# Comparison of the results of QSAR models for Bioconcentration Factor

Anna Lombardo[a], Rodolfo Gonella Diaza[a], Andrea Gissi[a,c], Emilio Benfenati[a], Frank Lemke[b]

[a] Istituto di Ricerche Farmacologiche Mario Negri, Laboratory of Environmental Chemistry and Toxicology, Via G. La Masa 19, 20156 Milan, Italy

[b] KnowledgeMiner Software Frank Lemke, Duererstrasse 40, Panketal, Germany

[c] Università degli Studi di Bari, Dipartimento Farmaco-Chimico, Via E. Orabona 4, 70125, Bari, Italy

## Introduction

Under REACH, **bioconcentration factor (BCF)** value of a chemical is required for several regulatory purposes. It is required above 100 t/y for registration and above 10 t/y for prioritisation (PBT/vPvB). A chemical is considerd B if BCF is above 2,000 l/kg, vB if it is above 5,000 l/kg. Other two thresholds exist for BCF: 100 l/kg for chemical safety assessmet and 500 l/kg for classification and labelling, but for these two purposes the use of BCF is not mandatory (log Kow can be used instead of it). BCF experimental tests are expensive in term of time, animals and money. Thus several *in silico* models have been developed.

For the project **ANTARES** a list of these models has been completed. We checked the performance of many of them, considering a large set of chemicals. Separate results are discussed considering if the chemicals are inside and outside the training set of each model, when this information is available, and according to the applicability domain, when defined by the model itself.

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

## Materials and Methods

Experimental data on 860 compounds have been taken from the literature *[1,2,3,4,5]*.
Models have been evaluated on the basis of the predictions of continuous values, and as classifiers for the different thresholds.

## Results

**Table 1** shows the models we used and their performance for the total set of 860 compounds. We have to remember that the experimental uncertainty is about 0.6 log unit *[6, 7]*. Models which are simply based on logP equations gave worst results. EPISuite, T.E.S.T. and VEGA seem to perform better.

| Models | TOT | $R^2$ | ACC |
|---|---|---|---|
| ACD | 859 | 0.49 | 0.77 |
| EpiSuite ARNOT GOBAS | 859 | 0.69 | 0.91 |
| CORAL | 860 | 0.73 | 0.89 |
| LogP-Equations (ACD LogP) | 768 | 0.52 | 0.76 |
| LogP-Equations (EPI LogP) | 762 | 0.46 | 0.74 |
| EpiSuite MEYLAN | 859 | 0.67 | 0.85 |
| TEST | 833 | 0.72 | 0.90 |
| VEGA (CAESAR) | 860 | 0.63 | 0.89 |
| VEGA (MEYLAN) | 860 | 0.65 | 0.84 |

**Table 1**. Global comparison of model performances. Both regression ($R^2$) and classification (Accuracy) are shown.

**Figure 1** shows detailed results. Values are lower for the compounds not in the training set, as expected.

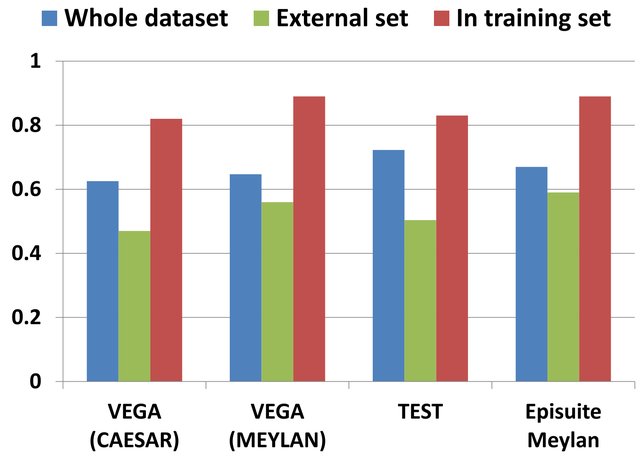


**Figure 1**. $R^2$ values considering chemicals which are inside or outside the training set. Only models for which this information is available are considered.

However, the results improve considering the chemicals inside the applicability domain of the model.
Unfortunately this information is not available for all models (**Figure 2**).

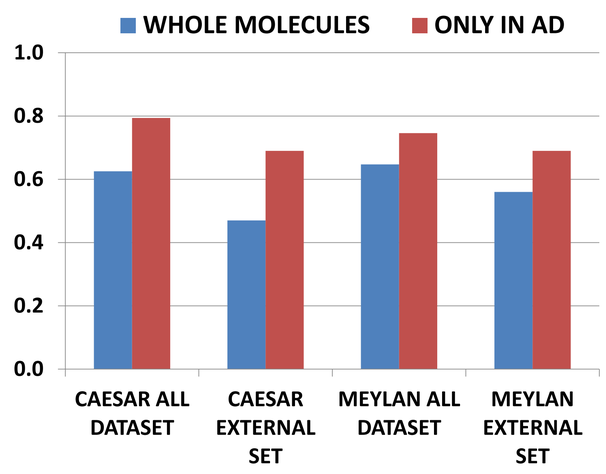


**Figure 2**. VEGA model $R^2$ values considering chemicals which are inside or outside the applicability domain.

Since EPISuite does not have an automatic system to evaluate the applicability domain, we implemented it within VEGA (http://www.vega-qsar.eu) and we applied the *VEGA applicability domain index*.
This is a quite valuable information, since the user can appreciate the expected reliability of the model according to the declared boundaries of the model.
The results on classification are biased by the low number of vB compounds, but also B are relatively low. Considering the prevalence of the chemicals in the different classes, **Figure 3** shows that VEGA gave reliable results, considering the applicability domain.

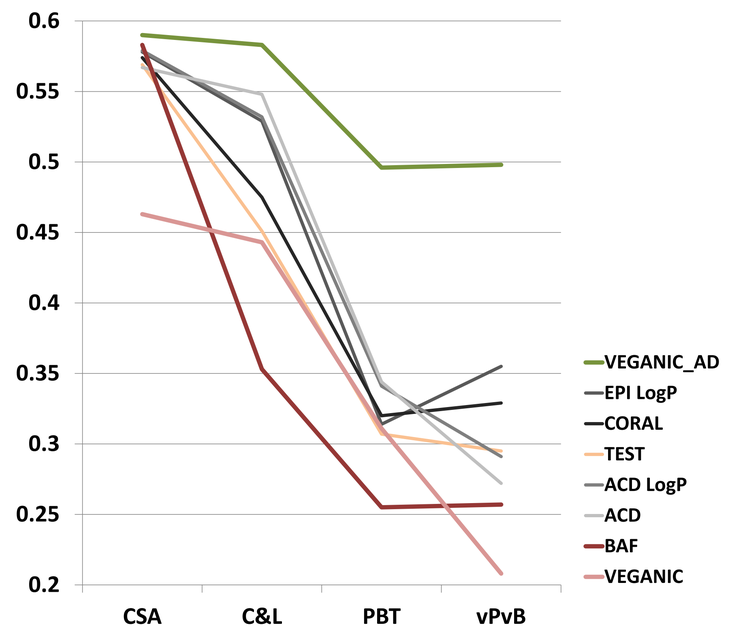


**Figure 3**. Model Scores based on a set of criteria to reduce the dependence on the number of compounds for each class.

## Conclusions

This evaluation shows that some QSAR models for BCF have reasonably good performance and can be useful for regulatory purposes. However, the user should use his own experience to evaluate the reliability of the prediction, with a careful consideration of the applicability domain and of the information provided by the software. This need is even more important in case of classification. Further studies about an integrated view of the output given by the best software are in progress with the aim to reduce error rate.

### REFERENCES

**1)** Arnot JA, Gobas FAPC (2006) A review of bioconcentration factor (BCF) and bioaccumulation factor (BAF) assessments for organic chemicals in aquatic organisms. Environ. Rev. 14: 257-297.
**2)** CEFIC LRI: http://www.cefic-lri.org/lri-toolbox/bcf
**3)** Dimitrov S, Dimitrova N, Parkerton T, Comber M, Bonnell M, Mekenyan O (2005). Base-line model for identifying the bioaccumulation potential of chemicals. SAR and QSAR in Environmental Research, 16 (6): 531-554.
**4)** Fu W, Franco A and Trapp S (2009). Methods for estimating the Bioconcentration Factor (BCF) of ionisable organic chemicals. Environ Toxicol Chem. 28(7): 1372–1379.
**5)** FOOTPRINT: http://www.eu-footprint.org/index.html
**6)** Lombardo A, Roncaglioni A, Boriani E, Milan C, Benfenati E. (2010) Assessment and validation of the CAESAR predictive model for Bioconcentration factor (BCF) in fish. Chemistry Central Journal, 4(Suppl 1):S1
**7)** Lombardo A, Roncaglioni A, Petoumenou MI, Nendza M, Benfenati E. Sources and data quality of the existing data for bioconcentration. SETAC Europe 21° Annual Meeting, 13-19 May 2011, Milan, Italy

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