



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

- 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

Visualizing Search Results with Annotation Context



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

Agnes L. Karmaus¹, Patricia Ceger¹, John Rooney¹, Shannon Bell¹, Dave Allen¹, Nicole Kleinstreuer² ¹Inotiv, Research Triangle Park, NC, USA; ²NIH/NIEHS/DNTP/NICEATM, Research Triangle Park, NC, USA



Searching Using cHTS Assay Annotation in ICE



- the Assay Selection feature.
- - concern.

Mechanistic Target Search

	0	∨ cH1	rs	
	0		Abnormal Growth a	nd Differentiation
	0		Angiogenic Process	S
	0	>	Cellular Processes	
	0	>	Cellular Stress Resp	ponse
	0	>	Endocrine-Related I	Processes
	0		Energy Metabolism	Process
	0	>	Epigenetic Process	÷
	0	\rightarrow	Gene Expression	
	0	>	Immune and Inflam	matory Response
	0	>	Neuronal Transmis	sion
÷.	0		Xenobiotic Metabo	lism
	0		Unannotated	

	CHTS		
	0	×	Acu
			>
			>
			\sim
			$^{\vee}$
	0		
	0		
	0		
	0		
	0		
	0		
	0		
Finished	ĩ		



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

				Substance Details	Curve Surfer
H ₃ C CH ₃		Hover over graphic for interactive tools. View interactive tools user guide. Plot Type	×		
HO		Stacked Bar Pie Select Assay Type(s) In Vitro × + × ×	100		
	UIT	Legend	80-		
PhysChem Property	Bisphenol	Active			
BP C n	343.19	Inactive			
HL log10, atm-m3/mole	-6.90	QC-omit	tin 60		
KOA log10	8.38	Flag-omit	Call C		
LogD. pH 5.5 log10	3.32	Not tested	Ŭ		
LogD, pH 7.4 log10	3.32				
LogP log10	3.32		40-		
MPC	152.70	Bisphenol A (80-05-7) Number of Assays=591			
MW g/mol	228.29	Number of Assay Categories=6			
pKa, Ionizations	1.00		20-		
pKa, Acidic 👩	9.46				
pKa, Basic 👩	NA	18.1% 81.9%			
VP log10, mmHg n	-7.17				
WS log10, moles/L	-3.13		0		
				Endother	Cell Pro.

• In the ICE Search tool, curated HTS (cHTS) data can be found via

 Assays are grouped by controlled vocabulary terminology to facilitate retrieval of orthologous or complementary assays:

. 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



	Cytotoxicity		2		
ermal halation	This MOA describes assays relating to cell survival and cell viability. It is composed of 117 assays relating to:				
oral	Cell Survival	CUI:C0007620	1		
> In Vivo Acute Oral 1	Cell Viability Process	CUI:C1516362			
> In Silico Acute Oral	Cellular Morphology	CUI:C1521816	1		
Node of Action	Cellular Processes	CUI:C1325880			
Cytotoxicity			-		
DNA Damage	Close				
Energy Metabolism P	Process				
Immune and Inflamn	natory Response				
Neuronal Transmissi	on				
Oxidative Stress					
p53 Signaling Pathw	ау				



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 Select Page Off Leaster by 1 ✓ 1 ✓ Asc assay details, e.g. Mechanistic ect All Filtered Clear Selected Overlay Selected Overlay Filtered Only show selected items Selected Item(s): 0/7255 Target terms, that can be used to Select this item filter and select subsets of data. Assay: ACEA_AR_agonist_AUC_viabil chanistic Target: Cell Viability Pro hemical Name: Bisp AC50 (uM): 39.9 ACC (uM): 13.7 Top of Curve: 148 ACEA_AR_agonist_AUC_viability Concentration Response Curve Overlay: Scaled Response



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.

Summary

- Search results can help identify data gaps.
- toxicologically relevant biological pathways.

Acknowledgments

This project was funded with federal funds from the National Institute of Environmental Health Sciences, National Institutes of Health, under Contract No. HHSN273201500010C.



The views expressed above do not necessarily represent the official positions of any federal agency. Since the poster was written as part of the official duties of the authors, it can be freely copied.

National Institutes of Health • U.S. Department of Health and Human Services



Abstract ID #12



• 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.

• Mode of Action groupings in ICE Search provide context and allow retrieval of assay data for

§ 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.



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