	QMRF identifier (JRC Inventory): **To be entered by JRC**
	QMRF Title: **QSPR model for the impact sensitivity of nitroaliphatic compounds using constitutional descriptors**
	Printing Date: **14 nov. 2019**

1.QSAR identifier

1.1.QSAR identifier (title):

QSPR model for the impact sensitivity of nitroaliphatic compounds using constitutional descriptors

1.2.Other related models:

1.3.Software coding the model:

2.General information

2.1.Date of QMRF:

November 2014

2.2.QMRF author(s) and contact details:

[1]Guillaume FAYET Ineris guillaume.fayet@ineris.fr www.ineris.fr

[2]Patricia ROTUREAU Ineris patricia.rotureau@ineris.fr www.ineris.fr

2.3.Date of QMRF update(s):

25/10/2012 - Version 1

14/11/2019 - Version 2

2.4.QMRF update(s):

14/11/2019 - Guillaume FAYET - corrections of the software name in sections 3.2, 4.4, 4.5, 4.6 and 8.2 ; update of the details of ref. 9 in 9.2

2.5.Model developer(s) and contact details:

[1]Vinca PRANA Ineris / Chimie ParisTech

[2]Guillaume FAYET Ineris guillaume.fayet@ineris.fr www.ineris.fr

[3]Patricia ROTUREAU Ineris patricia.rotureau@ineris.fr www.ineris.fr

[4]Carlo ADAMO Chimie ParisTech carlo-adamo@chimie-paristech.fr

2.6.Date of model development and/or publication:

2012

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

Vinca Prana, Guillaume Fayet, Patricia Rotureau and Carlo Adamo, Development of validated QSPR models for impact sensitivity of nitroaliphatic compounds, Journal of Hazardous Materials 235-236 (2012) 169-177 http://dx.doi.org/10.1016/j.jhazmat.2012.07.036

2.8.Availability of information about the model:

This model is non proprietary. Training and test sets are available.

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

3.Defining the endpoint - OECD Principle 1

3.1.Species:

3.2.Endpoint:

[1][2]QMRF 1. Physical Chemical Properties QMRF 1.21. Explosive Properties

3.3.Comment on endpoint:

The endpoint is related to explosive properties, namely the impact sensitivity. This property, characterizing the tendency of a material to react under the effect of a mechanical impact, is one of the most important to classify explosible substances according to the Classification, Labelling and Packaging of substances and mixtures (CLP regulation) and according to the Transport of Dangerous Goods (international regulation).

3.4.Endpoint units:

cm - logarithmic unit

3.5.Dependent variable:

log(h50%) - logarithm of the impact sensitivity (cm)

3.6.Experimental protocol:

The impact sensitivity, obtained by drop weight impact test, measures the height (in centimeters) from which the fall of a weight of a given mass on a sample causes a reaction with a 50% probability level.

3.7.Endpoint data quality and variability:

Data are taken from a single litterature reference to ensure consistency of experiments [ref1; sect 9.2]. This reference collects data which were obtained from the works of Kamlet and Adolph [ref 2-3; sect 9.2].

4.Defining the algorithm - OECD Principle 2

4.1.Type of model:

QSPR

4.2.Explicit algorithm:

multilinear regression model

Logh50% = -2.53 nN/natom + 0.07 nsingle – 0.25 nNO2 + 1.94

4.3.Descriptors in the model:

[1]nN/natom Relative number of N atoms

[2]nsingle Number of single bonds

[3]nNO2 Number of nitro groups

4.4.Descriptor selection:

A total of 66 constitutional descriptors were calculated using Codessa software and including some descriptors from examination of chemical structures. Then the best multi-linear regression algorithm (BMLR) implemented in the CodessaPro software was used to select descriptors. The first step in the BMLR analysis is to reduce the initial set of descriptors by rejecting all descriptors with insignificant variance. At the same time, if two descriptors are highly intercorrelated, only the one that has the strongest correlation with the property is retained. After that, starting from pairs of orthogonal descriptors, higher rank models are computed by successively including orthogonal descriptors as soon as an increase in correlation (based on Fisher coefficient F) is observed. Then, the BMLR analysis selects the best models at each 4.Defining the algorithm - OECD Principle 2 rank.The final model is chosen by expert knowledge considering the statistics of the model, the descriptors included in the model (chemical interpretation) and the quality of experimental data. For more details about descriptors and the BMLR

method, see ref 4 in section 9.2.

4.5.Algorithm and descriptor generation:

Multiple linear regression was computed by Codessa software to generate the model. Descriptors were calculated using the Codessa software and including some descriptors from examination of chemical structures such as the number of NO2 groups.

4.6.Software name and version for descriptor generation:

Codessa 2.7.16

Calculation, selection of descriptors and multilinear regression calculation

http://www.semichem.com/codessa/default.php

4.7.Chemicals/Descriptors ratio:

50 chemicals / 3 descriptors=16.6

The ratio for the training set is 34/3=11.3

5.Defining the applicability domain - OECD Principle 3

5.1.Description of the applicability domain of the model:

The applicability domain of the model is defined in terms of: 1) chemical family:nitroaliphatic compounds -chemical structure space of the training set based on the descriptors; 2) of the model using the method described in section 5.2.

Only one molecule of the validation set is out of the applicability domain: methylene-bis-N,N'-(2,2,2-trinitroacetamide).

5.2.Method used to assess the applicability domain:

The applicability domain (AD) was defined using an Euclidean distance based approach with the Ambit Discovery Software.

Euclidean distances between each molecule and the average of all molecules of the training set were calculated based on the descriptors included in the model. The AD was defined to include 95% of the molecules of the training set.

5.3.Software name and version for applicability domain assessment:

Ambit Discovery - version 1.20

http://ambit.sourceforge.net

5.4.Limits of applicability:

as defined in 5.1 and 5.2.

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: No

Formula: No

INChI: No

MOL file: Yes

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:

The training set contains 2/3 of the data: 34 nitroaliphatic compounds. Compounds were classified by increasing order of impact sensitivity and 2 molecules out of three molecules was regularly selected to constitute the training set.

No bias in representativeness was identified when inspecting the chemical structures of both sets.

6.6.Pre-processing of data before modelling:

6.7.Statistics for goodness-of-fit:

n=34; R^2=0.88; RMSE=0.17

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

Q^2=0.85

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

Q^2(5cv)=0.85 ; Q^2(10cv)=0.84

6.10.Robustness - Statistics obtained by Y-scrambling:

R^2(YS)=0.09 ; Standard Deviation(YS)=0.07 ; 500 iterations

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: No

Formula: No

INChI: No

MOL file: Yes

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:

The validation set contains 1/3 of the data: 16 nitroaliphatic compounds

7.6.Experimental design of test set:

Compounds were classified by increasing order of impact sensitivity and one molecule out of three molecules was regularly selected to constitute the test set.

No bias in representativeness was identified when inspecting the chemical structures of both sets.

7.7.Predictivity - Statistics obtained by external validation:

n=16; R^2ext =0.81 ; RMSE=0.22 ; Q^2(F1)=0.81; Q^2(F2)=0.81; Q^2(F3)=0.81; CCC=0.93

7.8.Predictivity - Assessment of the external validation set:

The external validation set is representative of the property distribution and of the structural domain of the training set (see section 7.6).

In the applicability domain, the predictivity is R^2in =0.78 , RMSE=0.23; Q^2(F1)=0.78; Q^2(F2)=0.78; Q^2(F3)=0.82 ; CCC=0.92

7.9.Comments on the external validation of the model:

8.Providing a mechanistic interpretation - OECD Principle 5

8.1.Mechanistic basis of the model:

From a chemical point of view, nitro groups play a critical role in the mechanism of decomposition of nitrocompounds. In particular, nitroaliphatic compounds are known to decompose by dissociation of the C-NO2 bond [ref 5, sect 9.2]. So the occurence of the number of nitro groups in the model is pertinent according to this statement. Moreover, this descriptor was also highlighted in a previous decision tree model for the prediction of the heat of decomposition of nitroaromatic compounds [ref 6, sect 9.2].

The 2 other descriptors are not so straightforwardly interpretable.

8.2.A priori or a posteriori mechanistic interpretation:

Constitutionnal descriptors were calculated using the Codessa software on the one hand and including additionnal descriptors from examination of chemical structures on the other hand as they could be able a priori to be linked to the property (for example, the number of NO2 groups).

Besides, in the final model developped by a statistical approach, the occurence of the number of nitro groups confirms a posteriori their role in the decomposition mechanism of nitroaliphatics.

8.3.Other information about the mechanistic interpretation:

9.Miscellaneous information

9.1.Comments:

9.2.Bibliography:

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[9]G. Fayet, P. Rotureau, V. Prana and C. Adamo, Global and local QSPR models to predict the impact sensitivity of nitro compounds, Process Safety Progress, 31, 291-303

9.3.Supporting information:

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

10.Summary (JRC QSAR Model Database)

10.1.QMRF number:

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10.2.Publication date:

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10.3.Keywords:

To be entered by JRC

10.4.Comments:

To be entered by JRC