	QMRF identifier (JRC Inventory): **To be entered by JRC**
	QMRF Title: **Total body elimination half-life (QSARINS) (version 1.0.1)**
	Printing Date: **06-02-2022**

1.QSAR identifier

1.1.QSAR identifier (title):

Total body elimination half-life (QSARINS) (version 1.0.1)

1.2.Other related models:

[1] S. Cassani, P. Gramatica, Identification of potential PBT behavior of personal care products by structural approaches. Sustain Chem Pharm, 2015;1:19-27

[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] A. Sangion, P. Gramatica, PBT assessment and prioritization of contaminants of emerging concern: pharmaceuticals. Environ Res, 2016a;147:297-306 [3]

1.3.Software coding the model:

PaDEL-Descriptor 2.18

A software to calculate molecular descriptors and fingerprints

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

QSARINS 2.0

Software for the development, analysis and validation of QSAR MLR models [5,6]

paola.gramatica@uninsubria.it

www.qsar.it

VEGA (https://www.vegahub.eu/)

The VEGA software provides QSAR models to predict tox, ecotox, environ, phys-chem and toxicokinetic properties of chemical substances.

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2.General information

2.1.Date of QMRF:

February 2022

2.2.QMRF author(s) and contact details:

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2.3.Date of QMRF update(s):

No update

2.4.QMRF update(s):

No update

2.5.Model developer(s) and contact details:

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

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[1] Emilio Benfenati Istituto di Ricerche Farmacologiche Mario Negri - IRCSS Via Mario Negri 2, 20156 Milano, Italy (Emilio.benfenati@marionegri.it) https://www.marionegri.it/

2.6.Date of model development and/or publication:

2016/2017

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

[1] S. Cassani, P. Gramatica, Identification of potential PBT behavior of personal care products by structural approaches. Sustain Chem Pharm, 2015;1:19-27

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

[3] A. Sangion, P. Gramatica, PBT assessment and prioritization of contaminants of emerging concern: pharmaceuticals. Environ Res, 2016a;147:297-306

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

[5] 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

[6] Gramatica P., et al. QSARINS-Chem: Insubria Datasets and New QSAR/QSPR Models for Environmental Pollutants in QSARINS, J. Comput. Chem. (Software News and Updates), 2014, 35, 1036-44.

[7] J.A. Arnot, T.N. Brown, F. Wania, Estimating screening-level organic chemical half-lives in humans. Environ Sci Technol, 2014; 48:723-730

[8] 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 model is non-proprietary and the training set is available.

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

Another QMRF is not available.

3.Defining the endpoint - OECD Principle 1

3.1.Species:

Human

3.2.Endpoint:

2. 4.a. Bioconcentration . BCF fish EC C.13 Bioconcentration: Flow-through Fish Test

3.3.Comment on endpoint:

This study addresses the development of QSAR models for the prediction of total body elimination half-lives. The first aim of this work is the creation of statistically valid and predictive models for the prediction of

half-lives in human; the second aim is to show how QSAR predictions can be used for the refinement of chemical screening procedures for hazard assessment.

3.4.Endpoint units:

kT (h-1) rate was converted to normalized biotransformation half-life value (HLT, h), and then expressed in base 10 log units LogHLT

3.5.Dependent variable:

Log(HLT)

3.6.Experimental protocol:

NA

3.7.Endpoint data quality and variability:

The dataset was taken from literature (J.A. Arnot, T.N. Brown, F. Wania, Estimating screening-level organic chemical half-lives in human. Environ Sci Technol. 2014; 48:723-730)

The HL dataset consists of the union of several datasets to obtain a variety of discrete organic chemical structures with a range of HL values.

Initially the dataset was composed of 1900 measured or estimated HLs for chemicals in human adults. Approximately 380 HLs were deemed inappropriate and were not used (e.i hormones, neurotransmitters, metallic compounds, tautomers, and large macrocyclic molecules). Approximately 410 HLs are repeated values from different data sources for the same chemical (pharmaceuticals). Another approximately 160 entries are different HLs for the same chemical (environmental contaminants) and it is necessary to select a single value for QSAR development; therefore, geometric means were calculated for these chemicals. The fragment method does not recognize differences in stereoisomers; therefore, in a few cases a geometric mean was also used when HLs for more than one stereoisomer were available. Screening-level QSAR predictions for stereoisomers need to be interpreted cautiously

The final data set is composed of 1105 chemicals with molar mass ranging from 30 (formaldehyde) to 960 (decabromodiphenyl ether) g/mol. The HLs span approximately 7.5 orders of magnitude from 0.05 h (0.002 d) for nitroglycerin to 2 × 106 h (83 000 d) for 2,3,4,5,2′,3′,5′,6′-octachlorobiphenyl with a median of 7.6 h (0.32 d). The corresponding rate constants range from 14/h (330/d) to 3.5 × 10–7/h (8.3 × 10–6)/d with a median of 0.091/h (2.2/d). Eighty percent of the chemicals in the HLT QSAR data set are pharmaceuticals (measured HLT) and 20% are environmental contaminants (estimated or assumed to approximate HLT).

The range of LogHLTare -1.30 / 6.30 for the training set and -1.08 / 5.83 for the test set. After successful validation, the model has been retrained on the entire dataset for implementation.

Dataset was splitted in training (552) and test set (553). For more details see section 6.6 and 7.6 of QMRF.

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:

LogHLT (total elimination half-life in human)

OLS-MLR method. Model developed on a training set of 552 compounds

LogHLT (total elimination half-life in human)_Full model

OLS-MLR method. Model developed on a training set of 1105 compounds

Split model equation: LogHLT= 0.5683 + 0.3299 ScCl + 0.6018AATS7p + 0.2385 nF - 0.0043 TopoPSA - 0.0484 gmax + 0.0778 GGI1 - 0.2404minsCl - 0.27 minsHsOH

Full model Equation:

LogHLT= 0.6577 + 0.351 ScCl + 0.5905AATS7p - 0.0042

TopoPSA + 0.2105 nF - 0.0495 gmax - 0.4298 minsCl +0.0686 GGI1 - 0.2927 minsHsOH

4.3.Descriptors in the model:

[1]nF Number of fluorine atoms

[2]minsHsOH minimum atom-type H E-state -OH

[3]gmax maximum electrotopological state

[4]SsCl sum of atom-type E-state -Cl

[5]AATS7p average Broto-Moreau autocorrelation of lag 7 weighted by polarizabilities

[6]TopoPSA topological polar surface area

[7]GGI1 topological charge index of order 1

[8]minsCl minimum atom-type E-state -Cl

4.4.Descriptor selection:

SMILES notation were used to encode for 2Dstructural information for all the molecules in the dataset; canonical smiles were derived by OpenBabel. The smiles string were used to calculate mono- and bidimensional descriptors by the software PaDEL-Descriptor. Constatnt descriptors and descriptors with a correlation greater than 0.98 were excluded from the total amout of descriptiors, using QSARINS software. The models were initially developed by the all-subset-procedure, and then GA was applied to obtain the final population of models (eight variables). The optimized parameter used was Q2LOO(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

Yap Chun Wei, Department of Pharmacy, National University of Singapore.
http://padel.nus.edu.sg/software/padeldescriptor/index.html

OpenBabel 2.3.2 Open Babel: the open source chemistry toolbox.

VEGA www.vegahub.eu

4.7.Chemicals/Descriptors ratio:

Split: 552 chemicals / 8 descriptors = 59

Full model: 1105 chemicals / 8 descriptors = 138

5.Defining the applicability domain - OECD Principle 3

5.1.Description of the applicability domain of the model:

The Applicability Domain (AD) is assessed using the original algorithm implemented within VEGA. An overall AD index is calculated, based on a number of parameters, which relate to the results obtained on similar chemicals within the training and test sets.

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 > 0.7, the predicted substance could be out of the Applicability Domain of the model. It corresponds to “moderate reliability” of prediction.

If AD index ≤ 0.7, the predicted substance is regarded out of the Applicability Domain of the model. It corresponds to “low reliability” of prediction.

No ADI threshold was used to provide performance calculations

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
1.5	1.5	1.5	0.85	1.0
0.8	0.8	0.8	0.7	0.85
All other cases				0.7

5.2. Method used to assess the applicability domain:

The AD 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 [14]. The 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 > 0.85, strongly similar compounds with known experimental value in the training set have been found

If 0.85 ≥ index > 0.7, only moderately similar compounds with known experimental value in the training set have been found

If index ≤ 0.7, 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 < 0.8, accuracy of prediction for similar molecules found in the training set is good

If 1.5 > index ≥ 0.8, accuracy of prediction for similar molecules found in the training set is not optimal

If index ≥ 1.5, 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 < 0.8, molecules found in the training set have experimental values that agree with the target compound predicted value

If 1.5 > index ≥ 0.8, similar molecules found in the training set have experimental values that slightly disagree with the target compound predicted value

If index ≥ 1.5, 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 < 0.8, the maximum error in prediction of similar molecules found in the training set has a low value, considering the experimental variability

If 1.5 > index ≥ 0.8, the maximum error in prediction of similar molecules found in the training set has a moderate value, considering the experimental variability

If index ≥ 1.5, 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:

The model is not applicable to inorganic chemicals and substances containing unusual elements (i.e., different from C, O, N, S, P, Cl, Br, F, I). Salts can be predicted only if converted to the neutralized form.

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:

To verify the predictive capability of the proposed models, the dataset (n=1105) was split, before model development, into a training set used for model development and a prediction set used later for external validation; the splitting scheme was the same as the one used prevously by Arnot (n training=552 , n prediction=553). The range of LogHLTare: -1.30 / 6.30

6.6.Pre-processing of data before modelling:

Transformation of kT (h-1) into LogHLT(h)

6.7.Statistics for goodness-of-fit:

R^2= 0.78 ; CCCtr[9,10]= 0.88 ; RMSEtr=0.62

The VEGA implementation returns the following statistics on the entire dataset (1105 compounds):

R^2 ext = 0.77 ; MAE = 0.489 ; MSE = 0.404 ; RMSE = 0.636

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

Q^2LOO= 0.77 ; CCCcv= 0.87; RMSEcv= 0.63

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

Q^2 (30% left out, 2000 iterations) LMO= 0.77

.

6.10.Robustness - Statistics obtained by Y-scrambling:

R^2yscr= 0.01

6.11.Robustness - Statistics obtained by bootstrap:

NA

6.12.Robustness - Statistics obtained by other methods:

NA

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:

To verify the predictive capability of the proposed models, the dataset (n=1105) was split, before model development, into a training set used for model development and a prediction set used later for external validation; the splitting scheme was the same as the one used prevously by Arnot (n training=552 , n prediction=553). The range of LogHLT are: -1.08 / 5.83

7.6.Experimental design of test set:

The splitting was the same as the one used previously by Arnot (Arnot et al., 2014)

7.7.Predictivity - Statistics obtained by external validation:

Q^2 extF1[11]= 0.74 ; Q^2extF2[12]= 0.74 ; Q^2 extF3[13]= 0.75 ; CCCex=0.86 ; RMSEex= 0.66

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 LogHLTvalues are [-1.30 / 6.30] and [-1.08 / 5.83] respectively for training and prediction sets.

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

[1] nF: training set (0 / 15), prediction set (0 / 17);

[2] SsCl: training set (0 / 8.48), prediction set (-0.22 / 10.86);

[3] minHsOH: training set (-0.19 / 0.94), prediction set (-0.19 / 0.98);

[4] AATS7p: training set (0 / 3.99), prediction set (0 / 5.97);

[5] TopoPSA: training set (0 / 321.17), prediction set (0 / 356.07);

[6] gmax: training set (1.35 / 17.24), prediction set (1.35 / 17.14);

[7] GGI1: training set (0 / 16.5), prediction set (0 / 16);

[8] minsCl: training set (0 / 1.35), prediction set (-0.11 / 1.35)

7.9.Comments on the external validation of the model:

The VEGA implementation returns the following statistics on the entire dataset (1105 compounds):

R^2 ext = 0.77 ; MAE = 0.489 ; MSE = 0.404 ; RMSE = 0.636

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 sum of atom-type electrotopological state -Cl (SsCl), the number of fluorine atoms (nF) and the average Broto-Moreau autocorrelation of lag7, weighted by polarizabilities (AATS7p). SsCl encodes for information about the electrotopological state of atom bounded to chlorine atoms. nF gives informations about the presence and the number of fluorine atoms, large nF values will increase the predicted biotransformation half-life; it is known that covalent bonds between aromatic carbon and halogen atoms are very stable and may induce persistance and biopersistence of chemicals. AATS7p is an autocorrelation descriptor that account for the intramolecular variation of the polarizability all over the molecular,structure, encodes for the presence of polar atoms in large molecules, it has direct effect on biopersistence. Another important descriptor is the

minimum atom-type H E-state -OH (minHsOH), it encodes for information about the electrotopological perturbation of the hydrogen atoms bonded to oxygen atoms; the electronic state of the hydrogen atoms is important since they are responsible for many intermolecular interactions of chemicals as hydrogen bonds; high values for this descriptor mean that the considered chemical has a high potential to form hydrogen bonds and to interact with other molecules in the surrounding media, it contributes in decreasing the predicted HLT

8.3.Other information about the mechanistic interpretation:

NA

9.Miscellaneous information

9.1.Comments:

NA

9.2.Bibliography:

[1]S. Cassani, P. Gramatica, Identification of potential PBT behavior of personal care products by structural approaches. Sustain Chem Pharm, 2015;1:19-27

[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]A. Sangion, P. Gramatica, PBT assessment and prioritization of contaminants of emerging concern: pharmaceuticals. Environ Res, 2016a;147:297-306

[4]Yap C. PaDEL-Descriptor: an open source software to calculate molecular desctriptors and fingerprints. J Comput Chem. 2011

[5]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

[6]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.

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

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[14] Floris et al. "A generalizable definition of chemical similarity for read-across." Journal of cheminformatics 6.1 (2014): 39

9.3.Supporting information:

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

All available dataset are present in the model inside the VEGA software.

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