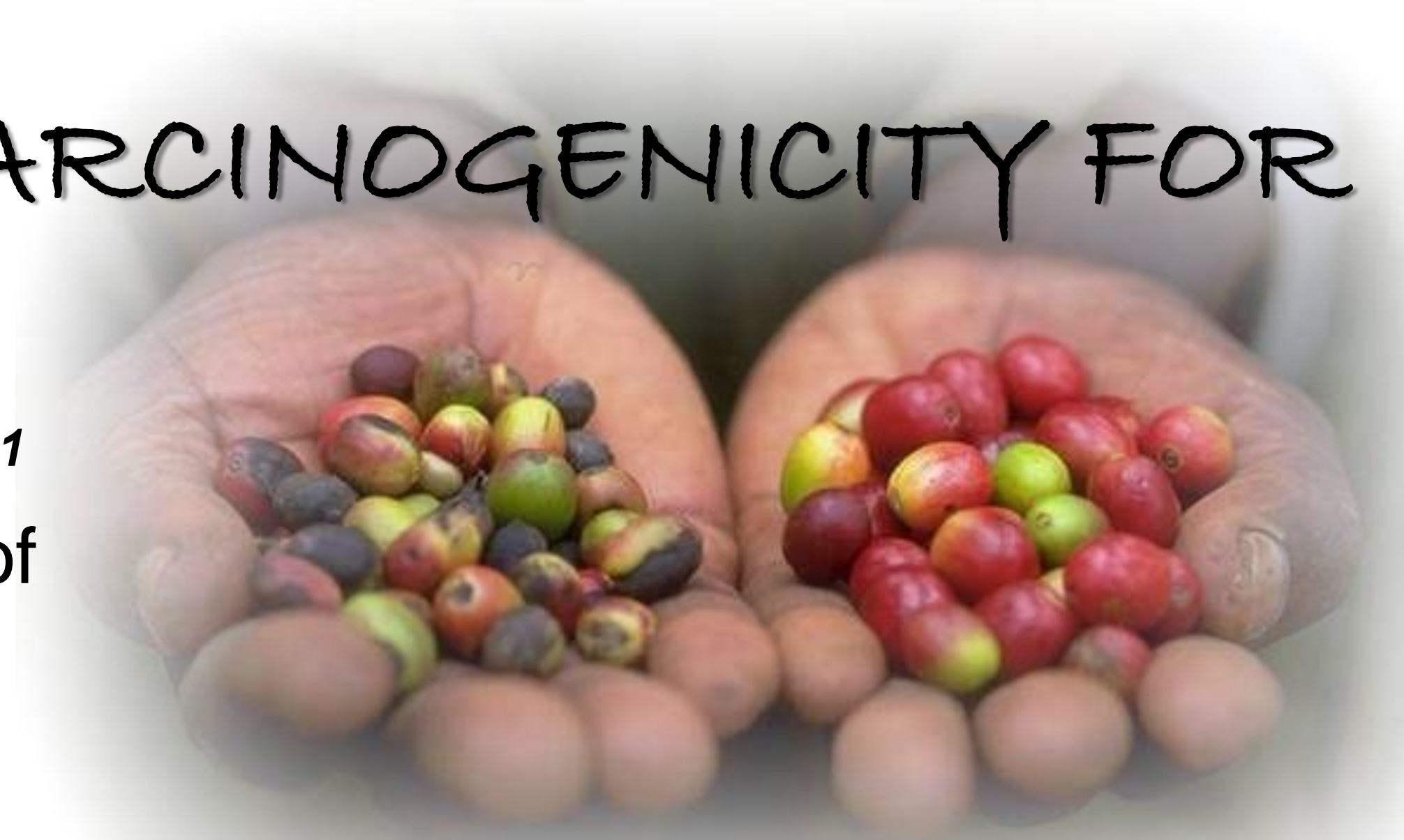


USE OF IN-SILICO MODELS TO ESTIMATE CARCINOGENICITY FOR PESTICIDES

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INTRODUCTION

The European legislative framework on pesticides aims to ensure better consumer protection throughout the EU. Compared to other legislations (such as REACH) there is a large demanding for experimental testing for plant protection products. Therefore there is room for the improvement of this situation by assessing if non testing methods may play a role, either in reducing the animal experiment need for active ingredients or to provide a more comprehensive overview of possible hazard posed by additional ingredients or metabolites.

MATERIALS & METHODS

In this case study, an evaluation of the applicability of QSARs models on pesticides and metabolites for carcinogenesis has been performed. QSARs are estimation methods to predict certain properties of chemicals which are based on the structure of the substance. Carcinogenicity, being directly related with human health, is one of the most relevant property to analyze. QSAR can be useful in particular for the evaluation of related compounds, such as impurities and metabolites. Seven software have been used to predict carcinogenicity endpoint using a specific set of 95 pesticides: Caesar, Derek, Hazard Expert (HE), Lazar, Multicase and Topkat, Toxtree. The predictions for this set of compounds have been compared with experimental results in order to assess and characterize the capability of each model.

RESULTS & DISCUSSIONS

The most important statistical measures of the performance of a binary classification test analyzed were the Accuracy, Sensibility and Specificity.

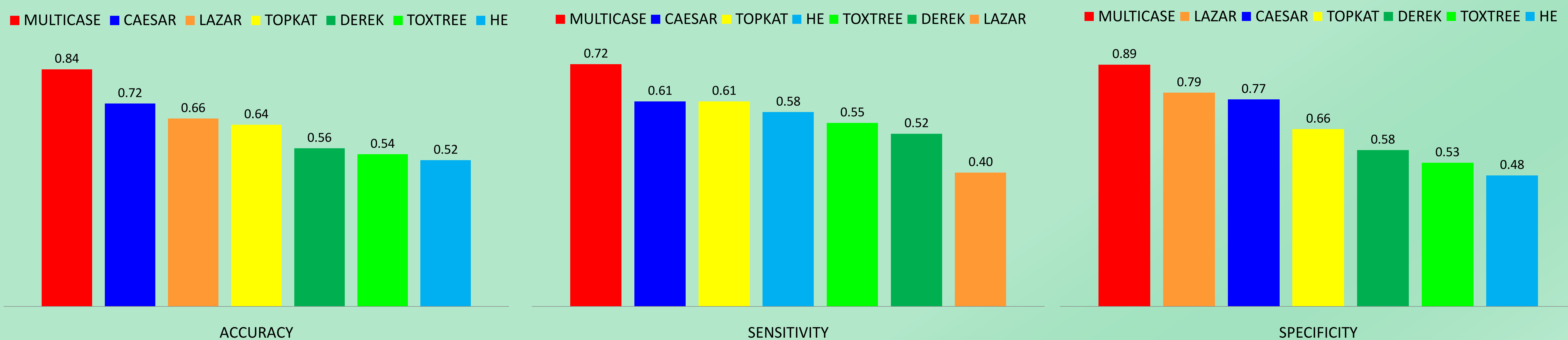


Figure 1.

Performance obtained by seven software. Results are given in percentage.

Accuracy is calculated by the ratio between $(TP+TN)/(TP+TN+FP+FN)$, Sensitivity by the ratio among $TP/(TP+FN)$ and Specificity by the ratio among $TN/(TN+FP)$, considering that TP are True Positive, TN True Negative, FP False Positive and FN False Negative.

Multicase performance is the best according to all the statistical analyses, but it does not handle all compounds (it does not provide prediction for nine compounds). Caesar shows a good prediction capability.

An useful issue is the capability to address the Applicability Domain (AD) of the model. This can help understanding if the model can be applied to a certain compound since the AD is the physico-chemical, structural or biological space, knowledge or information on which the training set of the model has been developed, and for which it is applicable to make predictions for new compounds.

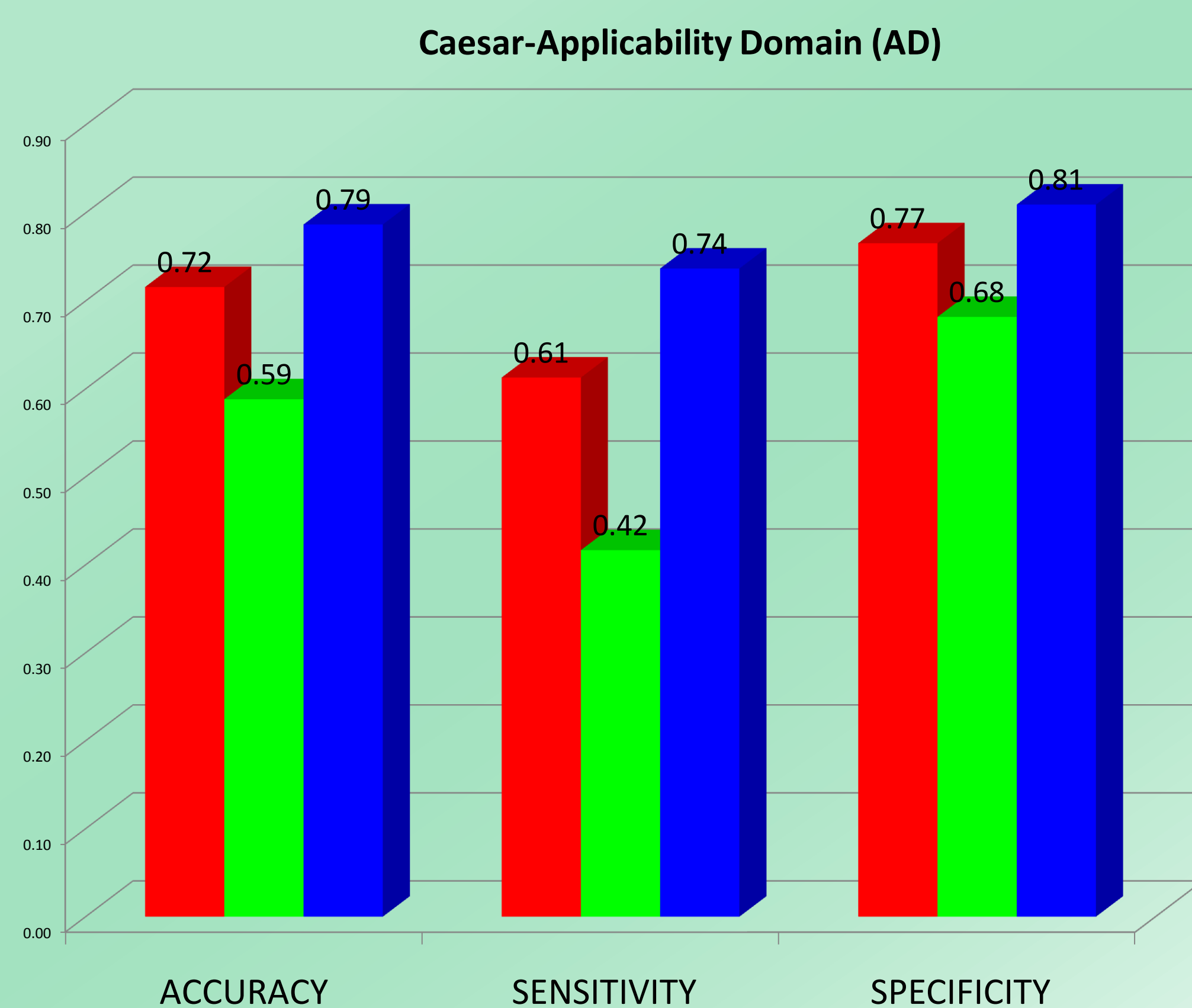


Figure 2.

Applicability Domain (AD), analyzed on Caesar, is based on:

- Similarity index with compounds in the training set;
- Concordance index, based on the similarity with experimental results;
- Accuracy index, calculated on the prediction accuracy of the most similar results;
- class membership score for the specific predicted chemicals.

CONCLUSION

- ✓ Pesticide toxicity is a complex field. Some QSAR models can be applied.
- ✓ Caesar predictions improve analyzing the AD. We discuss this point with the Caesar case. Figure 2 shows that applying the model to the correct cases, performances improves, producing more reliable results.
- ✓ Since carcinogenicity evaluation is typically done using a series of studies, an identification of a strategy using one, or a battery of in-silico models, will reduce the number of animal studies.