	QMRF identifier (JRC Inventory): **To be entered by JRC**
	QMRF Title: **Skin Sensitization Model (TOXTREE) v. 1.0.0**
	Printing Date: Nov 4, 2022

1.QSAR identifier

1.1.QSAR identifier (title):

Skin Sensitization Model (TOXTREE) version 1.0.0

1.2.Other related models:

NA

1.3.Software coding the model:

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:

04/11/2022

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:

[1] Alberto Manganaro, Kode s.r.l, Pisa, Italy a.manganaro@kode-solutions.net

2.6.Date of model development and/or publication:

2008

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

[1] Enoch SJ, Madden JC, Cronin MT. Identification of mechanisms of toxic action for skin sensitization using a SMARTS pattern based approach. SAR QSAR Environ Res. 2008; 19(5-6): 555-78. https://doi.org/10.1080/10629360802348985

2.8.Availability of information about the model:

The model is an implementation of the existing model implemented in the Toxtree software.

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

NA

3.Defining the endpoint - OECD Principle 1

3.1.Species:

Mouse

3.2.Endpoint:

Skin sensitization on mouse (local lymph node assay model) OECD 429.

Mechanisms of action.

3.3.Comment on endpoint:

Skin sensitizers are substances able to elicit an allergic response following contact with the skin, termed allergic contact dermatitis (ACD) in humans. The majority of skin sensitizers elicit their effect via covalent bond formation with skin proteins. These reactions have been understood in terms of well-defined nucleophilic-electrophilic reaction chemistry.

3.4.Endpoint units:

Adimensional

3.5.Dependent variable:

NA

3.6.Experimental protocol:

OECD 429 Test. The methods described here are based on the use of in vivo radioactive labelling to measure an increased number of proliferating cells in the draining auricular lymph nodes.

3.7.Endpoint data quality and variability:

For the endpoint data quality and variability please see the paper of Enoch et al. (2008): Enoch SJ, Madden JC, Cronin MT. Identification of mechanisms of toxic action for skin sensitization using a SMARTS pattern based approach. SAR QSAR Environ Res. 2008; 19(5-6): 555-78. https://doi.org/10.1080/10629360802348985

4.Defining the algorithm - OECD Principle 2

4.1.Type of model:

The majority of skin sensitizers elicit their effect via covalent bond formation with skin proteins. These reactions have been understood in terms of well-defined nucleophilic-electrophilic reaction chemistry. Thus, a first step in (Q)SAR analysis is the assignment of a chemical's potential mechanism of action enabling it to be placed in an appropriate reactivity domain. The aim of this model was to design a series of SMARTS patterns capable of defining these reactivity domains. This was carried out using a large database of local lymph node assay (LLNA) results that had potential mechanisms of action assigned to them using expert knowledge.

4.2.Explicit algorithm:

SMARTS patterns were developed to identify potential mechanisms of action regarded as being important for determining a chemical's skin sensitising potential. The initial set of SMARTS patterns developed have been used to obtain a framework on which to develop a larger set to train and improve mechanism identification. The training procedure then involved knowledge from Roberts et al. (2007) (in which potential mechanisms had been identified using expert knowledge) as the basis for the development of a final set of SMARTS patterns. This set of SMARTS patterns was assessed for their capability to identify correctly the potential mechanisms within this training dataset. Once the 'final' set of SMARTS patterns had been developed, the TIMES-SS dataset of 44 chemicals, which were not included in the training set, were used as a validation set. This dataset has also been subjected to a mechanistic assessment with mechanisms of action being assigned to each of the 44 chemicals by the same set of experts who assessed the training set.

For more information, please see the work of Enoch et al. (2008), listed in the bibliography and in sections 2.7 and 3.7.

4.3.Descriptors in the model:

NA

4.4.Descriptor selection:

NA

4.5.Algorithm and descriptor generation:

See section 9.2

4.6.Software name and version for descriptor generation:

NA

4.7.Chemicals/Descriptors ratio:

NA

5.Defining the applicability domain - OECD Principle 3

5.1.Description of the applicability domain of the model:

Unable to perform Applicability Domain check.

5.2.Method used to assess the applicability domain:

NA

5.3.Software name and version for applicability domain assessment:

VEGA

Included in the VEGA software and automatically displayed when running the model

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https://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:

No

6.2.Available information for the training set:

CAS RN: No

Chemical Name: No

SMILES: No

Formula: No

InChI: No

MOL file: No

NanoMaterial: null

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

NA

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

NA

6.5.Other information about the training set:

The training set is not included in the model, since this represents just a re-implementation of the model already implemented in the Toxtree software.

6.6.Pre-processing of data before modelling:

NA

6.7.Statistics for goodness-of-fit:

NA

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

NA

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

NA

6.10.Robustness - Statistics obtained by Y-scrambling:

NA

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:

No

7.2.Available information for the external validation set:

CAS RN: No

Chemical Name: No

SMILES: Yes

Formula: No

InChI: No

MOL file: No

NanoMaterial: null

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

NA

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

NA

7.5.Other information about the external validation set:

The test set is not included in the model, since this represents just a re-implementation of the model already implemented in the Toxtree software.

7.6.Experimental design of test set:

NA

7.7.Predictivity - Statistics obtained by external validation:

NA

7.8.Predictivity - Assessment of the external validation set:

NA

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 is based on a series of SMARTS patterns representing different mechanims of action related to skin sensitization toxicity.

8.2.A priori or a posteriori mechanistic interpretation:

A priori

8.3.Other information about the mechanistic interpretation:

NA

9.Miscellaneous information

9.1.Comments:

NA

9.2.Bibliography:

[1] Enoch SJ, Madden JC, Cronin MT. Identification of mechanisms of toxic action for skin sensitization using a SMARTS pattern-based approach. SAR QSAR Environ Res. 2008; 19(5-6): 555-78. https://doi.org/10.1080/10629360802348985

9.3.Supporting information:

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

Data used to build the model are available in the paper of Enoch et al. (2008).

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