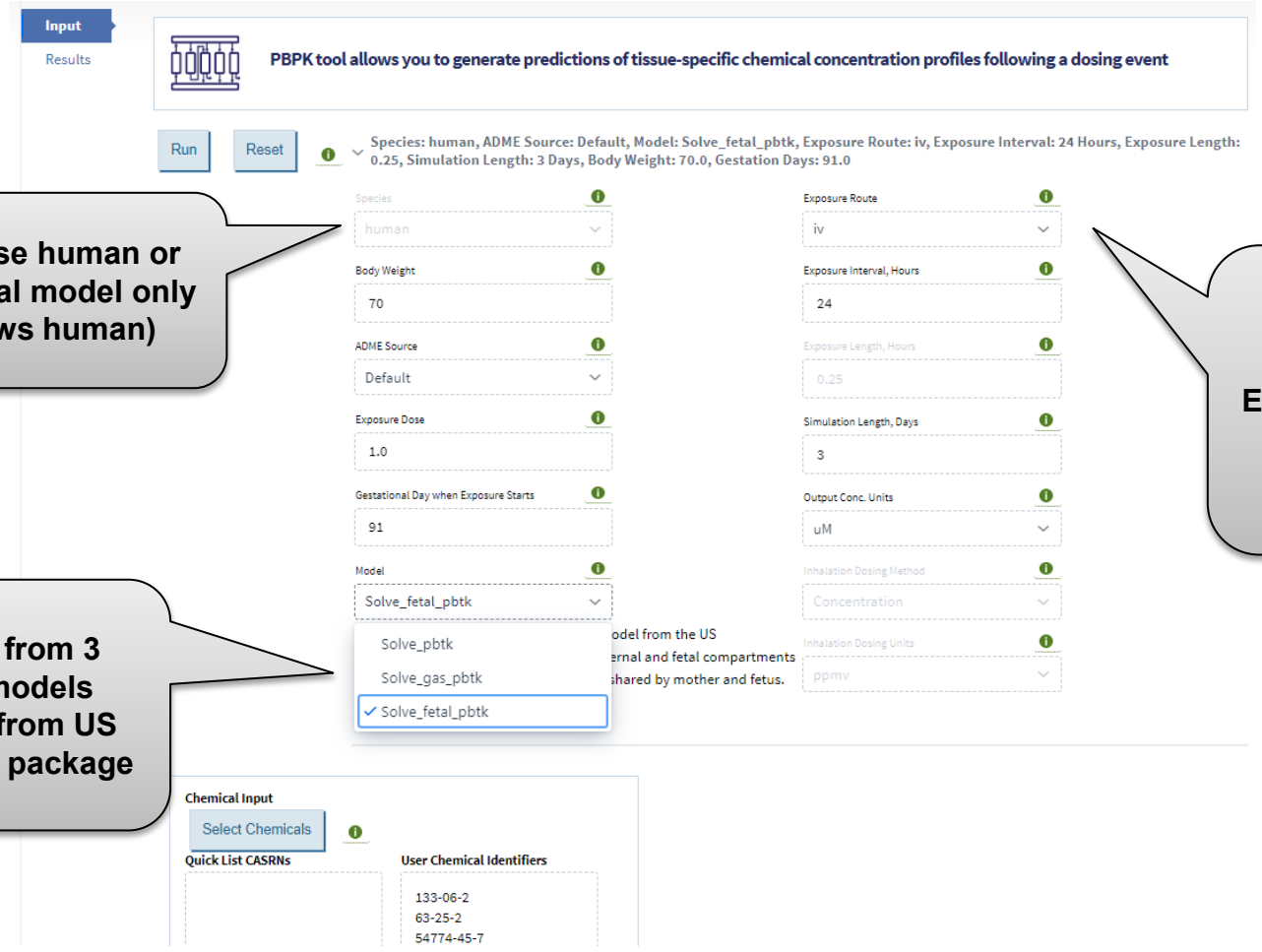
PBPK

PBPK Analysis Tool

Perform a search → Identify similar chemicals → Characterize chemical inventory → Review in vitro data details → **Generate chemical concentration predictions** → Predict equivalent administered dose



Choose human or rat (fetal model only allows human)

Customize model parameters such as Exposure Route, Exposure Length, and Simulation Length

Choose from 3 PBPK models sourced from US EPA's httk package

httk v2.2.2 (Pearce et al., 2017)

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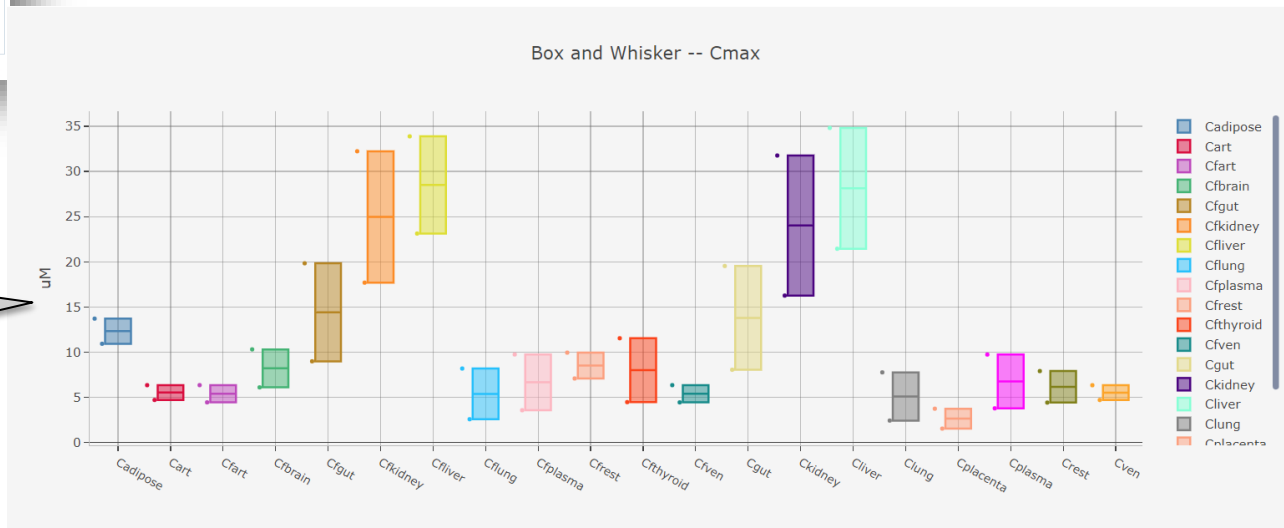
PBPK

PBPK Analysis Tool

Perform a search → Identify similar chemicals → Characterize chemical inventory → Review in vitro data details → **Generate chemical concentration predictions** → Predict equivalent administered dose

For each input chemical, the results show the concentration of the chemical over time in plasma and each tissue compartment

Boxplots show the Cmax distribution across all returned chemicals for each compartment



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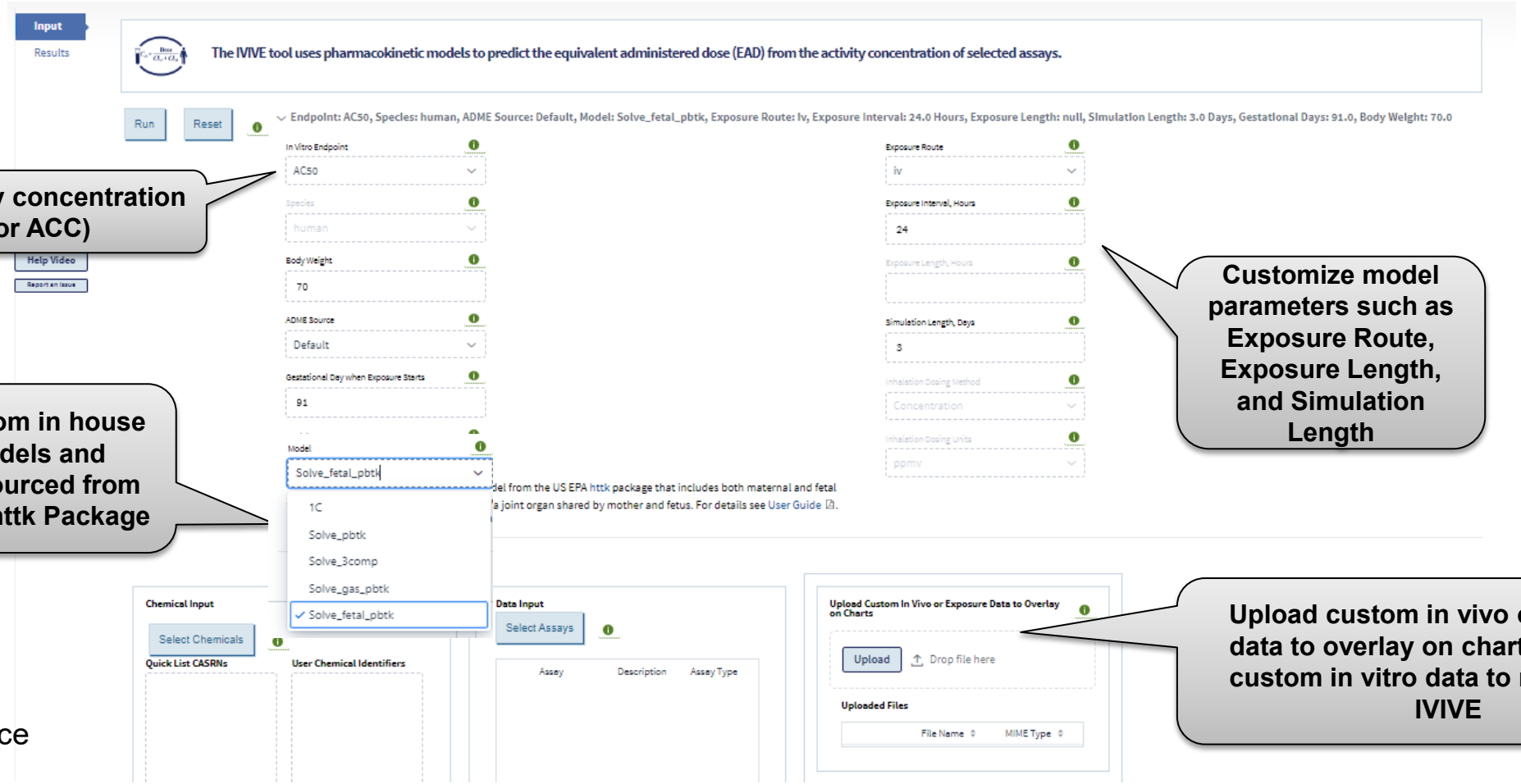
IVIVE

IVIVE Analysis Tool

Perform a search → Identify similar chemicals → Characterize chemical inventory → Review in vitro data details → Generate chemical concentration predictions → **Predict equivalent administered dose**



Type of activity concentration (AC50 or ACC)

Choose from in house ICE models and models sourced from US EPA's httk Package

Customize model parameters such as Exposure Route, Exposure Length, and Simulation Length

Upload custom in vivo or exposure data to overlay on charts or upload custom in vitro data to run through IVIVE

httk v2.2.2 (Pearce et al., 2017)

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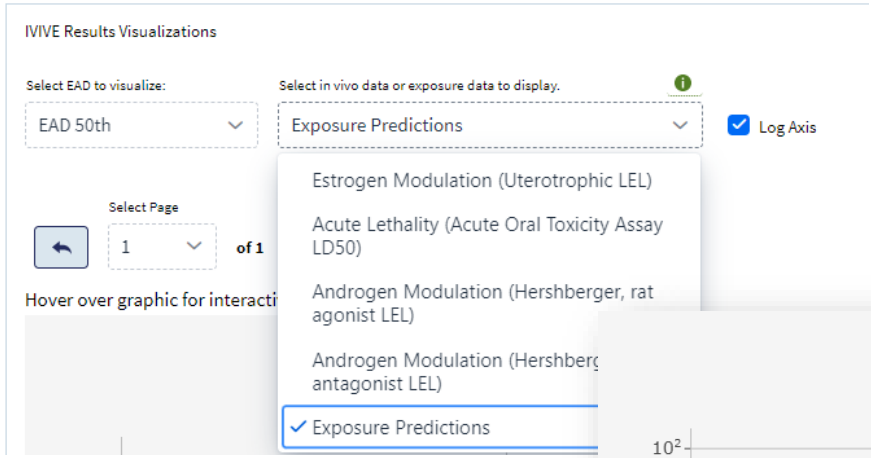
IVIVE

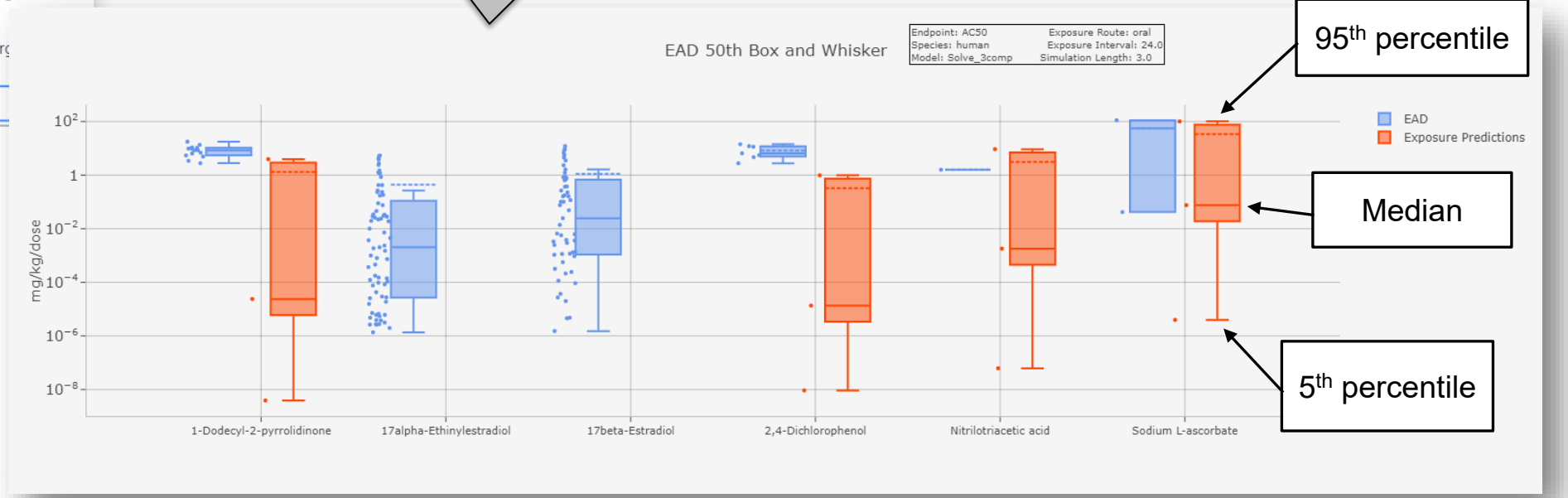
IVIVE Analysis Tool

Perform a search → Identify similar chemicals → Characterize chemical inventory → Review in vitro data details → Generate chemical concentration predictions → **Predict equivalent administered dose**



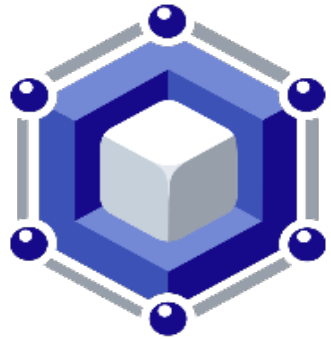
Box and whisker plots show Equivalent Administered Dose (EAD) based on in vitro inputs

Users can now overlay Exposure Predictions from EPA's SEEM3 model



SEEM3 (Ring et al., 2019)

Summary of changes and enhancements in ICE v4.1



Data updates

- Added links to the NTP CEBS database and EPA CompTox Chemicals Dashboard in data downloads
- Updated cHTS data: Inclusion of annotations to OBO Foundry ontologies

Tool updates

- Additional information regarding data flags on Curve Surfer results cards.
- Chemical Quick Lists: New PFAS Quick List, Updated RoC Classifications Quick List

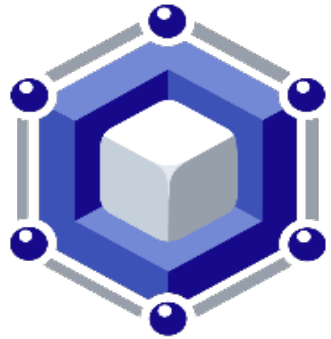
REST API

- Inclusion of applicability domain information for OPERA predictions
- Inclusion of Curve Surfer raw data

Documentation

- Updated manuals, html pages, and help videos

Strategic activities to improve ICE



External review

- A team from ICF (a toxicologist, environmental scientist, computational chemist, and experienced software developer) recently conducted a review of ICE
- They assessed the usability of the front-end user interface and categorizing their findings in terms of (i) Functionality & Usability, (ii) Intuitiveness & Familiarity, (iii) Regulatory Utility, and (iv) Wishlist Functions
- They also conducted a full audit of the backend database schema and software stack

Their findings were provided in written reports and during an all-hands ICE Review and Planning Meeting on August 23, 2024

Sample Slide from the External Reviewers

Functionality & Usability

- Having web-based brief user guides, tutorial videos, and more detailed PDFs each serve useful purposes depending on how well versed the user is in each Tool or topic.
- Info bubbles are well written and prevent users from needing to search help pages, thus saving time.
- Sometimes links to cebs.niehs.nih.gov are broken or land on an empty page. For example, Test Article Not Found (nih.gov). If the CEBS website is the source of the issue, then a notice to the user would be helpful.

Intuitiveness & Familiarity

- Overall interface is user friendly. Users can get from input to result in seconds.
- The time or root cause of expiring sessions is unknown and when it happens, work is unsaved and the tool is refreshed.
- Refreshing browser pages always brings the user back to the Quest tool instead of whichever tool they were working in.
- For many of the tools, the “Select Chemicals” button seems like an option to upload a list.
- Results download options are labeled inconsistently and differences in outputs could use descriptions.

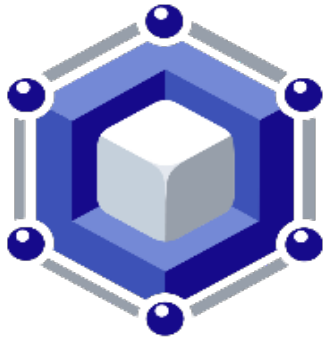
Regulatory Utility

- Widespread use would likely require an increase in data coverage, especially for chemicals in classes of regulatory interest and for representative chemicals in data poor classes.
- More backend transparency is required for regulatory use, especially for EPA. For example, model coefficient values and statistical metrics are missing in the outputs. This is also important for non-regulatory purposes.

Wishlist Functions

- Increase in data coverage, especially for chemicals in classes of regulatory interest.
  - Tox based assays only had data for 4/14 test chemicals (data available in other platforms for chemicals not covered in ICE).
- Interoperability between all the tools. For example, selecting from output in IVIVE to carry to PBPK.
- A tool for QSAR or read across that includes tox outcomes for comparing chemicals. A "next step" to chemical quest.
- Adding a pause or cancel once a run starts.
- Listing the maximum number of input chemicals on each page.

Strategic activities to improve ICE (2)



All-Hands ICE Review and Planning Meeting: August 23, 2024

Objective: Characterize the current state of ICE, identify challenges and opportunities, and discuss potential future directions

Participants from NIEHS, Inotiv, Sciome, ICF

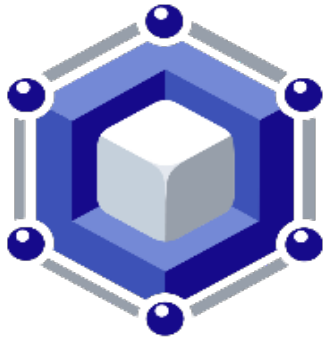
Agenda

- Reports from Inotiv tool leads and ICF consultants about what elements are working well, as well as challenges and opportunities related to the ICE front end
- Report from the Sciome leads and an ICF consultant about the overall backend architecture, code base quality, and state of the databases and servers
- Discussion about future directions for ICE

Output

- A unified list of items related to ICE improvement, growth, and sustainability for future focused discussions and prioritization.

Ongoing work and future enhancements



Items in progress and planned for ICE v4.2

Based on feedback/requests from stakeholders, and informed by discussions at the recent ICE Review and Planning Meeting…

- Update cHTS data to align with invitrodb v4.1
- Update Tox21 quick list
- Integrate chemical quick lists into data pipeline
- IVIVE tool: Add feature to allow user-provided data
- PBPK tool: Add feature to allow user-provided data
- Chemical Characterization tool: update PCA plots

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Acknowledgments

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

The NICEATM Group

Integrated Chemical Environment

https://github.com/NIEHS/OPERA

OPERA OPEn (q)saR App

https://www.sciome.com/

CEBS Chemical Effects in Biological Systems

https://cebs.niehs.nih.gov/cebs/

https://comptox.epa.gov/dashboard

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