User-friendly Toxicology Tools from ICE Workflows

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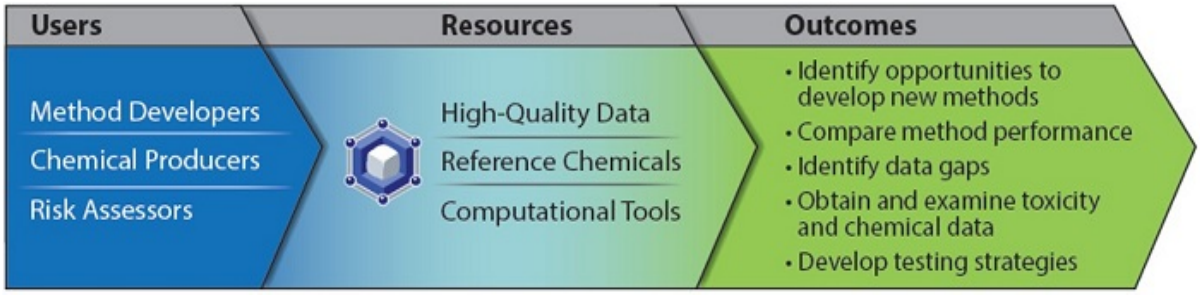
The Integrated Chemical Environment



ICE provides free online access to:

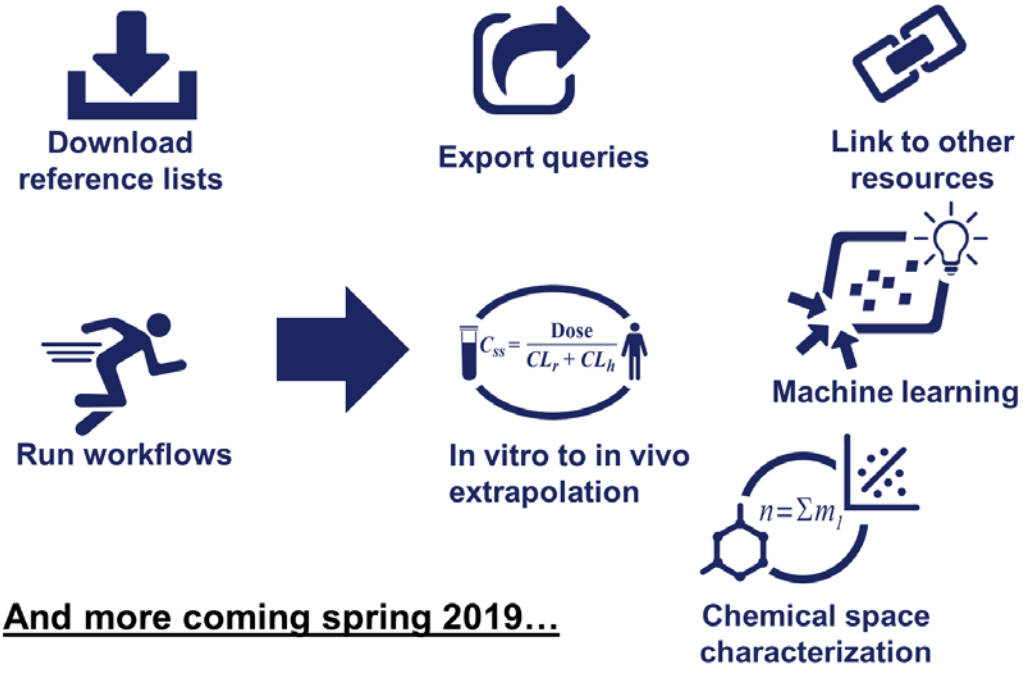
- Curated in vivo and in vitro test data
- In silico toxicity predictions and chemical property data
- Reference chemical lists
- Computational tools and workflows related to chemical characterization and predicting toxicity

ICE supports:

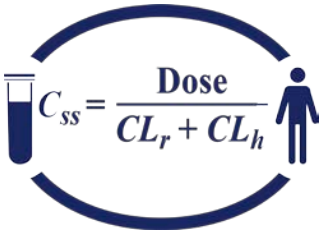
- Data integration: brings together available data, including data on formulations
- Results exploration: enables dynamic, graphical exploration with publication-quality graphics
- Data analysis: allows characterization of data using online workflows
- FAIR data access

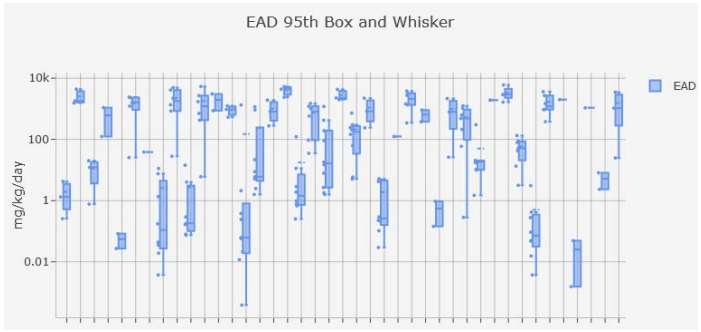
What Goes into ICE?

Making Data and Tools Available



In Vitro to In Vivo Extrapolation





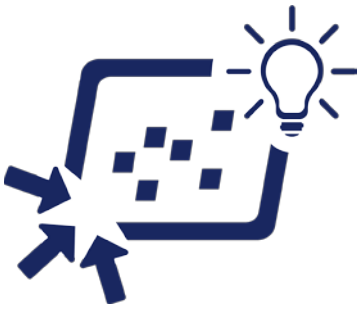
Use high-throughput in vitro data available from ICE to estimate external dose via a one-compartment model

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

```
Models: knn, rf
Metrics: ROC, Sens, Spec
Number of differences: 1
p-value adjustment: bonferroni
[1] ------------------------   knn   ----------
[1] Machine Learnin
Confusion Matrix a

          Referenc
Prediction Active
  Active       61
  Inactive      4

               Acc
                 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
```

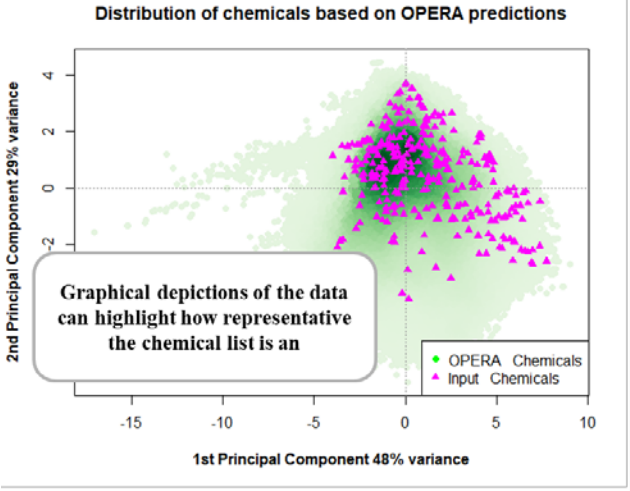
Performance statistics of the model including the confusion matrix (classification) and RMSE (regression) are available to compare method performance

	A	B	C	D	E
1	CASRN	knn	svmRadial	toPredict	PhysChem
2	95-70-5	Active	Active	Active	0.355
3	26172-55-4	Active	Active	Act	
4	81406-37-3	Active	Active	A	
5	119-36-8	Inactive	Inactive	In	
6	87-86-5	Active	Active	A	
7	862892-90	Active	Active	A	
8	531-95-3	Active	Active	Ina	
9	66422-95-5	Active	Active	Active	-0.816
10	122-57-6	Active	Active	Active	1.826
11	150114-71	Inactive	Inactive	Inactive	0.675
12	1154-59-2	Active	Active	Active	4.99
13	89-25-8	Active	Active	Active	0.929

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.



Graphical depictions of the data can highlight how representative the chemical list is an

```
[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
 Mean   :278.46   Mean   : 145.91   Mean
 3rd Qu.:317.59   3rd Qu.: 195.41   3rd Q
 Max.   :780.43   Max.   : 302.06   Max.
       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.   :  4.043
 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."

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