Chemical Exploration: Identifying Bioactivity with the Use of Structural Features

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U.S. Department of Health and Human Services

New Approach Methodologies

- New approach methodologies (NAMs) include in vitro and in silico techniques used to query a specific toxicity endpoint.
- Because NAMs are often developed to address a specific set of regulatory or research needs, there may be a lack of diversity in chemicals used to develop them. This can hinder further evaluations of their usefulness and limitations.
- Structure-based information for chemicals used to validate NAMs and for candidates for testing in NAMs is important for advancing and implementing these methods.
- This poster describes a freely available web tool for exploring, comparing, and visualizing structure-based chemical information.

The Integrated Chemical Environment (ICE)

- To provide access to data, predictions, and structure-based information, the National Toxicology Program maintains the Integrated Chemical Environment (ICE).
- ICE provides resources and tools to examine chemical activity and properties that are accessible to users with a broad range of chemistry expertise, with a focus on on non-animal approaches.

Integrated Chemical Environment

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 CASRNs.
- Includes computational tools for chemical characterization and predictive toxicology.

Search

Data

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

IVIVE

ICE supports:

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

Chemical Characterization

Acknowledgements and Contact Us

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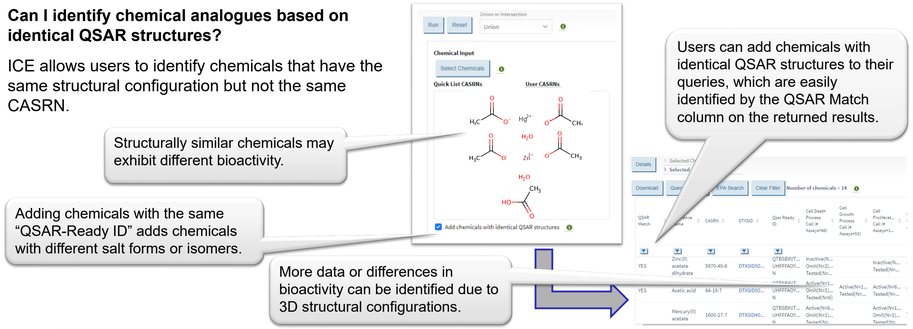
Visit ICE
https://ice.ntp.niehs.nih.gov/

Chemical Exploration: ICE Case Studies

Users can obtain a wide range of information through ICE queries, from chemical properties to bioactivity data. ICE can be used to identify available data across different toxicity endpoints or explore why differences in bioactivity are observed. Below are case studies to illustrate the functionality of the ICE web interface.

Can I identify chemical analogues based on identical QSAR structures?

ICE allows users to identify chemicals that have the same structural configuration but not the same CASRN.



Structurally similar chemicals may exhibit different bioactivity.

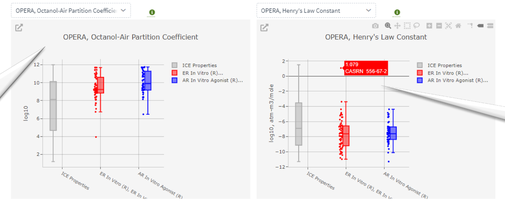
Adding chemicals with the same "QSAR-Ready ID" adds chemicals with different salt forms or isomers.

Users can add chemicals with identical QSAR structures to their queries, which are easily identified by the QSAR Match column on the returned results.

More data or differences in bioactivity can be identified due to 3D structural configurations.

Do these two chemical sets of interest have different properties?

The ICE Chemical Characterization tool provides Visualization of Chemical Properties box-and-whisker plots.

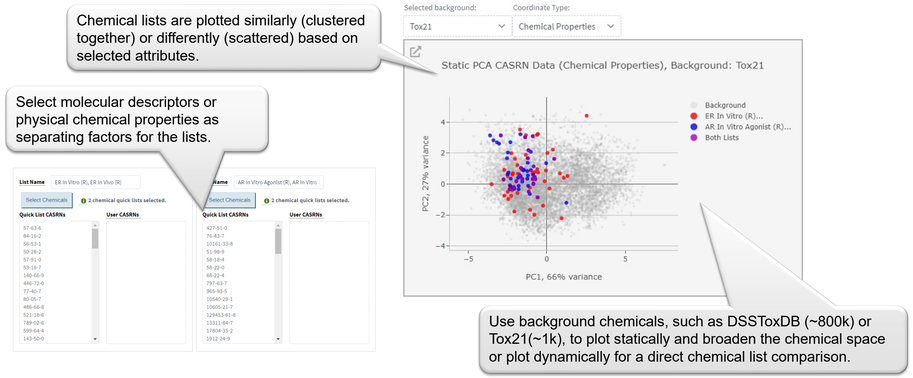


Visual comparison of properties highlights differences represented by one or two lists of chemicals to all chemicals in ICE.

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

How do my chemicals of interest compare in terms of physicochemical property or structural space coverage?

The ICE Chemical Characterization tool provides principal component analysis (PCA) plots to show comparison through chemical properties or molecular descriptors.



Chemical lists are plotted similarly (clustered together) or differently (scattered) based on selected attributes.

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

Use background chemicals, such as DSSToxDB (~800k) or Tox21(~1k), to plot statically and broaden the chemical space or plot dynamically for a direct chemical list comparison.

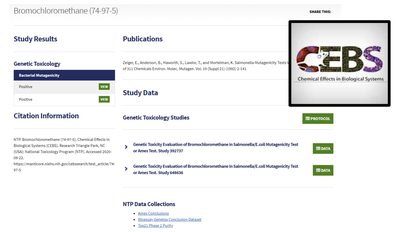
Linking ICE With Other Resources

Information obtained from ICE can be combined with other data resources for additional insight into the chemicals of interest.

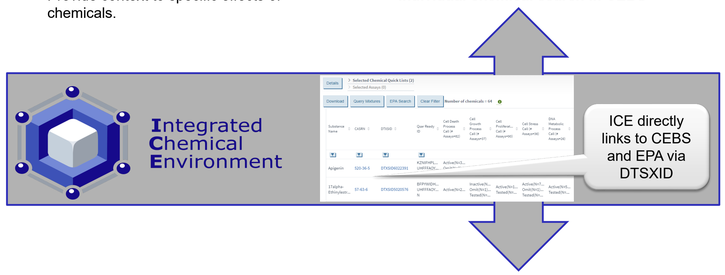
- CEBS allows users to obtain information on individual test articles.
- EPA resources can provide experimental results as well as chemical categorization.

NTP Chemical Effects in Biological Systems (CEBS)

- Users can expand their ICE analysis by exploring detailed study results available in CEBS, including histopathology and clinical chemistry data.
- By combining ICE and CEBS, users can:
  - Identify biological effects.
  - Investigate the bioactivity and the chemical characterization of chemicals of interest.
  - Provide context to specific effects of chemicals.



Individual chemical search in CEBS



ICE directly links to CEBS and EPA via DTXSID

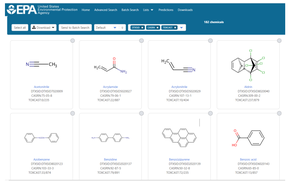
U.S. Environmental Protection Agency (EPA) CompTox Chemical Dashboard and Chemical and Products Database (https://comptox.epa.gov/dashboard)

CompTox Chemical Dashboard

- The Chemical Dashboard provides information on individual chemicals from environmental fate and transport to exposure and usage.
- ICE users can query the CompTox Chemical Dashboard with chemical lists to further explore properties of individual chemicals and how chemical structure and bioactivity can influence experimental factors.

Chemical and Products Database (CPDat)

- CPDat offers categorical mapping (e.g., consumer products) to ~50,000 chemicals based on functionality.
- Combining ICE and CPDat data can allow users to explore characteristics of chemicals. Users can also classify chemicals analyzed in ICE and compare their chemicals of interest to others in the category.



Batch Search on CompTox Chemical Dashboard

Carcinogenicity Data from ICE grouped by CPDat categories