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| | *QMRF identifier (JRC Inventory):* **To be entered by JRC** |
| | *QMRF Title:* **Thyroid Receptor Alpha effect (NRMEA) - v. 1.0.1** |
| | *Printing Date:* **June 8, 2022** |
| | |

## 1.QSAR identifier

### 1.1.QSAR identifier (title):

Thyroid Receptor Alpha effect (NRMEA) - v. 1.0.1

### 1.2.Other related models:

This is the description of the VEGA model that implements the “Thyroid Receptor Alpha effect (NRMEA) - v. 1.0.0” developed by the group of Prof. Wei Shi, University of Nanjing

### 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:

June 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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### 2.6.Date of model development and/or publication:

24 sept 2019

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

Benfenati E, Roncaglioni A, Lombardo A, Manganaro A. Integrating QSAR, Read-Across, and Screening Tools: The VEGAHUB Platform as an Example. Advances in Computational Toxicology; Springer; 2019. p. 365-81

**2.8.Availability of information about the model:**

The model is non-proprietary and the training, test and validation sets are available.

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

QMRF Title: Nuclear Receptor-mediated Endocrine Activity (NRMEA)

Printing Date: June 9,2022

## 3.Defining the endpoint - OECD Principle 1

**3.1.Species:**

Homo sapiens

**3.2.Endpoint:**

Endocrine disrupting chemicals Nuclear receptor-mediated endocrine disruption Thyroid Receptor Alpha effect

**3.3.Comment on endpoint:**

The effect of compound on Thyroid receptor alpha (classification)

**3.4.Endpoint units:**

Model is a classification so there is no units, possible results should be Active/Inactive prediction and Agonist/A-Anta/Antagonist.

**3.5.Dependent variable:**

The dependent variable is Endocrine effect, as binary classification: 0 (inactive), 1 (active).

**3.6.Experimental protocol:**

Model are built based on two in vitro assays: i) reporter gene assay and ii) cytotoxicity.

**3.7.Endpoint data quality and variability:**

Chemical data were collected from two open free libraries, including ToxCast/Tox21 (https://www.epa.gov/chemical-research/toxcast-dashboard) and ChEMBL (https://www.ebi.ac.uk/chembl/).

All of the chemical data were prepared by removing all false SMILES strings, and deleting all duplicate compounds. Then, the data set was split randomly into training set and test set in the ratio of 4:1 (KNIME Analytics Platform, https://www.knime.com/).

## 4.Defining the algorithm - OECD Principle 2

**4.1.Type of model:**

Hierarchy featured fragments-based model.

**4.2.Explicit algorithm:**

Hierarchy fragment features

model is a hierarchical tree on three levels: fragments on first and second levels define if a compound is active on receptor, third fragments define the type of activity of the compounds on the receptor

**4.3.Descriptors in the model:**

Structural fragment based. The model is a structure-based model and does not make use of Descriptors.

**4.4.Descriptor selection:**

Structure alerts selected are described in the guide associated at the model present in the Vega platform.

### 4.5.Algorithm and descriptor generation:

Firstly, we took advantage of primary fragments to select compounds have the possibility of being active. Secondly, compounds were screened by secondary fragments according to their different types of primary fragments. Each compound contains primary and secondary fragments simultaneously, would be predicted as active compounds. Next, the types of disrupting activities of identified active compounds would be distinguished based on their tertiary fragments. This hierarchy fragments allow the exploration of a wide range of structurally diverse active compounds which could bind to receptors, and build up an array of rules focusing on Agonist/A-Anta/Antagonist disruption.

Structural fragments are calculating using substructure frequency analysis and substructure percentage analysis, and PubChem fingerprint database was used to generate primary fragments to describe active disruptors as much as possible. According to the structural features, chemicals were divided into several subtypes based on their primary fragments. Then, specific secondary fragments were generated by using SARpy software (https://www.vegahub.eu/portfolio-item/sarpy/). Active disruptors, containing primary and related secondary fragments, were used to extracted disrupting tertiary fragments. Disruptors were clustered according to their primary and secondary fragments, then, tertiary fragments were extracted independently by using SARpy software.

### 4.6.Software name and version for descriptor generation:

Padel-descriptor

Padel-descriptor (for primary fragment) https://www.softpedia.com/get/Science-CAD/PaDEL-Descriptor.shtml

SARpy software

SARpy software (for secondary and tertiary fragment) https://www.vegahub.eu/portfolio-item/sarpy/

### 4.7.Chemicals/Descriptors ratio:

5462 chemicals/ 26 structural alerts

## 5.Defining the applicability domain - OECD Principle 3

### 5.1.Description of the applicability domain of the model:

The 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 and is defined in this way for this QSAR model´s predictions.

If $1 \geq$ AD index $\geq 0.8$, the predicted substance is in the Applicability Domain of the model. It corresponds to “good reliability of prediction”.

If $0.8 >$ AD index $\geq 0.6$, the predicted substance could be out of the Applicability Domain of the model. It corresponds to “moderate reliability of prediction”.

If AD index $< 0.6$, the predicted substance is out of the Applicability Domain of the model and corresponds to “low reliability of prediction”.

### 5.2.Method used to assess the applicability domain:

The Applicability Domain and chemical similarity is measured with the algorithm developed for VEGA. Full details in the VEGA website (www.vegahub.eu), including the open access paper describing it [15]. The VEGA 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.

Information on these indices is given below:

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 > 0.8, strongly similar compounds with known experimental value in the training set have been found

If 0.8 ≥ index > 0.6, only moderately similar compounds with known experimental value in the training set have been found

If index ≤ 0.6, no similar compounds with known experimental value in the training set have been found

Accuracy 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 < 0.6, accuracy of prediction for similar molecules found in the training set is good

If 0.8 > index ≥ 0.6, accuracy of prediction for similar molecules found in the training set is not optimal

If index ≥ 0.8, 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 < 0.6, similar molecules found in the training set have experimental values that agree with the predicted value

If 0.8 > index ≥ 0.6, some similar molecules found in the training set have experimental values that disagree with the predicted value

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

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:

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 < 0.6, 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

**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: No

Smiles: Yes

Formula: No

INChI: No

MOL file: No

NanoMaterial: 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:**

**6.6.Pre-processing of data before modelling:**

All of the chemical data were prepared by removing all false SMILES strings, and deleting all duplicate compounds. Then, the data set was split randomly into training set and test set in the ratio of 4:1 (KNIME Analytics Platform, https://www.knime.com/). The training set was used to provide feature fragments and local physicochemical properties present across the completely active set. The test set was used in the external validation.

**6.7.Statistics for goodness-of-fit:**

We Active/Inactive prediction

Training set: n = 5462, accuracy: 0.998; sensitivity: 0.87; specificity: 1.0, MCC 0.94. TP 109, TN 5338, FP 0, FN 15

Agonist /Antagonist/inactive prediction

Training set accuracy:0.99

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

**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:**

No

**7.2.Available information for the external validation set:**

NA

**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:**

**7.6.Experimental design of test set:**

**7.7.Predictivity - Statistics obtained by external validation:**

NA

**7.8.Predictivity - Assessment of the external validation set:**

**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:**

With NRMEA, you can predict chemicals Thyroid Receptor Alpha effect.

**8.2.A priori or a posteriori mechanistic interpretation:**

NA

**8.3.Other information about the mechanistic interpretation:**

NA

## 9.Miscellaneous information

**9.1.Comments:**

NA

**9.2.Bibliography:**

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[15] Floris, M., Manganaro, A., Nicolotti, O. et al. A generalizable definition of chemical similarity for read-across. J Cheminform 6, 39 (2014). https://doi.org/10.1186/s13321-014-0039-1

**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