The Integrated Chemical Environment: Tools and Data to Support Toxicity Assessments

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The Integrated Chemical Environment

ICE provides free online access to:

- Curated in vivo and in vitro data related to toxicity testing
- In silico toxicity predictions and chemical property data
- Curated lists of chemicals with defined assays (reference chemical lists)
- Computational tools 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 (findable, accessible, interoperable, and reusable) data access
ICE 2.0

New features in ICE 2.0:

- Expand your search by adding chemicals in ICE with the same QSAR-ready structures as your chemical
- Simplified assay selection
- Updated tools

![Diagram showing computational models, published data, databases, validation studies, download reference lists, export queries and results, integrate data, in vitro to in vivo extrapolation, chemical space characterization, and machine learning.]
Overview of the Integrator

- Pop-up assay selection groups assays by common features/toxicity endpoints.
- Select chemicals to query from chemical quick list and/or entering CASRN.
- Further filter query results and export in a variety of computer-friendly and human-readable formats.
- Run tools to explore ICE data and generate predictions.
In Vitro to In Vivo Extrapolation

\[ C_{ss} = \frac{\text{Dose}}{CL_r + CL_h} \]

Use high-throughput in vitro data available from ICE to estimate external dose.

Choose from:

- One-compartment pharmacokinetic (1C PK) model including population simulation
- Two three-compartment physiologically based pharmacokinetic (PBPK) models:
  - 3C Glu: incorporates gut glucuronidation for BPA-family compounds
  - 3C HTTK: uses the httk package model
- Three-compartment models include gut, liver, and kidney
- Rat and human predictions
- A stand-alone version available for use with custom datasets: [https://github.com/NIEHS/](https://github.com/NIEHS/)
- Find out more about the IVIVE workflow: Abstract 3138/Poster P886, Wednesday, March 13
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.

Predicts endpoints for in vivo assays:

- Local lymph node assay (skin sensitization)
- Uterotrophic (estrogenic activity)
- Human skin sensitization potency

Machine learning methods available*

- cforest: conditional random forest
- rpart: recursive partitioning
- knn: k-nearest neighbor
- svmRadial: support vector machine with a radial kernel
- pls: partial least squares regression

*Machine learning tool uses imputation and/or removes sparse assays/chemicals to permit use of methods requiring complete cases.

Stand-alone version available for use with custom datasets: https://github.com/NIEHS/Machine-Learning-Pipeline
Performance statistics of the model including the confusion matrix (classification) and RMSE (regression) are available to compare method performance.

Models: knn, rf
Metrics: ROC, Sens, Spec
Number of differences: 1
p-value adjustment: bonferroni

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Accuracy: 0.9519
95% CI: (0.8914, 0.9842)
No Information Rate: 0.625
P-Value [Acc > NIR]: 4.602e-15

Kappa: 0.899
McNemar's Test P-Value: 0.3711

Sensitivity: 0.9385
Specificity: 0.9744
Pos Pred Value: 0.9839
Neg Pred Value: 0.9048
Prevalence: 0.6250
Detection Rate: 0.5865
Detection Prevalence: 0.5962
Balanced Accuracy: 0.9564

'Positive' Class: Active

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

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<th>C</th>
<th>D</th>
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Chemical Characterization

Leverage ICE models to characterize a user-supplied chemical list, getting information on the chemical space covered based on different physicochemical properties.

Graphical outputs highlight how representative the input chemical list (purple) is compared to the available chemical space in ICE (green).
Tabular summary comparing input chemicals to the >700,000 chemicals in ICE

Future plans for Chemical Characterization tool:

- 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 ([https://www.epa.gov/chemical-research/chemical-and-products-database-cpdat](https://www.epa.gov/chemical-research/chemical-and-products-database-cpdat))
- Integration with ChemMaps ([http://www.chemmaps.com](http://www.chemmaps.com))
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