

The Integrated Chemical Environment (ICE): Advancing Data Availability and Computational Tool Accessibility for the Development, Evaluation, and Application of New Approach Methods

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Integrated Chemical Environment (ICE)

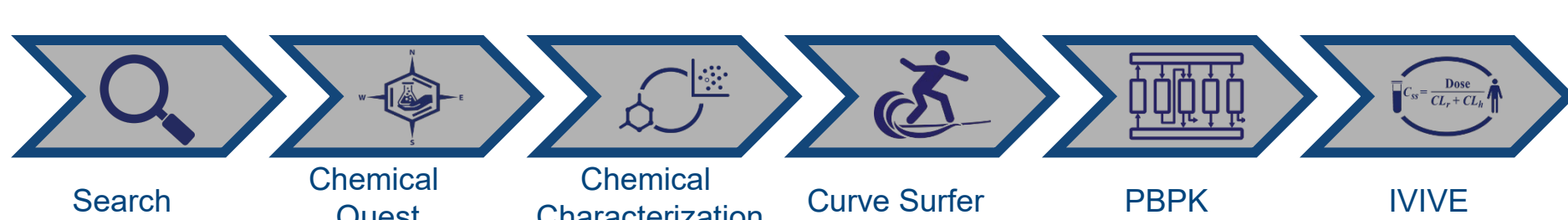
- The Integrated Chemical Environment (ICE: <https://ice.ntp.niehs.nih.gov/>) is an open access resource comprising curated chemical property and bioactivity data, as well as tools for summarizing, analyzing, and visualizing these data.
- ICE was developed by the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) to support development and evaluation of new approach methodologies (NAMs) in toxicology testing [1].
- ICE aims to democratize the usage of in silico methods in toxicology by providing a suite of user-friendly tools to conduct a variety of searches, visualizations, characterizations, and analyses on underlying sets of highly curated data.
- As part of ongoing efforts to improve user experience and address stakeholder requests, we released two ICE updates in 2024: v4.0.2 in March 2024 and v4.1 in September 2024.

ICE provides

- Curated in vivo and in vitro toxicity testing data, in silico toxicity predictions, and experimental or predicted physicochemical property and exposure data.
- Interactive computational tools that characterize, analyze, and predict bioactivity for user-defined or ICE-provided curated lists of chemicals with well-characterized toxic effects.

ICE supports

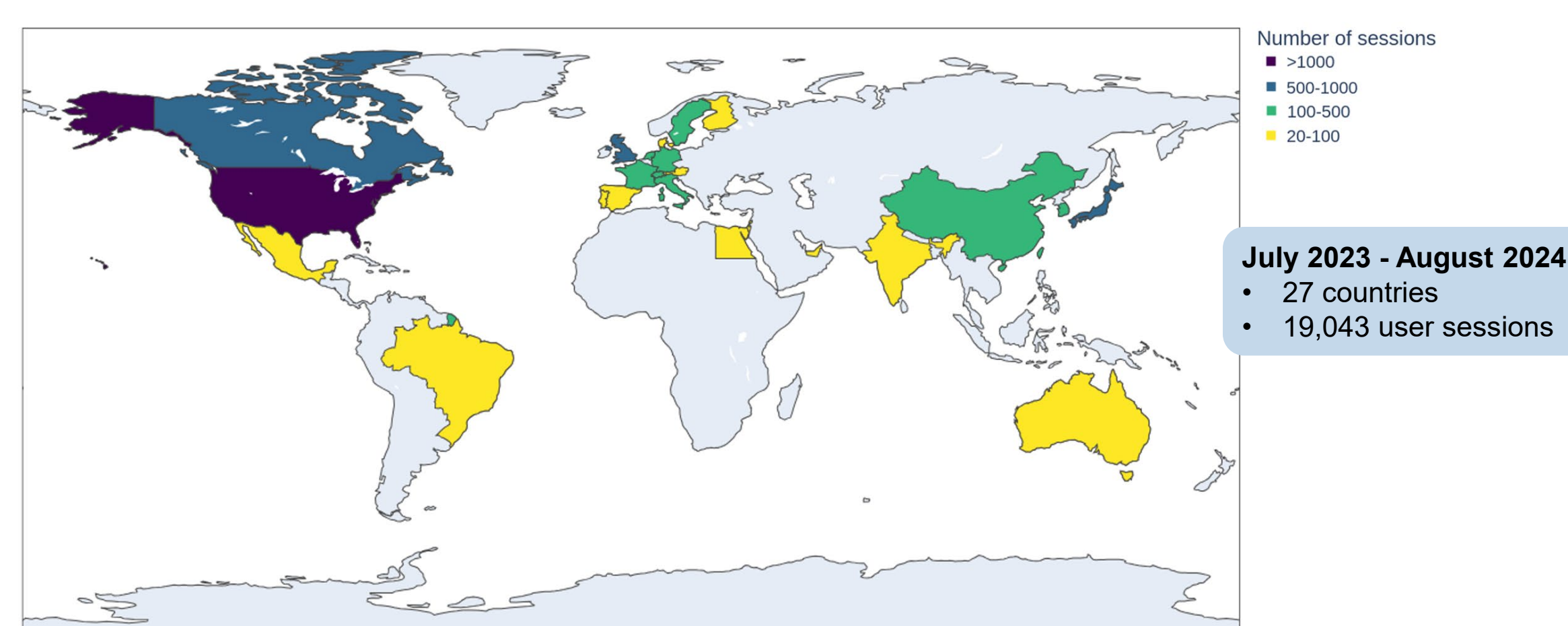
- FAIR (findable, accessible, interoperable and reusable) principles.
- Approaches using the 3Rs (reduce, refine, and replace animal tests).
- Data integration: Brings together disparate data types.
- Data analyses: Data characterization and interpretation with user-friendly workflows.
- Filtering: Allows data-driven interactive filtering options.
- Tool interoperability: Facilitates passing selected chemicals from results across multiple ICE tools and to other resources.
- Results exploration: Enables dynamic interactive visualizations yielding high-quality graphics.



ICE Usage

ICE tools and data have been used for numerous applications, including supporting chemical prioritization [2], connecting biomonitoring and computational toxicology studies [3], assessing biological points of departure [4–6], and in vitro to in vivo extrapolation (IVIVE) [7, 8].

As indicated in the figure below, which was derived from website analytics, the ICE platform has seen robust usage globally.



Summary of ICE Improvements in 2024

Data updates

- Added links to the NTP Chemical Effects in Biological Systems (CEBS) database and U.S. Environmental Protection Agency (EPA) CompTox Chemicals Dashboard for chemicals in data download files.
- Updated curated high-throughput screening (cHTS) data by expanding annotations based on the Open Biological and Biomedical Ontologies (OBO) (see Hill et al. poster PSII-01).
- New cHTS flags: Technological interference flags warn users of potential interference between chemicals and fluorescence and luciferase readout technologies.
- Improved data curation and harmonization pipelines (see Unnikrishnan et al. poster PSII-02).

Tool updates

- Additional information regarding data flags on Curve Surfer results cards.
- Chemical Quick Lists: New EPA per- and polyfluoroalkyl substances (PFAS) Quick List, updated Report on Carcinogens (RoC) Classifications Quick List.
- Major updates in the data visualizations for Search tool query summary results.

REST API

- Inclusion of applicability domain information for OPERA predictions.
- Inclusion of concentration-response data for cHTS results.
- Ability to query by cHTS assay name.

Documentation

- Updated documentation and help videos.



Updates to ICE Data

In Vivo and In Vitro

Toxicity endpoint	Assay	# of chemicals
Acute Toxicity	In vivo acute oral, dermal, and inhalation toxicity	~10000
ADME Parameters	Fraction unbound, intrinsic clearance, Caco2 permeability	~3000
Cancer	In vivo and in vitro cancer, and weight-of-evidence	~3000
Chemical Parameters	Experimental physicochemical properties	~20000
cHTS	Curated EPA ToxCast and federal Tox21 assays (in vitro)	~10000
DART	In vivo and in vitro developmental and reproductive toxicity	~600
Endocrine	In vivo and in vitro data on androgen receptor and estrogen receptor agonist and antagonist activity	~1700
Eye Irritation	In vivo and in vitro eye irritation/corrosion	~500
Skin Irritation	In vivo and in vitro skin irritation/corrosion	~600
Skin Sensitization	In vivo and in vitro skin sensitization	~1800

New in v4.1:
Expanded annotations to cHTS data based on OBO Foundry ontologies.
New in v4.1:
• Versioning information in data sets.
• Links to the NTP CEBS database and EPA CompTox Chemicals Dashboard in data file downloads.

In Silico Models and Integrated Approaches

Endpoint	Model	# of chemicals
Physicochemical Properties	OPEN (qsaR App (OPERA) Mansouri et al. J Cheminform 2018	1M+
	OPEN (qsaR App (OPERA) Mansouri et al. J Cheminform 2018	1M+
Structural Properties	OPEN (qsaR App (OPERA) Mansouri et al. J Cheminform 2018	1M+
	OPEN (qsaR App (OPERA) Mansouri et al. J Cheminform 2018	1M+
Predicted ADME Properties	OPEN (qsaR App (OPERA) Mansouri et al. J Cheminform 2018	1M+
	OPEN (qsaR App (OPERA) Mansouri et al. J Cheminform 2018	1M+
Environmental Fate	Collaborative Acute Toxicity Modeling Suite (CATMoS) - Rat acute oral toxicity, Mansouri et al. EHP 2021	1M+
	Collaborative Acute Toxicity Modeling Suite (CATMoS) - Rat acute oral toxicity, Mansouri et al. EHP 2021	1M+
Acute Oral Toxicity	Estrogen receptor pathway model. Browne et al. ES&T 2015	~1800
	Androgen receptor pathway model. Kleinstreuer et al. Chem Res Tox 2017	~1900
Endocrine	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 (EPA SEEM3), Ring et al. Environ Sci Technol 2019	475,000+

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

Updates to REST API

Highlight: Inclusion of Curve Surfer raw data in the REST API

Users can employ the HTTP GET protocol to submit an ICE REST API query using any of several accepted chemical identifiers, including DTXSID, CASRN, InChIKey, or chemical name.

For example, the Curve Surfer data for chlordecone (CASRN 143-50-0) may be requested via a browser (or other tools, such as curl).

<https://ice.ntp.niehs.nih.gov/api/v1/curves?chemid=143-50-0>

The result is returned as a JSON representation, a partial view of which is shown to the right.

```
{
  "curves": [
    {
      "assay": "143-50-0",
      "chemid": "143-50-0",
      "casrn": "143-50-0",
      "dtxsid": "DTXSID0020966",
      "inchi": "ClC1=CC=CC=C1",
      "name": "Chlordecone",
      "pubchem": "274886",
      "url": "https://ice.ntp.niehs.nih.gov/api/v1/curves?chemid=143-50-0",
      "version": "1.0"
    }
  ]
}
```

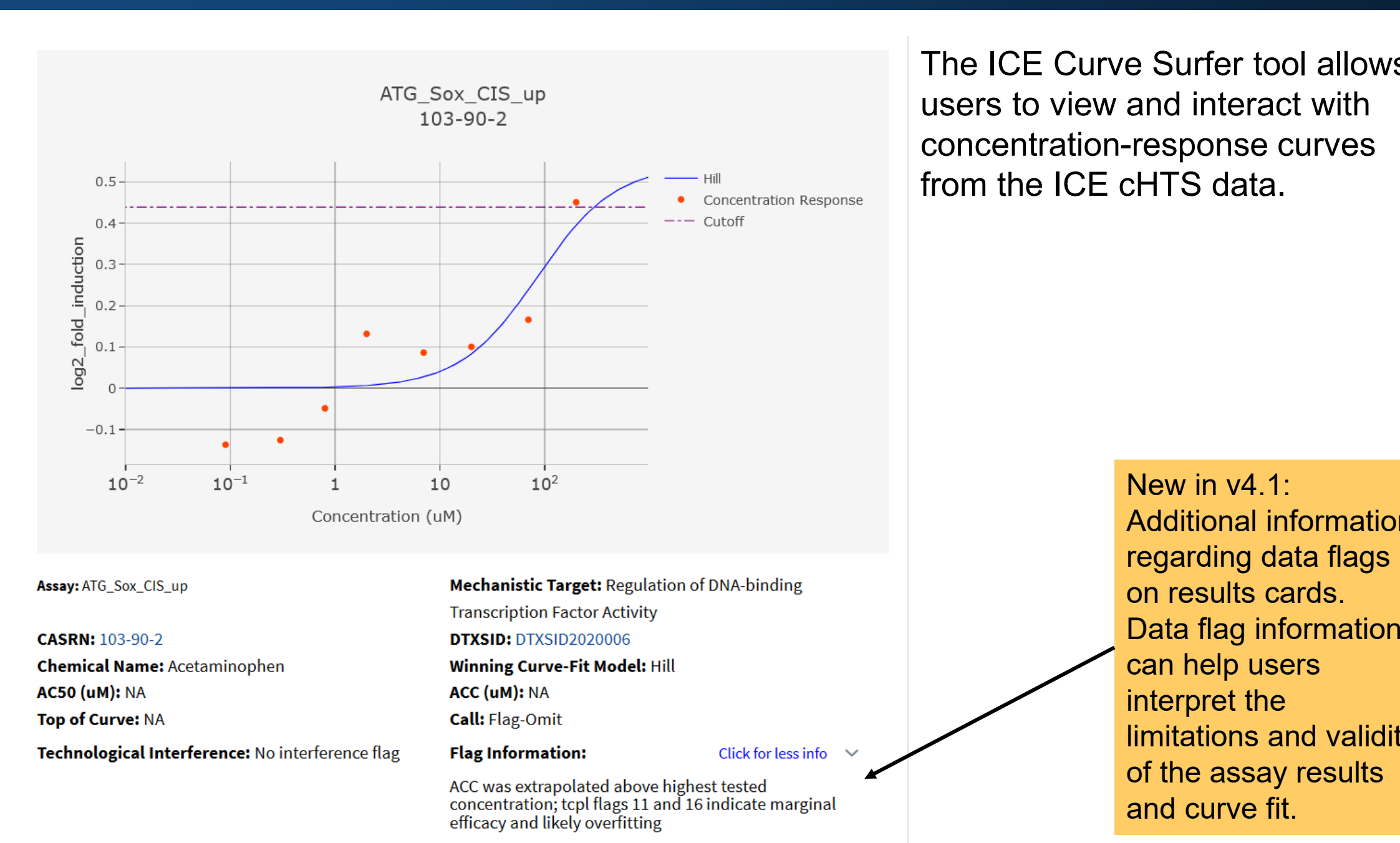
Summary and Impact of Improvements to ICE

ICE provides high-quality curated data and tools to support development of new, revised, and alternative methods. ICE provides free online access to (i) curated in vivo and in vitro test data (ii) in silico toxicity predictions and chemical property data, (iii) reference and non-reference chemical lists, and (iv) computational tools for chemical characterization and predicting toxicity.

During 2024, ICE has been updated with improved data and tools to facilitate more efficient and informed queries and analyses. Specific enhancements include the following:

- Expanded cHTS annotations using terminologies and taxonomies from the OBO Foundry ontologies. This change will allow increased interoperability with other databases such as CEBS that use ontologies for their data dictionaries. This change may also facilitate efforts to incorporate these data into AOPs and standardized reporting efforts such as the OECD Harmonized Templates.
- Enhanced data flag information on Curve Surfer results cards. Data flag information can help users understand cHTS flags and bolster confidence in interpreting and applying assay results.
- New EPA PFAS Quick List and updated RoC Classifications Quick List. These enhancements should improve the user experience in making certain queries throughout the ICE toolset.
- Inclusion of Curve Surfer data as part of the REST API. This will provide users with further flexibility in incorporating cHTS assay results into other applications/pipelines and help in automated retrieval of these results for external analyses or completion.

Updates to the Curve Surfer Tool



New in v4.1:
Additional information regarding data flags on results cards. Data flag information can help users interpret the limitations and validity of the assay results and curve fit.

Updates to Chemical Quick Lists

ICE Chemical Quick Lists can be used to quickly populate an ICE query.

Reference Chemical List	Non-reference Chemical List
Androgen receptor In Vitro Agonist	Androgen receptor In Vivo Agonists
Androgen receptor In Vitro Antagonist	Androgen receptor In Vivo Antagonists
Estrogen receptor In Vivo Agonist	EPA Pesticide Active Ingredients
Eye Irritation-Corrosion	EPA Pesticide Inert Ingredients, Food and Nonfood Use
Genotoxicity	EPA IRIS Cancer Assessment
OECD Defined Approach to Skin Sensitization: Human	EPA IRIS Non-Cancer Assessment
OECD Defined Approach to Skin Sensitization: Local lymph node assay	EPA PFAS Master List
Skin Corrosion	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

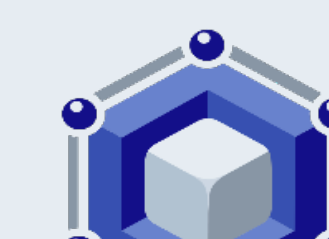
New in release v4.1:
• New EPA PFAS Quick List.
• Updated RoC Classifications Quick List based on the 15th Report on Carcinogens.

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More Information and Acknowledgments

Visit ICE at <https://ice.ntp.niehs.nih.gov>



To get announcements of ICE updates and other NICEATM activities, visit the NIH mailing list page for NICEATM News and subscribe.



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The NICEATM team

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