Developing In Vitro Assay Annotations to Provide Context and Facilitate Interpretation Toward Toxicological Endpoints

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Introduction

- Building confidence in new approach methodologies (NAMs) for chemical evaluation requires access to reliable and relevant data that are interpretable, openly accessible, and approachable via tools for easy use by all stakeholders.

- To address these needs, the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) developed the user-friendly Integrated Chemical Environment (ICE). ICE provides data and computational tools to aid in finding, analyzing, and contextualizing NAMs.

- ICE includes high-throughput screening (HTS) data from Tox21 and ToxCast assays. HTS data in ICE have been:
  - § Curated by experts to identify the most robust data.
  - § Annotated by experts using controlled terminology.

- ICE tools integrate multiple assay and chemical data, and ICE visualizations allow quick summaries and data evaluation.

- This presentation describes how the curation, annotation, and ICE Search and Curve Surfer tools can make HTS data accessible and transparent for all users.

Developing cHTS Annotations

1. Literature was mined to help identify known modes of action (MOA) contributing to toxicological outcomes of regulatory interest, such as developmental and reproductive toxicity and acute toxicity.

2. The EPA's invitrodb database was mined to retrieve technological assay information including "intended_target_family" and "biological_process_target".

3. Terms were curated to ensure consistency and mapped to the NCI Metathesaurus (https://ncim.nci.nih.gov/ncimbrowser/), creating a connection to widely used and established terminology with controlled identifiers.

4. Annotations are continuously being updated and refined. Any feedback can be submitted to ICE-support@niehs.nih.gov

Searching Using cHTS Assay Annotation in ICE

- In the ICE Search tool, curated HTS (cHTS) data can be found via the Assay Selection feature.

- Assays are grouped by controlled vocabulary terminology to facilitate retrieval of orthologous or complementary assays:
  1. Mechanistic Target terms organize assays based on biological processes to facilitate assay interpretation.
  2. Mode of Action (MOA) terms organize assays based on pathways relevant to toxicological outcomes of regulatory concern.
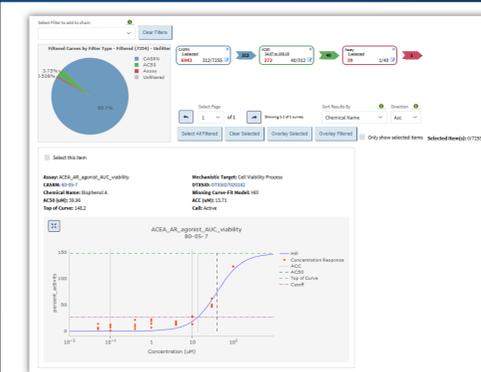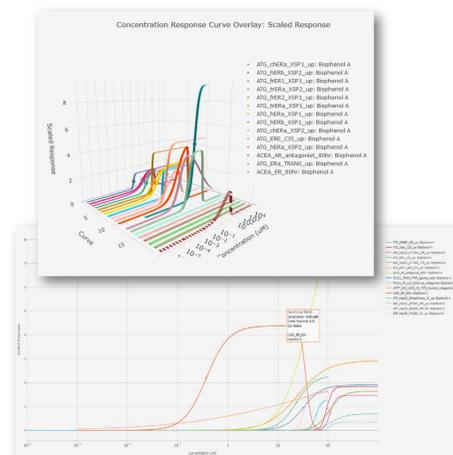
Mechanistic Target Search

Mode of Action Search
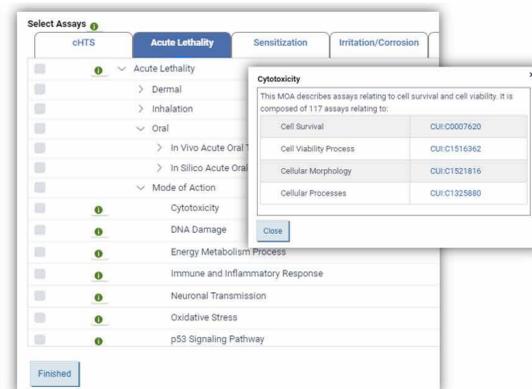
Visualizing Concentration-Response Details for cHTS Assays

Concentration-response curves from cHTS assays can be viewed using the ICE Curve Surfer tool. Results include chemical and assay details, e.g. Mechanistic Target terms, that can be used to filter and select subsets of data.


Concentration-response curves for multiple chemical/assay combinations can be viewed using the curve overlay tool (in 2D or 3D) to facilitate comparisons.

The dashed lines help review how inactive or curation-omitted responses compare to active responses.

Visualizing Search Results with Annotation Context

Example: Searching by MOA "cytotoxicity" yields bar plots summarizing activity calls for all annotation terms related to "cytotoxicity". Boxplots summarize all chemical AC50 values per assay within a specific annotation term (in this example, "cell viability process").
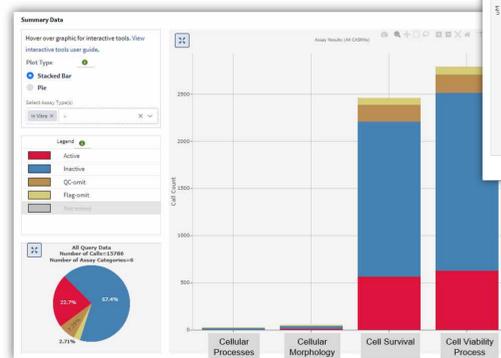
Results can also be viewed by chemical. A table lists chemical properties, bar plots summarize activity calls for each MOA term, and boxplots show potency for active endpoints within specific MOAs.

Summary

- Controlled vocabulary annotations facilitate accessing and interpreting cHTS assay data.
  - § Users can easily compare orthologous or complementary assays.
  - § Outputs help review data in support of building weight-of-evidence evaluations.
  - § Search results can help identify data gaps.

- Mode of Action groupings in ICE Search provide context and allow retrieval of assay data for toxicologically relevant biological pathways.
  - § Results are grouped based on toxicological endpoints of regulatory significance.

- Visualizations in ICE help with interpreting query results by grouping per assays or chemical.
  - § ICE Curve Surfer for individual concentration-response curve viewing can help build confidence, improve understanding of data, and provide context for activity calls.

Acknowledgments