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

Building Confidence in Alternative Methods Through ICE

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Abstract 4000
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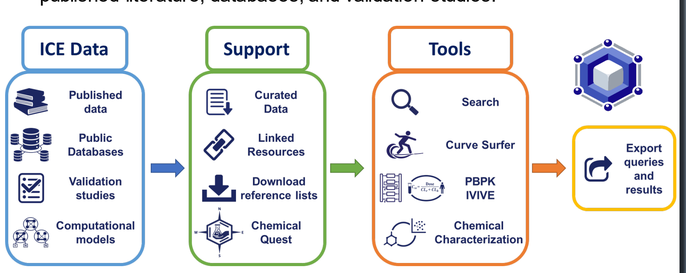
New Approach Methodologies

- New approach methodologies (NAMs) are non-animal methods that use in vitro assays or in silico tools to provide insight on chemical hazard.
- While some NAMs have been adopted for specific policy applications, barriers remain to broader acceptance of NAMs for regulatory purposes.
- One approach to addressing these barriers is increasing access to the data and tools used to develop and validate NAMs.

The Integrated Chemical Environment

- The National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) developed and maintains the Integrated Chemical Environment (ICE) as a resource to promote NAM development.
- 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.
- Defined terminology to group in vitro assays by mechanistic target or modes of action contributing to toxicity endpoints.
- Curated chemical lists and chemical identifiers for building queries.
- Workflows for pharmacokinetic modeling, structural similarity searching, and chemical characterization.

ICE supports:

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

Acknowledgements

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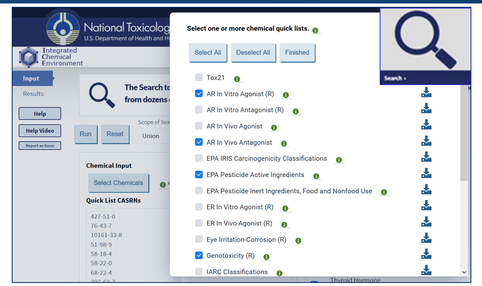
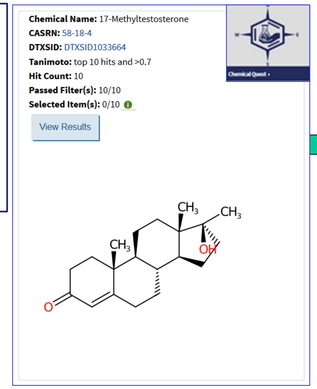
Data Access



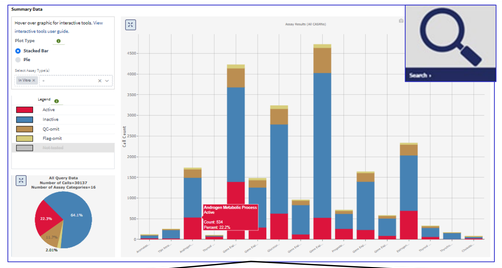
- Use the ICE **Search** Tool to query assay and chemical property data for over 10,000 chemicals and mixtures.
- Build queries using CASRNs, DTSXIDs, InChiKeys, or SMILES.
- Predefined chemical quick lists and reference lists are related to defined outcomes.

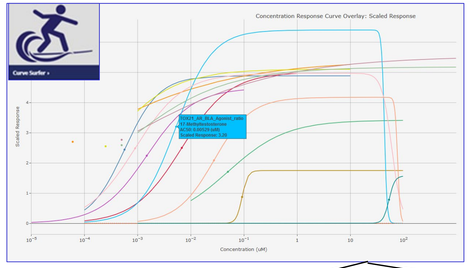
- Use the ICE **Chemical Quest** tool to search for chemicals that are structurally similar to novel query chemicals.
- Chemical Identifiers and 2D structures are accepted for queries.



- Structural analogs found by **Chemical Quest** can be examined and selected for export or sent to other ICE tools.
- Newly added advanced filtration of results includes SMARTs strings with substructure highlighting.

Curated, Contextualized HTS Data

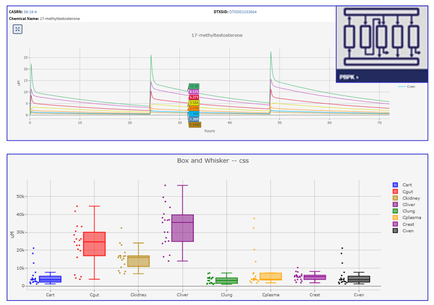




- ICE **Search** query results provide graphical visualizations of chemical bioactivity data for selected assays.
- The ICE curated high-throughput screening data (cHTS) workflow applies chemical QC information and technology-specific flags to data obtained from the U.S. Environmental Protection Agency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

- ICE **Curve Surfer** is an interactive concentration–response visualization tool for cHTS data that now features customizable curve overlays.

PBPK and IVIVE Tools Provide Context



The ICE **PBPK** tool allows users to calculate internal chemical concentrations through a simple interface using physiologically based pharmacokinetic (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** (in vivo to in vitro extrapolation) tool uses in vitro assay bioactivity concentrations to predict relevant in vivo exposures.

- User can overlay relevant in vivo assay results.
- Users can upload custom in vitro or in vivo data.

Summary

- ICE provides free and open access to curated data to support improved understanding and appropriate application of NAMs.
- User-friendly tools permit data exploration and visualization to build users' confidence in new approaches and facilitate communication among domain experts.
- ICE provides detailed user guides and help videos.
- Query results can be exported to the EPA CompTox Chemicals Dashboard and NTP Chemical Effects in Biological Systems (CEBS).
- Curated data is organized by toxicity endpoint, and exported data includes standard formatting and units.
- 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 and ICE tools at SOT:
  - Abedini et al. Abstract 4004 / Poster P702
  - Karmaus et al. Abstract 4005 / Poster P703
  - Mumtaz et al. Abstract 5042 / Poster P146
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