Chemical exploration: providing biological context for NAMs

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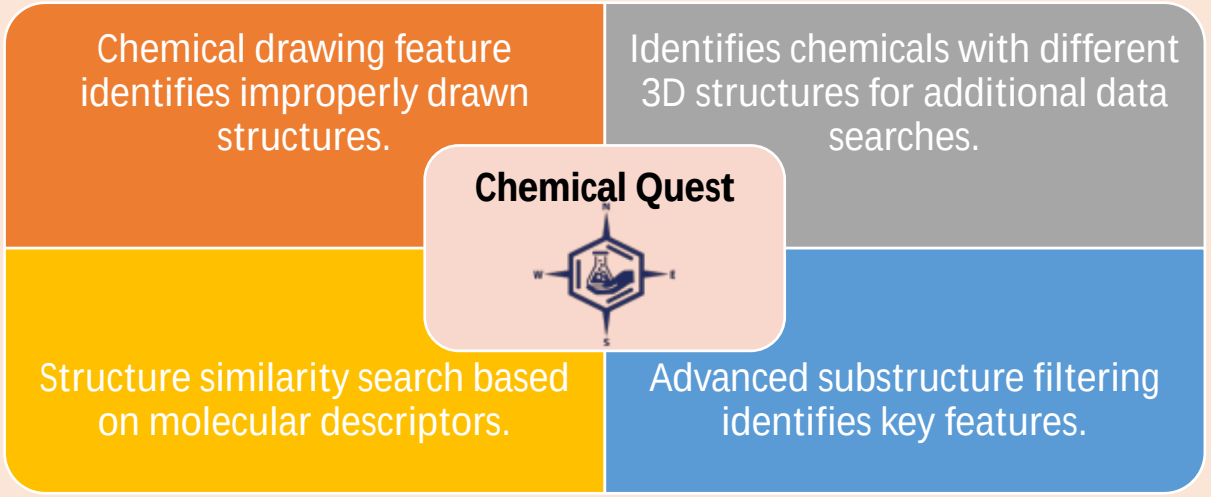
OBJECTIVES

- This presentation describes how ICE supports developing new approach methodologies (NAMs) for predicting toxicity.
- ICE provides improved access to data, predictions and structure-based information through:
  - Structure-based queries to expand data acquisition and read across for complex molecules.
  - Expanded data and modeling tools needed for biological context.

APPROACH

- Updates to ICE:
  - Enhanced PBPK and IVIVE tools, updated QSAR models for parameters.
  - Expanded tool capabilities to include new search identifiers: SMILES, DTXSID and InChiKey
  - Added ability to identify structurally similar chemicals through molecular descriptors: identified chemicals can be sent to all ICE tools, enabling structure-based support.

MAIN RESULTS



IMPACT

- ICE has several tools and features to promote easily accessible data.
  - Updated annotation expands tool access.
- New search capabilities include three new identifier types and support structure-based queries.
- Queried chemicals can be sent to other ICE tools or external databases.

- **For more information visit ICE: https://ice.ntp.niehs.nih.gov/**

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OBJECTIVES

New Approach Methodologies and the Integrated Chemical Environment

Integrated Chemical Environment

Data resources are needed to support development of NAMs:

- New approach methodologies (NAMs) include in vitro and in silico techniques used to query a specific toxicity endpoint.
- NAMs are often developed for a specific set of regulatory needs, using chemicals with established bioactivity.
- The finite set of chemicals used for validation may not provide definitive insight regarding a NAMs domain of applicability.

Structure-based queries can maximize data availability and facilitate searches for chemical information:

- Availability of structure-based information for chemicals used to validate NAMs and for candidates tested in NAMs is important for advancing and implementing these methods.
- National Toxicology Program's Integrated Chemical Environment (ICE) provides resources and tools to examine chemical bioactivity and structural properties that are accessible to users with a broad range of chemistry expertise.

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APPROACH

Key features of ICE:

- Contains data and information for over 800,000 chemicals.
- Allows users to construct queries with curated chemical quick lists or user-specified chemical identifiers.
- Includes computational workflows for chemical characterization and predictive toxicology.
- Links to additional chemical resources:
  - NTP Chemical Effects in Biological Systems (CEBS): CEBS provides detailed testing information from NTP studies.
  - CompTox Chemical Dashboard: This U.S. Environmental Protection Agency (EPA) resource provides individual chemical information ranging from toxicity values to exposure and usage.
  - EPA Chemical and Products Database (CPDat): CPDat offers functionality based-mapping for ~50,000 chemicals on categories such as consumer use.

ICE supports:

- Data integration: bringing together data from different endpoints and experiments for comparison.
- Results exploration: dynamic, graphical exploration of query results with capability to refine and send chemicals to additional tools.
- Data analyses and graphical display of chemical characteristics.

New tool application:

- Chemical Quest: chemical structure similarity search based on chemical identifiers including SMILES strings and hand-drawn structures.
- Structure similarity is determined through a combination of molecular descriptors.

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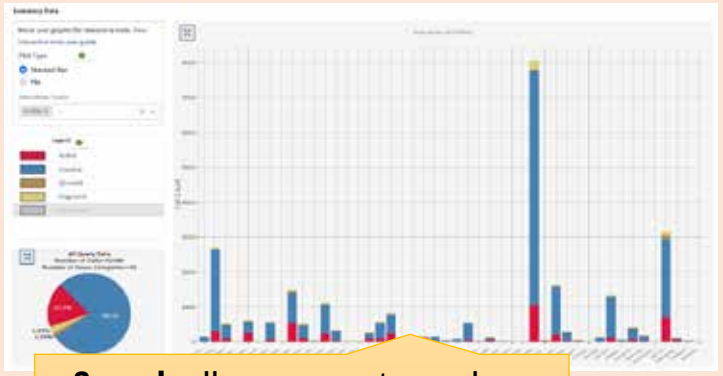
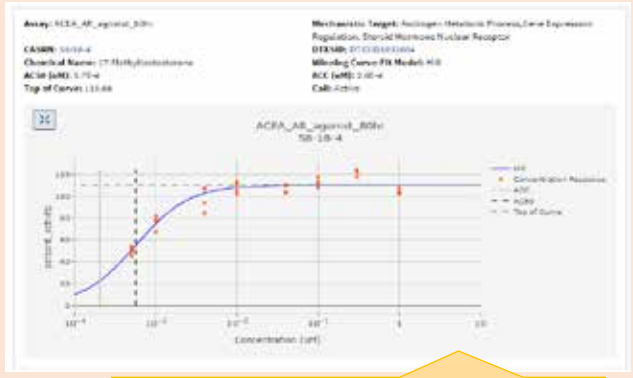
MAIN RESULTS

Search, Curve Surfer, IVIVE and PBPK

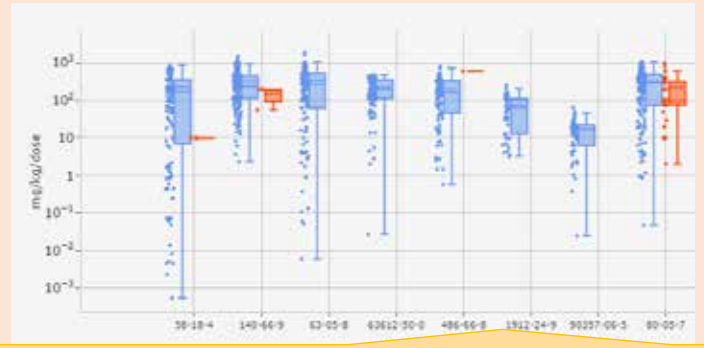
- All ICE tools accept a variety of chemical identifiers: CASRN, DTXSID, SMILES, and InChiKey.
- Queried and filtered chemicals can be sent to other tools within ICE or to the EPA's CompTox Chemicals Dashboard; can also be copied to the user clipboard.
- All data can be exported as text or Excel files. Curve Surfer graphic outputs can also be exported to a PDF.



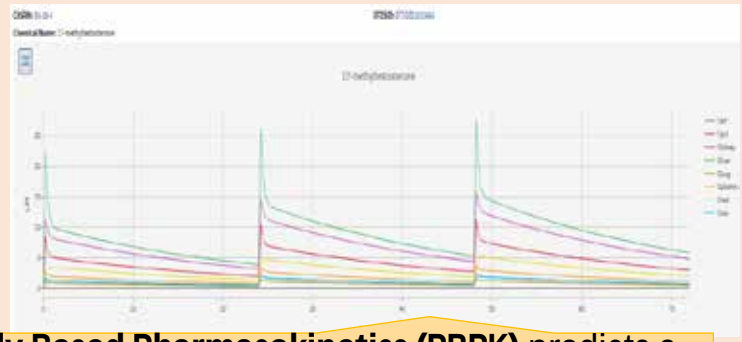
Search allows users to explore bioactivity and chemical property data for individual chemicals or mixtures



Curve Surfer shows concentration-response curves for assay and mechanistic targets. For each curve, the winning curve fit model is identified.



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



Physiologically Based Pharmacokinetics (PBPK) predicts a tissue-specific chemical concentration following an administered dose. Results are returned for the chemical concentration over time in plasma and tissue compartments.

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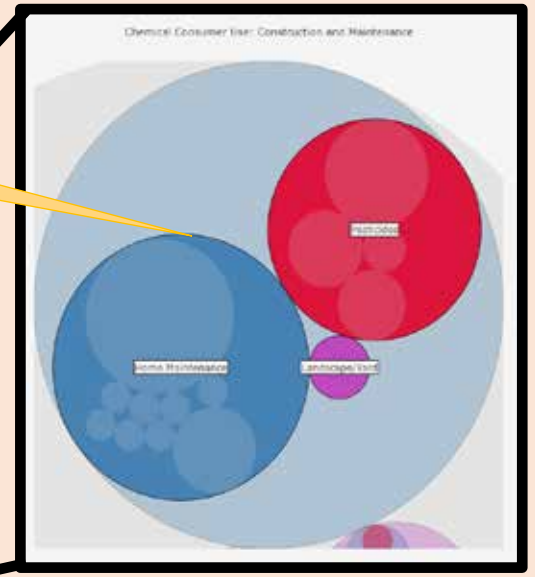
MAIN RESULTS

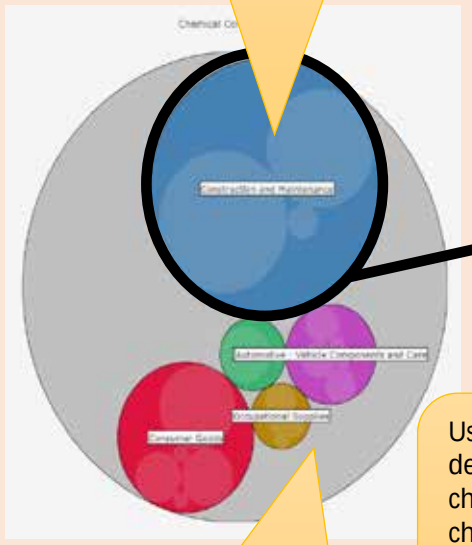
Chemical Characterization

- The ICE Chemical Characterization tool provides a comprehensive list and statistical summary of predicted chemical properties for quantitative assessments.
- Chemical properties are reported based on measured values and quantitative structure-activity/property relationship model predictions.
- Data can be viewed as:
  - Lists of chemical properties (individual and summary).
  - Box-and-whisker plots for visual investigation of chemical property distributions.
  - Principal component analysis plots for a comparison of chemical properties, molecular descriptors or bioactivity.
  - Bubble plots for emphasis on product use data (U.S. EPA's CPDat).

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

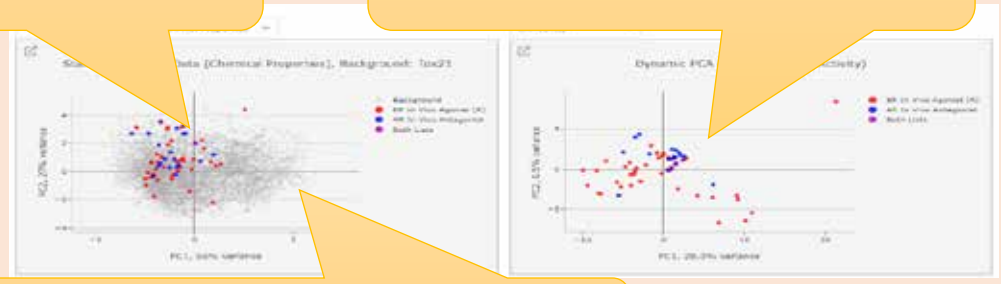


Product use categories can have several subcategories for target-specific analysis.



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

View direct spatial comparisons between two user-defined chemical lists for bioactivity, chemical properties, or molecular descriptors.



Examine chemical diversity relative to large reference datasets such as DSSToxDB (~800k) or Tox21(~1k).

User-defined chemical lists are plotted based on product use as classified in the CPDat Database.

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

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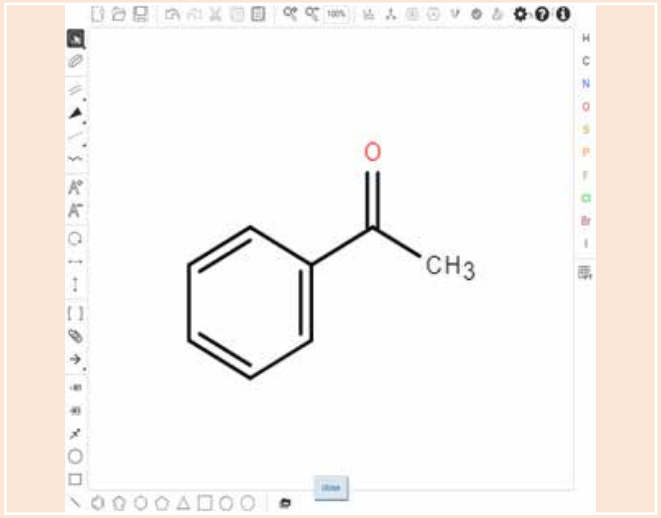
MAIN RESULTS

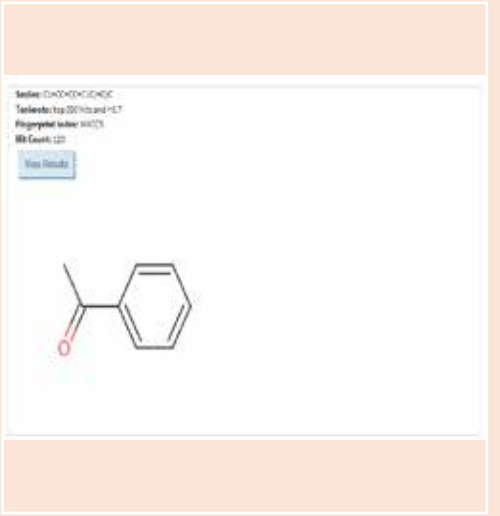
Chemical Quest

- The ICE Chemical Quest tool allows users to perform a structure similarity search of chemicals within the ICE database.
- Similar structures are identified using fingerprints to represent individual chemical features.
- Tanimoto scores are provide for each returned chemical to show level of potential similarity.
  - Users can specify the desired Tanimoto score range to narrow results.
- Advanced filter options are available for returned results to include a substructure search feature.



Users can manually draw their chemicals of interest or input a list of chemical identifiers including SMILES strings

Results are returned for each individual chemical searched by the user



All structurally similar chemicals are returned with a 2D structure, Tanimoto score, and chemical identifiers. Results can be used to query other ICE tools or sent to external EPA or NTP databases.

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IMPACT/SIGNIFICANCE

- New Approach Methodologies (NAMs)
  - In vitro and in silico techniques.
  - Structure based information.
  - Non-animal research approaches.

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

- Integrated Chemical Environment (ICE)
  - Freely available data and tools.
  - Chemical information based on experimental and computationally predicted data.
  - New features enhance the development of computational alternative methods:
    - Additional search identifiers – allows for a variety of search options.
    - Updated QSAR models – enhanced and more accurate predictions.
    - Similarity search tool – users can identify a large selection of similar chemicals that could be ideal for testing.

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