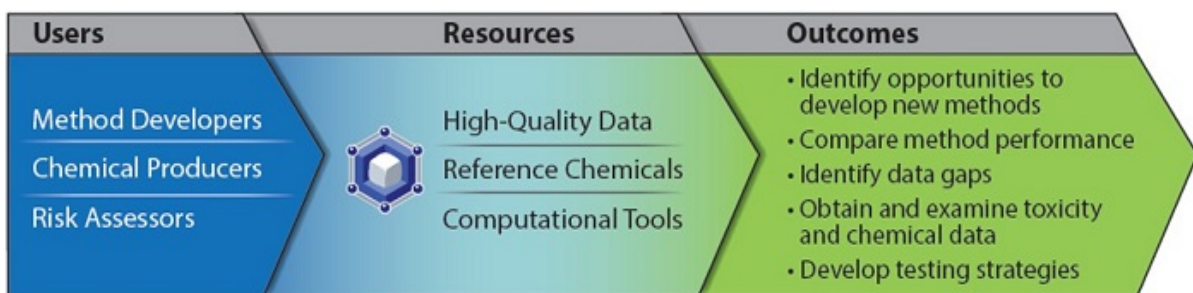


User-friendly Toxicology Tools from ICE Workflows

S. Bell¹, J. Phillips², N. Cariello¹, P. Ceger¹, X. Chang¹, F. Hermes¹, K. Mansouri¹, R. Rai¹, D. Allen¹, W. Casey³, N. Kleinstreuer³

¹ILS, RTP, NC, USA; ²Sciome LLC, RTP, NC, USA; ³NIH/NIEHS/DNTP/NICEATM, RTP, NC, USA

The Integrated Chemical Environment



ICE provides free online access to:

- Curated in vivo and in vitro test data
- In silico toxicity predictions and chemical property data
- Reference chemical lists
- Computational tools and workflows related to chemical characterization and predicting toxicity

ICE supports:

- Data integration: brings together available data, including data on formulations
- Results exploration: enables dynamic, graphical exploration with publication-quality graphics
- Data analysis: allows characterization of data using online workflows
- FAIR data access

What Goes into ICE?



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

Integrated Chemical Environment

Home Integrator Formulations Workflows Reference Data About Help

Search the NTP Website

Selected Reference Lists: ICDMM Cystos Acute Oral 2008, ICDMM Skin Corrosion

Substance Name	CASRN	DTXSID
Diphenol	20630-75-5	DTXSID0022834
Trichloroacetic acid	76-03-9	DTXSID1021378
Triphenyltin hydroxide	76-87-9	DTXSID1021409
Fenitronol	60168-88-8	DTXSID2032390
Triethylenemelamine	51-10-3	DTXSID3026225
Sodium carbonate	497-19-8	DTXSID1029621

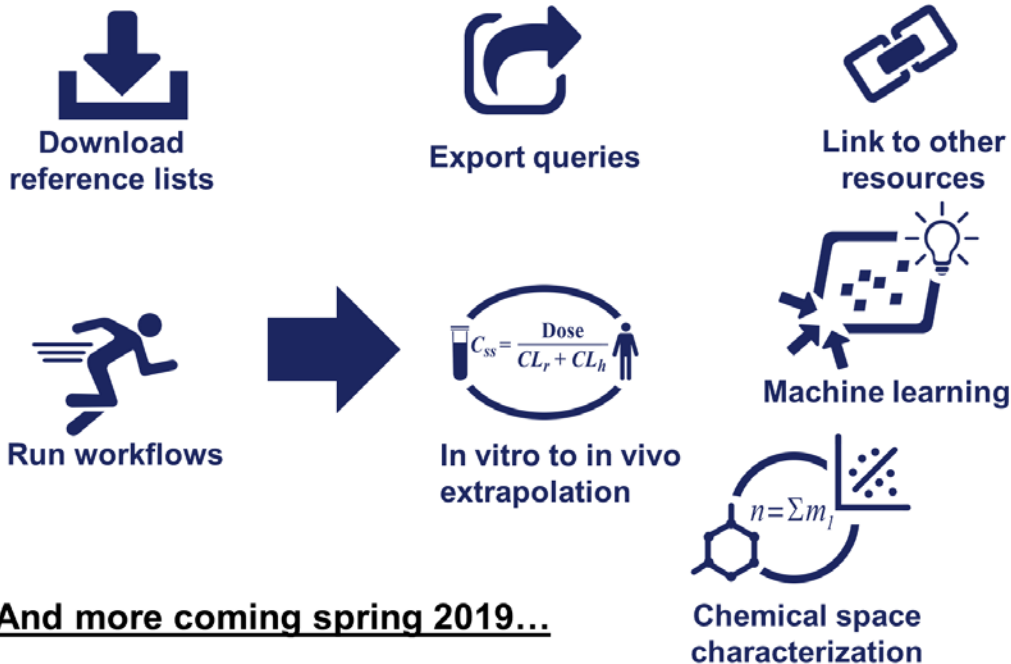
Chemical Breakdown

Assay	in silico	in vitro	in silico+in vitro	in vitro+in vivo	in silico+in vitro+in vivo
Acute Oral Toxicity	40	10	35	0	84
Skin Sensitization	0	10	0	0	10
Skin Irritation	0	0	61	0	61
Eye Irritation	0	0	10	0	10
Endocrine	0	0	40	72	112
CHTS	0	0	0	111	111

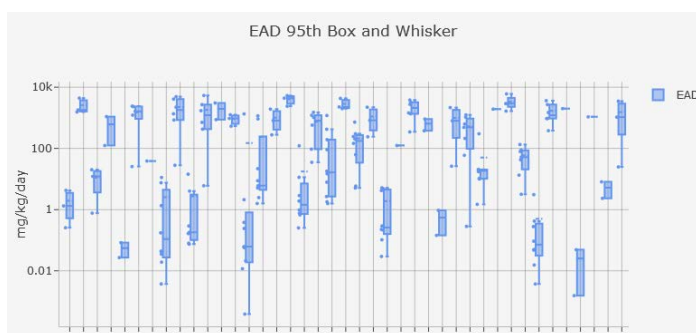
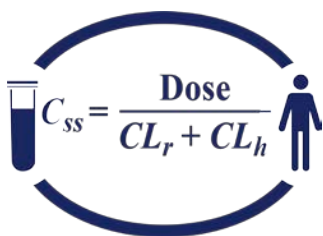
Chemical structure: CC(C)C(=O)Nc1ccc(Cl)c(Cl)c1
pKa: 4.55
logP: 3.71

3 chemical reference lists selected
Enter one CASRN per line.

Making Data and Tools Available



In Vitro to In Vivo Extrapolation



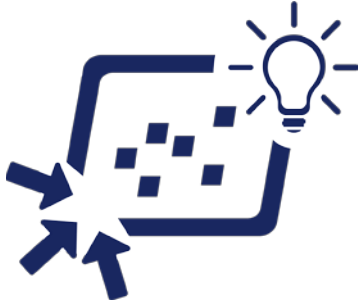
Use high-throughput in vitro data available from ICE to estimate external dose via a one-compartment model

IVIVE tools planned for future releases:

- Three-compartment physiologically based pharmacokinetic model
- Glucuronidation and sulfation predictions

- Reverse toxicokinetics predictions
- Calculations with user-provided data on ICE platform

Machine Learning



Use the machine learning tool for hypothesis generation and to explore different machine learning approaches using ICE data. Selected endpoints (for classification and regression modeling) and algorithms are available through ICE to facilitate the ease of use by those with limited background in computational toxicology

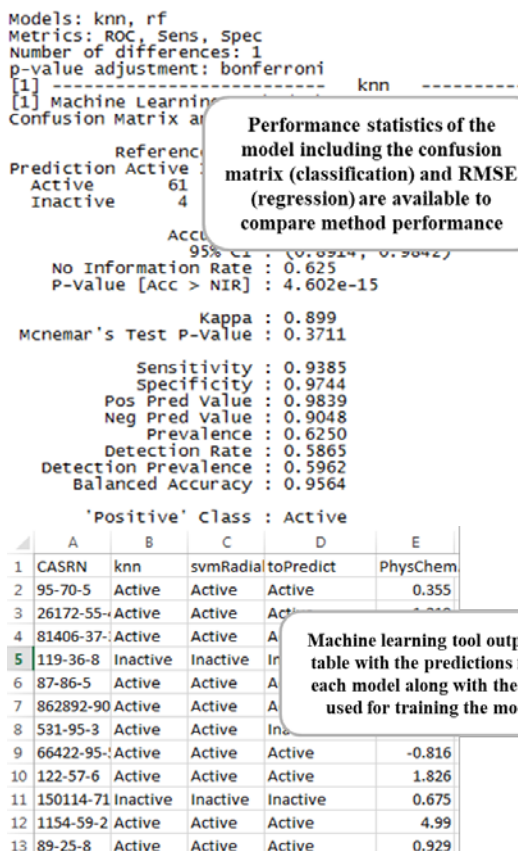
Endpoints for prediction

- LLNA: call
- Uterotrophic: call, LEL
- Human Potency: call, NOEL/LOEL

Machine learning methods available

- rf: random forest
- rpart: recursive partitioning
- knn: k-nearest neighbor
- svmRadial: support vector machine with a radial kernel

- pls: partial least squares regression

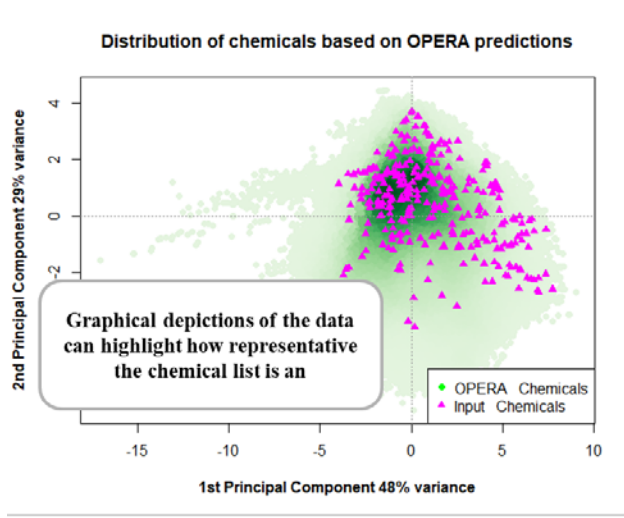


Performance statistics of the model including the confusion matrix (classification) and RMSE (regression) are available to compare method performance

Machine learning tool outputs a table with the predictions from each model along with the data used for training the model

Chemical Characterization

Leverage ICE models to characterize a chemical list, getting information on the chemical space covered (or not covered) based on different physchem properties.



```

[1] "----- Summary of Input Data -----"
MW      MP      BP      HL      VP
Min.   : 46.04   Min.   :-109.62   Min.   : 79.62   Min.   : -10.988   Min.   : -10.213
1st Qu.:220.06   1st Qu.: 93.95   1st Qu.:295.79   1st Qu.: -9.256   1st Qu.: -9.069
Median :270.16   Median : 152.53   Median : 308.70   Median : -7.276   Median : -5.542
Mean   :278.46   Mean   : 145.91   Mean   : 308.70   Mean   : -7.276   Mean   : -5.542
3rd Qu.:317.59   3rd Qu.: 195.41   3rd Qu.: 345.40   3rd Qu.: -6.002   3rd Qu.: -3.258
Max.   :780.43   Max.   : 302.06   Max.   : 482.74   Max.   : 1.374   Max.   : 4.843
WS
Min.   : -8.169
1st Qu.: -4.338
Median : -3.568
Mean   : -3.162
3rd Qu.: -2.253
Max.   : 1.218
[1] "----- Summary of Available OPERA Data -----"
MW      MP      BP      HL      VP
Min.   : 0.0     Min.   : -177.46   Min.   : -139.2   Min.   : -12.880   Min.   : -12.744
1st Qu.:199.0   1st Qu.: 64.21   1st Qu.: 274.3   1st Qu.: -8.833   1st Qu.: -8.062
Median :253.0   Median : 120.53   Median : 314.0   Median : -7.498   Median : -5.981
Mean   :277.5   Mean   : 113.68   Mean   : 308.7   Mean   : -7.276   Mean   : -5.542
3rd Qu.:322.0   3rd Qu.: 172.31   3rd Qu.: 345.4   3rd Qu.: -6.002   3rd Qu.: -3.258
Max.   :8435.5   Max.   : 482.74   Max.   : 541.5   Max.   : 1.374   Max.   : 4.843
NA's   :232
WS
Min.   : -12.080
1st Qu.: -4.354
Median : -3.045
Mean   : -3.154
3rd Qu.: -1.834
Max.   : 1.417

```

Tabular output of the data to compare the distribution of the input list to that of the >700,000 chemicals in ICE

In the pipeline:

- Generate physchem and other structure-based predictions from user-provided chemical lists
- Prediction of chemical parameters for use in modeling (example. fraction unbound, pka)
- Chemical use category overview provided by EPA's Consumer Products Database (cpDAT)
- Integration with ChemMaps (<http://www.chemmaps.com/>)

Contact Us



To get announcements of ICE updates and other NICEATM activities, visit the NIH mailing list page for NICEATM News at <https://list.nih.gov/cgi-bin/wa.exe?SUBED1=niceatm-l&A=1> and click “Subscribe.”

Visit ICE



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

Acknowledgements

ICE has been funded in whole or in part with federal funds from the National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, 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.