Acute-Tox™

iS Tox Platform™
Machine-learning models for a new toxicology

Report

Client:
Altox

Username:
Tiago

Study Number:
Acute-Tox_Compound5_

Date:
2019/06/19 - 15:24:37

Program Version: 1.7

Molecular Query

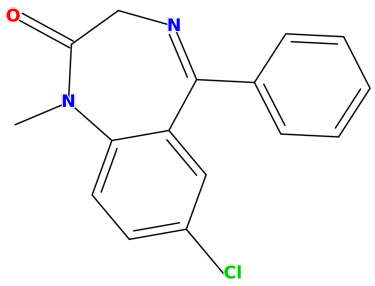
Name:
Compound 5

CAS:
NA

SMILES:
CN1c2ccc(Cl)cc2C(=NCC1=O)c1ccccc1

logK$_{ow}$:
3.15

logD:
2.75



Model Summary

Acute-Tox™ is a computational tool for prediction of the acute oral toxicity by statistical and machine learning-models. The method permits estimation of an LD_{50} and the results allow a substance to be classified for acute toxicity according to the Globally Harmonised System of classification and labeling of chemicals. The models are in compliance with 3Rs in acute systemic toxicity testing, as well they were validated following the OECD (Organisation for Economic Co-operation and Development) Principles for the Validation for Regulatory Purposes of (Q)SAR Models. These OECD principles are discussed in each section of this report.

This tool is powered with artificial intelligence models developed with a rigorously curated rat acute oral toxicity dataset, containing 11,723 chemical structures (defined endpoint - OECD principle 1).

The final result is provided in a table summarising all the individual predictions, the applicability domain (AD) confidence levels, with a decision for the outcome.

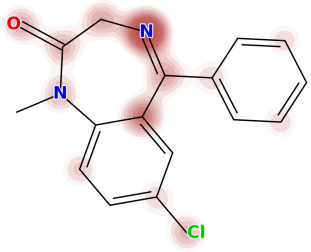
Artificial Intelligence Models

The individual predictions below were obtained for the oral acute toxicity estimation by Artificial Neural Networks (ANN). To ensure transparency in the description of the model (an unambiguous algorithm - OECD Principle 2), more detailed information about each model is presented below.

The STR (Structure–toxicity relationship) Probability Mapping indicates the fragments that decrease toxicity (-) (green) or increase toxicity (+) (red), useful for hypotheses and mechanistic interpretations (OECD Principle 5).

STR Contribution Map

Increase toxicity (+) Decrease toxicity (-)

Predicted endpoint/Method	Predicted Category/Value (Confidence)	STR Contribution Mapping
Rat Oral Acute Toxicity (OECD 423) Deep Learning decision model implemented with hybrid descriptors	Category 4 2.9 -log10(mol/Kg) 365.1 mg/Kg (94.0%)	

Prediction Confidence (Based on the most similar molecules)

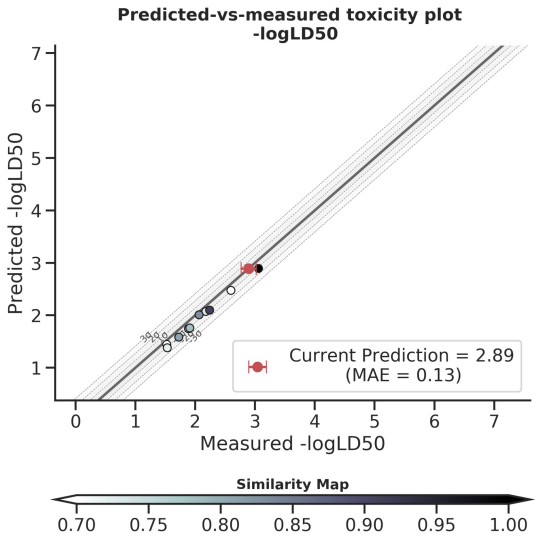
With appropriate measures of goodness-of-fit, robustness, and predictivity (OECD Principle 4). The graph below plots measured versus predicted acute oral toxicity values for each most similar compound and, the mean absolute error (MAE) for each prediction.

Experimental vs predicted toxicity values

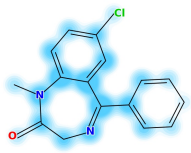
for the six most similar molecules (Dice) with the prediction confidence level

Similarity Map

Low High

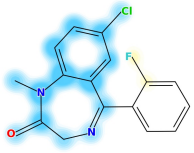


Similarity: 1.00



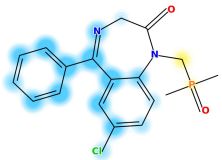
Exp. value: 3.1
Ext. Pred. value: 2.9
(Confidence: 95%)

Similarity: 0.91



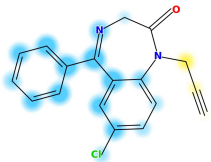
Exp. value: 2.2
Ext. Pred. value: 2.1
(Confidence: 94%)

Similarity: 0.83



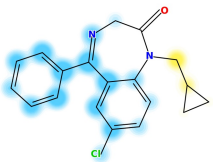
Exp. value: 2.1
Ext. Pred. value: 2.0
(Confidence: 97%)

Similarity: 0.81



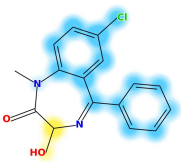
Exp. value: 1.7
Ext. Pred. value: 1.6
(Confidence: 92%)

Similarity: 0.78



Exp. value: 1.9
Ext. Pred. value: 1.8
(Confidence: 92%)

Similarity: 0.73



Exp. value: 2.2
Ext. Pred. value: 2.1
(Confidence: 95%)

To assess the confidence of the Acute-Tox ™ predictions, after of to assess the applicability domain of the model by the Visual applicability domain (AD) Inspection®, is recommended assess the model performance by the predicted-vs-measured toxicity plot and confidence level for the most similar molecules.

To assess the chemical space of the prediction and its mean absolute error (MAE), this section presents the model performance for the most similar molecules (Dice) during 5-Fold external validation, also, for the six most similar molecules (Dice) with the confidence level side-by-side to each acute toxicity prediction. If the predicted value matches the experimental values for the test set chemicals, the model has a low MAE and greater confidence.

Detailed data about the dataset of chemicals, including endpoint and descriptor values; derivation of the descriptors; test and training sets; removed outliers; statistical parameters and others are available in the QMRF (QSAR Model Reporting Format) report under a confidentiality agreement. Altox Ltda assures scientific integrity of the data.

The Deep learning model has components with multiple hidden layers that can learn increasingly abstract representations of the chemical hybrid descriptors. The chemical hybrid descriptor. Then, every 4 subsequent layers learn more complex representations. Finally, the last layer can evaluate the acute oral toxicity LD_{50} values of the given compound.

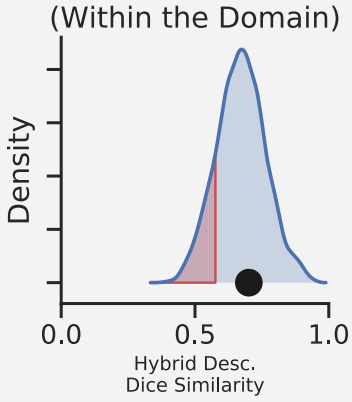
Visual AD Inspection®

The applicability domain (AD) is defined by the chemical structure space and the toxicological response encoded by the developed model, to make new predictions with a given reliability (a defined domain of applicability - OECD Principle 3). Our visual AS Inspection® is used to establish the scope and limitations of the models. Basically, new chemicals must be reasonably similar to training set compounds or a prediction cannot be accepted.

Our visual AD inspection is represented by a density plot of the average fingerprint-dice similarity for the k-nearest neighbors of each compound during the 5-Fold external validation. The chemical structure is represented by a hybrid descriptor composed by ECFP4 fingerprints and physicochemical measurements: molecular weight (MW), topological polar surface area (TPSA), octanol-water partition coefficient for neutral compounds (log K_{ow}) or at different pH states (logD). At the visual AD inspection, the black circle represents the evaluated compound, the highlighted red area means the restricted similarity region, and the blue region is the allowed similarity of the chemical space to predict new compounds.

Even though a well-designed AD helps the user to assess the reliability of predictions made by the model, it should not automatically be assumed that all predictions within the defined AD are necessarily reliable.

Rat Oral Acute Toxicity (OECD 423)



Final Result

The oral acute toxicity results according to GHS are presented below; Category 1 (red), or Category 2 (red), or Category 3 (red), or Category 4 (yellow), or Category 5 (yellow), and/or Not Classified (Green) predictions are presented with applicability domain (AD) and confidence level (robustness, OECD principle 4) for the physical-chemical properties and advanced statistical systems.

Predicted endpoint/Method	Predicted Category/Value (Confidence)	Applicability Domain
Physical-chemical Properties		
log_{kow}	3.15	-
logD	2.75	-
Advanced Statistical System		
Rat Oral Acute Toxicity (OECD 423) Deep Learning decision model implemented with hybrid descriptors	Category 4 2.9 -log10(mol/Kg) 365.1 mg/Kg (94.0%)	Within