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| | *QMRF identifier (JRC Inventory):* **To be entered by JRC** |
| | *QMRF Title:* **VEGA implementation of Cramer classification - v. 1.0.1** |
| | *Printing Date:* **September 2022** |
| | |

## 1.QSAR identifier

### 1.1.QSAR identifier (title):

VEGA implementation of Cramer classification (version 1.0.1)

### 1.2.Other related models:

This is the description of the VEGA model that mimic the “Cramer rules” as implemented in the software ToxTree version 3.1.0

### 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:

September 2022

### 2.2.QMRF author(s) and contact details:

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[2] Erika Colombo Istituto di Ricerche Farmacologiche Mario Negri - IRCSS Via Mario Negri 2, 20156 Milano, Italy erika.colombo@marionegri.it https://www.marionegri.it/

### 2.3.Date of QMRF update(s):

No update

### 2.4.QMRF update(s):

No update

### 2.5.Model developer(s) and contact details:

The original model implements the conceptual scheme developed by Cramer. For the implementation in ToxTree:

[1] Nina jeliazkova; IDEA Consult, Joseph II straat 40 B1, 1000 Brussels, Belgium; jeliazkova.nina@gmail.com

For the implementation in VEGA of the Toxtree model:

[2] Alberto Manganaro; IRCCS-Istituto di Ricerche Farmacologiche Mario Negri, Via La Masa 19, 20156 Milano, Italy; alberto.manganaro@marionegri.it

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

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

[1] Cramer G. M., R. A. Ford, R. L. Hall, Estimation of Toxic Hazard - A Decision Tree Approach, J. Cosmet. Toxicol., Vol.16, pp. 255-276, Pergamon Press, 1978

[2] I.C. Munro, R.A. Ford, E. Kennepohl, and J.G. Sprenger, Correlation of structural class with No-Observed-Effect Levels: A proposal for establishing a threshold of concern, Food Chem. Toxicol. 34 (1996), pp. 829-867.

[3] Patlewicz G, Jeliazkova N, Safford RJ, Worth AP, Aleksiev B. (2008) An evaluation of the implementation of the Cramer classification scheme in the Toxtree software. SAR QSAR Environ Res. ;19(5-6):495-524.

[4] Benfenati E, Manganaro A, Gini G

VEGA-QSAR: AI inside a platform for predictive toxicology

Proceedings of the workshop "Popularize Artificial Intelligence 2013", December 5th 2013, Turin, Italy Published on CEUR Workshop Proceedings Vol-1107

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

The model is non-proprietary and the training set is available.

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

Another QMRF is not available.

## 3.Defining the endpoint - OECD Principle 1

### 3.1.Species:

Not applicable. Ideally it refers to human toxicity.

### 3.2.Endpoint:

This model does not refer to a collection of experimental data on a certain endpoint. It aims to identify rules of concern, and thus it is not a statistical model, but it is closer to an expert system.

### 3.3.Comment on endpoint:

NA

### 3.4.Endpoint units:

Adimensional.

### 3.5.Dependent variable:

The dependent variable is the severity of the effect, as three classes: 1 (lower concern), 2 (intermediate concern), 3 (higher concern).

### 3.6.Experimental protocol:

NA

### 3.7.Endpoint data quality and variability:

NA

## 4.Defining the algorithm - OECD Principle 2

### 4.1.Type of model:

Structure-based model

### 4.2.Explicit algorithm:

The Cramer rules Model is based on the Cramer classification scheme as implemented in the module Cramer rules of Toxtree, which is an open source application.

### 4.3.Descriptors in the model:

The model is a structure-based model and does not make use of descriptors

### 4.4.Descriptor selection:

No descriptor is used.

### 4.5.Algorithm and descriptor generation:

A decision tree has been implemented within Toxtree, and the same tree is implemented in VEGA.

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

Ad hoc decision tree has been implemented within Toxtree

### 4.7.Chemicals/Descriptors ratio:

Not applicable; the software is an expert system, not a statistical one. There is no training set.

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

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

The decision tree is not a statistical model, with a training set. The software identifies the presence of certain fragments and features associated to the Cramer classes. The model is applicable to organic substances. Since there is not a training set, the Applicability Domain Index, as typically applied within VEGA, is not applicable in this case

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

Not applicable. See 5.1.

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

Not applicable. See 5.1.

### 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

This is not a formal QSAR model developed through statistical methods so no specific internal and external validation has been performed.

### 6.1.Availability of the training set:

The decision tree is not a statistical model, with a training set. The software identifies the presence of certain fragments and features associated to the Cramer classes.

### 6.2.Available information for the training set:

NA

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

The model does not use descriptors and does not use a training set.

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

NA

### 6.5.Other information about the training set:

NA

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

NA

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

This is not a formal QSAR model developed through statistical methods so no specific internal and external validation has been performed.

### 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:

NA

### 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:

All

### 7.5.Other information about the external validation set:

NA

### 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 fragments and features use by the conceptual scheme of the Cramer model have been described and discussed within the original paper:

Cramer G. M., R. A. Ford, R. L. Hall, Estimation of Toxic Hazard - A Decision Tree Approach, J. Cosmet. Toxicol., Vol.16, pp. 255-276, Pergamon Press, 1978

These are not related to a specific mechanism, but represent a sequence of rules to identify substances of higher concern.

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

A priori, however, the mechanism is not an explicit one.

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

NA

## 9.Miscellaneous information

### 9.1.Comments:

NA

### 9.2.Bibliography:

[1] Cramer G. M., R. A. Ford, R. L. Hall, Estimation of Toxic Hazard - A Decision Tree Approach, J. Cosmet. Toxicol., Vol.16, pp. 255-276, Pergamon Press, 1978

[2] I.C. Munro, R.A. Ford, E. Kennepohl, and J.G. Sprenger, Correlation of structural class with No-Observed-Effect Levels: A proposal for establishing a threshold of concern, Food Chem. Toxicol. 34 (1996), pp. 829-867.

[3] Patlewicz G, Jeliazkova N, Safford RJ, Worth AP, Aleksiev B. (2008) An evaluation of the implementation of the Cramer classification scheme in the Toxtree software. SAR QSAR Environ Res. ;19(5-6):495-524.

**9.3.Supporting information:**

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

NA

## 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