National Institute of Environmental Health Sciences
*Division of the National Toxicology Program*

# Providing Context For Chemical Effects Through Compound Structure Similarity

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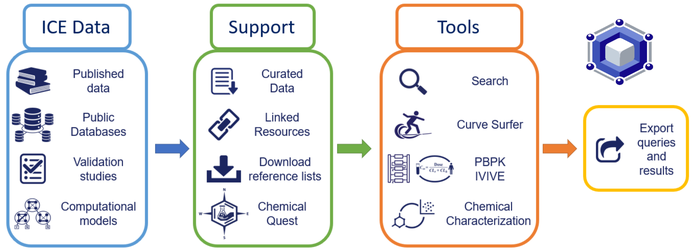
## The Integrated Chemical Environment (ICE)

- Developers of alternatives to animal-based chemical testing need access to chemical safety and bioactivity data, predictions, and structure-based characteristic information.
- To address this need, the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) maintains the **Integrated Chemical Environment (ICE)**.
- ICE provides resources, data, and tools to examine chemical bioactivity and properties that are accessible to users with a broad range of chemistry expertise.




**Key features of ICE:**

- Freely available.
- Contains data and information for over 800,000 chemicals.
- Users can construct queries with curated chemical quick lists or user-specified chemical identifiers (CASRN, DTXSID, InChiKey, and SMILES).
- Queried and filtered chemicals can be sent to other tools within ICE and can also be copied to the user clipboard.
- All data can be exported as text or Excel files. Curve Surfer graphics can also be exported to a PDF.

**ICE supports:**

- FAIR (findable, accessible, interoperable and reusable) data.
- Data integration: combine data from different endpoints for comparison and exploration.
- Results exploration: dynamic, graphical exploration of query results with capability to refine.
- Data analysis: computational tools for chemical characterization and predictive toxicology.

## Linking ICE With Other Resources

- Information obtained from ICE can be combined with other data resources for additional insight into the chemicals of interest.
- ICE users can click on chemical identifiers to directly access the **NTP Chemical Effects in Biological Systems (CEBS)** database and the **U.S. Environmental Protection Agency (EPA) CompTox Chemical Dashboard**.
- By linking to CEBS, ICE users can explore a chemical's biological effects, investigate its bioactivity, determine property characterization, and provide context to specific effects of chemicals.
- ICE users can query the CompTox Chemical Dashboard to further explore properties of individual chemicals and how chemical structure and bioactivity can influence experimental variables.
- The **EPA Chemical and Products Database (CPDat)** offers categorical mapping (e.g., consumer products) to ~50,000 chemicals based on functionality.

## Acknowledgements/Contact Us

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**Visit ICE**
**https://ice.ntp.niehs.nih.gov/**

## Chemical Exploration

**"My structure is unique; can I identify chemical analogues by searching on a structure?"**

**ICE Chemical Quest Tool**

**Tool Input**

Identify structurally similar chemicals from in vivo, in vitro, and in silico data for over 800,000 chemicals. Chemical similarity is determined by Saagar fingerprints (Sedykh et al. 2021).

Specify Tanimoto score range and max number of returned results.

Search for similar chemicals from ICE or determine the similarity of chemicals in two user-defined lists.

Query structurally similar chemicals based on 2D structures or other chemical identifiers (CASRN, DTXSID, InChiKey).

**Tool Output**

Filter by a range of chemical characteristics including chemical identifiers, SMARTS strings, Tanimoto scores, and if availability of bioactivity data. Combine and rearrange filters to refine results.

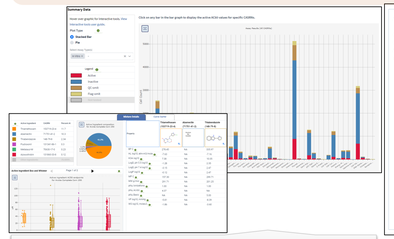
Filter by SMARTS strings to reduce results and highlight desired structural features.

Filter numeric results using sliding bar filters with curves to show the range of data being selected.

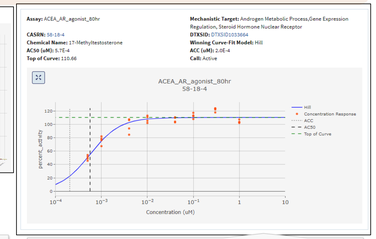
## Building Biological Context for Similar Chemicals

**"What data are available on chemicals with similar structures?"**

**ICE Search and Curve Surfer Tools**



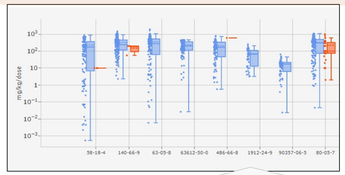
The ICE **Search** tool provides bioactivity and chemical property data for individual chemicals or mixtures.



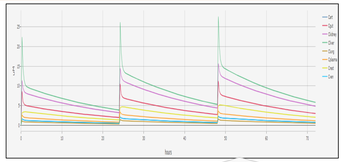
The ICE **Curve Surfer** tool shows concentration-response curve and some assay details.

**"How can chemical exposure affect biological response?"**

**ICE IVIVE and PBPK Tools**



The ICE **In Vitro to In Vivo Extrapolation (IVIVE) tool** estimates an equivalent administered dose for plasma concentration of a chemical based on the activity concentration in an in vitro assay, based on U.S. EPA's httk R package.



The ICE **Physiologically Based Pharmacokinetics (PBPK)** tool predicts a tissue-specific chemical concentration of an administered dose. Results are chemical concentration over time in plasma and tissue compartments.

**"How do my chemicals of interest relate in terms of physicochemical properties or structural space coverage?"**

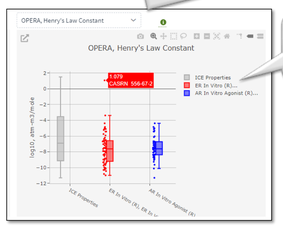
**ICE Chemical Characterization Tool**

**Visualization of Chemical Properties**

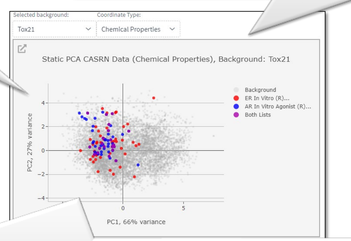
Box-and-whisker plots of individual chemical properties highlight differences between one or two lists of chemicals and the properties represented by all chemicals in ICE.

PCA plots cluster or scatter chemicals depending on their degree of similarity for selected attributes.

Select molecular descriptors or physical chemical properties as separating factors for the lists.



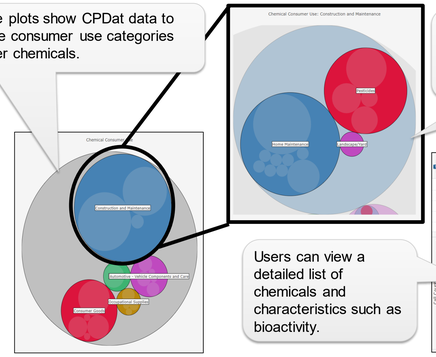

Chemicals that stand out may be incompatible with desired assay platform.




Use background chemicals, such as DSSToxDB for predictive toxicology (~800k) or Tox21(~10k screened in more than 70 high-throughput assays), to plot statically and broaden the chemical space or plot dynamically for a direct comparison.

**Consumer Use Explorer**

Bubble plots show CPDat data to provide consumer use categories for user chemicals.



Users can click on categories of interest to magnify the number of chemicals located in each subcategory.

Users can view a detailed list of chemicals and characteristics such as bioactivity.