Building Confidence in Alternative Methods Through ICE

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Highlights

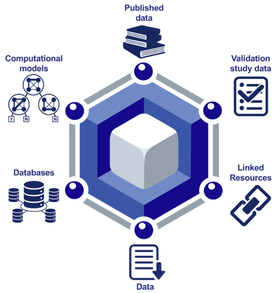
- Building confidence in new approach methodologies (NAMs) for chemical evaluation requires **access to reliable data** and other technical information, as well as **increased familiarity, use of interpretable, approachable** language, and opportunities for stakeholder engagement.
- NICEATM provides **user friendly**, **openly accessible resources** including curated data and computational tools to aid in finding, analyzing, and providing context for that data.

New Approach Methodologies

- New approach methodologies are generally defined as non-animal methods using one or more in vitro assays or in silico tools to provide insight on chemical hazard.
- While scientific and policy advances have enabled adoption of some NAMs for specific applications, barriers remain to broader acceptance of NAMs for regulatory purposes.

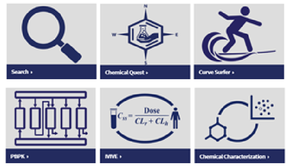
The Integrated Chemical Environment (ICE)

- The National Toxicology Program (NTP) developed and maintains the Integrated Chemical Environment (ICE) as a resource for NICEATM stakeholders.
- ICE provides user-friendly access to high-confidence data curated from published literature, databases, and validation studies.



ICE provides:

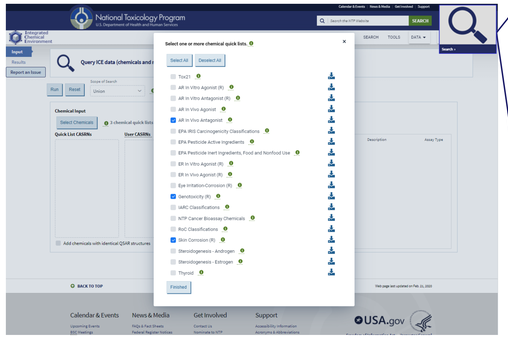
- Data and information for over 800,000 chemicals.
- Reference chemical lists with classifications and bioactivity data**.**
- In vitro assays grouped by mechanistic target and mode of action and linked with defined terminology.
- Ability for user to query with curated chemical quick lists or user-specified chemical identifiers**.**
- Computational workflows for PBPK and IVIVE modeling, structural similarity searching, and chemical characterization.



ICE supports:

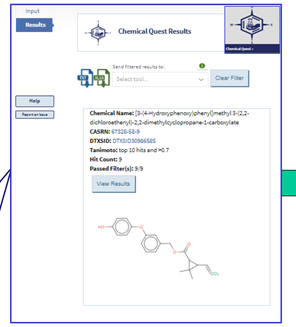
- FAIR (findable, accessible, interoperable and reusable) principles.
- Data integration: brings together data from different endpoints / experiments.
- Results exploration: dynamic, graphical exploration of query results.

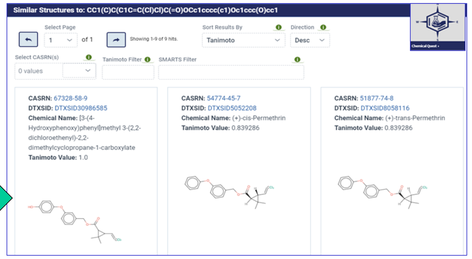
Data Access



- The ICE **Search** Tool allows users to query assay and chemical property data for over 10,000 chemicals and mixtures.
- Build queries using CASRNs, DTSXIDs, InChiKeys, or SMILES.
- ICE includes in silico property predictions for >800,000 chemicals.
- Predefined chemical quick lists and reference lists are related to specific toxicity endpoints.

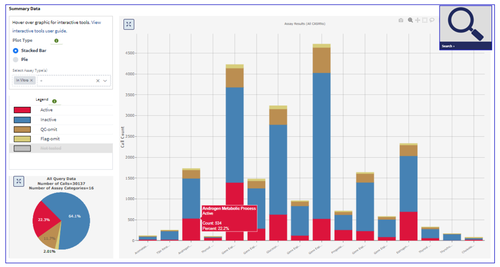
- The **Chemical Quest** tool can be used to search for chemicals that are structurally similar to target chemicals.
- Chemical Identifiers and 2D structures are accepted for queries.

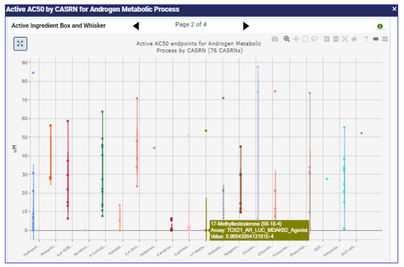


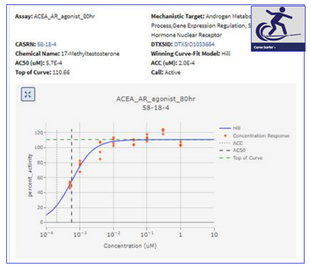


- Structural analogs found by **Chemical Quest** can be examined and individually selected for export or sent to other ICE tools.

Curated, Contextualized HTS Data



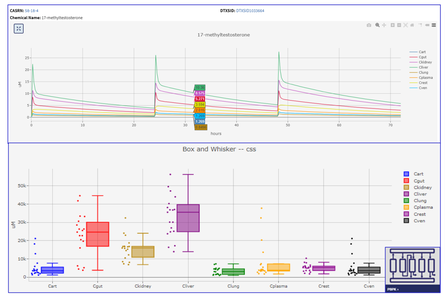




- ICE **Search** query results provide graphical visualizations of chemical bioactivity data for selected assays.
- Curated high-throughput screening data (cHTS) workflow applies chemical QC information and technology-specific flags to data obtained from the U.S. Environmental Protection Agency's invitrodb.
- Assays are curated using a controlled terminology and linked to mechanistic targets, as well as modes of action, to facilitate meaningful assay selection.

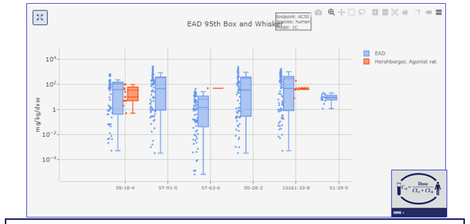
- **Curve Surfer** is an interactive concentration–response visualization tool for cHTS data.

PBPK and IVIVE Tools Provide Context



The ICE **PBPK** tool allows users to calculate internal chemical concentrations through a simple interface using PBPK models from the EPA httk R package. Outputs provide:

- Tissue-level concentrations.
- Individual chemical curves.
- Overall distribution in different tissue compartments for all query chemicals.



The ICE **IVIVE** tool relates in vitro assay bioactivity concentrations to predicted in vivo exposures.

- User can overlay comparable in vivo assay results.

Conclusions

- ICE provides free and open access to curated data to support improved understanding and appropriate application of NAMs.
- User-friendly tools within ICE permit data exploration and visualization thus enabling increased confidence in approaches and facilitating communication between domain experts.
- Detailed user guides and help videos provide support.
- Use of standard IDs (CASRN, DTXSIDs) aids linkage between ICE, the EPA CompTox Chemicals Dashboard, and NTP Chemical Effects in Biological Systems (CEBS).
- Curated data is organized by toxicity endpoint, with standard formatting and units provided in downloads.
- All data and tools are designed to be accessed by diverse users and require no specific knowledge of computational methods.

More Information

- Learn more about NICEATM tools at ASCCT platform presentations by Karmaus et al. and Abedini et al.: Thursday, October 14.
- Subscribe to the NICEATM News email list: **https://list.nih.gov/cgi-bin/wa.exe?SUBED1=niceatm-l&A=1**

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