QMRF Title:
Mutagenicity (Ames test) CONSENSUS model (version 1.0.2)

1. QSAR identifier

1.1. QSAR identifier (title): VEGA Mutagenicity (Ames test) CONSENSUS model (version 1.0.2)

1.2. Other related models:
The model provides a qualitative prediction of mutagenicity on Salmonella typhimurium (Ames test), applying a consensus approach based on the four QSAR models currently available in VEGA. It is implemented inside the VEGA online platform, accessible at: www.vegahub.eu. See QMRF of the 4 individual models as further reference.

1.3. Software coding the model:
VEGA platform available at www.vegahub.eu

Version 1.0.1: changed weights for Applicability Domain conversion.

Version 1.0.2: changed the main algorithm when experimental values are found.

2. General Information

2.1. Date of QMRF: 15 April 2019

2.2. QMRF author(s) and contact details:

<table>
<thead>
<tr>
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<th>Affiliation</th>
<th>e-mail</th>
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<tbody>
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</tbody>
</table>

2.3. Date of QMRF update(s)

2.4. QMRF update(s)

2.5. Model developer(s) and contact details:
Alberto Manganaro, IRCSS-Istituto di Ricerche Farmacologiche "Mario Negri", Milan, Italy
Emilio Benfenati, IRCSS-Istituto di Ricerche Farmacologiche "Mario Negri", Milan, Italy

2.6. Date of model development and/or publication:
2014 [ref.2, sect.9.2]
2.7. Reference(s) to main scientific papers and/or software package:
- www.vegahub.eu

2.8. Availability of information about the model:
Complete documentation about the model is available on the guideline of the model, inside the VEGA application [ref.1, sect.9.2]

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

Endpoint

3. Defining the endpoint - OECD Principle 1

3.1. Species:
Histidine-dependent strains of *Salmonella typhimurium* (Ames test)

3.2. Endpoint:
Mutagenicity bacterial reverse mutation test

3.3. Comment on endpoint:
Mutagenic toxicity is the capacity of a substance to cause genetic mutations. This property is of high public concern because it has a close relationship with carcinogenicity and eventually reproductive toxicity: most of the mutagenic substances are suspected carcinogenic substance in case a genotoxic mechanism is considered. The Ames test is the basic in vitro assay to detect mutagens.

3.4. Endpoint units:
Adimensional

3.5. Dependent variable:
Binary classification as: Mutagenic / Non-Mutagenic.

3.6. Experimental protocol:
Ames test is an in vitro model of chemical mutagenicity and consists of a range of bacterial strains that together are sensitive to a large array of DNA-damaging agents.

3.7. Endpoint data quality and variability:
The estimated inter-laboratory reproducibility rate of *S. typhimurium* test data is 85% [ref.3, sect.9.2]
Algorithm

4. Defining the algorithm - OECD Principle 2

4.1. Type of model:
The model performs a consensus assessment based on the predictions of the available VEGA mutagenicity models (CAESAR, SARpy, ISS and KNN). See the individual QMRF [1].

4.2. Explicit algorithm:
The consensus algorithm uses the Applicability Domain assessment of each single model's prediction as its weight, so that the final assessment will be more influenced by the single models that produced more reliable predictions.
The Applicability Domain assessment of each model is converted to a numerical value in the range [0..1] with the following scheme:

<table>
<thead>
<tr>
<th>VEGA AD qualitative assessment</th>
<th>AD reference value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good reliability</td>
<td>0.9</td>
</tr>
<tr>
<td>Moderate reliability</td>
<td>0.6</td>
</tr>
<tr>
<td>Low reliability</td>
<td>0.2</td>
</tr>
</tbody>
</table>

The consensus score (CS) is calculated separately for the two outcomes as follow:

\[
\begin{align*}
CS_M &= \frac{\sum IR_M}{nr.\, tot\, models} \\
CS_{nM} &= \frac{\sum IR_{nM}}{nr.\, tot\, models}
\end{align*}
\]

The final class assignment is done according to the value of the CS: the compound is assigned to the positive class if \( CS_M \geq CS_{nM} \).

If at least one experimental value is available the CS is calculated as 1 if all values are concordant or as a ratio depending on the prevalence of the experimental responses. In this case, the reported number of models used refers only to the number of models having an experimental value.

For the purpose of this consensus approach, the “suspect mutagenic / non-mutagenic” predictions are considered simply as “mutagenic / non-mutagenic” predictions.

4.3. Descriptors in the model:
The input for this model are the predictions of the other models so no other types of descriptors are directly used by the consensus

4.4. Descriptor selection:
Not applicable

4.5. Algorithm and descriptor generation:
Not applicable

4.6. Software name and version for descriptor generation:
4.7. Chemicals/Descriptors ratio:
Not applicable

App. Domain

5. Defining the applicability domain - OECD Principle 3

5.1. Description of the applicability domain of the model
With this approach, the score of the final prediction can be used as a measure of the reliability of the produced consensus assessment. Indeed, the score would achieve its maximum value (1) only if one or more models found experimental values and these values are in agreement. In all other cases, the score will result in lower values.

5.2. Method used to assess the applicability domain:
See 4.2

5.3. Software name and version for applicability domain assessment:
VEGA

5.4. Limits of applicability:

Robustness

6. Internal validation - OECD Principle 4

6.1. Availability of the training set:
The model performs a consensus assessment based on the predictions of the available VEGA mutagenicity models (CAESAR, SARpy, ISS and KNN) and their training sets are available.

6.2. Available information for the training set:
CAS RN: No
Chemical Name: No
Smiles: No
Formula: No
INChI: No
MOL file: No

6.3. Data for each descriptor variable for the training set: No

6.4. Data for the dependent variable for the training set: No, the datasets are available for the 4 individual models.

6.5. Other information about the training set:
6.6. Pre-processing of data before modelling:
All chemical structures have been checked manually.

6.7. Statistics for goodness-of-fit:
No statistics are provided since in presence of experimental data the outcome of the consensus will be calculated according to experimental data only. The statistics of each individual model is provided within the relative QMRF.

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:

Predictivity

7. External validation - OECD Principle 4

7.1. Availability of the external validation set:
The model performs a consensus assessment based on the predictions of the available VEGA mutagenicity models (CAESAR, SARpy, ISS and KNN) and their individual external validation sets are available as in the relative QMRF.

7.2. Available information for the external validation set:
CAS RN: No
Chemical Name: No
Smiles: No
Formula: No
INChI: No
MOL file: No

7.3. Data for each descriptor variable for the external validation set: No

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

7.5. Other information about the external validation set:
7.6. Experimental design of test set:
No selection of chemicals prior to experimentation

7.7. Predictivity - Statistics obtained by external validation:

7.8. Predictivity - Assessment of the external validation set:

7.9. Comments on the external validation of the model:

Interpretation

8. Providing a mechanistic interpretation - OECD Principle 5

8.1. Mechanistic basis of the model:
The model provides a qualitative prediction of mutagenicity on Salmonella typhimurium (Ames test), applying a consensus approach based on the four QSAR models currently available in VEGA. Two models of them (ISS and SARpy) are structural alerts based. In particular, ISS structural alerts are expert based meanwhile SARpy includes statistical alerts to identify both toxic and non-toxic compounds. Thus, the mechanisms associated to the effect can be explored in this way.

8.2. A priori or a posteriori mechanistic interpretation:
The ISS model is based on a priori knowledge. The SARpy model is based on a posteriori interpretation.

8.3. Other information about the mechanistic interpretation:
Bibliography

9. Miscellaneous information

9.1. Comments:

9.2. Bibliography:

1) Guide to Mutagenicity Consensus version 1.0.2. Available as software help guide to the models when installing it.
