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Modeling quantitative acute oral systemic toxicity based on a k-Nearest Neighbor (k-NN) algorithm

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Introduction

Laboratory of Environmental Chemistry and Toxicology

- Modeling exercise based on the dataset released by the NICEATM team
- 2 months, 5 people involved using different tools and algorithms (more results on posters)
- Common internal procedure for the dataset curation

Data preparation: LD_{50} values

Aggregation of entries

- De-salting
- Duplicated structures

Data variability analysis

- Removed entries:
  - with SD ≥ 0.5 for data point values
  - Conflicting classes

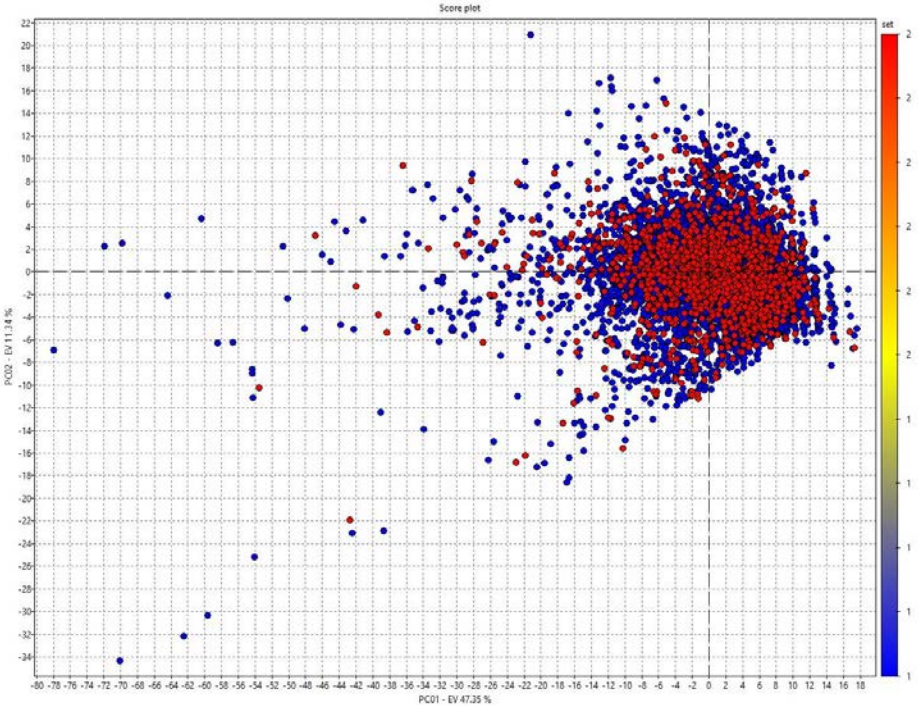
Final dataset: 8476 unique structures

- Median 1st quantile LD_{50} (mmol/kg)
- Univocal label for classification

Count (single point)	Canonical_QSARr	Salt_Solvent	Mean	1st Quantile median	Standard Deviation
4	COP(=S)(OC)SCN1N=NC2C=CC=CC=2C1=O		-0.71	-1.84	1.90
4	NC1CCCCC1	Cl(1), C(C)(=O)O(1)	0.25	-0.95	0.87
2	CC[P+](C1C=CC=CC=1)(C1C=CC=CC=1)C1C=CC=CC=1	[Br-](1), [I-](1)	-0.50	-0.72	0.32
5	NCCO		1.72	1.45	0.30

Dataset preparation

- Training and validation set splitting (80%/20%)
- Indigo fingerprints calculated in KNIME and compared using the Tanimoto score
- stratified sampling based on clusters obtained with the k-Means clustering algorithm
- nearly-common dataset to all the 5 modeled endpoints



Data distribution

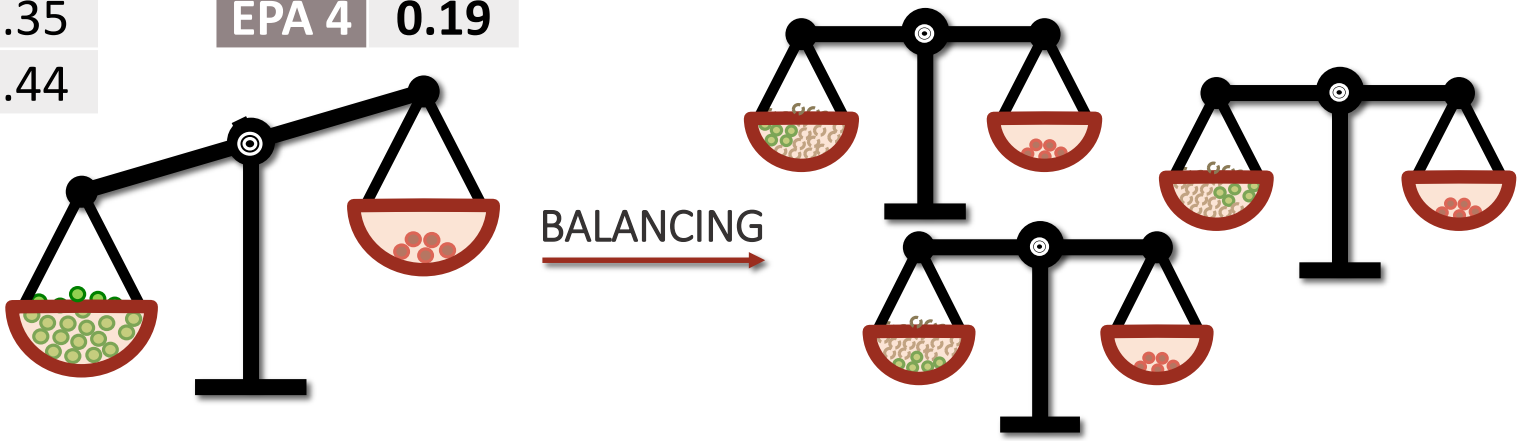
	n	Min logLD50 (mmol/kg)	Max logLD50 (mmol/kg)	Mean	St.dev	Skewness
TS	5029	-4.66	2.71	0.44	0.90	-0.98
VS	1251	-3.70	2.38	0.44	0.90	-1.05

	%
GHS 1	**0.02**
GHS 2	**0.06**
GHS 3	**0.13**
GHS 4	0.35
GHS 5	0.44

	%
EPA 1	**0.09**
EPA 2	**0.22**
EPA 3	0.50
EPA 4	**0.19**

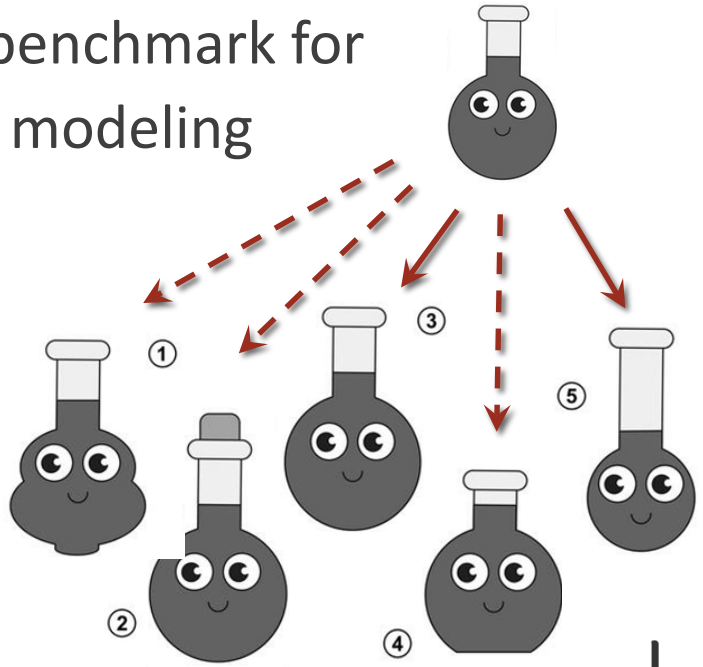
	%
nT	0.43
T	0.57

	%
vT	**0.92**
not vT	0.08



Modeling approach

- K-nn algorithm as implemented into in house software (istKNN by A. Manganaro, Kode srl)
- Simple method, internal benchmark for other more sophisticated modeling techniques (see posters)
- Allows a read-across like approach



kode chemoinformatics

Similarity Index (SI)

- accounting for different chemical and structural features of the molecules

- considering different relevant structural aspects, including the size of the molecules

$$SI = S(FP)^{0.4} * S(CD)^{0.35} * S(HE)^{0.1} * S(FG)^{0.15}$$

FP → Fingerprints

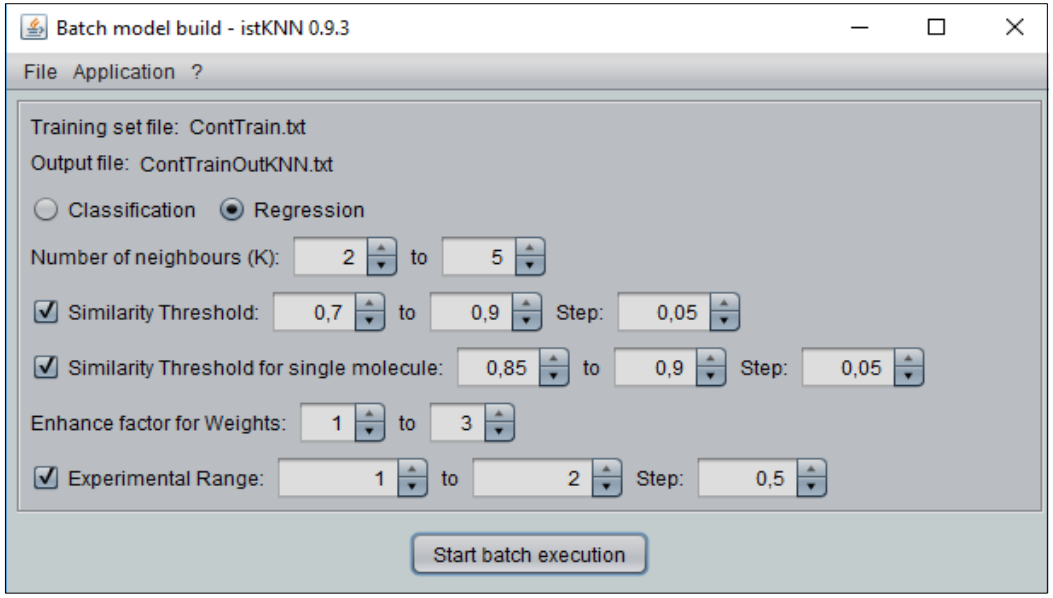
CD → Structural key with 35 Constitutional descriptors (MW, nr of skeleton atoms, etc.)

HE → Structural key with 11 Hetero-atoms descriptors

FG → Structural key with 154 Functional groups (specific chemical moieties)

- FP similarity → Maxwell-Pilliner index
- CD, HE, FG similarities → Bray-Curtis index

Software setting



Batch model development

> 300 models optimizing 5 parameters

Batch models on training set

Select best setting with R^2_{LOO} and check VS with best model

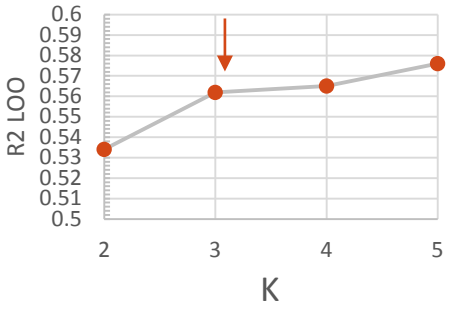
Use this setting to run a new model on the entire dataset

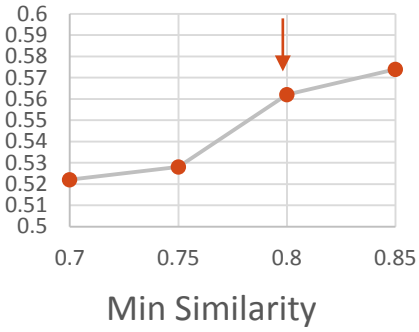
Results

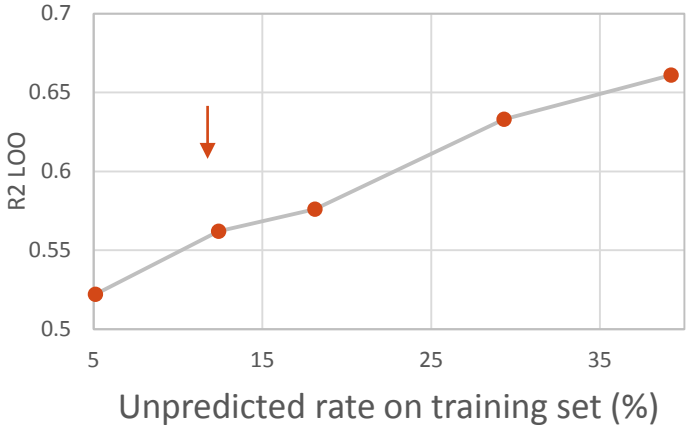
Model parameters						Training Set (TS)			Validation Set (VS)		
Model No.	K	Min Similarity	Min Similarity for single molecule	Enhance factor	Exper. range	R^2 (LOO)	RMSE (LOO)	Unpred. rate	R^2	RMSE	Unpred. rate
135	3	0.8	0.85	3	2	0.56	0.59	13.2%	0.56	0.59	12.4%

TS + VS

R2 (LOO)	RMSE (LOO)	Unpred. rate
0.583	0.575	11.9%



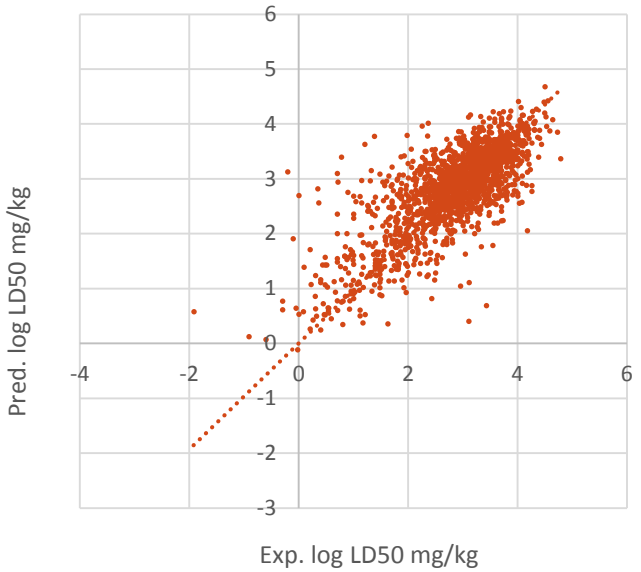




Results on the evaluation set

Evaluation set (n = 1865)

R2	RMSE	Unpred. rate
0.58	0.56	14%

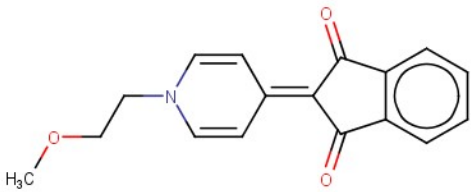


Applicability domain

Chemical domain: Inorganic chemicals and chemicals with unusual elements (i.e., B and Se) are excluded during the data curation. Silicates are included.

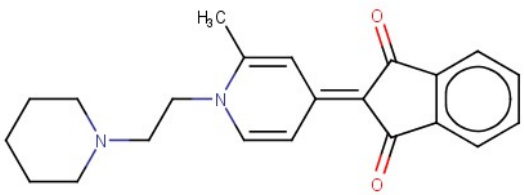
Model domain: No prediction if 1) too high experimental range of similar molecules or 2) no similar molecules present in the dataset

Examples



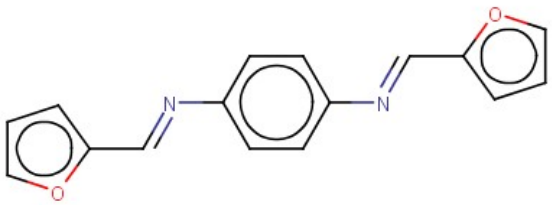
Sim. = 0.881

Exp. LD_{50} = 350 mg/kg



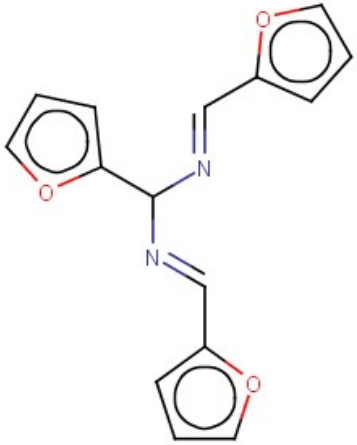
Exp. = 390 mg/kg

Pred. = 439 mg/kg



Sim. = 0.83

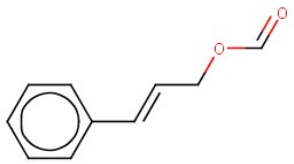
Exp. LD_{50} = 1220 mg/kg



Exp. = 400 mg/kg

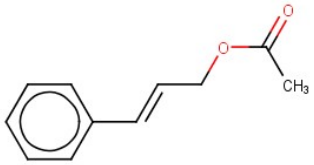
No Prediction

Examples



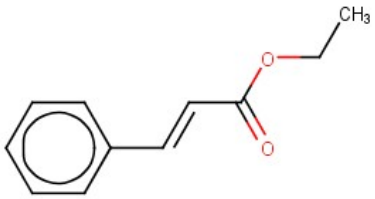
Sim. = 0.941

Exp. LD_{50} = 2900 mg/kg



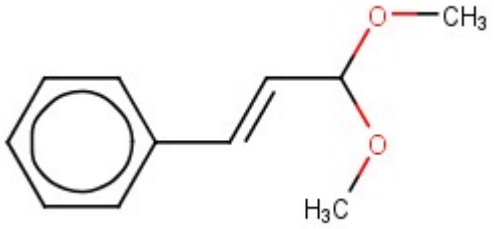
Sim. = 0.94

Exp. LD_{50} = 3300 mg/kg



Sim. = 0.931

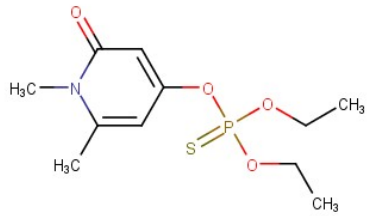
Exp. LD_{50} = 4000 mg/kg



Exp. = 3700 mg/kg

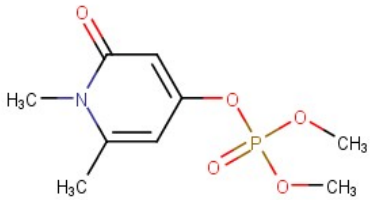
Pred. = 3497 mg/kg

Examples



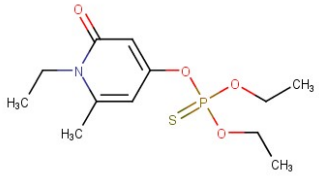
Sim. = 0.964

Exp. LD_{50} = 5.97 mg/kg



Sim. = 0.958

Exp. LD_{50} = 2.91 mg/kg



Sim. = 0.946

Exp. LD_{50} = 7070 mg/kg

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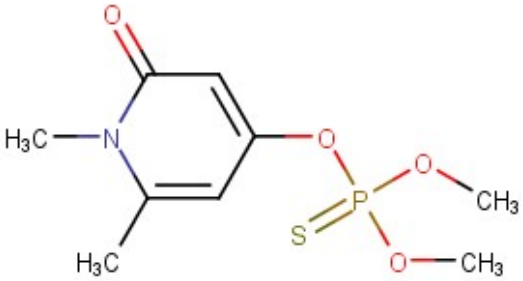


Exp. = 0.812 mg/kg

No Prediction

Conclusions & perspectives

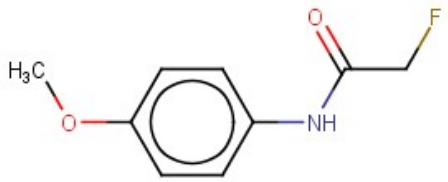
- k-NN demonstrated to be a simple method capable to obtain acceptable results
- Easily adapted for two prediction strategies:
  - automatic way for **screening** large inventories
  - read-across setting for allowing expert reasoning around available information for **hazard assessment**
- Easily implementable (freely available) in VEGA (www.vegahub.eu)

Thank you!

Questions?

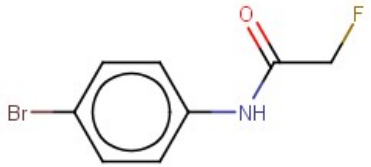
alessandra.roncaglioni@marionegri.it

Examples



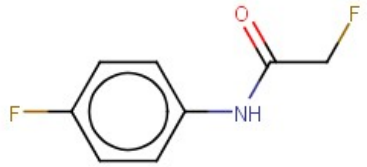
Sim. = 0.913

Exp. LD_{50} = 10 mg/kg



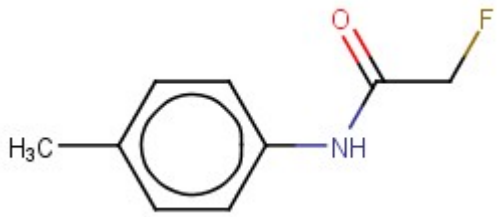
Sim. = 0.912

Exp. LD_{50} = 29 mg/kg



Sim. = 0.931

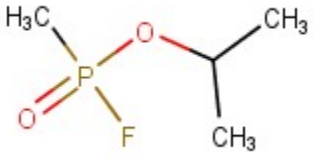
Exp. LD_{50} = 2 mg/kg



Exp. = 7 mg/kg

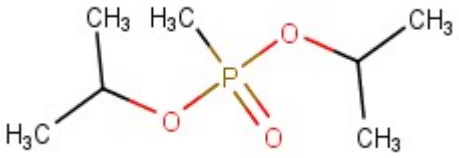
Pred. = 7.27 mg/kg

Examples



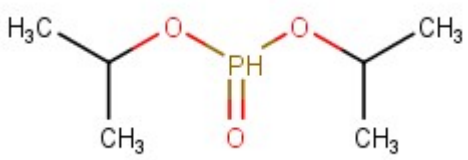
Sim. = 0.898

Exp. LD_{50} = 0.55 mg/kg



Sim. = 0.877

Exp. LD_{50} = 826 mg/kg



Sim. = 0.842

Exp. LD_{50} = 1700 mg/kg

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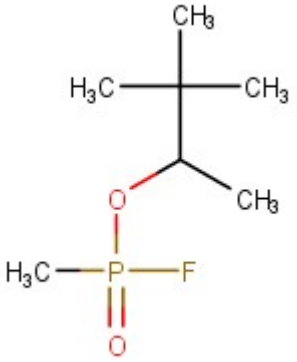

Exp. = 0.4 mg/kg

No Prediction