SciMatics SciQSAR model for maximum recommended daily dose (MRDD) in humans

1. QSAR identifier

1.1 QSAR identifier (title)

SciMatics SciQSAR model for maximum recommended daily dose (MRDD) in humans, Danish QSAR Group at DTU Food.

1.2 Other related models

MultiCASE CASE Ultra model for maximum recommended daily dose (MRDD) in humans, Danish QSAR Group at DTU Food.

Leadscope Enterprise model for maximum recommended daily dose (MRDD) in humans, Danish QSAR Group at DTU Food.

1.3. Software coding the model

SciQSAR version 3.1.00.

2. General information

2.1 Date of QMRF

January 2015.

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

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2.6 Date of model development and/or publication

January 2014.

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

Contrera, J.F., Matthews, E.J., Kruhlak, N.L., and Benz, R.D. (2004) Estimating the safe starting dose in phase I clinical trials and no observed effect level based on QSAR modelling of the human maximum recommended daily dose. *Regulatory Toxicology and Pharmacology*, 40, 185 – 206.

SciQSAR (2009) Reference guide: *Statistical Analysis and Molecular Descriptors*. Included within the SciMatics SciQSAR software.

2.8 Availability of information about the model

The training set is non-proprietary and was compiled from the Maximum Recommended Daily Dose (MRDD) Database which is publically available at the FDA/CDER Webpage (http://www.epa.gov/comptox/dsstox/sdf_fdamdd.html, accessed 9th of July 2013). The model algorithm is proprietary from commercial software.

2.9 Availability of another QMRF for exactly the same model

3. Defining the endpoint

3.1 Species

Human (phase 1 clinical trial).

3.2 Endpoint

QMRF 4. Human Health Effects

QMRF 4.14. Repeated dose toxicity

3.3 Comment on endpoint

The Maximum Recommended Daily Dose (MRDD) for a pharmaceutical is an estimated upper dose limit beyond which a drug's efficacy is not increased and/or undesirable adverse effects begin to outweigh beneficial effects. The MRDD is related to the No Observed Effect Level (NOEL) for non-pharmaceuticals (NOEL equals 1/10 MRDD), a dose at which there are no statistically or biologically significant increases in the frequency or severity of any effect between the exposed population and its appropriate control. Because of this relation this model can be used to estimate both the MRDD and NOEL values for a given compound.

Data for this model was compiled from FDA's Center for Drug Evaluation and Research, Office of Pharmaceutical Science, Informatics and Computational Safety Analysis Staff's Maximum Recommended Daily Dose (FDAMDD) database. Most of the MRDD values in the FDAMDD database were determined from pharmaceutical phase 1 human clinical trials that employed an oral route of exposure and daily treatments, usually for 3 - 12 months. The pharmaceuticals were given as single or divided dose treatment regimens to achieve desired pharmacological effects. In contrast, roughly 5% of the pharmaceuticals in the FDAMDD database were anti-neoplastics and anesthetics and these were administered intravenously and/or intramuscularly. When separate MRDDs were reported for different routes of exposure, only the oral MRDD was included in the database. In addition, some pharmaceuticals have different MRDD values for male and female adults, children, or elderly patients. In this situation only MRDD values for the average adult patient were used.

Pharmaceuticals that are administered orally are usually tested over a limited range of doses and have MRDDs reported as mg/day. The MRDDs were converted from the mg/day unit to mg/kg body weight (bw)/day based upon an average adult weighing 60 kg. In contrast, the dose unit for most antineoplastic drug MRDDs is reported as mg/m^2 which was converted to mg/kg bw/day using the formula mg/kg bw/day = $mg/m^2/37$ for an average adult. Additionally, a few drugs had MRDDs reported in parts per million (ppm) which were converted to mg/kg bw/day on the basis that 1000 ppm equals 25 mg/kg bw/day for an average 60 kg adult. MRDD values for the 1,220 chemicals in this training set range from 0.00001 to 1000 mg/kg bw/day (Matthews *et al.* 2004).

As data for this model is derived directly from human data it can be argued that the model predictions can give a more accurate estimate of human MRDD than data derived from repeat-dose tests in rodents.

To make a categorical model compounds with a MRDD value between 0.0167-2.69 mg/kg bw/day were defined as positive and compounds with MRDD values between 5.00-1000 mg/kg bw/day were defined as negative. Intermediate compounds were defined as marginal.

3.4 Endpoint units

No units, 1 for positives and 0 for negatives.

3.5 Dependent variable

Maximum recommended daily dose (MRDD) in humans, positive or negative.

3.6 Experimental protocol

Data originate from pharmaceutical phase 1 human clinical trials that employed an oral route of exposure and daily treatments, usually for 3 - 12 months. The pharmaceuticals were given as single or divided dose treatment regimens to achieve desired pharmacological effects. In contrast, roughly 5% of the pharmaceuticals in the FDAMDD database were anti-neoplastics and anesthetics and these were administered intravenously and/or intramuscularly (Matthews *et al.* 2004).

3.7 Endpoint data quality and variability

According to (http://www.epa.gov/comptox/dsstox/sdf_fdamdd.html) "Several features of DSSTox FDAMDD have the potential to impact on SAR analysis and should be taken into account in any future use of these data. Most prominent among these is the imprecise nature of the reported MRDD value, both in terms of the wide range of adverse or toxic effects that would be considered in assigning the MRDD, and in terms of the ambiguous chemical structure association with this dose measure. In DSSTox FDAMDD and the corresponding Source FDA MRDD database, there are several cases where a single Dose_MRDD_mg value is assigned to multiple related structural derivatives of a pharmaceutical, i.e., the same activity is assigned to multiple Structure/CASRN records in the database. In theory, an MRDD value will reflect the lowest dose of a drug producing adverse effects but for the FDA MRDD database this value has been derived from pooled clinical reports where more than one form of a drug may have been administered. When MRDD mg mass units are converted to mmol units for SAR analysis, a single Dose_MRDD_mg is converted to a range of mmol doses, taking into account the different molecular weights of the various drug derivatives. Assuming that these various drug derivatives have similar or equal molar potencies, the reported Dose_MRDD_mg could be presumed to reflect the dose of the smallest STRUCTURE_MolecularWeight derivative that would register as the highest molar content and, therefore, most potent for a given mass dose."

4. Defining the algorithm

4.1 Type of model

This is a categorical (Q)SAR model based on calculated molecular descriptors, and if available the modeller's own or third-party descriptors or measured endpoints can be imported and used as descriptors.

4.2 Explicit algorithm

This is a categorical (Q)SAR model made by use of the non-parametric discriminant analysis (DA) kernel method (see 4.5). The specific implementation is proprietary within the SciQSAR software.

4.3 Descriptors in the model

Molecular connectivity indices

Molecular shape indices

Topological indices

Electrotopological (Atom E and HE-States) indices

Electrotopological bond types indices

SciQSAR software provides over 400 built-in molecular descriptors. Additionally, SciQSAR makes it possible to import the modeller's own or third-party descriptors or use measured endpoints as custom descriptors.

4.4 Descriptor selection

The initial descriptor set is manually chosen by the model developer from the total set of built-in descriptors. Furthermore, the set of descriptors applied in the modelling by the program is on top of this selection determined by thresholds for descriptor variance and number of nonzero values likewise defined by the model developer.

67 descriptors were selected from the initial pool of descriptors by the system and used to build the model.

4.5 Algorithm and descriptor generation

For a binary classification problem SciQSAR uses discriminant analysis (DA) to make a (Q)SAR model. SciQSAR implements a broad range of discriminant analysis (DA) methods including parametric and non-parametric approaches. The classic parametric method of DA is applicable in the case of approximately normal within-class distributions. The method generates either a linear discriminant function (the within-class covariance matrices are assumed to be equal) or a quadratic discriminant function (the within-class covariance matrices are assumed to be unequal). When the distribution is assumed to not follow a particular law or is assumed to be other than the multivariate normal distribution, non-parametric DA methods can be used to derive classification criteria. The non-parametric DA methods available within SciQSAR include the kernel and *k*-nearest-neighbor (kNN) methods. The main types of kernels implemented in SciQSAR include uniform, normal, Epanechnikov, bi-weight, or tri-weight kernels, which are used to estimate the group specific density at each observation. Either Mahalanobis or Euclidean distances can be used to determine proximity between compound-vectors in multidimensional descriptor space. When the

kNN method is used, the Mahalanobis distances are based on the pooled covariance matrix. When the kernel method is used, the Mahalanobis distances are based on either the individual within-group covariance matrices or the pooled covariance matrix. (Contrera *et al*. 2004)

If the data outcome is continuous, regression analysis is used to build the predictive model. Within SciQSAR several regression methods are available: ordinary multiple regression (OMR), stepwise regression (SWR), all possible subsets regression (PSR), regression on principal components (PCR) and partial least squares regression (PLS). The choice of regression method depends on the number of independent variables and whether correlation or multicollinearity among the independent variables exists: OMR is acceptable with a small number of independent variables, which are not strongly correlated. SWR is used under the same circumstances as OMR but with greater number of variables. PSR is used for problems with a great number of independent variables. PCR and PLS are useful when a high correlation or multicollinearity exist among the independent variables. (SciQSAR 2009)

To test how stable the developed models are, SciQSAR have built-in cross-validation procedures (see 6.).

For this model, the kernel method was used.

4.6 Software name and version for descriptor generation

SciQSAR version 3.1.00.

4.7 Descriptors/chemicals ratio

In this model 67 descriptors were used. The training set consists of 1106 compounds. The descriptor/chemical ratio is 1:16.5 (67:1106).

5. Defining Applicability Domain

5.1 Description of the applicability domain of the model

The definition of the applicability domain consists of two components; the definition in SciQSAR and the in-house further refinement algorithm on the output from SciQSAR to reach the final applicability domain call.

1. SciQSAR

The first criterion for a prediction to be within the models applicability domain is that all of the descriptor values for the test compound can be calculated by SciQSAR. If SciQSAR cannot calculate each descriptor value for the test chemical no prediction value is given by SciQSAR and it is considered outside the model's applicability domain.

2. The Danish QSAR group

The Danish QSAR group has applied a stricter definition of applicability domain for its SciQSAR models. In addition to the applicability domain definition made by SciQSAR a second criterion has been applied for predictions generated from (Q)SAR models with a binary endpoint. For each prediction SciQSAR calculates the probability (p) for the test compound's membership in one of the two outcome classes (positive or negative). The probability of membership in a class is a measure of how well training set knowledge is able to discriminate a positive prediction from a negative prediction within the nearest space of the subject compound-vector. The probability of membership value is also a measure of the degree of confidence of a prediction. The Danish QSAR group uses this probability for a prediction to further define the model's applicability domain. Only positive predictions with a probability equal to or greater than 0.7 and negative predictions with a probability equal to or less than 0.3 are accepted. Positive predictions with a probability between 0.5 and 0.7 as well as negative predictions with a probability between 0.3 and 0.5 are considered outside the model's applicability domain. When these predictions are wed out the accuracy of the model in general increases at the expense of reduced model coverage. Furthermore, as SciQSAR does not define a structural domain, only predictions which were within either Leadscope structural domain (defined as at least one training set chemical within a Tanimoto distance of 0.7) or CASE Ultra structural domain (no unknown fragments for negatives and maximum 1 unknown fragment for positives) were defined as being inside the SciQSAR applicability domain.

5.2 Method used to assess the applicability domain

The system does not generate predictions if it cannot calculate each descriptor value for the test compound.

Only positive predictions with probability equal to or greater than 0.7 and negative predictions with probability equal to or less than 0.3 were accepted.

5.3 Software name and version for applicability domain assessment

SciQSAR version 3.1.00.

5.4 Limits of applicability

The Danish QSAR group applies an overall definition of structures acceptable for QSAR processing which is applicable for all the in-house QSAR software, i.e. not only SciQSAR. According to this definition accepted structures are organic substances with an unambiguous structure, i.e. so-called discrete organics defined as: organic compounds with a defined two dimensional (2D) structure containing at least two carbon

atoms, only certain atoms (H, Li, B, C, N, O, F, Na, Mg, Si, P, S, Cl, K, Ca, Br, and I), and not mixtures with two or more 'big components' when analyzed for ionic bonds (for a number of small known organic ions assumed not to affect toxicity the 'parent molecule' is accepted). Structures with less than two carbon atoms or containing atoms not in the list above (e.g. heavy metals) are rendered out as not acceptable for further QSAR processing. Calculation 2D structures (SMILES and/or SDF) are generated by stripping off accepted organic and inorganic ions. Thus, all the training set and prediction set chemicals are used in their non-ionized form. See 5.1 for further applicability domain definition.

6. Internal validation

6.1 Availability of the training set

Yes

6.2 Available information for the training set

Yes

6.3 Data for each descriptor variable for the training set

No

6.4 Data for the dependent variable for the training set

Yes

6.5 Other information about the training set

1106 compounds are in the training set: 524 positives and 582 negatives.

6.6 Pre-processing of data before modelling

Data was originally collected from the FDAMDD database. Only compounds for which SMILES codes could be found and that had a structure acceptable for the commercial software were used in the final training set, that is only discrete organic chemicals as described in 5.4 were used. In case of replicate structures, one of the replicates was kept if all the compounds had the same activity and all were removed if they had different activity.

6.7 Statistics for goodness-of-fit

SciQSARs own internal performance test of the model gave the following Cooper's statistics for predictions within the applicability domain as defined by SciQSAR (i.e. the first criterion described in 5.1):

- Sensitivity (true positives / (true positives + false negatives)): 100%
- Specificity (true negatives / (true negatives + false positives)): 100%
- Concordance ((true positives + true negatives) / (true positives + true negatives + false positives + false negatives)): 100%

6.8 Robustness – Statistics obtained by leave-one-out cross-validation

Not performed.

6.9 Robustness – Statistics obtained by leave-many-out cross-validation

SciQSAR's own internal 10-fold cross-validation (10*10% out) procedure was used for predictions within the applicability domain as defined by SciQSAR (i.e. the first criterion described in 5.1). As the probability domain was not applied (i.e. the second criterion described in 5.2) the accuracy of the predictions when

applying this domain can be expected to be higher than reflected in these cross-validation results. This gave the following Cooper's statistics:

- Sensitivity (true positives / (true positives + false negatives)): 73.1%
- Specificity (true negatives / (true negatives + false positives)): 77.3%
- Concordance ((true positives + true negatives) / (true positives + true negatives + false positives + false negatives)): 75.3%

6.10 Robustness - Statistics obtained by Y-scrambling

Not performed.

6.11 Robustness - Statistics obtained by bootstrap

Not performed.

6.12 Robustness - Statistics obtained by other methods

Not performed.

7. External validation

7.1 Availability of the external validation set

7.2 Available information for the external validation set

7.3 Data for each descriptor variable for the external validation set

7.4 Data for the dependent variable for the external validation set

7.5 Other information about the validation set

7.6 Experimental design of test set

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

External validation has not been performed for this model.

8. Mechanistic interpretation

8.1 Mechanistic basis of the model

The SciQSAR software provides over 400 calculated physico–chemical, electrotopological E-state, connectivity and other molecular descriptors. The descriptors selected for the model may indicate modes of action that are obvious for persons with expert knowledge about the endpoint.

8.2 A priori or posteriori mechanistic interpretation

A posteriori mechanistic interpretation. The descriptors selected for the model may provide a basis for mechanistic interpretation.

8.3 Other information about the mechanistic interpretation

9. Miscellaneous information

9.1 Comments

The model can be used to predict the human MRDD in a categorical way: Positive means MRDD value between 0.0167-2.69 mg/kg bw/day, negative means MRDD values between 5.00-1000 mg/kg bw/day and marginal means intermediate in between 2.69 and 5.00 mg/kg bw/day. It can be argued that the predictions from this (Q)SAR model give a more accurate estimate of human MRDD/NOEL than those derived from animal toxicity studies, where multiple uncertainty/safety factors are necessary to compensate for incompatibility and uncertainty underlying the extrapolation of animal toxicity to humans.

9.2 Bibliography

Matthews, E.J, Kruhlak, N.L, Benz, R.D and Contrera, J.F. (2004) Assessment of the Health Effects of Chemicals in Humans: I. QSAR Estimation of the Maximum Recommended Daily Dose (MRDD) and No Effect Level (NOEL) of Organic Chemicals Based on Clinical Trial Data. *Current drug Discovery Technologies,* 1, 61-76.

Maximum recommended daily dose (MRDD) Database: http://www.epa.gov/comptox/dsstox/sdf_fdamdd.html. Accessed 9th of July 2013. According to which the data originates from:

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9.3 Supporting information