

Integrated Chemical Environment

Nicole C. Kleinstreuer, PhD
NICEATM Deputy Director

NTP BSC Meeting
December 7-8, 2017





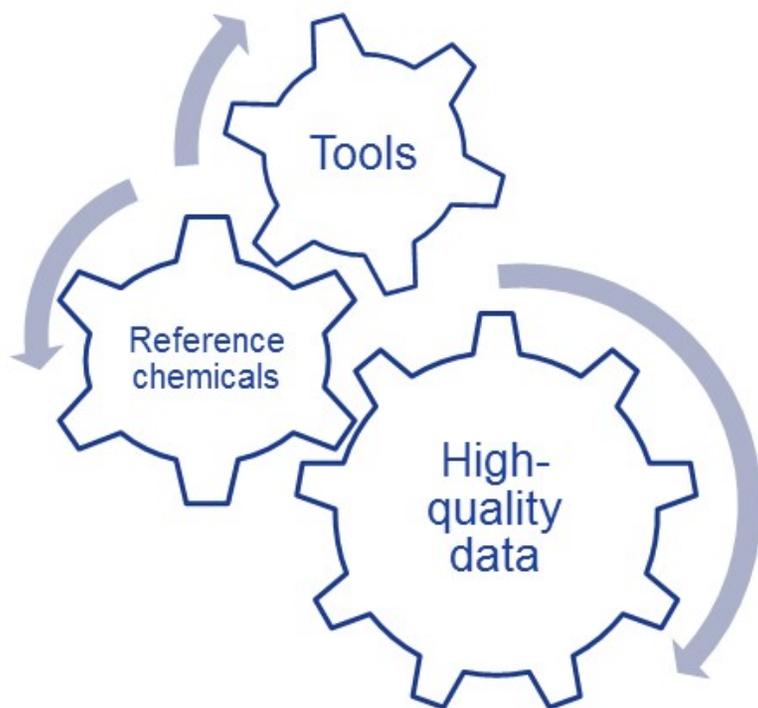
Strategic Roadmap Goal

Foster the use of efficient, flexible, and robust practices to establish confidence in new methods

- Identify and collate sources of high-quality human toxicological data.
- Create centralized data access points that are publicly available and easily accessible.
- Actively solicit the submission and collation of parallel data from animal studies and alternative methods.
- Leverage partnerships and complimentary initiatives
 - FAIR Principles, NIH Data Commons, NCATS Data Translator, EPA Chemistry Dashboard, NLM Databases, Biomed21 recommendations, SEND reporting, etc.



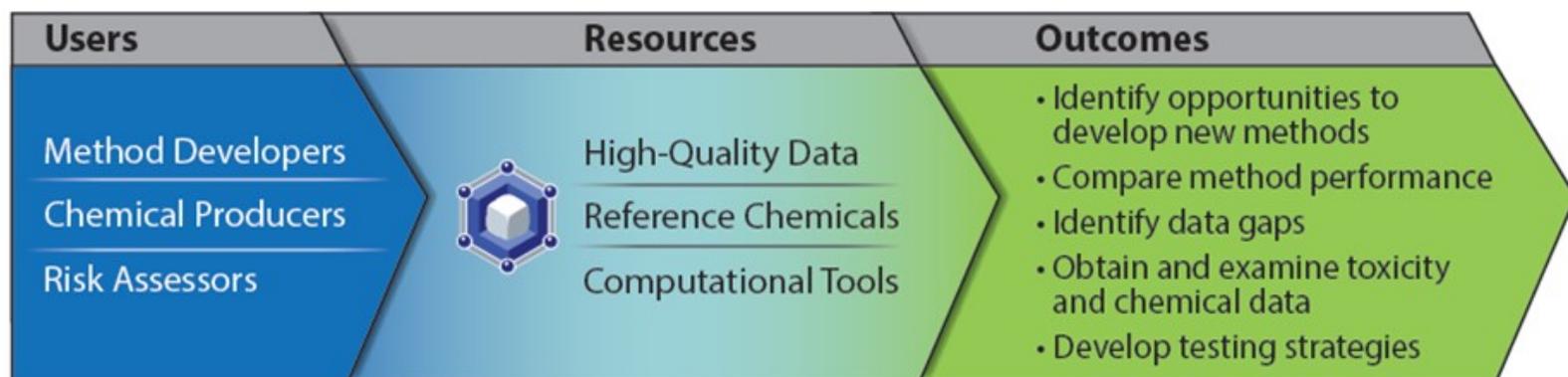
Developing Web-based Data Resources



- Who needs them?
 - NTP & ICCVAM scientists
 - Researchers from other institutes/companies
 - Regulators looking for information
 - Assay/model developers looking for data (or opportunities)
- What do they need?
 - Data supporting chemical evaluation and model development
 - High quality and open access
 - Context and meta data available
 - Centrally available (one stop shop)
 - Easy to use, free, transparent



Integrated Chemical Environment: ICE



<https://ice.ntp.niehs.nih.gov/>

Bell et al. 2017 EHP

- **Data integrator:**
 - Structured format designed for ease of use
 - Allows access to data for multiple regulatory endpoints
 - Query by CASRN or established reference chemical lists
 - Flexible, exportable results
- **Workflows:**
 - Property predictions, Chemical space characterization, IVIVE, Mechanistic models, AOP mapping



Goals of ICE

- Uphold FAIR principles for ICCVAM Data
- Provide intuitive access to high quality (curated) data and tools to support:
 - chemical evaluations,
 - data integration, and
 - model development
- Enable wider community to engage in the use of alternative and computational approaches for assessing chemical safety





State of FAIRness at NICEATM

Integrated Chemical Environment (ICE)

<https://ice.ntp.niehs.nih.gov/>



- Provides FAIR for ICCVAM data
- Communication with other applications and data systems
 - Chemical Effects in Biological Systems (CEBS)
 - NIEHS Data Commons
 - EPA Dashboard, CTD, NLM databases, etc.
- Significant ongoing efforts to improve data and tool utility
 - Intuitive user interface
 - Web-based visual analytics
 - Improved search functionality
 - Improving capture of data provenance
 - Web application programming interfaces (APIs)
 - Interactive web-based workflows
 - Many more...

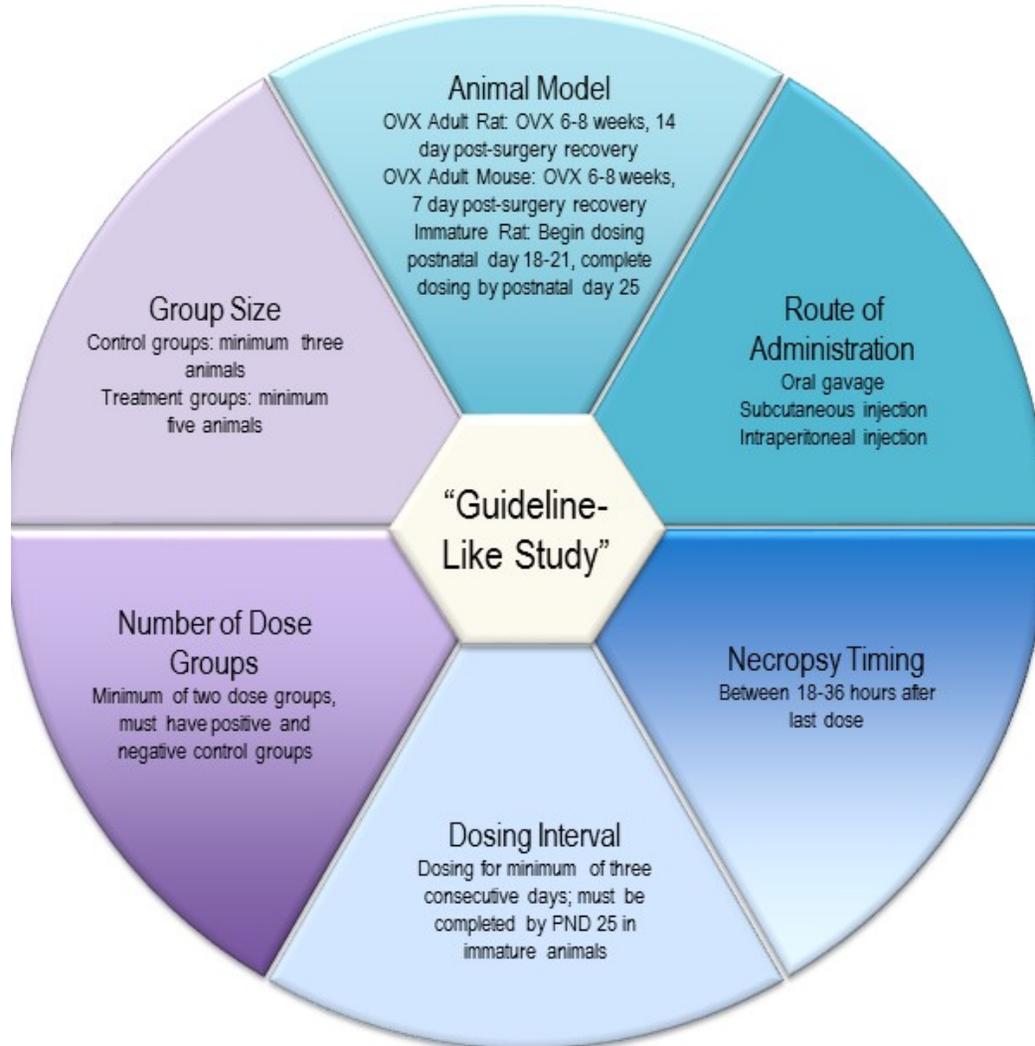


Data in ICE

Endpoint	In vitro	In vivo animal	In vivo human	In silico	Chemicals (+ Als)	Formulations
Acute Oral	x	x			35 (145)	627
Acute Inhalation		x			(119)	460
Acute Dermal		x			(134)	537
Skin Sensitization	x	x	x		578 (115)	506
Eye Irritation/Corrosion	x	x			183 (127)	570
Skin Irritation/Corrosion		x	x		120 (128)	523
Endocrine Disruption	x	x		x	8824	
cHTS	x				9076	
PhysChem Properties	x			x	42976	



Data Curation Process



Example: Uterotrophic Data (endocrine *in vivo*)

- Systematic literature review of publically available data
- Extract all study protocol and effect details
- Identify chemical activities measured in “guideline-like” uterotrophic studies
- Identify a subset of *in vivo* reference chemicals

Kleinstreuer et al. 2015 EHP



Live Demo

<https://ice.ntp.niehs.nih.gov/>



Backup Slides

National Toxicology Program
U.S. Department of Health and Human Services

Integrated Chemical Environment | Home | Integrator | Workflows | Reference Data | About | Help

Search the NTP Website [SEARCH]

Run Search [Clear]

Select Assays [Unson]

Select Assay Target | Activity

- Acute Oral Toxicity
- Skin Sensitization
- Skin Irritation
- in vivo
- Acute skin irritatic
- 4h HPT
- Eye Irritation
- in vivo
- in vitro
- Vitrigel
- Endocrine
- Androgen
- in vitro

Select Chemicals

Select Reference Lists.
Enter one CASRN per line.

Substance Name	CASRN	Acute Oral Toxicity ...	Acute Oral Toxicity ...	DPR
1-Chloro-2,4-dinitr...	97-00-7			[97.5]
Benzaldehyde	100-52-7			
Bisphenol A diglyci...	1675-54-3			
Ethyl 4-(2,6-dichlor...	96569-04-6			
2-Ethylbutyraldehyde	97-96-1			
Monobutyl phthalate	131-70-4			
alpha-Bromotoluene	100-39-0			

Download

Number of chemicals = 1044. Showing 20 out of 28 Endpoints. All Endpoint columns

Select Reference Chemical Lists

Select one or more reference chemical lists:

- Reference Chemical Lists
- AR in vitro Agonist 2016
- AR in vitro Antagonist 2016
- ER in vitro Agonist 2015
- ER in vitro Agonist 2015
- ICCVAM Cytotox Acute Oral 2006
- ICCVAM Eye Corrosion 2006
- ICCVAM LLNA 2009
- ICCVAM Skin Corrosion 2004
- OECDTG455

Chemical

Number of Unique Chemicals

Endpoint	in vitro	in vitro+in vivo	in vivo
Acute Oral Toxicity	35	30	0
Skin Sensitization	456	113	576
Skin Irritation	120	0	120
Eye Irritation	66	52	117
Endocrine	53	52	112

Skin Sensitization Call Breakdown

Call Counts

Endpoint	active	inactive	
DPRA	204	127	331
hCLAT	200	85	285
Human Potency	142	149	291
KeratinoSens	472	309	781
LLNA	701	287	988



Backup Slides

National Toxicology Program
U.S. Department of Health and Human Services

Integrated Chemical Environment

Home Integrator Workflows Reference Data About Help

Search the NTP Website SEARCH

Decision/Call Summary

Filter results

Assay Filter

Assays: 20

- Assay
- NHK NRU
- Acute eye irritation/corrosion
- Binding
- Transactivation-Agonist
- DPRA
- hCLAT
- Human maximization
- Draize eye
- Vitrigel
- LLNA

Close

Chemical Name	CASRN	Assay	Endpoint	Value	Unit	NCLAT CD96, EC1...	NCLAT Call	Human Potency
Bisphenol A				3.35	NA	[0.71-5.31], n=12, ...	Active c...	
Bisphenol B				9.3E-7	NA	300.26	Active	
Bisphenol A				1.8	NA	18.27	Active	
Bisphenol A				8.1E-5	NA		Active	
Vinclozolin				4.8E-8	NA			
Cyproterone acetate				5.1	NA	3.2	Active	
Hydroxyflutamide				2.4E-4	NA			
Vinclozolin				1.9E-6	NA			
Flutamide				512.0	nM			
2,2',4,4'-Tetrahydroxyflutamide				1323.0	nM			
Flutamide				300.0	nM			
Flutamide				639.0	nM			
Butylparaben				7.1E-6	nM			
Bisphenol A				1.5E-6	NA			
4-Nonylphenol				781.0	nM			
Flutamide				933875.0	ng/t			
Procymidone				560.0	nM			
Procymidone				310.0	nM			
Cyproterone acetate				9.4	nM			
Procymidone				200.0	nM			
Flutamide				292.0	nM			
Flutamide				398.0	nM			
Procymidone				270.0	nM			
Flutamide	13311-84-7	Transactivation-An...	AC50/EC50/IC50	640.0	nM			

Decision Breakdown

inactive: 38
active: 79

2b: 29
1: 109
ghg: classification, eye
nc: 62
2a: 34
1: 76

eye
epa classification, eye
eu classification, eye



Backup Slides



National Toxicology Program
U.S. Department of Health and Human Services

Search the NTP Website

SEARCH



Home Integrator Workflows Reference Data About Help

ICE Workflows

NICEATM and partners have generated several software programs and workflows designed to improve predictions of chemical safety. Currently available workflows:

- Physicochemical property predictions
- Skin sensitization potency
- AOP overlay and ontology

[Physicochemical property predictions](#)

[Skin Sensitization potency](#)

[AOP overlay and ontology](#)



Physicochemical property predictions

Generates in silico predictions of octanol-water partition coefficient (logP), water solubility (logS), boiling point (BP), melting point (MP), vapor pressure (logVP), and bioconcentration factor (logBCF) using QSAR models developed in R. These constants are useful in the calculation of some modeling parameters as well as for chemical characterization.

Reference: Zang et al 2017. *Journal of Applied Toxicology*, 37(7):792-805

Software Requirements: Requires [R](#) version 3.4 or above

How to access: [Physicochemical_Property_Prediction_github](#)

Data inputs: a data frame with PaDEL descriptors for each chemical to be predicted

Returns: a data frame with predictions of the desired physicochemical property for each chemical





Backup Slides



National Toxicology Program
U.S. Department of Health and Human Services

Search the NTP Website

SEARCH



Integrated Chemical Environment

Home

Integrator

Workflows

Reference Data

About

Help

On This Page

- ICE Reference Chemical Lists
- Download Reference Lists
- AR in vitro Agonist 2016
- AR in vitro Antagonist 2016
- ER in vitro Agonist 2015
- ER in vivo Agonist 2015
- ICCVAM Cytotox Acute Oral 2006
- ICCVAM Eye Corrosion 2006
- ICCVAM LLNA 2013
- ICCVAM Skin Corrosion 2004
- OECDTG455

Reference Chemical Lists

Reference chemicals are chemicals that cause a specific well-characterized biological effect and therefore can be used to assess the performance of an assay designed to measure that effect. NICEATM compiled reference chemical lists in the context of assay validation studies conducted or sponsored by NICEATM and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). These lists are available on the [NICEATM website](#). "ICCVAM reference lists" were compiled through ICCVAM activities or working groups, while the other lists were developed for studies conducted by NICEATM or other partners. Reference chemical lists may be issued as part of protocols or test guidelines describing accepted procedures for specific tests, or in performance standards documents describing essential test method components for tests intended to measure similar biological outcomes. Some reference chemical lists are designed to assess the performance of assays conducted for a specific regulatory purpose, and thus may not be entirely applicable for assessing the performance of similar assays applied to different endpoints or used in different contexts. Please consult the background references listed below to determine the suitability of these reference chemical lists for a particular purpose.

Download Reference Chemical Lists

The reference chemical lists used in ICE with the supporting information for the specified biological effect are available [here](#) for quick download



Under Development: Formulations

 **Integrated Chemical Environment**

Home Integrator **Formulations** Workflows

Run Search Clear

Select Chemicals 

<input type="checkbox"/> Acute Dermal Toxicity	
<input type="checkbox"/> Acute Oral Toxicity	
<input type="checkbox"/> Acute Inhalation Toxicity	
<input type="checkbox"/> Primary Skin Irritation	
<input type="checkbox"/> Primary Eye Irritation	
<input type="checkbox"/> Dermal Sensitization	

 Select Reference Lists.

Enter one CASRN per line.

Download full data



Under Development: Formulations

Run Search Clear

Select Chemicals ?

- Acute Dermal Toxicity
- Acute Oral Toxicity
- Acute Inhalation Toxicity
- Primary Skin Irritation
- Primary Eye Irritation
- Dermal Sensitization

+ Select Reference Lists.

Enter one CASRN per line.

172345-26-5
1928-43-4
1918-00-9
10007-85-9
120068-37-3
106-24-1
1071-83-6

Download Query Integrator

Send the CASRNs to the Integrator

Formulation ID	Active Ingredient	CASRN	Percent AI
▶ Not Stated	-	ICE_42094346618	-
▶ Glyphosate	-	ICE_729956234	-
▶ Albaugh Glyphosate Acid	-	ICE_1757011315	-
▶ Touchdown Diquat Home and Garden Concentrate	-	ICE_1433817882	-
▶ SYN 1219 Herbicide	-	ICE_1506463698	-
▶ Sharda Glyphosate	-	ICE_4646586107	-
▶ Celsius WG	-	ICE_1839890958	-
▶ M1750 Herbicide	-	ICE_41910034923	-
▶ Glyphosate Acid	-	ICE_1327297599	-
▶ Navigator 80WG Termicide/Insecticide	-	ICE_1010954240	-
▶ CSI Imidacloprid + Fipronil SC	-	ICE_1054278024	-
▶ Proflaminate/Diquat/Glyphosate EW Ready to Use	-	ICE_4660223765	-
▶ NUP-07003 Herbicide	-	ICE_4509740805	-
▶ SM-9 Tergitol	-	ICE_42020205260	-
▶ Proflaminate/Diquat/Glyphosate EW Manufacturing	-	ICE_1385261692	-
▶ Glyphosate XG	-	ICE_1408275449	-
▶ Craze Herbicide	-	ICE_1119858598	-
▶ Certifect for Dogs	-	ICE_1932298155	-
▶ Tradename for Dogs	-	ICE_42117480911	-
▶ Proflaminate/Diquat/Glyphosate EW Concentrate	-	ICE_19848904	-
▶ Regent 500TS Insecticide	-	ICE_41998701941	-
▶ Shooter Insecticide	-	ICE_41759811876	-
▶ Departure Herbicide	-	ICE_41502273265	-
▶ EH-1446 Herbicide	-	ICE_41541177964	-
▶ EH-1534 Herbicide	-	ICE_777883124	-
▶ LDI Glyphosate	-	ICE_4510677064	-



Interoperability Across Systems

Consistent & compatible web-APIs



CEBS



ICE

Others...



Data Commons

NIEHS Data Systems

Consistent data set access & retrieval



CSS Dashboard

PubChem

Many others...



External Data Systems



Current timeline

Initial 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) January 2018

- Data updates

Update (V1.3) March 2018

- Data updates
- Interactive workflows



Acknowledgments



– Shannon Bell



– Jason Phillips

National Toxicology Program



– Andy Shapiro

– Charles Schmitt

– Stephanie Holmgren



For any comments please contact:

ICE-support@nih.gov

Visit us online

<https://ice.ntp.niehs.nih.gov/>