	QMRF identifier (JRC Inventory): **To be entered by JRC**
	QMRF Title: **BCF model (CAESAR) (version 2.1.15)**
	Printing Date: **Apr 15, 2022**

1.QSAR identifier

1.1. QSAR identifier (title):

Model to predict bioconcentration factors (BCF) v 2.1.15.

1.2. Other related models:

Two models, model A and model B, have been used to build hybrid model, model C.

In the proposed approach, the outputs of the individual models (model A and B) were used as inputs of the hybrid model.

Model A was developed by Radial Basis Function Neural Networks (RBFNN) using a heuristic method to select the optimal descriptors; model B was developed by Radial Basis Function Neural Networks (RBFNN) using genetic algorithm for the descriptors selection.

1.3. Software coding the model:

The combined model C (hybrid) was built by an in house software made as PC-Windows Excel macro;

Codessa software, version 2.21 for HM (Heuristic Method);

Moby Digs, version 1.0 (http://www.talete.mi.it), genetic algorithm for GA-VSS (variable selection strategy);

RBFNN (Wan and Harrington, 1999)

2D descriptors: DRAGON version 5.4, MDL descriptors, ACD labs (version 9.08), Kowin (version 1.67)

2.General information

2.1. Date of QMRF:

April 2022

2.2. QMRF author(s) and contact details:

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2.3. Date of QMRF update(s):

NA

2.4. QMRF update(s):

2.5. Model developer(s) and contact details:

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2.6. Date of model development and/or publication:

2008

2.7. Reference(s) to main scientific papers and/or software package:

[1] Zhao, C., Boriani, E., Chana, A., Roncaglioni,A., Benfenati, E. A new hybrid system of QSAR models for predicting bioconcentration factors (BCF). Chemosphere (2008), 73, 1701-1707.

[2] Lombardo A, Roncaglioni A, Boriani E, Milan C, Benfenati E. Assessment and validation of the CAESAR predictive model for bioconcentration factor (BCF) in fish. Chemistry Central Journal (2010), 4 (Suppl 1).

[3] Benfenati E, Manganaro A, Gini G

VEGA-QSAR: AI inside a platform for predictive toxicology

Proceedings of the workshop "Popularize Artificial Intelligence 2013", December 5th 2013, Turin, Italy

Published on CEUR Workshop Proceedings Vol-1107

2.8. Availability of information about the model:

The hybrid model is available.

2.9. Availability of another QMRF for exactly the same model:

Other QMRF is not available

3.Defining the endpoint - OECD Principle 1

3.1. Species:

Fish species: Cyprinos Carpio and salmonids

3.2. Endpoint:

2.Environmental fate parameters 4. Bioconcentration 2.4.a.BCF fish

3.3. Comment on endpoint:

This endpoint is particularly required under REACH regulation. A good prediction for BCF endpoint may reduce the number of animal (fish)in experimental tests. REACH regulation states that a substance is identified as bioaccumulative (B) when BCF>2000 (log BCF>3.301) and very bioaccumulative (vB) when BCF>5000 (logBCF>3.699). Thus the endpoint could also be treated in classification and distinguish not B from v+vBcompounds (it is not possible to distinguish V from vB because of the high variability in experimental data). This hybrid model performed well as classifier for B and vB chemicals

3.4. Endpoint units:

no units (concentration/concentration)

3.5. Dependent variable:

Log BCF

3.6. Experimental protocol:

OECD TG 305 OECD GUIDELINES FOR TESTING OF CHEMICALS:

a) OECD TG 305A: Bioaccumulation:Sequential Static Fish Test, 1981
b) OECD TG 305B: Bioaccumulation: Semi-Static Fish Test 1981
c) OECD TG 305C: Bioaccumulation: Test for the Degree of Bioaccumulation in Fish, 1981
d) OECD TG 305D: Bioaccumulation: Static Fish Test, 1981
e) OECD TG 305E: Bioaccumulation: Flow-through Fish Test, 1981,
f) OECD TG 305: Bioconcentration: Flow-through Fish Test (1996) &
g) OECD TG 305: Bioaccumulation in Fish: Aqueous and Dietary Exposure (2012)

It is noted that all OECD TG 305 under point a) to e) above has been deleted but the versions from 1981 was used until 1996 when replaced by the joint version from 1996 (c.f. point f) above) which were then used until it was significantly updated in 2012 (c.f. point g above), to the version which has been employed since then.

3.7. Endpoint data quality and variability:

Variability of the test data: 0.75 log units (Dimitrov at al., 2005), reference in *section 9.2*

The data set of 511 compounds and the measured log BCF values were from Dimitrov et al. (2005) [1]. The biological data are of high quality. Values were obtained only according to official guidelines, which makes the data suitable for regulatory purposes, such as REACH.

All structures were checked one-by-one within the EC funded project CAESAR, by at least two scientists. For a quality check of the chemical information, using the molecule names and/or CAS numbers from the literature, we checked the two-dimensional (2D) chemical structures at five online databases: ChemFinder (http://chemfinder.cambridgesoft.com), ChemIDPlus (http://chem.sis.nlm.nih.gov/chemidplus/), Safe Nite (http://www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html), Biodegradability Database and Estimation (http://qsar.cerij.or.jp/cgi-bin/QSAR/index) and PubChem Compound (http://www.ncbi.nlm.nih.gov/sites/). Some ambiguities or errors were found. Some compounds were omitted according to the following criteria: (a) too little information to find the structure; (b) mixtures; (c) diastereo-isomers; (d) metal complexes; (e) some compounds were repeated in the original paper. We used the neutral form of salts. With diastereo-isomers we kept only one compound, using the average BCF value. The final database is composed of 473. The data set covers a wide range of log BCF and calculated log Kow (log BCF from −1.00 to 4.85; log Kow from −4.3 to 12.7), with molecular weights from 68 to 943. The 473 mono-constituent organic substances were randomly split into a training (n = 378) and a test set (n = 95) using Statistica 6.0 random number generator (http://www.statsoft.com)

The experimental BCF data collection includes historical fish BCF data based on previous versions of OECD TG 305 (c.f. point 3.6). But as these experimental data have undergone significant expert evaluations, it is generally believed that the BCF data collection employed in many cases may be of almost similar reliability as BCF data obtained by employing the newest OECD TG 305 version.

4.Defining the algorithm - OECD Principle 2

4.1. Type of model:

The hybrid model provides a quantitative prediction of bioconcentration factor (BCF) in fish (Cyprinos Carpio and salmonids), given in log(L/kg).

It is implemented inside the VEGA online platform, accessible at: https://www.vegahub.eu/

The model extends the original CAESAR model, previously available at http://www.caesar-project.eu, no longer supported

The basic idea of a hybrid model is that each model brings a different content of the complex system which is modelled. (Amaury et al., 2007)

4.2. Explicit algorithm:

If mean (value given by models to combine) > 2.410

log BCF = 1.052 * [mean (value given by models to combine)] - 0.065

If 1.355 < mean (value given by models to combine) ≤ 2.410

log BCF = 0.996 * [min (value given by models to combine)] + 0.042

Otherwise

log BCF = 0.936 * [mean (value given by models to combine)] - 0.123

4.3. Descriptors in the model:

[1] Moriguchi octanol-water partition coefficient (MlogP).

[2] Moran autocorrelation of lag 5, weighted by atomic van der Waals volumes (MATS5V): molecular descriptor calculated from the molecular graph by summing the products of atom weights of the terminal atoms of all paths of the considered path length (the lag).

[3] Number of chlorine atoms (Cl-089), Cl attached to carbon (sp2).

[4] Second highest eigenvalue of Burden matrix, weighted by atomic polarizabilities (BEHp2).

[5] Geary autocorrelation of lag 5, weighted by atomic van der Waals volumes (GATS5V): molecular descriptor calculated from the molecular graph by summing the products of atom weights of the terminal atoms of all paths of the considered path length (the lag).

[6] Solvation connectivity index chi-0 (XOSolv): molecular descriptor designed for modeling solvation entropy and describing dispersion interactions in solution.

[7] Sum of all -Cl groups E-state values in molecule (SsCl).

[8] Absolute eigenvalues sum from electronegativity weighted distance matrix (Aeige).

These descriptors are calculated within the VEGA software.

4.4. Descriptor selection:

The set of descriptors initially screened is made of 2D molecular descriptors, calculated by DRAGON version 5.4 (759 descriptors), MDL descriptors (249 descriptors), ACD labs version 9.08, (13 descriptors) and KOWIN (1 descriptor).

Thus, 1022 descriptors were obtained including different logP and logD values calculated with these programs.

Heuristic and genetic algorithm methods were then used to select the optimal descriptors.

4.5. Algorithm and descriptor generation:

Multiple Linear Regression (MLR) was used to develop the linear model of the property of interest, with CODESSA software.

Radial Basis Function Neural Network (RBFNN) (Wan and Harrington, 1999) was used with a Matlab function for building the models. This function and result files containing the models are available on request. The hybrid model approach is based on the idea of using more representations of the problem, more paradigms of knowledge representation, and more algorithms to find a solution. As in other cases (Lo Piparo, 2006; Amaury et al., 2007), the outputs of the individual models were used as inputs of the hybrid model.

4.6. Software name and version for descriptor generation:

DRAGON, version 5.4

Calculation of several sets of molecular descriptors from molecular geometries (topological, geometrical, WHIM, 3D-MoRSE, molecular profiles, etc.)

Prof. R.Todeschini - distributed by Talete srl, via Pisani 13, 20124 Milano, Italyhttp://www.talete.mi.it

Then, the model in VEGA has implemented the descriptors internally.

4.7. Chemicals/Descriptors ratio:

378 chemicals training/8 descriptors = 47

5.Defining the applicability domain - OECD Principle 3

5.1. Description of the applicability domain of the model:

Outliers where these classes of compounds: perfluorinated sulfonic acid derivatives, phosphonothioate, phosphorothioate, compounds including thioester functions, compound highly reactive and highly degradable by humidity and light, i.e double peroxide, and Michael acceptor with high probability of reacting with a carbanion, compound with high degree of topological symmetry. Within CAESAR a special tool was developed for all models. This tool, available at the website, shows the six most similar compounds present in our data set, and the related experimental and predicted values. In this way the user can have a direct, transparent, and clear assessment of the errors for similar compounds, and thus have a good basis for the evaluation of the applicability domain specific for a certain compound. Indeed, this information is related to the compound of interest.

For this model the ADI is calculated based on the AD indices under point 5.2 below in this way:

Indices are calculated on the first k = 2 most similar molecules, each having S_k similarity value with the target molecule.

Similarity index (*IdxSimilarity*) is calculated as:

$$\frac{\sum_k S_k}{k} \times (1 - Diam^2)$$

where *Diam* is the difference in similarity values between the most similar molecule and the *k*-th molecule.

Accuracy index (*IdxAccuracy*) is calculated as:

$$\frac{\sum_c^k |exp_c - pred_c|}{k}$$

where exp_c is the experimental value of the c-*th* molecule in the training set and $pred_c$ is the c-*th* molecule predicted value by the model.

Concordance index (*IdxConcordance*) is calculated as:

$$\frac{\sum_c^k |exp_c - pred_{target}|}{k}$$

where exp_c is the experimental value of the c-*th* molecule in the training set and $pred_{target}$ is the predicted value for the input target molecule.

Max Error index (*IdxMaxError*) is calculated as:

$$max(|exp_c - pred_c|)$$

where exp_c is the experimental value of the c-*th* molecule in the training set and $pred_{target}$ is the predicted value for the input target molecule, evaluated over the k molecules.

ACF contribution (*IdxACF*) index is calculated as

$$ACF = rare \times missing$$

where: *rare* is calculated on the number of fragments found in the molecule and found in the training set in less than 3 occurences as following: if the number is 0, *rare* is set to 1.0; if the number is 1, *rare* is set to 0.6; otherwise *rare* is set to 0.4

missing is calculated on the number of fragments found in the molecule and never found in the training set as following: if the number is 0, *missing* is set to 1.0; if the number is 1, *missing* is set to 0.6; otherwise *missing* is set to 0.4

Descriptors Range (*IdxDescRange*) index is calculated as 1.0 if all molecular descriptors used in the prediction fall within the range of descriptors used in the whole training set, 0.0 otherwise.

AD final index is calculated as following:

$$ADI = IdxSimilarity \times IdxACF \times IdxDescRange$$

The initialADI index is the used together with the other sub-indices to calculate the final ADI, on the basis of the assessment class in which each sub-index falls:

IdxAccuracy ≥	IdxConcordance ≥	IdxMaxError ≥	InitialADI ≥	ADI
1.0	1.0	1.0	0.85	1.0
0.5	0.5	0.5	0.75	0.85
All other cases				0.75

The ADI is defined in this way for this QSAR model´s predictions:

If 1 ≥ AD index > 0.85, the predicted substance is regarded in the Applicability Domain of the model. It corresponds to “good reliability” of prediction.

If 0.85 ≥ AD index > 0.75, the predicted substance could be out of the Applicability Domain of the model. It corresponds to “moderate reliability” of prediction.

If AD index ≤ 0.75, the predicted substance is regarded out of the Applicability Domain of the model. It corresponds to “low reliability” of prediction.

5.2. Method used to assess the applicability domain:

The AD and the chemical similarity is measured with the algorithm developed for VEGA. Full details are in the VEGA website (www.vegahub.eu), including the open access paper describing it [11]. The VEGA AD also evaluates the correctness of the prediction on similar compounds (accuracy), the consistency between the predicted value for the target compound and the experimental values of the similar compounds, the range of the descriptors, and the presence of unusual fragments, using atom centred fragments.

These indices are defined in this way for this QSAR model:

Similar molecules with known experimental value:

This index takes into account how similar are the first two most similar compounds found. Values near 1 mean that the predicted compound is well represented in the dataset used to build the model, otherwise the prediction could be an extrapolation. Defined intervals are:

If 1 ≥ index > 0.9, strongly similar compounds with known experimental value in the training set have been found

If 0.9 ≥ index > 0.75, only moderately similar compounds with known experimental value in the training set have been found

If index ≤ 0.75, no similar compounds with known experimental value in the training set have been found

Accuracy (average error) of prediction for similar molecules:

This index takes into account the classification accuracy in prediction for the two most similar compounds found. Values near 1 mean that the predicted compounds fall in an area of the model's space where the model gives reliable predictions (no misclassifications), otherwise the lower is the value, the worse the model behaves. Defined intervals are:

If index < 0.5, accuracy of prediction for similar molecules found in the training set is good

If 1.0 ≥ index ≥ 0.5, accuracy of prediction for similar molecules found in the training set is not optimal

If index > 1.0, accuracy of prediction for similar molecules found in the training set is not adequate

Concordance for similar molecules:

This index takes into account the difference between the predicted value and the experimental values of the two most similar compounds. Values near 0 mean that the prediction made disagrees with the values found in the model's space, thus the prediction could be unreliable. Defined intervals are:

If index < 0.5, molecules found in the training set have experimental values that agree with the target compound predicted value

If 1.0 ≥ index ≥ 0.5, similar molecules found in the training set have experimental values that slightly disagree with the target compound predicted value

If index > 1.0, similar molecules found in the training set have experimental values that completely disagree with the target compound predicted value

Maximum error of prediction among similar molecules:

This index takes into account the maximum error in prediction among the two most similar compounds. Values near 0 means that the predicted compounds fall in an area of the model's space where the model gives reliable predictions without any outlier value. Defined intervals are:

If index < 0.5, the maximum error in prediction of similar molecules found in the training set has a low value, considering the experimental variability

If 1.0 ≥ index ≥ 0.5, the maximum error in prediction of similar molecules found in the training set has a moderate value, considering the experimental variability

If index > 1.0, the maximum error in prediction of similar molecules found in the training set has a high value, considering the experimental variability

Atom Centered Fragments similarity check:

This index takes into account the presence of one or more fragments that aren't found in the training set, or that are rare fragments. First order atom centered fragments from all molecules in the training set are calculated, then compared with the first order atom centered fragments from the predicted compound; then the index is calculated as following: a first index RARE takes into account rare fragments (those who occur less than three times in the training set), having value of 1 if no such fragments are found, 0.85 if up to 2 fragments are found, 0.7 if more than 2 fragments are found; a second index NOTFOUND takes into account not found fragments, having value of 1 if no such fragments are found, 0.6 if a fragments is found, 0.4 if more than 1 fragment is found. Then, the final index is given as the product RARE * NOTFOUND. Defined intervals are:

If index = 1, all atom centered fragment of the compound have been found in the compounds of the training set

If 1 > index ≥ 0.7, some atom centered fragment of the compound have not been found in the compounds of the training set or are rare fragments

If index < 0.7, a prominent number of atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments

Model descriptors range check:

This index checks if the descriptors calculated for the predicted compound are inside the range of descriptors of the training and test set. The index has value 1 if all descriptors are inside the range, 0 if at least one descriptor is out of the range. Defined intervals are:

Index = TRUE, descriptors for this compound have values inside the descriptor range of the compounds of the training set

Index = FALSE, descriptors for this compound have values outside the descriptor range of the compounds of the training set

5.3. Software name and version for applicability domain assessment:

VEGA (www.vegahub.eu)

5.4. Limits of applicability:

See outliers description in 7.9

6.Internal validation - OECD Principle 4

6.1. Availability of the training set:

Yes

6.2. Available information for the training set:

CAS RN: Yes

Chemical Name: Yes

Smiles: Yes

Formula: No

INChI: No

MOL file: No

6.3. Data for each descriptor variable for the training set:

All

6.4. Data for the dependent variable for the training set:

All

6.5. Other information about the training set:

Classification for REACH for compounds v+vB and notB.

6.6. Pre-processing of data before modelling:

6.7. Statistics for goodness-of-fit:

After the implementation in VEGA:

Training set: n = 378; R^2 = 0.81; RMSE = 0.58

6.8. Robustness - Statistics obtained by leave-one-out cross-validation:

6.9. Robustness - Statistics obtained by leave-many-out cross-validation:

Leave many out (20%) cross validation models (20% of the compounds on the training set were randomly selected (sub-test set) and a model developed with the remaining ones (sub-training set). This procedure was repeated 10 times. Results is: Rcv^2= 0.79 SDEP = 0.66

6.10. Robustness - Statistics obtained by Y-scrambling:

6.11. Robustness - Statistics obtained by bootstrap:

6.12. Robustness - Statistics obtained by other methods:

7.External validation - OECD Principle 4

7.1. Availability of the external validation set:

Yes

7.2. Available information for the external validation set:

CAS RN: Yes

Chemical Name: Yes

Smiles: Yes

Formula: No

INChI: No

MOL file: No

7.3. Data for each descriptor variable for the external validation set:

All

7.4. Data for the dependent variable for the external validation set:

All

7.5. Other information about the external validation set:

Classification for REACH for compounds v+vB and notB.

7.6. Experimental design of test set:

See 6.9

Later, the model was validated with external test as described in [2].

7.7. Predictivity - Statistics obtained by external validation:

Test set: n = 95; R^2 = 0.78; RMSE = 0.62

Test set in AD: n = 31; R^2 = 0.85; RMSE = 0.52

Test set could be out of AD: n = 34; R^2 = 0.75; RMSE = 0.60

Test set out of AD: n = 30; R^2 = 0.67; RMSE = 0.72

Only five of the outliers (55, 57, 90, 291, 476) are false negatives (see 5.1 applicability domain)

7.8. Predictivity - Assessment of the external validation set:

In view of the large number of chemicals, the random splitting for training and test set does not affect the predictivity of the model

7.9. Comments on the external validation of the model:

NA

8.Providing a mechanistic interpretation - OECD Principle 5

8.1. Mechanistic basis of the model:

The model largely relies on logP, which typically is the main descriptor used for BCF. Corrections are applied to balance the use of the specific logP calculator, MLogP. Indeed, this particular descriptor gives good results when chemicals contain C,N,O, but it may be less accurate in case of compounds with other atoms, like Cl and P.

8.2.A priori or a posteriori mechanistic interpretation:

The mechanistic interpretation of the model is provided a posteriori i.e. by interpretation of the final set of the selected descriptors

8.3. Other information about the mechanistic interpretation:

NA

9.Miscellaneous information

9.1. Comments:

Prediction accuracy was 98%, sensitivity 96%, specificity 100% and geometric mean 0.98. Thus, the hybrid model also performed well as a classifier for “B” and “vB” chemicals.

9.2. Bibliography:

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[3] Zhao, C., Boriani, E., Chana, A., Roncaglioni,A., Benfenati, E. A new hybrid system of QSAR models for predicting bioconcentration factors (BCF). Chemosphere (2008), 73, 1701-1707.

[4] Lombardo A, Roncaglioni A, Boriani E, Milan C, Benfenati E. Assessment and validation of the CAESAR predictive model for bioconcentration factor (BCF) in fish. Chemistry Central Journal (2010), 4 (Suppl 1)

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a) ECD TG 305A: Bioaccumulation:Sequential Static Fish Test, 1981
b) OECD TG 305B: Bioaccumulation: Semi-Static Fish Test 1981
c) OECD TG 305C: Bioaccumulation: Test for the Degree of Bioaccumulation in Fish, 1981
d) OECD TG 305D: Bioaccumulation: Static Fish Test, 1981
e) OECD TG 305E: Bioaccumulation: Flow-through Fish Test, 1981,
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g) OECD TG 305: Bioaccumulation in Fish: Aqueous and Dietary Exposure. Paris: Organisation for Economic Co-operation and Development, 2012. https://www.oecd-ilibrary.org/environment/test-no-305-bioaccumulation-in-fish-aqueous-and-dietary-exposure_9789264185296-en.

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9.3. Supporting information:

Training set(s)Test set(s)Supporting information:

10.Summary (JRC QSAR Model Database)

10.1. QMRF number:

To be entered by JRC

10.2. Publication date:

To be entered by JRC

10.3. Keywords:

To be entered by JRC

10.4. Comments:

To be entered by JRC