	QMRF identifier (JRC Inventory): **Q13-46-0010**
	QMRF Title: **QSAR for skin sensitisation via Schiff base formation**
	Printing Date: **Dec 11, 2019**

1.QSAR identifier

1.1.QSAR identifier (title):

QSAR for skin sensitisation via Schiff base formation

1.2.Other related models:

1.3.Software coding the model:

N/A

2.General information

2.1.Date of QMRF:

26 March 2009

2.2.QMRF author(s) and contact details:

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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]David W Roberts Liverpool John Moores University D.W.Roberts@ljmu.ac.uk
[2]Aynur Aptula SEAC Unilever nora.aptula@unilever.com
[3]Grace Patlewicz DuPont Haskell Global Centers for Health & Environmental Sciences
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2.6.Date of model development and/or publication:

May 2006

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

Roberts DW, Aptula AO & Patlewicz G (2006). Mechanistic Applicability Domains for Non-Animal Based Prediction of Toxicological Endpoints. QSAR Analysis of the Schiff Base Applicability Domain for Skin Sensitization. Chemical Research in Toxicology 19, 1228-1233.

2.8.Availability of information about the model:

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

3.Defining the endpoint - OECD Principle 1

3.1.Species:

Mouse

3.2.Endpoint:

4.Human Health Effects 4.6.Skin sensitisation

3.3.Comment on endpoint:

The EC3 as derived from the Local Lymph Node Assay (LLNA). This is the dose (expressed as percent concentration by weight) giving a stimulation index (SI) of 3 in the LLNA. The SI is the ratio of tritiated thymidine uptake in treated animals to uptake in control animals.

3.4.Endpoint units:

The EC3 is typically expressed as a percentage.

3.5.Dependent variable:

The EC3 has been converted to its molar log equivalent, so pEC3. pEC3 = log EC3-logMW where MW refers to the Molecular Weight

3.6.Experimental protocol:

The LLNA is described in OECD TG 429.

3.7.Endpoint data quality and variability:

The LLNA is subject to biological variability. The EC3 can vary by a factor of 2, the general rule of thumb being that an EC3 can be doubled or halved. The training dataset used in this study is of high quality and taken from Unilever and Procter and Gamble in-house sources which has since been published as a compilation in Gerberick et al (2005).

4.Defining the algorithm - OECD Principle 2

4.1.Type of model:

QSAR

4.2.Explicit algorithm:

multilinear regression QSAR

multilinear regression QSAR based on more than 1 descriptor

pEC3 = 1.12(sum sigma*) + 0.42(LogP) -0.62

4.3.Descriptors in the model:

[1]sum of sigma* constant Taft coefficients

[2]Log P log of the octanol water partition coefficient

4.4.Descriptor selection:

A chemical needs to undergo a set of hurdles in order to induce skin sensitisation. The rate determining step is covalent binding. This is thought to be modelled effectively by hydrophobicity and reactivity. The reactivity is modelled by the sum of the sigma* coefficients and Log P for hydrophobicity.

4.5.Algorithm and descriptor generation:

Multiple Linear Regression was used to derive a statistical model relating Log P and sum sigma* to the pEC3 data.

4.6.Software name and version for descriptor generation:

CLogP (Version 4)

www.biobyte.com

sigma* coefficients

Taken from the book of Perrin et al 198: pKa prediction of organic acids and bases. Sigma* values can also be calculated within the commercial ChemSketch package part of the suite of tools from ACD Labs software (www.acdlabs.com).

4.7.Chemicals/Descriptors ratio:

There were 2 descriptors for the 10 original chemicals in the training set. The final equation reported is based on a combined training and test set comprising 16 compounds and the use of the same 2 descriptors. Thus 8 chemicals/descriptor (16/2).

5.Defining the applicability domain - OECD Principle 3

5.1.Description of the applicability domain of the model:

The QSAR is applicable for the whole domain of Schiff base formers. To use it confidently requires a degree of chemistry expertise to assign a chemical to the appropriate domain - general rules and principles are described in Aptula and Roberts (2006). All aliphatic aldehydes and ketones belong in this domain unless they have additional functional groups that enable them to react by alternative reaction routes. Aromatic aldehydes and ketones are excluded from this domain. For the prediction of pEC3 there is a cut off of LogP = 4. Chemicals with Log P values in excess of this might well be overpredicted.

5.2.Method used to assess the applicability domain:

No specific method - based on organic chemistry principles as published in Aptula and Roberts (2006).

5.3.Software name and version for applicability domain assessment:

N/A

5.4.Limits of applicability:

See 5.1

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: 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:

Data in Roberts et al (2006)

6.6.Pre-processing of data before modelling:

The EC3 values were converted in their pEC3s as described in section 3.5. The negative logarithm of the molar EC3 or pEC3 = Log EC3 – Log MW

6.7.Statistics for goodness-of-fit:

r^2= 0.937; r^2adj = 0.919; s = 0.11; F = 52.2

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

No cross validation was carried out.

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

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: No

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:

Validation set of 6 compounds is available in Roberts et al (2006).

7.6.Experimental design of test set:

Compounds expected to be schiff base formers though not necessarily aldehydes (as in the training set) were selected

7.7.Predictivity - Statistics obtained by external validation:

n = 6; r^2 = 0.957; r^2adj = 0.946; s = 0.17; F = 88.1

7.8.Predictivity - Assessment of the external validation set:

7.9.Comments on the external validation of the model:

The test set of compounds was found to agree well in terms of their predicted pEC3 values. Accordingly the test set and training set were combined to create one overall equation relating the sum of the sigma* and Log P to pEC3.

pEC3 = 1.12(sum sigma*) + 0.42(LogP) -0.62

n = 16; r^2= 0.952; r^2adj = 0.945; s = 0.12; F = 129.6

8.Providing a mechanistic interpretation - OECD Principle 5

8.1.Mechanistic basis of the model:

The mechanistic basis is clear. The model is based on the assumption that covalent binding is a rate determining step for sensitisation induction to occur and therefore sensitisation can be modelled using electrophilic reactivity and hydrophobicity.

8.2.A priori or a posteriori mechanistic interpretation:

A priori

8.3.Other information about the mechanistic interpretation:

There are many references describing this type of approach - see papers by Aptula et al (2005); Roberts et al (2008); Roberts et al (2007); Roberts and Aptula (2008).

9.Miscellaneous information

9.1.Comments:

This model could be used as a standalone QSAR for the prediction of sensitisation potential and potency for schiff base forming compounds.

9.2.Bibliography:

[1]Gerberick GF, Ryan CA, Kern PS, Schlatter H, Dearman RJ, Kimber I, Patlewicz G & Basketter DA (2005). Compilation of historical local lymph node data for the evaluation of skin sensitization alternatives. Dermatitis 16, 157-202.

[2]Aptula AO, Patlewicz G & Roberts DW (2005). Skin Sensitization: Reaction Mechanistic Applicability Domains for Structure-Activity Relationships. Chemical Research in Toxicology 18, 1420-1426.

[3]Roberts DW, Aptula AO, Patlewicz G & Pease C (2008). Chemical reactivity indices and mechanism-based read-across for non-animal based assessment of skin sensitisation potential. Journal of Applied Toxicology 28, 443-454.

[4]Roberts DW, Patlewicz G, Kern PS, Gerberick F, Kimber I, Dearman RJ, Ryan CA, Basketter DA & Aptula AO.(2007). Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chemical Research in Toxicology 20, 1019-1030.

[5]Roberts DW & Aptula AO (2008). Determinants of skin sensitisation potential. Journal of Applied Toxicology 28, 377–387.

[6]Aptula AO & Roberts DW (2006). Mechanistic applicability domains for nonanimal-based prediction of toxicological end points: general principles and application to reactive toxicity. Chemical Research in Toxicology 19, 1097-1105.

9.3.Supporting information:

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

10.Summary (JRC QSAR Model Database)

10.1.QMRF number:

Q13-46-0010

10.2.Publication date:

2013-06-21

10.3.Keywords:

skin sensitisation;local lymph node assay;LLNA;EC3;Schiff base;

10.4.Comments:

former Q2-15-8-108