An Integrated Chemical Environment to Support 21st Century Toxicology

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Integrated Chemical Environment

What is ICE?

ICE is the Integrated Chemical Environment, which houses:

- High quality, curated in vivo, in vitro, and in silico data from the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and partners
- Reference chemical lists (chemicals that can be used as a reference for a given assay or endpoint) and associated data
- Computational tools and workflows (Summer 2017)

Users	Resources	Outcomes
Method Developers	High-Quality Data	• Identify opportunities to develop new methods
Chemical Producers	Reference Chemicals	• Compare method performance • Identify data gaps
Risk Assessors	Computational Tools	• Obtain toxicity and chemical data • Develop testing strategies

What need does ICE fill?

NICEATM developed ICE to:

- Provide a central location for computer-friendly versions of NICEATM data and computational models
- Facilitate data use by NICEATM stakeholders

What can ICE do?

Currently 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 within query results
- Data accession: obtaining reference chemical lists and supporting data

Resources available soon (Summer 2017):

- Data analysis: downloadable computational tools and workflows to support test method development

Search by Chemicals and Integrate Data from Multiple Assays

ICE data are searchable by chemical and/or assay:

Select chemicals:

- Input user-defined CASRN(s)
  or
- Select reference chemical lists to combine with your custom list or use on their own
  or
- Search selected datasets for all chemicals in ICE by leaving the input chemical field blank
- Chemicals not found in the results will be listed in a separate download file

Reference Chemical Lists

- AR Agonist 2016
- AR Antagonist 2016
- ICCVAM Cytotox Acute Oral 2006
- ICCVAM Eye Corrosion 2006
- ICCVAM LLNA 2013
- ICCVAM Skin Corrosion 2004
- Uterotrophic 2016

Select assay data:

- Data Integrator allows users to combine selected data streams of interest
- Assay Selection field enables organization of data either by endpoints of regulatory interest or by data type (e.g., in vitro and in silico data)
- Queries are joined using "or" logic (e.g., ocular irritation or dermal irritation) by default
- Explore view allows users to dynamically refine queries
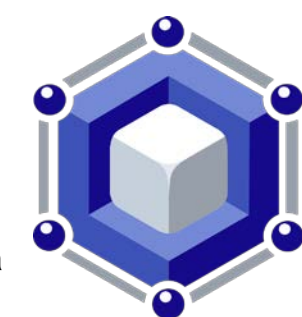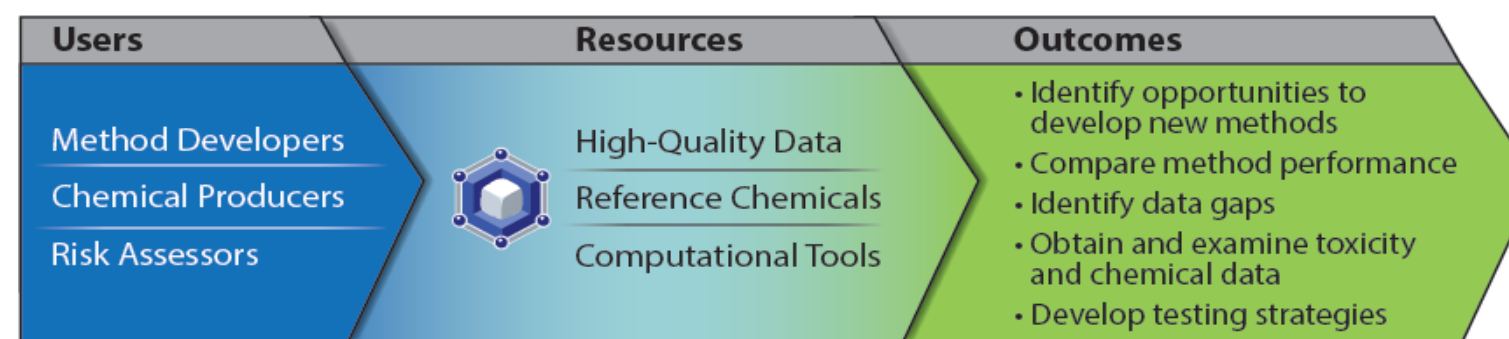
Assay Selection

- Acute Oral Toxicity
- Dermal Sensitization
- Dermal Irritation
- Ocular Irritation
- Endocrine
- in vitro (all)
- in silico

Analyze and Export Your Query

Get data for your analysis

- Quick view of full query results prior to exporting
- Export data to Excel and tab delimited files
- See which chemicals were not found
- Query parameters are documented in export screen to ensure queries can be replicated, supporting reproducibility

Query Parameters

Date Run:2017-02-21 15:01:49.086
App Version: BETA 1.00.622

Chemical Reference Lists
****
AR Agonist 2016
ICCVAM Eye
2004, Uterot...

Workflows (launching July 2017)

- Physicochemical property predictions
- Physiologically based pharmacokinetic and toxicokinetic models for in vitro to in vivo extrapolation

Record ID	Chemical Name	CASRN	Assay
R_00075693	(2E)-3-Phenylprop-2-enal	14371-10-9	ATG_ERE_CIS_up
R_00075700	(2E)-3-Phenylprop-2-enal	14371-10-9	ATG_PXRE_CIS_up
R_00075700	(2E)-3-Phenylprop-2-enal	14371-10-9	ATG_VDRE_CIS_up
R_00075714	(2E)-3-Phenylprop-2-enal	14371-10-9	OT_NURR1_NURR1R
R_00075716	(2E)-3-Phenylprop-2-enal	14371-10-9	TOX21_ERa_LUC_BG
R_00075702	(2E)-3-Phenylprop-2-enal	14371-10-9	ATG_ERa_TRANS_up
R_00075704	(2E)-3-Phenylprop-2-enal	14371-10-9	ATG_PPARg_TRANS_
R_00075705	(2E)-3-Phenylprop-2-enal	14371-10-9	ATG_PXR_TRANS_u
R_00075693	(2E)-3-Phenylprop-2-enal	14371-10-9	ATG_DR5_CIS_up
R_00075699	(2E)-3-Phenylprop-2-enal	14371-10-9	ATG_PPRE_CIS_up
R_00075698	(2E)-3-Phenylprop-2-enal	14371-10-9	ATG_PBREM_CIS_up
R_00075701	(2E)-3-Phenylprop-2-enal	14371-10-9	ATG_VDRE_CIS_up
R_00075703	(2E)-3-Phenylprop-2-enal	14371-10-9	ATG_NURR1_TRANS_

What Data Are in ICE?

Available data

- High quality, curated data from scientific literature sources
- Data used to support the reference chemical lists
- High-throughput screening Tox21/ToxCast data, curated by chemical QC results
- Computational predictions useful in developing models of health impacts or chemical characterization
- Other data useful in developing/evaluating new approaches or chemical safety

Data Types	Availability	Type	Endpoint Examples
Acute dermal toxicity	October 2017 (tentative)	in vivo	Rodent LD50
Acute inhalation toxicity	October 2017 (tentative)	in vivo	Rodent LC50
Acute oral toxicity	March 2017	in vivo	Rodent LD50
Acute oral toxicity	March 2017	in vitro[a]	Basal cytotoxicity IC50
Androgenic activity	March 2017	in vitro	Androgen receptor binding and transactivation (agonist and antagonist activity)
Androgenic activity	July 2017 (tentative)	in vivo	Lowest effect level in the rodent Hershberger assay
Androgenic activity	March 2017	in silico	Androgen receptor pathway model scores
Curated HTS	March 2017	in vitro	Assay ACC, AC50
Dermal irritation	March 2017	in vivo	Skin irritation/corrosion classification categories
Dermal sensitization	March 2017	in vivo	Mouse LLNA EC3 and human patch test lowest effect level
Dermal sensitization	March 2017	in vitro	KeratinoSens, DPRA, hCLAT assay results
Dermal sensitization	July 2017 (tentative)	in silico	Binary sensitizer/nonsensitizer call
Estrogenic activity	March 2017	in vivo	Lowest effect level in the rodent uterotrophic assay
Estrogenic activity	March 2017	in silico	Estrogen receptor pathway model scores
Ocular irritation	March 2017	in vivo	Eye irritation/corrosion classification categories
Physicochemical property predictions	March 2017	in silico	LogP, logVP, logBCF, logS, melting point, boiling point

AC50, concentration that increases activity by 50%; ACC, activity concentration at cut-off, a measure of the activity threshold for an assay response based on curve-fitting models; BCF, bioconcentration factor; DPRA, direct peptide reactivity assay; EC3, in the LLNA, a test chemical concentration that produces a stimulation index of 3; hCLAT, human cell line activation test; HTS, high throughput screening; IC50, concentration that inhibits activity (in this context, decreases cell viability) by 50%; LC50, inhalation concentration expected to produce lethality in 50% of animals tested; LD50, dose expected to produce lethality in 50% of animals tested; LLNA, local lymph node assay; logP, octanol-water partition coefficient; logVP, vapor pressure; logBCF, bioconcentration factor; logS, water solubility.

[a]In vitro basal cytotoxicity assays proposed for setting starting doses for in vivo acute oral toxicity studies.

Explore Query Results

Interactive data exploration

- ICE displays results graphically with real-time updated exportable graphics
- User can filter search output to further refine results based on assay and/or chemicals
- User can dynamically explore results or export them to Excel or tab delimited files

Endpoint Record Count: 167597
One line is returned per endpoint record.

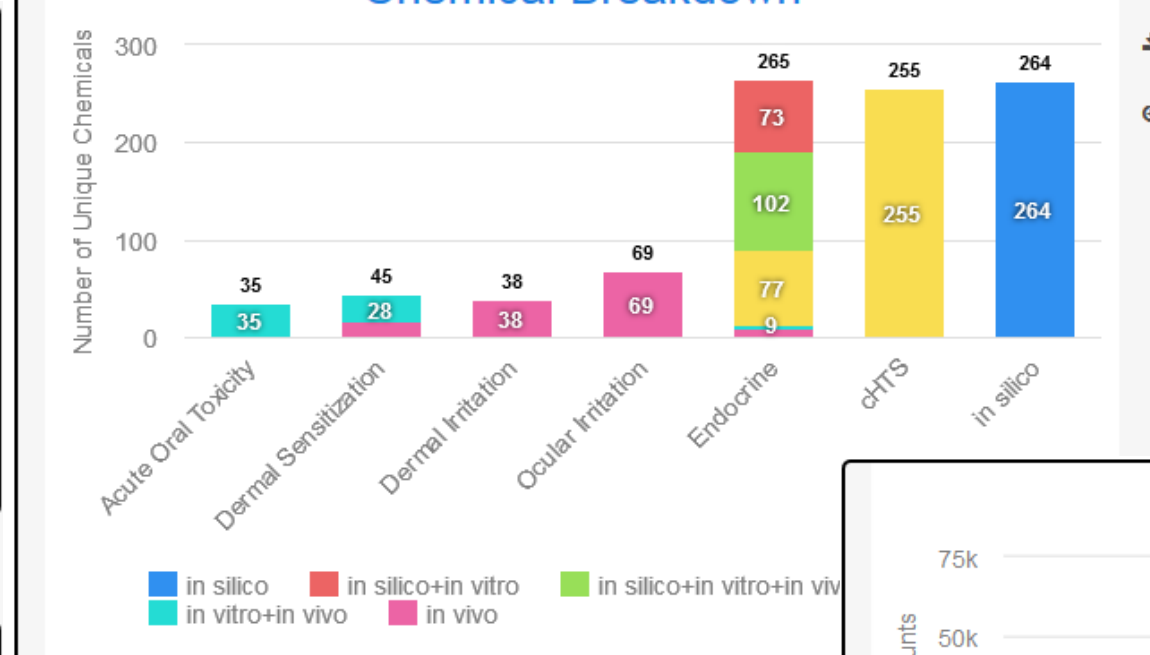| Chemical Name	CASRN	Assay	Endpoint	Value	Unit
(2E)-3-Phenylprop-2-enal	14371-10-9	ZangPhysChem MP	MP	74.8	NA
(2E)-3-Phenylprop-2-enal	14371-10-9	ATG_ERE_CIS_up	ACC	1.40157742699894	log10 uM
(2E)-3-Phenylprop-2-enal	14371-10-9	ATG_NRF2_ARE_CIS_up	ACC	1.48556830968425	log10 uM
(2E)-3-Phenylprop-2-enal	14371-10-9	ATG_PXRE_CIS_up	ACC	0.632172604720532	log10 uM
(2E)-3-Phenylprop-2-enal	14371-10-9	ATG_VDRE_CIS_up	ACC	2.02761108774535	log10 uM
(2E)-3-Phenylprop-2-enal	14371-10-9	OT_NURR1_NURR1RXRa_0480	ACC	1.51194289217381	log10 uM
(2E)-3-Phenylprop-2-enal	14371-10-9	TOX21_ERa_LUC_BG1_Agonist	ACC	1.36131688594952	log10 uM
(2E)-3-Phenylprop-2-enal	14371-10-9	ATG_ERa_TRANS_up	ACC	1.40970100375982	log10 uM

Filter

Assay Groups: 25

	Assay Group
	Acute Oral Toxicity
	DPRA
	hCLAT
	Human Potency
	KeratinoSens
	LLNA
	Dermal Irritation
	Ocular Irritation
	AR Transactivation-Antagonist
	AR Transactivation-Agonist

Chemicals: 305

CASRN	Chemical Name
36734-19-7	Iprodione
103-90-2	Acetaminophen
330-55-2	Linuron
14075-53-7	Potassium tetrafluoroborat
5392-28-9	tetra-Aminopyrimidine sulf
71-58-9	Medroxyprogesterone acet
501-53-1	Benzyl chloroformate
62-76-0	Sodium oxalate
75-26-3	2-Bromopropane
40487-42-1	Pendimethalin

Chemical Breakdown

Number of Unique Chemicals

in silico / in silico+in vitro / in silico+in vitro+in vivo / in vitro+in vivo / in vitro / in vivo

Visualize

cHTS Call Breakdown

Call Counts

active / inactive / qc-omit
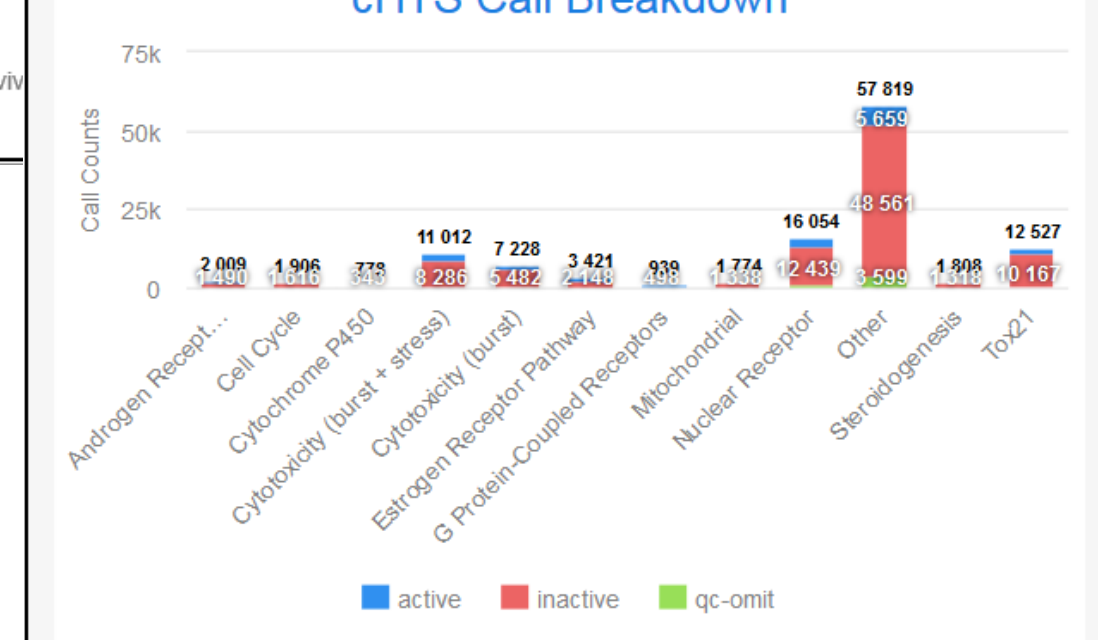
Current Timeline

Launch (v1.0)	March 2017, SOT Annual Meeting	• Launch of web resource highlighting the data integrator
Update (v1.1)	July 2017	• Launch of tools/workflows section • Data updates
Update (v1.2)	October 2017	• Data updates
Update (v1.3)	January 2018	• Data updates
Update (v1.4)	April 2018	• Interactive workflows • Data updates

Quarterly updates will be conducted with notification and details of updates on the ICE webpage and announced through NICEATM News.

Contact Us

Access ICE
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Bell SM, Phillips J, Sedykh A, Tandon A, Sprankle C, Morefield SQ, Shapiro A, Allen D, Shah R, Maull EA, Casey WM, Kleinstreuer NC. 2017. An Integrated Chemical Environment to support 21st century toxicology (in press). Environmental Health Perspectives. DOI 10.1289/EHP1759

Acknowledgements