Comparison of the results of QSAR models for LD50

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Introduction

Within **ANTARES** we compared a series of **QSAR models for LD50**: ACD, T.E.S.T., TOPKAT, ADMET Predictor, TerraQSAR. The comparison was done using a large set of chemicals (>7,000). The values have been taken from the US EPA web site (http://www.epa.gov/nrmrl/std/qsar/qsar.html). The models for LD50 have been check for these chemicals. Since the LD50 is a continuous dose, but the regulation also identifies toxicity classes related to LD50 values, we considered both the results in classification and in regression.
The results have been also evaluated separately for the chemicals inside and outside the training set of each model, when possible, and inside and outside the applicability domain, when defined by the model itself.

http://www.antares-life.eu/software.php

Materials and Methods

- **DATASET**: 7,420 Compounds with Rat Oral LD_{50} expressed in - Log mol/kg
- **MODELS**: US EPA T.E.S.T. (free), ACD/ToxSuite, Accelrys TopKat, ADMET Predictor and TerraQSAR (commercial)

In order to standardize the input, all molecules have been converted to SMILES using an *in house* software.

Three molecules couldn't be converted and they have been excluded.

Table 1. LD50 toxicity category defined by regulation

Toxicity Category	Thresholds
CAT1	LD50 <= 5
CAT2	5 < LD50 <= 50
CAT3	50 < LD50 <= 300
CAT4	300 < LD50 <= 2,000
NON TOX	LD50 > 2,000

EVALUATION OF THE PERFORMANCES:

- R^2 – regression
- Accuracy of prediction – classification using thresholds defined by regulation (see **Table 1**).
- Evaluation performed on entire dataset and, where available, using information about **Applicability Domain** and molecules in **model training set**.

Results

The performances of the selected models, evaluated using the entire dataset are reported in **Table 2**.

T.E.S.T. does not provide predictions for molecules out of its Applicability Domain.

The best models seems to be ACD/ToxSuite and US EPA T.E.S.T.

Table 2. Regression and classification performances of the selected models

	N. molecules	R2	ACC
ACD	7,417	0.77	0.66
ADMET	7,417	0.54	0.53
TERRA	7,417	0.64	0.65
T.E.S.T.	7,406	0.71	0.69
TOPKAT	7,417	0.40	0.48

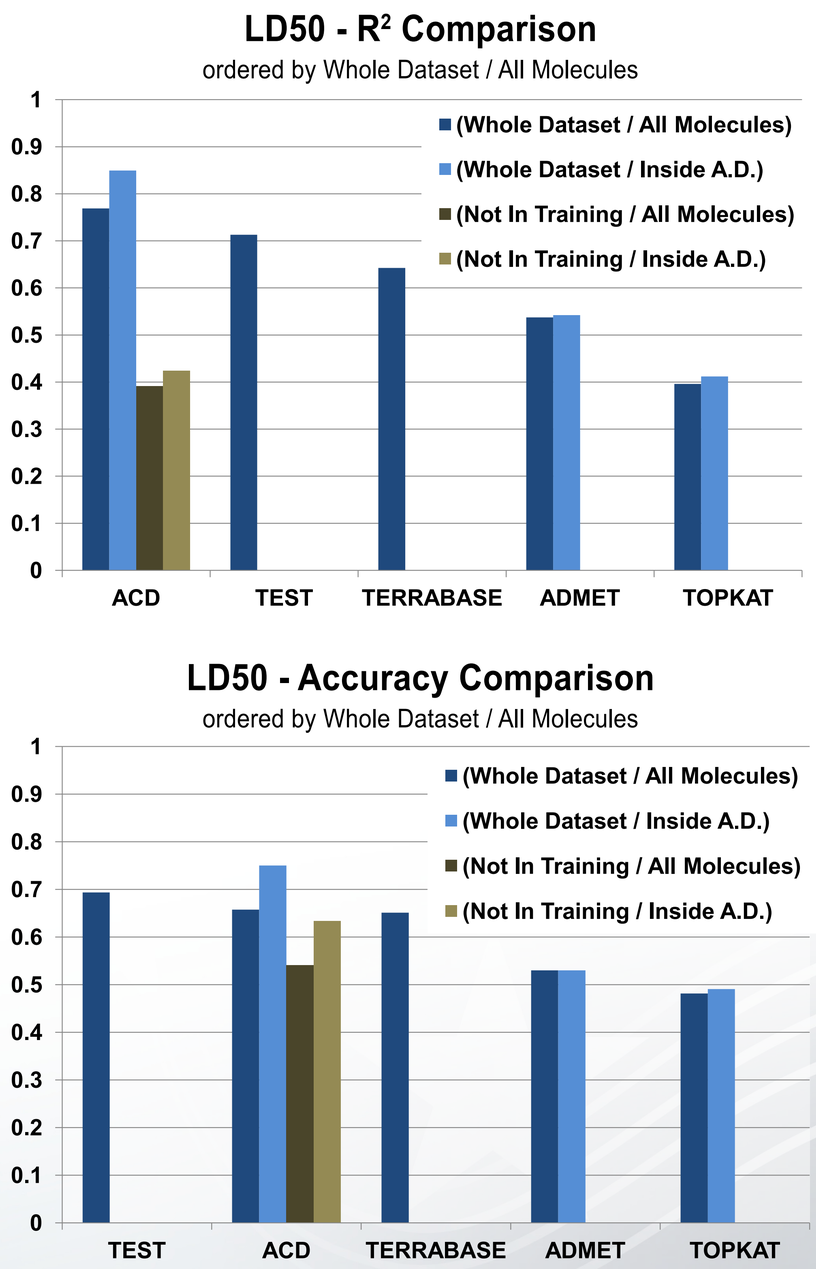

Figure 1.Comparison of the 5 models considering A.D. and models' training set.

Figure 1 shows the results. Good results in regression have been obtained with ACD/ToxSuite and US EPA T.E.S.T.
In classification we also found quite different results, depending on the model and the categories. We considered 5 categories, according to the regulatory thresholds. Some models, such as ACD and T.E.S.T., gave good accuracy, while other models showed low accuracy.
This study can help user in the identification of useful tools for REACH.

Conclusions

This evaluation shows that there are few models with good performance for LD50 for continuous values. However, results get worst considering chemicals in a test set. To improve this picture, the user should evaluate the applicability domain of the model.
A similar trend appears in classification.

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