	QMRF identifier (JRC Inventory): **To be entered by JRC**
	QMRF Title: **Insubria QSAR PaDEL-Descriptor model for prediction of metabolic biotranformation half-life in fish. (Split 1)** **Keywords: Biotransformation rate; metabolic half-life; QSAR; consensus modelling; risk assessment; chemical prioritization.**
	Printing Date: **30-gen-2018**

1.QSAR identifier

1.1.QSAR identifier (title):

Insubria QSAR PaDEL-Descriptor model for prediction of metabolic biotranformation half-life in fish. (Split 1)

Keywords: Biotransformation rate; metabolic half-life; QSAR; consensus modelling; risk assessment; chemical prioritization.

1.2.Other related models:

T.Brown, J.A. Arnot, F. Wania, Iterative fragment selection: a group contribution approach to predictiong fish biotrasformation half-lives. Environ Sci Technol. 2012; 46:8253-60 [1]

E. Papa, L. van der Wal, J.A. Arnot, P. Gramatica, Metabolic biotransformation half-lives in fish: QSAR modelling and consensus analysis. STOTEN. 2014;470-471:1040-1046 [2]

1.3.Software coding the model:

PaDEL-Descriptor 2.18

A software to calculate molecular descriptors and fingerprints [3]

http://padel.nus.edu.sg/software/padeldescriptor/index.html

QSARINS 2.0

Software for the development, analysis and validation of QSAR MLR models [4,5]

paola.gramatica@uninsubria.it

www.qsar.it

HyperChem ver.7.3

Software used to design, check and optimize chemical structures.

Instant JChem 5.5.0

software for calculating acid and basic pKas

Http://www.chemaxon.com

ACD Labs 12.5

software for calculating acid and basic pKas

2.General information

2.1.Date of QMRF:

02/10/17

2.2.QMRF author(s) and contact details:

[1]Alessandro Sangion DiSTA, University of Insubria (Varese - Italy) alessandro.sangion@uninsubria.it www.qsar.it

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2.3.Date of QMRF update(s):

2.4.QMRF update(s):

2.5.Model developer(s) and contact details:

[1]Ester Papa DiSTA, University of Insubria (Varese - Italy) ester.papa@uninsubria.it www.qsar.it

[2]Paola Gramatica DiSTA, University of Insubria (Varese - Italy) paola.gramatica@uninsubria.it www.qsar.it

[3]Leon van der Wal REACH Mastery, Como, Italy

[4]Jon A. Arnot ARC Arnot Research & Consulting, Toronto, ON, Canada ; Department of Physical and Environmental Science, University of Toronto, ON, Canada

2.6.Date of model development and/or publication:

2013/2014

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

[1]Gramatica P., et al. QSARINS: A new software for the development, analysis and validation of QSAR MLR models, J. Comput. Chem. (Software News and Updates), 2013, 34 (24), 2121-2132 [4]

[2]Gramatica P., et al. QSARINS-Chem: Insubria Datasets and New QSAR/QSPR Models for Environmental Pollutants in QSARINS, submitted to J. Comput. Chem. (Software News and Updates), 2013. [5]

[3]Papa E., et al. Metabolic biotransformation half-lives in fish: QSAR modelling and consensus analysis, STOTEN. 2014;470-471:1040-1046 [2]

[4]Yap, C.W. PaDEL descriptor: an open source software to calculate molecular descriptors and fingerprints., J. Comput. Chem. 2011 32, 1466-1474 [3]

2.8.Availability of information about the model:

Non-proprietary. Defined algorithm, available in QSARINS [4, 5]. Training and prediction sets are available in the attached sdf file of this QMRF (section 9) and in the QSARINS-Chem database [5].

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

No other information available.

3.Defining the endpoint - OECD Principle 1

3.1.Species:

Range of fish species, body sizes and temperatures were normalized.

3.2.Endpoint:

Bioaccumulation Metabolic biotransformation in fish

3.3.Comment on endpoint:

The biotransformation rate constants from a range of fish species, body sizes and temperatures were normalized to rate constants for fish with a body weight of 0.01kg at 15°C

3.4.Endpoint units:

km (day^{-1}) rate was converted to normalized biotransformation half-life value (HL_ndays), and then expressed in base 10 log

units $LogHL_n$

3.5.Dependent variable:

Log (HL_n)

3.6.Experimental protocol:

No information available

3.7.Endpoint data quality and variability:

A mass balance method was developed to estimate in vivo whole body metabolic biotransformation rate costants in fish from laboratory bioaccumulation data. The method includes a screening level uncertainty analysis for the km estimates and was applied to a database of evaluated laboratory bioaccumulation test data to derive an in vivo km database.

4.Defining the algorithm - OECD Principle 2

4.1.Type of model:

QSAR - Multiple linear regression model (OLS - Ordinary Least Square)

4.2.Explicit algorithm:

LogHLn (fish biotransformation half-life)_Split-1

OLS-MLR method. Model developed on a training set of 421 compounds

LogHLn (fish biotransformation half-life)_Full Model

OLS-MLR method. Model developed on a training set of 632 compounds

Split-1 model equation: $LogHL_n$= -4.081 + 1.082 VAdjMat - 0.122 gmax - 0.205 nHBAcc + 0.119 nX - 0.116 SaaaC + 0.387 FP503 + 2.294 FP29 - 0.666 minHBd + 0.241 ndSCH

Full model Equation: $LogHL_n$= -4.1059 + 1.096 VAdjMat - 0.1284 gmax - 0.1785 nHBAcc + 0.1116 nX - 0.118 SaaaC + 0.3938 FP503 + 2.098 FP29 - 0.6584 minHBd + 0.1606 ndSC

4.3.Descriptors in the model:

[1]VAdjMat Vertex adjacency index

[2]nX Number of halogens

[3]minHBd Minimum E-States for (strong) Hydrogen Bond donors

[4]gmax maximum electrotopological state

[5]SaaaC sum of atom-type E-state

[6]nHBAcc number of hydrogen bond acceptor (using CDK algorithm)

[7]ndSCH count of atom-type =CH-

[8]FP29 count of individual chemical atoms 2Si

[9]FP503 simple smart pattern Cl-C:C-[#1]

4.4.Descriptor selection:

A total of 1567 molecular descriptors of differint types (0D, 1D, 2D) and fingerprints were calculated in PaDEL-Descriptor 2.18. Constant and semi-constant values and descriptors found to be correlated pairwise were excluded in a pre-reduction step (one of any two descriptors with a correlation greater than 0.98 was removed to reduce redundant information), and a final set of 520 molecular descriptors were used as input variables for variable subset selection. The models were initially

developed by the all-subset-procedure, and then GA was applied to obtain the final population of models (nine variables). The optimized parameter used was Q^2_{LOO}(leave-one-out).

4.5.Algorithm and descriptor generation:

Multiple linear regression (Ordinary Least Square method) was applied to generate the model.

Molecular descriptors were generated by PaDEL-Descriptor software. The input files for descriptor calculation contain information on atom and bond types, presence of halogens, E-state energy, electrotopological state,molecular dimension and hydrofobicity.

4.6.Software name and version for descriptor generation:

PaDEL-Descriptor 2.18

A software to calculate molecular descriptors and fingerprints [3]

Yap Chun Wei, Department of Pharmacy, National University of Singapore.

http://padel.nus.edu.sg/software/padeldescriptor/index.html

HYPERCHEM - ver. 7.03

Software for molecular drawing and conformational energy optimization

4.7.Chemicals/Descriptors ratio:

Split: 421 chemicals / 9 descriptors = 46.8

Full model: 632 chemicals / 9 descriptors = 70.2

5.Defining the applicability domain - OECD Principle 3

5.1.Description of the applicability domain of the model:

The applicability domain of the model was verified by the identification of response outliers (i.e.compounds with cross-validated standardized residuals greater than 2.5 standard deviation units) and structural outliers with leverage value (h) greater than 3p'/n (h*) (where p' is the number of model variables plus one, and n is the number of the objects used to calculate the model). The applicability domain was also graphically investigated through the William plot of hat value versus standardized residuals.

Response and descriptor space:

Range of experimental $LogHL_n$values: -1.56 / 3

Range of descriptor values: VAdjMat 2.58 / 6.75 ; nX 0 /12 ; minHBd 0 / 0.91 ; gmax 1.35 / 14.8 ; SaaaC 0 / 10.9 ; nHBAcc 0 / 11; FP503 0 / 1 ; FP29 0 / 1 ; ndSCH 0 / 6 .

5.2.Method used to assess the applicability domain:

As it has been stated in section 5.1, the structural applicability domain of the model was assessed by the leverage approach, providing a cut-off hat value (h*=0.0475). HAT values are calculated as the diagonal elements of the HAT matrix:

$H = X(X^TX)^{-1}X^T$

The response applicability domain can be verified by the standardized

residuals in cross-validation greater than 2.5 standard deviation units.

5.3.Software name and version for applicability domain assessment:

QSARINS 2.0

Software for the development, analysis and validation of QSAR MLR models

paola.gramatica@uninsubria.it

www.qsar.it

5.4.Limits of applicability:

FULL model domain: Outliers for structure, hat>3p'/n(h*):
Octaethylene glycol monotridecyl ether, Benzo[a]pyrene,
Dibenzo[a,h]anthracene, 'Cyclohexene,4-ethenyl-',
Tetradecamethylcycloheptasiloxane (D7), PeryleneBenzo(k)fluoranthene,
Benzo[b]chrysene, Dodecamethylcyclohexasiloxane (D6),
Decamethylcyclopentasiloxane (D5), Cyclotetrasiloxane, octamethyl-,
1,5,9-cyclododecatriene, Ethylidene norbornene, 175 Factor L, 175 Factor
J, Spinosad Factor D, Spinosad Factor A.
Outliers for response, standardised residuals > 2.5 standard deviation
units: Benzene, 1,1,1-(chloromethylidyne)tris-, Cyclohexane,
1,2,3,4,5-pentabromo-6-chloro-, Dibenzofuran,
2,4-Dichloro-1-(trifluoromethyl)benzene, Phenol,
2,4,6-tris(1,1-dimethylethyl)-, Pentachloroanisole,
1,4-dichloronaphthalene, 1,3,5-trimethyl cyclohexane,
'Oxirane,[(dibromomethylphenoxy)methyl]-', Cis 1,1,3,5 tetramethyl
cyclohexane, Isodecanol.

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

NanoMaterial: null

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:

To verify the predictive capability of the proposed models, the dataset
(n=632) was split, before model development, into a training set used
for model development and a prediction set used later for external
validation, in a 2:1 prportion using different approach, analyzing
structural similarity so that both sets would cover the same structural
domain (n training=421 , n prediction=211). The range of LogHLn are:

-1.57 / 3

6.6.Pre-processing of data before modelling:

Transformation of km (day^{-1}) into LogHLn (day)

6.7.Statistics for goodness-of-fit:

Ordered response split model:

R^2= 0.74 ; CCC_{tr}[6,7]=0.85; RMSE= 0.60

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

Ordered response Split model:

Q^2_{LOO}= 0.73 ; CCC_{cv}= 0.84 ; $RMSE_{cv}$= 0.61

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

Q^2_{LMO}= 0.75

6.10.Robustness - Statistics obtained by Y-scrambling:

R^2_{yscr}= 0.02

6.11.Robustness - Statistics obtained by bootstrap:

No information available

6.12.Robustness - Statistics obtained by other methods:

No information available

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

NanoMaterial: null

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:

To verify the predictive capability of the proposed models, the dataset (n=632) was split, before model development, into a training set used for model development and a prediction set used later for external validation, in a 2:1 prportion using different approach, analyzing structural similarity so that both sets would cover the same structural domain (n training=421 , n prediction=211); the range of $LogHL_n$are: -1.33 / 2.79

7.6.Experimental design of test set:

The splitting was the same as the one used previously by Arnot (Arnot et al., 2009)[8]

7.7.Predictivity - Statistics obtained by external validation:

Ordered response split model:

Q^2_{extF1}[9]= 0.76; Q^2_{extF2}[10]=
0.76 ; Q^2_{extF3}[11]= 0.77; CCC_{ex}=0.87;
RMSE= 0.56

7.8.Predictivity - Assessment of the external validation set:

The splitting methodology based on similarity analysis allowed for the selection of meaningful training sets and representative prediction sets. Training and prediction sets are balanced according to structure . In particular, for response the range of $LogHL_n$values are [-1.57 /3] and [-1.33 / 2.79] respectively for training and prediction sets.

As much as concern structural representativity, the range of descriptors values is:

nX: training set (0 / 12), prediction set (0 / 9);
SaaaC: training set (0 / 10.82), prediction set (0 / 10.88);
minHBd: training set (0 / 0.753), prediction set (0 / 0.915);
nHBAcc: training set (0 / 11), prediction set (0 / 11);
ndSCH: training set (0 / 6), prediction set (0 / 3);
gmax: training set (1.35 / 14.76), prediction set (1.348 / 14.70);
VAdjMAT: training set (2.58 / 6.75), prediction set (2.58 / 6.72);
FP29: training set (0 / 1), prediction set (0 / 1);
FP503: training set (0 / 1), prediction set (0 / 1);

7.9.Comments on the external validation of the model:

no other information available

8.Providing a mechanistic interpretation - OECD Principle 5

8.1.Mechanistic basis of the model:

The model was developed by statistical approach. No mechanistic basis for this physico-chemical property was set a priori, but a mechanistic interpretation of molecular descriptors was provided a posteriori (see 8.2).

8.2.A priori or a posteriori mechanistic interpretation:

The most relevant descriptors for the modeling of the selected response are the vertex adjacemcy index (VAdjMAT), the number of haogens (nX) and the minumun E-state energy for hydrogen bond donors (minHBd). The first two descriptors gave information abut molecular dimension, hydrophobicity and presence of halogen atoms; the correlation among VAdjmat e LogKow is 62%, and the correlation among nX and VAdjMAT and molecular weight is 61% and 75% respectively. The last descriptor describes the ability of the chemical to participate in intramoleular interactions. Two other important descriptors are the maximum electrotopological state (gmax), the sum of atom-type E-state which describes the number of ring juncture carbons in fused rings (SaaaC). Also there are other variables selected in the proposed model encode for specific information related to structural domains, atoms fingerprints, functional groups and bonds. Moving from slowly biotransformated chemicals to chemicals that are relatively quickly

biotransformated, is observed an increase in gmax and minHBd values while VAdjMAT and nX values decrease; in particular most of the slowly metabolized compounds have VAdjMAT values between 4.5 and 6, gmax values between 1 and 3, and minHBd = 0. This means that in the current dataset, slower biotransformation is associated to chemicals with no, or limited, ability to participate in non-covalent intramolecuar interactions. These chemicals are characterized by large hydrophobic, halogenated structures, with few or no ramifications, and one or more aromatic rings. The increasing presence of polar and ionizable groups as well as the number and variety of reactive functional groups simultaneously present in the molecule is generally associated with faster biotransformation rates (shorter HL_n)

8.3.Other information about the mechanistic interpretation:

no other information available

9.Miscellaneous information

9.1.Comments:

Given the good results of the external validation, this model has a good applicability domain and therefore unsuccessful applications are probably very reduced. Anyhow, the check of outliers by the Williams plot and the Insubria graph for chemicals without experimental data will allow to verify the model applicability. To predict $LogHL_n$for new chemicals without experimental data, it is suggested to apply the equation of the full model, developed on all the available chemicals (n training = 632)$LogHL_n$ = -4.1059 + 1.096 VAdjMat - 0.1284 gmax - 0.1785 nHBAcc + 0.1116 nX - 0.118 SaaaC + 0.3938 FP503 + 2.098 FP29 - 0.6584 minHBd + 0.1606 ndSC

n training set =632 ; R^2= 0.75 ; Q^2_{LOO}= 0.74 ; $Q^2_{lmo30\%}$= 0.72 ; CCC_{tr}= 0.86 ; CCC_{cv}= 0.85 ; $RMSE_{tr}$= 0.58 ; $RMSE_{cv}$= 0.59

9.2.Bibliography:

[1]T.Brown, J.A. Arnot, F. Wania, Iterative fragment selection: a group contribution approach to predictiong fish biotrasformation half-lives. Environ Sci Technol. 2012; 46:8253-60

[2]E. Papa, L. van der Wal, J.A. Arnot, P. Gramatica, Metabolic biotransformation half-lives in fish: QSAR modelling and consensus analysis. STOTEN. 2014;470-471:1040-1046

[3]Yap C. PaDEL-Descriptor: an open source software to calculate molecular desctriptors and fingerprints. J Comput Chem. 2011;32:1466-74

[4]Gramatica P., et al. QSARINS: A new software for the development, analysis and validation of QSAR MLR models, J Comput Chem (Software News and Updates). 2013, 34 (24), 2121-2132

[5]Gramatica P., et al. QSARINS-Chem: Insubria Datasets and New QSAR/QSPR Models for Environmental Pollutants in QSARINS, submitted to J Comput Chem (Software News and Updates). 2013.

[6]Chirico N., Gramatica P., Real external predictivity of QSAR models: how to evaluate it? Comparison of different validation criteria and proposal of using the concordance correlation coefficient. J Chem Inf Model. 2011;51:2320-2335

[7]Chirico N., Gramatica P., Real external predictivity of QSAR models. Part 2. New intercomparable thresholds for different validation criteria and the need for scatter plot inspection. J Chem Inf Model. 2012;52:2044-2058

[8]Arnot J.A., Meylan W., Tunkel J., Howard P., Macklay D., Bonnell M., et al. Quantitative structure activity relationship for predicting metabolic biotransformation rates for organic chemicals in fish. Environ Toxicol Chem. 2009;28:1168-1177

[9]Shi L.M. et al. QSAR models using a large diverse set of estrogens, J Chem Inf Comput Sci. 2001;41:186-195

[10]Schuurman G. et al. External validation and prediction employing the predictive squared correlation coefficient - Test set activity mean vs training set activity mean, J Chem Inf Model. 2008;48:2140-2145

[11]Consonni V., Ballabio D., Todeschini R., Comments on the definition of the Q2 parameter for QSAR validation. J Chem Inf Model. 2009;49:1669-1678

9.3.Supporting information:

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

10.Summary (JRC Inventory)

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