Table S2. Evaluation of QSARs according to the 49 assessment criteria for uncertainty, variability and bias.

|  |  |
| --- | --- |
| Low Uncertainty, Variability, Bias or Influence |  |
| Moderate Uncertainty, Variability, Bias or Influence |  |
| High Uncertainty, Variability, Bias or Influence |  |

Table S2a. QSAR Study #1. Luan *et al*.

|  |  |  |  |
| --- | --- | --- | --- |
| ID | Area of Uncertainty, Variability, Bias or Influence | Assignment of Uncertainty, Variability, Bias or Influence | Reason |
|  |  |  |  |
| Model Creation | | | |
|  |  |  |  |
| *1.1 Definition of Chemical Structures* | | | |
|  |  |  |  |
| 1.1a | Accuracy of chemical structure |  | Structures unambiguously defined including any isomerism |
| 1.1b | Assessment of significant impurities or mixtures |  | No mention of impurities or mixtures |
|  |  |  |  |
| *1.2* *Biological Data* | | | |
|  |  |  |  |
| 1.2a | Quality of individual studies in the data set |  | Quality of data not discussed within paper |
| 1.2b | Consistency of the data set including comparability of data |  | No mention of assays used, or testing laboratories utilised |
| 1.2c | Checking of toxicological data |  | No checking mentioned or apparent. |
| 1.2d | Error associated with biological data |  | Some mention of experimental error, but not stated what would be typically associated with the test |
| 1.2e | (if required) Units of concentration known, stated and appropriate for use |  | Units not stated |
| 1.2f | (If appropriate) Nominal or measured concentrations |  | Nominal concentrations used. Not stated in paper but can be assumed from Schultz et al (2003). |
| 1.2g | Internal exposure known |  | Internal exposure not known |
|  |  |  |  |
| *1.3 Measurement and / or Estimation of Physico-Chemical Properties and Structural Descriptors* | | | |
|  |  |  |  |
| 1.3a | Measurement of physico-chemical properties | N/A |  |
| 1.3b | Calculation of properties and 2-D descriptors |  | Well characterised software providing unambiguous properties |
| 1.3c | Calculation of 3-D descriptors |  | Structure optimisation performed without need for conformational analysis |
| 1.3d | Software utilised |  | Full details of software provided |
| 1.3e | Definition of molecular fragments | N/A |  |
|  |  |  |  |
| *1.4 Creation of the Data Set for QSAR Modelling* | | | |
|  |  |  |  |
| 1.4a | Data set is complete |  | Descriptor values have not been provided |
| 1.4b | Data set has appropriate variation in potency (quantitative) or balance of actives vs inactives (qualitative) |  | Good variation in potency |
| 1.4c | Selection of training set data |  | Randomly divided into training set without bias |
| 1.4d | Training set homogeneity |  | Training set is homogeneous |
| 1.4e | Suitable training and test sets defined and utilised |  | As required, appropriate training and test sets |
|  |  |  |  |
| *1.5 Modelling Approach* | | | |
|  |  |  |  |
| 1.5a | How appropriate is the modelling approach for the endpoint and to deal with the complexity / non-linearity of the data |  | Some modelling approaches e.g. RBFNN likely to be too complex for this simple cytotoxicity endpoint |
|  |  |  |  |
| Description of the QSAR Model | | | |
|  |  |  |  |
| *2.1 Description of Model* | | | |
|  |  |  |  |
| 2.1a | Documentation and reporting |  | Model fully defined |
| 2.1b | Data set is complete and described | ` | The data set is described/provided partially, descriptor values are not reported |
| 2.1c | Transparency of the model |  | MLR model is transparent in terms of the algorithm. PLS and RFBNN are not reported |
|  |  |  |  |
| *2.2 Statistical Performance* | | | |
|  |  |  |  |
| 2.2a | Statement of statistical fit, performance and predictivity |  | Full description of model performance |
| 2.2b | Interpretation of statistical fit etc with respect to biological error (see Criterion 1.2d) |  | Not interpretation is provided. Root Mean Square (RMS) error for RFBNN model is lower than would usually be expected for experimental error |
|  |  |  |  |
| *2.3 Applicability Domains* | | | |
|  |  |  |  |
| 2.3a | Chemical applicability domain of model |  | Domain defined but not in terms of all key aspects such as hydrophobicity and reactivity |
| 2.3b | Mechanistic applicability domain of model |  | Not defined |
| 2.3c | Biological applicability domain of model |  | Not defined |
|  |  |  |  |
| *2.4 Mechanistic Relevance, Interpretability and Transparency* | | | |
|  |  |  |  |
| 2.4a | Mechanistic justification |  | Grouped based upon special substituents that contribute to toxicity, however no mechanistic rationale mentioned |
| 2.4b | Presence / availability of other and supporting information |  | No supporting information |
| 2.4c | Relevance to descriptors to mechanism of action / AOP |  | Partial or correlated relationship to mechanism |
|  |  |  |  |
| *2.5 Adequate coverage of ADME effects* | | | |
|  |  |  |  |
| 2.5a | Metabolism and / or effect of significant metabolites have been considered |  | Role of metabolism not addressed |
| 2.5b | Toxicokinetics have been addressed in the model |  | Model does not relate to toxicokinetic considerations |
|  |  |  |  |
| Application of the QSAR Model | | | |
|  |  |  |  |
| *3.1 Documentation and Reproducibility* | | | |
|  |  |  |  |
| 3.1a | Reproducibility of the models |  | No descriptor values given |
| 3.1b | Reproducibility of the prediction |  | No descriptor values given |
|  |  |  |  |
| *3.2 Usability* | | | |
|  |  |  |  |
| 3.2a | Implementation of the model |  | Not implemented into software but it could be possible |
| 3.2b | Software accessibility |  | Software may be obtained on specific license |
| 3.2c | Software transparency | N/A |  |
| 3.2d | Relative cost |  | Cheap to use compared to a standard test |
| 3.2e | Sustainability |  | Need for licencing of software |
| 3.2f | Maintenance and support | N/A |  |
| 3.2g | Intellectual Property |  | No IP considerations i.e. open access |
| 3.2h | Ownership |  | Model in public domain |
| 3.21 | Ethics |  | No ethical concerns due to use of an in vitro assay |
|  |  |  |  |
| *3.3 Relevance* | | | |
|  |  |  |  |
| 3.3a | Heterogeneity and density of chemical space |  | Well populated and distributed chemical space |
| 3.3b | Relevance of the predicted endpoint for the regulatory risk assessment purpose/protection goal |  | Not a regulatory endpoint. However, likely to provide an estimate that could support e.g. hazard identification |
| 3.3c | Adequacy |  | Adequate for stated purpose |
| 3.3d | Extrapolation and relevance to humans | N/A |  |
| 3.3.e | Extrapolation and relevance to environmental biota |  | Relevant to environmental biota |
|  |  |  |  |

Table S2b. QSAR Study #2. Pal *et al*.

|  |  |  |  |
| --- | --- | --- | --- |
| ID | Area of Uncertainty, Variability, Bias or Influence | Assignment of Uncertainty, Variability, Bias or Influence | Reason |
|  |  |  |  |
| Model Creation | | | |
|  |  |  |  |
| *1.1 Definition of Chemical Structures* | | | |
|  |  |  |  |
| 1.1a | Accuracy of chemical structure |  | Structures unambiguously defined including any isomerism |
| 1.1b | Assessment of significant impurities or mixtures |  | No mention of impurities or mixtures |
|  |  |  |  |
| *1.2* *Biological Data* | | | |
|  |  |  |  |
| 1.2a | Quality of individual studies in the data set |  | Non-standard test, quality of individual studies not stated |
| 1.2b | Consistency of the data set including comparability of data |  | Assays used or laboratories not mentioned |
| 1.2c | Checking of toxicological data |  | No checking |
| 1.2d | Error associated with biological data |  | Unknown error |
| 1.2e | (if required) Units of concentration known, stated and appropriate for use |  | Not known or not stated |
| 1.2f | (If appropriate) Nominal or measured concentrations |  | Nominal concentrations used |
| 1.2g | Internal exposure known |  | Internal exposure not known |
|  |  |  |  |
| *1.3 Measurement and / or Estimation of Physico-Chemical Properties and Structural Descriptors* | | | |
|  |  |  |  |
| 1.3a | Measurement of physico-chemical properties | N/A | Measured properties not used |
| 1.3b | Calculation of properties and 2-D descriptors |  | Well characterised software providing unambiguous properties |
| 1.3c | Calculation of 3-D descriptors |  | Full structure optimisation performed, conformational analysis not required |
| 1.3d | Software utilised |  | Full details of software provided |
| 1.3e | Definition of molecular fragments | N/A | Molecular fragments not used in model |
|  |  |  |  |
| *1.4 Creation of the Data Set for QSAR Modelling* | | | |
|  |  |  |  |
| 1.4a | Data set is complete |  | Electrophilicity descriptor has not been reported within dataset |
| 1.4b | Data set has appropriate variation in potency (quantitative) or balance of actives vs inactives (qualitative) |  | Good variation in potency (e.g. several log units) |
| 1.4c | Selection of training set data |  | Data selection reported to be without bias using threefold cross-validation |
| 1.4d | Training set homogeneity |  | Training set is homogeneous |
| 1.4e | Suitable training and test sets defined and utilised |  | Only small test utilised |
|  |  |  |  |
| *1.5 Modelling Approach* | | | |
|  |  |  |  |
| 1.5a | How appropriate is the modelling approach for the endpoint and to deal with the complexity / non-linearity of the data |  | Regression analysis is an appropriate modelling approach for the endpoint |
|  |  |  |  |
| Description of the QSAR Model | | | |
|  |  |  |  |
| *2.1 Description of Model* | | | |
|  |  |  |  |
| 2.1a | Documentation and reporting |  | Model fully defined |
| 2.1b | Data set is complete and described |  | The data set is described/provided partially, descriptors values are not reported |
| 2.1c | Transparency of the model |  | Model is transparent in terms of the algorithm |
|  |  |  |  |
| *2.2 Statistical Performance* | | | |
|  |  |  |  |
| 2.2a | Statement of statistical fit, performance and predictivity |  | Full description of model performance |
| 2.2b | Interpretation of statistical fit etc with respect to biological error (see Criterion 1.2d) |  | No interpretation is provided, although the standard errors of models are possibly consistent with experimental error |
|  |  |  |  |
| *2.3 Applicability Domains* | | | |
|  |  |  |  |
| 2.3a | Chemical applicability domain of model |  | Defined as substituted benzenes, however key aspects are missing |
| 2.3b | Mechanistic applicability domain of model |  | Not defined |
| 2.3c | Biological applicability domain of model |  | Not defined |
|  |  |  |  |
| *2.4 Mechanistic Relevance, Interpretability and Transparency* | | | |
|  |  |  |  |
| 2.4a | Mechanistic justification |  | No mechanistic basis |
| 2.4b | Presence / availability of other and supporting information |  | No supporting information |
| 2.4c | Relevance to descriptors to mechanism of action / AOP |  | No mechanistic basis of descriptors |
|  |  |  |  |
| *2.5 Adequate coverage of ADME effects* | | | |
|  |  |  |  |
| 2.5a | Metabolism and / or effect of significant metabolites have been considered |  | No reference to metabolism |
| 2.5b | Toxicokinetics have been addressed in the model |  | No reference to toxicokinetics |
|  |  |  |  |
| Application of the QSAR Model | | | |
|  |  |  |  |
| *3.1 Documentation and Reproducibility* | | | |
|  |  |  |  |
| 3.1a | Reproducibility of the models |  | Descriptor values are not available, therefore the model cannot be reproduced |
| 3.1b | Reproducibility of the prediction |  | Descriptor values are not available, therefore the predictions cannot be reproduced |
|  |  |  |  |
| *3.2 Usability* | | | |
|  |  |  |  |
| 3.2a | Implementation of the model |  | Model has the potential to be implemented but this has not been undertaken |
| 3.2b | Software accessibility |  | Software may be obtained on specific license |
| 3.2c | Software transparency | N/A |  |
| 3.2d | Relative cost |  | Cheap to use compared to a standard test |
| 3.2e | Sustainability |  | Need for licencing of the Gaussian 09 program package |
| 3.2f | Maintenance and support | N/A |  |
| 3.2g | Intellectual Property |  | No IP considerations i.e. open access |
| 3.2h | Ownership |  | Model in public domain |
| 3.21 | Ethics |  | No ethical concerns |
|  |  |  |  |
| *3.3 Relevance* | | | |
|  |  |  |  |
| 3.3a | Heterogeneity and density of chemical space |  | Well populated and distributed chemical space |
| 3.3b | Relevance of the predicted endpoint for the regulatory risk assessment purpose/protection goal |  | Endpoint sufficient for purpose, can be used as an estimation in hazard assessment |
| 3.3c | Adequacy |  | Adequate for stated purpose |
| 3.3d | Extrapolation and relevance to humans | N/A |  |
| 3.3.e | Extrapolation and relevance to environmental biota |  | Relevant to environmental biota |
|  |  |  |  |

Table S2c. QSAR Study #3. de Morais e Silva *et al*.

|  |  |  |  |
| --- | --- | --- | --- |
| ID | Area of Uncertainty, Variability, Bias or Influence | Assignment of Uncertainty, Variability, Bias or Influence | Reason |
|  |  |  |  |
| Model Creation | | | |
|  |  |  |  |
| *1.1 Definition of Chemical Structures* | | | |
|  |  |  |  |
| 1.1a | Accuracy of chemical structure |  | Structures fully defined in terms of SMILES |
| 1.1b | Assessment of significant impurities or mixtures |  | No mention of impurities or mixtures |
|  |  |  |  |
| *1.2* *Biological Data* | | | |
|  |  |  |  |
| 1.2a | Quality of individual studies in the data set |  | Quality not known or stated |
| 1.2b | Consistency of the data set including comparability of data |  | No checking of assays or laboratories used |
| 1.2c | Checking of toxicological data |  | No checking |
| 1.2d | Error associated with biological data |  | Unknown error |
| 1.2e | (if required) Units of concentration known, stated and appropriate for use |  | Appropriate units stated |
| 1.2f | (If appropriate) Nominal or measured concentrations |  | Nominal concentrations used |
| 1.2g | Internal exposure known |  | Internal exposure not known |
|  |  |  |  |
| *1.3 Measurement and / or Estimation of Physico-Chemical Properties and Structural Descriptors* | | | |
|  |  |  |  |
| 1.3a | Measurement of physico-chemical properties | N/A |  |
| 1.3b | Calculation of properties and 2-D descriptors | N/A |  |
| 1.3c | Calculation of 3-D descriptors |  | Full structure optimisation without the need of conformational analysis |
| 1.3d | Software utilised |  | Full details of software and any options/non defaults |
| 1.3e | Definition of molecular fragments | N/A |  |
|  |  |  |  |
| *1.4 Creation of the Data Set for QSAR Modelling* | | | |
|  |  |  |  |
| 1.4a | Data set is complete |  | Descriptor values not given |
| 1.4b | Data set has appropriate variation in potency (quantitative) or balance of actives vs inactives (qualitative) |  | Good variation in potency |
| 1.4c | Selection of training set data |  | Data selection assumed to be without bias, although not reported |
| 1.4d | Training set homogeneity |  | Multiple toxicity values for single chemicals are included instead of taking an average |
| 1.4e | Suitable training and test sets defined and utilised |  | Replicate structures are present within both the training and test dataset |
|  |  |  |  |
| *1.5 Modelling Approach* | | | |
|  |  |  |  |
| 1.5a | How appropriate is the modelling approach for the endpoint and to deal with the complexity / non-linearity of the data |  | Appropriate modelling approach for the endpoint |
|  |  |  |  |
| Description of the QSAR Model | | | |
|  |  |  |  |
| *2.1 Description of Model* | | | |
|  |  |  |  |
| 2.1a | Documentation and reporting |  | Model fully defined |
| 2.1b | Data set is complete and described |  | Descriptor values are not provided |
| 2.1c | Transparency of the model |  | Model is transparent in terms of the algorithm |
|  |  |  |  |
| *2.2 Statistical Performance* | | | |
|  |  |  |  |
| 2.2a | Statement of statistical fit, performance and predictivity |  | Full description of model performance |
| 2.2b | Interpretation of statistical fit etc with respect to biological error (see Criterion 1.2d) |  |  |
|  |  |  |  |
| *2.3 Applicability Domains* | | | |
|  |  |  |  |
| 2.3a | Chemical applicability domain of model |  | Defined as organic compounds, however key aspects are missing such as fundamental physico-chemical property ranges |
| 2.3b | Mechanistic applicability domain of model |  | Fully defined in terms of relevant mechanism(s) of action |
| 2.3c | Biological applicability domain of model |  | Not defined |
|  |  |  |  |
| *2.4 Mechanistic Relevance, Interpretability and Transparency* | | | |
|  |  |  |  |
| 2.4a | Mechanistic justification |  | Definition of non-polar narcosis mechanism of action |
| 2.4b | Presence / availability of other and supporting information |  | No supporting information |
| 2.4c | Relevance to descriptors to mechanism of action / AOP |  | Descriptors or properties clearly related to mechanism |
|  |  |  |  |
| *2.5 Adequate coverage of ADME effects* | | | |
|  |  |  |  |
| 2.5a | Metabolism and / or effect of significant metabolites have been considered |  | No reference to metabolism |
| 2.5b | Toxicokinetics have been addressed in the model |  | Model relates to toxicokinetic considerations that affect toxicity or potency |
|  |  |  |  |
| Application of the QSAR Model | | | |
|  |  |  |  |
| *3.1 Documentation and Reproducibility* | | | |
|  |  |  |  |
| 3.1a | Reproducibility of the models |  | Descriptor values are not provided, therefore the models cannot be reproduced |
| 3.1b | Reproducibility of the prediction |  | Descriptor values are not provided, therefore the predictions cannot be reproduced |
|  |  |  |  |
| *3.2 Usability* | | | |
|  |  |  |  |
| 3.2a | Implementation of the model |  | Model has the potential to be implemented but this has not been undertaken |
| 3.2b | Software accessibility |  | Software may be obtained on specific license |
| 3.2c | Software transparency | N/A |  |
| 3.2d | Relative cost |  | Cheap to use compared to a standard test |
| 3.2e | Sustainability |  | Need for licensing of software |
| 3.2f | Maintenance and support | N/A |  |
| 3.2g | Intellectual Property |  | No IP considerations i.e. open access |
| 3.2h | Ownership |  | Model in public domain |
| 3.21 | Ethics |  | No ethical concerns |
|  |  |  |  |
| *3.3 Relevance* | | | |
|  |  |  |  |
| 3.3a | Heterogeneity and density of chemical space |  | Well populated and distributed chemical space |
| 3.3b | Relevance of the predicted endpoint for the regulatory risk assessment purpose/protection goal |  | Endpoint not sufficiently defined for regulatory use. However, likely to provide an estimate that could support e.g. hazard identification as part of a weight of evidence. |
| 3.3c | Adequacy |  | Adequate for stated purpose |
| 3.3d | Extrapolation and relevance to humans | N/A |  |
| 3.3.e | Extrapolation and relevance to environmental biota |  | Relevant to environmental biota |

Table S2d. QSAR Study #4. Toropova and Toropov

|  |  |  |  |
| --- | --- | --- | --- |
| ID | Area of Uncertainty, Variability, Bias or Influence | Assignment of Uncertainty, Variability, Bias or Influence | Reason |
|  |  |  |  |
| Model Creation | | | |
|  |  |  |  |
| *1.1 Definition of Chemical Structures* | | | |
|  |  |  |  |
| 1.1a | Accuracy of chemical structure |  | Structures fully defined in terms of SMILES |
| 1.1b | Assessment of significant impurities or mixtures |  | No mention of impurities or mixtures |
|  |  |  |  |
| *1.2* *Biological Data* | | | |
|  |  |  |  |
| 1.2a | Quality of individual studies in the data set |  | Quality not known or stated |
| 1.2b | Consistency of the data set including comparability of data |  | No checking of assay or laboratories used |
| 1.2c | Checking of toxicological data |  | No checking |
| 1.2d | Error associated with biological data |  | Not stated |
| 1.2e | (if required) Units of concentration known, stated and appropriate for use |  | Appropriate units stated |
| 1.2f | (If appropriate) Nominal or measured concentrations |  | Nominal concentrations used |
| 1.2g | Internal exposure known |  | Internal exposure not known |
|  |  |  |  |
| *1.3 Measurement and / or Estimation of Physico-Chemical Properties and Structural Descriptors* | | | |
|  |  |  |  |
| 1.3a | Measurement of physico-chemical properties | N/A |  |
| 1.3b | Calculation of properties and 2-D descriptors |  | Well characterised software providing unambiguous properties |
| 1.3c | Calculation of 3-D descriptors | N/A |  |
| 1.3d | Software utilised |  | Full details of software provided |
| 1.3e | Definition of molecular fragments | N/A |  |
|  |  |  |  |
| *1.4 Creation of the Data Set for QSAR Modelling* | | | |
|  |  |  |  |
| 1.4a | Data set is complete |  | Descriptor values not given |
| 1.4b | Data set has appropriate variation in potency (quantitative) or balance of actives vs inactives (qualitative) |  | Good variation in potency |
| 1.4c | Selection of training set data |  | Data selection assumed to be without bias, although not reported |
| 1.4d | Training set homogeneity |  | Multiple toxicity values for single chemicals are included instead of taking an average |
| 1.4e | Suitable training and test sets defined and utilised |  | Replicate structures are present within both the training and test dataset |
|  |  |  |  |
| *1.5 Modelling Approach* | | | |
|  |  |  |  |
| 1.5a | How appropriate is the modelling approach for the endpoint and to deal with the complexity / non-linearity of the data |  | Appropriate modelling approach for the endpoint |
|  |  |  |  |
| Description of the QSAR Model | | | |
|  |  |  |  |
| *2.1 Description of Model* | | | |
|  |  |  |  |
| 2.1a | Documentation and reporting |  | Model fully defined |
| 2.1b | Data set is complete and described |  | Descriptor values are not provided |
| 2.1c | Transparency of the model |  | Model is transparent in terms of algorithm |
|  |  |  |  |
| *2.2 Statistical Performance* | | | |
|  |  |  |  |
| 2.2a | Statement of statistical fit, performance and predictivity |  | Full description of model performance |
| 2.2b | Interpretation of statistical fit etc with respect to biological error (see Criterion 1.2d) |  |  |
|  |  |  |  |
| *2.3 Applicability Domains* | | | |
|  |  |  |  |
| 2.3a | Chemical applicability domain of model |  | Partially defined in supplementary with respect to SMILES |
| 2.3b | Mechanistic applicability domain of model |  | Not defined |
| 2.3c | Biological applicability domain of model |  | Not defined |
|  |  |  |  |
| *2.4 Mechanistic Relevance, Interpretability and Transparency* | | | |
|  |  |  |  |
| 2.4a | Mechanistic justification |  | No mechanistic basis |
| 2.4b | Presence / availability of other and supporting information |  | No supporting information |
| 2.4c | Relevance to descriptors to mechanism of action / AOP |  | No mechanistic basis of descriptors |
|  |  |  |  |
| *2.5 Adequate coverage of ADME effects* | | | |
|  |  |  |  |
| 2.5a | Metabolism and / or effect of significant metabolites have been considered |  | No reference to metabolism |
| 2.5b | Toxicokinetics have been addressed in the model |  | No reference to toxicokinetics |
|  |  |  |  |
| Application of the QSAR Model | | | |
|  |  |  |  |
| *3.1 Documentation and Reproducibility* | | | |
|  |  |  |  |
| 3.1a | Reproducibility of the models |  | Descriptor values are not provided, therefore the models cannot be reproduced |
| 3.1b | Reproducibility of the prediction |  | Descriptor values are not provided, therefore the predictions cannot be reproduced |
|  |  |  |  |
| *3.2 Usability* | | | |
|  |  |  |  |
| 3.2a | Implementation of the model |  | Model has been implemented into CORAL software |
| 3.2b | Software accessibility |  | Software is publicly and freely available |
| 3.2c | Software transparency | N/A |  |
| 3.2d | Relative cost |  | Cheap to use compared to that of a standard test |
| 3.2e | Sustainability |  | Published QSAR |
| 3.2f | Maintenance and support | N/A |  |
| 3.2g | Intellectual Property |  | No IP considerations i.e. open access |
| 3.2h | Ownership |  | Model in public domain |
| 3.21 | Ethics |  | No ethical concerns |
|  |  |  |  |
| *3.3 Relevance* | | | |
|  |  |  |  |
| 3.3a | Heterogeneity and density of chemical space |  | Well populated and distributed chemical space |
| 3.3b | Relevance of the predicted endpoint for the regulatory risk assessment purpose/protection goal |  | Endpoint not sufficiently defined for regulatory use. However, likely to provide an estimate that could support e.g. hazard identification as part of a weight of evidence. |
| 3.3c | Adequacy |  | Adequate for stated purpose. Likely to provide an estimate that could support e.g. hazard identification. |
| 3.3d | Extrapolation and relevance to humans | N/A |  |
| 3.3.e | Extrapolation and relevance to environmental biota |  | Relevant to environmental biota |
|  |  |  |  |

Table S2e. QSAR Study #5. Wang *et al*.

|  |  |  |  |
| --- | --- | --- | --- |
| ID | Area of Uncertainty, Variability, Bias or Influence | Assignment of Uncertainty, Variability, Bias or Influence | Reason |
|  |  |  |  |
| Model Creation | | | |
|  |  |  |  |
| *1.1 Definition of Chemical Structures* | | | |
|  |  |  |  |
| 1.1a | Accuracy of chemical structure |  | Structures not fully defined |
| 1.1b | Assessment of significant impurities or mixtures |  | No mention of impurities or mixtures |
|  |  |  |  |
| *1.2* *Biological Data* | | | |
|  |  |  |  |
| 1.2a | Quality of individual studies in the data set |  | Quality not known |
| 1.2b | Consistency of the data set including comparability of data |  | Laboratories/assay unknown |
| 1.2c | Checking of toxicological data |  | No checking |
| 1.2d | Error associated with biological data |  | Unknown error |
| 1.2e | (if required) Units of concentration known, stated and appropriate for use |  | Appropriate units stated |
| 1.2f | (If appropriate) Nominal or measured concentrations |  | Nominal concentrations used |
| 1.2g | Internal exposure known |  | Internal exposure not known |
|  |  |  |  |
| *1.3 Measurement and / or Estimation of Physico-Chemical Properties and Structural Descriptors* | | | |
|  |  |  |  |
| 1.3a | Measurement of physico-chemical properties |  | Reliabile and reproducible physico-chemical properties have been calculated |
| 1.3b | Calculation of properties and 2-D descriptors | N/A |  |
| 1.3c | Calculation of 3-D descriptors | N/A |  |
| 1.3d | Software utilised |  | Software known, but not fully described |
| 1.3e | Definition of molecular fragments | N/A |  |
|  |  |  |  |
| *1.4 Creation of the Data Set for QSAR Modelling* | | | |
|  |  |  |  |
| 1.4a | Data set is complete |  | Descriptor values not given |
| 1.4b | Data set has appropriate variation in potency (quantitative) or balance of actives vs inactives (qualitative) |  | Good variation in potency |
| 1.4c | Selection of training set data |  | Data selection assumed to be without bias, although not reported |
| 1.4d | Training set homogeneity |  | Training set is homogenous |
| 1.4e | Suitable training and test sets defined and utilised |  | Appropriate training and test sets |
|  |  |  |  |
| *1.5 Modelling Approach* | | | |
|  |  |  |  |
| 1.5a | How appropriate is the modelling approach for the endpoint and to deal with the complexity / non-linearity of the data |  | Regression analysis is an appropriate modelling approach for the endpoint |
|  |  |  |  |
| Description of the QSAR Model | | | |
|  |  |  |  |
| *2.1 Description of Model* | | | |
|  |  |  |  |
| 2.1a | Documentation and reporting |  | Model fully defined |
| 2.1b | Data set is complete and described |  | Chemical names and toxicological values only provided |
| 2.1c | Transparency of the model |  | Model is transparent in terms of algorithm |
|  |  |  |  |
| *2.2 Statistical Performance* | | | |
|  |  |  |  |
| 2.2a | Statement of statistical fit, performance and predictivity |  | Full description of model performance |
| 2.2b | Interpretation of statistical fit etc with respect to biological error (see Criterion 1.2d) |  |  |
|  |  |  |  |
| *2.3 Applicability Domains* | | | |
|  |  |  |  |
| 2.3a | Chemical applicability domain of model |  | Defined as alcohol organic small molecule compounds, however key aspects are missing |
| 2.3b | Mechanistic applicability domain of model |  | Not defined |
| 2.3c | Biological applicability domain of model |  | Not defined |
|  |  |  |  |
| *2.4 Mechanistic Relevance, Interpretability and Transparency* | | | |
|  |  |  |  |
| 2.4a | Mechanistic justification |  | No mechanistic basis |
| 2.4b | Presence / availability of other and supporting information |  | No supporting information |
| 2.4c | Relevance to descriptors to mechanism of action / AOP |  | No mechanistic basis of descriptors |
|  |  |  |  |
| *2.5 Adequate coverage of ADME effects* | | | |
|  |  |  |  |
| 2.5a | Metabolism and / or effect of significant metabolites have been considered |  | No reference to metabolism |
| 2.5b | Toxicokinetics have been addressed in the model |  | No reference to toxicokinetics |
|  |  |  |  |
| Application of the QSAR Model | | | |
|  |  |  |  |
| *3.1 Documentation and Reproducibility* | | | |
|  |  |  |  |
| 3.1a | Reproducibility of the models |  | Descriptor values are not provided, therefore the models cannot be reproduced |
| 3.1b | Reproducibility of the prediction |  | Descriptor values are not provided, therefore the predictions cannot be reproduced |
|  |  |  |  |
| *3.2 Usability* | | | |
|  |  |  |  |
| 3.2a | Implementation of the model |  | Model has the potential to be implemented but that has not been undertaken |
| 3.2b | Software accessibility |  | Software is publicly and freely available |
| 3.2c | Software transparency | N/A |  |
| 3.2d | Relative cost |  | Cheap to use compared to standard test |
| 3.2e | Sustainability |  | Published QSAR |
| 3.2f | Maintenance and support | N/A |  |
| 3.2g | Intellectual Property |  | No IP considerations i.e. open access |
| 3.2h | Ownership |  | Model in public domain |
| 3.21 | Ethics |  | No ethical concerns |
|  |  |  |  |
| *3.3 Relevance* | | | |
|  |  |  |  |
| 3.3a | Heterogeneity and density of chemical space |  | Well populated and distributed chemical space |
| 3.3b | Relevance of the predicted endpoint for the regulatory risk assessment purpose/protection goal |  | Endpoint not sufficiently defined for regulatory use. However, likely to provide an estimate that could support e.g. hazard identification as part of a weight of evidence. |
| 3.3c | Adequacy |  | Adequate for stated purpose. Likely to provide an estimate that could support e.g. hazard identification. |
| 3.3d | Extrapolation and relevance to humans | N/A |  |
| 3.3.e | Extrapolation and relevance to environmental biota |  | Relevant to environmental biota |
|  |  |  |  |

Table S2g. QSAR Study #6. Yan *et al*.

|  |  |  |  |
| --- | --- | --- | --- |
| ID | Area of Uncertainty, Variability, Bias or Influence | Assignment of Uncertainty, Variability, Bias or Influence | Reason |
|  |  |  |  |
| Model Creation | | | |
|  |  |  |  |
| *1.1 Definition of Chemical Structures* | | | |
|  |  |  |  |
| 1.1a | Accuracy of chemical structure |  | Only CAS numbers provided, structures not defined |
| 1.1b | Assessment of significant impurities or mixtures |  | Impurities/mixtures not stated |
|  |  |  |  |
| *1.2* *Biological Data* | | | |
|  |  |  |  |
| 1.2a | Quality of individual studies in the data set |  | Quality of individual studies not known |
| 1.2b | Consistency of the data set including comparability of data |  | No mention of assays used, or testing laboratories utilised |
| 1.2c | Checking of toxicological data |  | No checking |
| 1.2d | Error associated with biological data |  | Unknown error |
| 1.2e | (if required) Units of concentration known, stated and appropriate for use |  | Appropriate units stated |
| 1.2f | (If appropriate) Nominal or measured concentrations |  | Nominal concentrations used |
| 1.2g | Internal exposure known |  | Internal exposure not known |
|  |  |  |  |
| *1.3 Measurement and / or Estimation of Physico-Chemical Properties and Structural Descriptors* | | | |
|  |  |  |  |
| 1.3a | Measurement of physico-chemical properties | N/A |  |
| 1.3b | Calculation of properties and 2-D descriptors | N/A |  |
| 1.3c | Calculation of 3-D descriptors |  | Full structure optimisation performed |
| 1.3d | Software utilised |  | Full details of software provided |
| 1.3e | Definition of molecular fragments | N/A |  |
|  |  |  |  |
| *1.4 Creation of the Data Set for QSAR Modelling* | | | |
|  |  |  |  |
| 1.4a | Data set is complete |  | Majority of dataset is provided, albeit with structures lacking |
| 1.4b | Data set has appropriate variation in potency (quantitative) or balance of actives vs inactives (qualitative) |  | Good variation in potency |
| 1.4c | Selection of training set data |  | Data selection assumed to be without bias |
| 1.4d | Training set homogeneity |  | Chemicals are homogenous across chemical space |
| 1.4e | Suitable training and test sets defined and utilised |  | Appropriate training and test sets |
|  |  |  |  |
| *1.5 Modelling Approach* | | | |
|  |  |  |  |
| 1.5a | How appropriate is the modelling approach for the endpoint and to deal with the complexity / non-linearity of the data |  | Regression analysis is an appropriate modelling approach for the endpoint |
|  |  |  |  |
| Description of the QSAR Model | | | |
|  |  |  |  |
| *2.1 Description of Model* | | | |
|  |  |  |  |
| 2.1a | Documentation and reporting |  | Model fully defined |
| 2.1b | Data set is complete and described |  | Dataset is described/provided partially |
| 2.1c | Transparency of the model |  | Model is transparent in terms of the algorithm and can be interpreted and reproduced |
|  |  |  |  |
| *2.2 Statistical Performance* | | | |
|  |  |  |  |
| 2.2a | Statement of statistical fit, performance and predictivity |  | Full description of the model performance |
| 2.2b | Interpretation of statistical fit etc with respect to biological error (see Criterion 1.2d) |  | No consideration of experimental error given |
|  |  |  |  |
| *2.3 Applicability Domains* | | | |
|  |  |  |  |
| 2.3a | Chemical applicability domain of model |  | Domain defined but not in terms of all key aspects |
| 2.3b | Mechanistic applicability domain of model |  | Not defined |
| 2.3c | Biological applicability domain of model |  | Not defined |
|  |  |  |  |
| *2.4 Mechanistic Relevance, Interpretability and Transparency* | | | |
|  |  |  |  |
| 2.4a | Mechanistic justification |  | No mechanistic basis |
| 2.4b | Presence / availability of other and supporting information |  | No supporting information |
| 2.4c | Relevance to descriptors to mechanism of action / AOP |  | No mechanistic basis of descriptors |
|  |  |  |  |
| *2.5 Adequate coverage of ADME effects* | | | |
|  |  |  |  |
| 2.5a | Metabolism and / or effect of significant metabolites have been considered |  | No reference to metabolism |
| 2.5b | Toxicokinetics have been addressed in the model |  | No reference to toxicokinetics |
|  |  |  |  |
| Application of the QSAR Model | | | |
|  |  |  |  |
| *3.1 Documentation and Reproducibility* | | | |
|  |  |  |  |
| 3.1a | Reproducibility of the models |  | Model transparent and fully documented |
| 3.1b | Reproducibility of the prediction |  | All parameters are available allowing for predictions to be reproduced |
|  |  |  |  |
| *3.2 Usability* | | | |
|  |  |  |  |
| 3.2a | Implementation of the model |  | Model has potential to be implemented but this has not been undertaken |
| 3.2b | Software accessibility |  | Software may be obtained on specific license |
| 3.2c | Software transparency | N/A |  |
| 3.2d | Relative cost |  | Cheap to use compared to a standard test |
| 3.2e | Sustainability |  | Need for licencing of the HyperChem software |
| 3.2f | Maintenance and support | N/A |  |
| 3.2g | Intellectual Property |  | No IP considerations i.e. open access |
| 3.2h | Ownership |  | Model in public domain |
| 3.21 | Ethics |  | No ethical concerns |
|  |  |  |  |
| *3.3 Relevance* | | | |
|  |  |  |  |
| 3.3a | Heterogeneity and density of chemical space |  | Well populated and distributed chemical space |
| 3.3b | Relevance of the predicted endpoint for the regulatory risk assessment purpose/protection goal |  | Endpoint sufficient for purpose, can be used as an estimation in hazard assessment |
| 3.3c | Adequacy |  | Adequate for stated purpose |
| 3.3d | Extrapolation and relevance to humans | N/A |  |
| 3.3e | Extrapolation and relevance to environmental biota |  | Relevant to environmental biota |
|  |  |  |  |

Table S2h. QSAR Study #7. He *et al*.

|  |  |  |  |
| --- | --- | --- | --- |
| ID | Area of Uncertainty, Variability, Bias or Influence | Assignment of Uncertainty, Variability, Bias or Influence | Reason |
|  |  |  |  |
| Model Creation | | | |
|  |  |  |  |
| *1.1 Definition of Chemical Structures* | | | |
|  |  |  |  |
| 1.1a | Accuracy of chemical structure |  | Structures unambiguously defined including any isomerism |
| 1.1b | Assessment of significant impurities or mixtures |  | Impurities/mixtures defined and removed |
|  |  |  |  |
| *1.2* *Biological Data* | | | |
|  |  |  |  |
| 1.2a | Quality of individual studies in the data set |  | Quality of the individual studies are not known |
| 1.2b | Consistency of the data set including comparability of data |  | Assays used or laboratories not mentioned |
| 1.2c | Checking of toxicological data |  | UNSURE, Records reported to be verified by two individuals simultaneously |
| 1.2d | Error associated with biological data |  |  |
| 1.2e | (if required) Units of concentration known, stated and appropriate for use | N/A |  |
| 1.2f | (If appropriate) Nominal or measured concentrations | N/A |  |
| 1.2g | Internal exposure known | N/A |  |
|  |  |  |  |
| *1.3 Measurement and / or Estimation of Physico-Chemical Properties and Structural Descriptors* | | | |
|  |  |  |  |
| 1.3a | Measurement of physico-chemical properties | N/A | Measured properties not used |
| 1.3b | Calculation of properties and 2-D descriptors |  | Well characterised software providing unambiguous properties |
| 1.3c | Calculation of 3-D descriptors | N/A | 3-D descriptors not used |
| 1.3d | Software utilised |  | Software is known, but not fully described |
| 1.3e | Definition of molecular fragments | N/A | Molecular fragments not used |
|  |  |  |  |
| *1.4 Creation of the Data Set for QSAR Modelling* | | | |
|  |  |  |  |
| 1.4a | Data set is complete |  | Descriptors values have not been provided |
| 1.4b | Data set has appropriate variation in potency (quantitative) or balance of actives vs inactives (qualitative) |  | Well balanced data set of actives and inactives |
| 1.4c | Selection of training set data |  |  |
| 1.4d | Training set homogeneity |  | Training set is homogenous |
| 1.4e | Suitable training and test sets defined and utilised |  | As required, appropriate |
|  |  |  |  |
| *1.5 Modelling Approach* | | | |
|  |  |  |  |
| 1.5a | How appropriate is the modelling approach for the endpoint and to deal with the complexity / non-linearity of the data |  | Modelling approach likely, but unproven, to be appropriate for the hepatotoxicity endpoint |
|  |  |  |  |
| Description of the QSAR Model | | | |
|  |  |  |  |
| *2.1 Description of Model* | | | |
|  |  |  |  |
| 2.1a | Documentation and reporting |  | Model non-defined |
| 2.1b | Data set is complete and described |  | The data set is described/provided partially, descriptor values are not reported |
| 2.1c | Transparency of the model |  | Non-transparent model |
|  |  |  |  |
| *2.2 Statistical Performance* | | | |
|  |  |  |  |
| 2.2a | Statement of statistical fit, performance and predictivity |  | Full description of model performance |
| 2.2b | Interpretation of statistical fit etc with respect to biological error (see Criterion 1.2d) | N/A |  |
|  |  |  |  |
| *2.3 Applicability Domains* | | | |
|  |  |  |  |
| 2.3a | Chemical applicability domain of model |  | Not defined |
| 2.3b | Mechanistic applicability domain of model |  | Not defined |
| 2.3c | Biological applicability domain of model |  | Not defined |
|  |  |  |  |
| *2.4 Mechanistic Relevance, Interpretability and Transparency* | | | |
|  |  |  |  |
| 2.4a | Mechanistic justification |  | No mechanistic basis |
| 2.4b | Presence / availability of other and supporting information |  | No supporting information |
| 2.4c | Relevance to descriptors to mechanism of action / AOP |  | No mechanistic basis of descriptors |
|  |  |  |  |
| *2.5 Adequate coverage of ADME effects* | | | |
|  |  |  |  |
| 2.5a | Metabolism and / or effect of significant metabolites have been considered |  | No reference to metabolism |
| 2.5b | Toxicokinetics have been addressed in the model |  | No reference to toxicokinetics |
|  |  |  |  |
| Application of the QSAR Model | | | |
|  |  |  |  |
| *3.1 Documentation and Reproducibility* | | | |
|  |  |  |  |
| 3.1a | Reproducibility of the models |  | Descriptor values are not available, therefore the model cannot be reproduced |
| 3.1b | Reproducibility of the prediction |  | Descriptor values are not available, therefore the predictions cannot be reproduced |
|  |  |  |  |
| *3.2 Usability* | | | |
|  |  |  |  |
| 3.2a | Implementation of the model |  | Model has the potential to be implemented, but this has not been undertaken |
| 3.2b | Software accessibility |  | Software is publicly and freely available |
| 3.2c | Software transparency | N/A |  |
| 3.2d | Relative cost |  | Cheap to use compared to that of a standard test |
| 3.2e | Sustainability |  | Published model |
| 3.2f | Maintenance and support | N/A |  |
| 3.2g | Intellectual Property |  | No IP considerations i.e. open access |
| 3.2h | Ownership |  | Model in public domain |
| 3.21 | Ethics |  | No ethical concerns |
|  |  |  |  |
| *3.3 Relevance* | | | |
|  |  |  |  |
| 3.3a | Heterogeneity and density of chemical space |  | Well populated and distributed chemical space |
| 3.3b | Relevance of the predicted endpoint for the regulatory risk assessment purpose/protection goal |  | Not a regulatory endpoint, although may be used as part of a weight of evidence for chronic toxicity in some circumstances |
| 3.3c | Adequacy |  | Adequate for stated purpose |
| 3.3d | Extrapolation and relevance to humans |  | Relevant to humans |
| 3.3.e | Extrapolation and relevance to environmental biota | N/A |  |
|  |  |  |  |

Table S2h. QSAR Study #8. Jiang *et al*.

|  |  |  |  |
| --- | --- | --- | --- |
| ID | Area of Uncertainty, Variability, Bias or Influence | Assignment of Uncertainty, Variability, Bias or Influence | Reason |
|  |  |  |  |
| Model Creation | | | |
|  |  |  |  |
| *1.1 Definition of Chemical Structures* | | | |
|  |  |  |  |
| 1.1a | Accuracy of chemical structure |  | Structures unambiguously defined including any isomerism |
| 1.1b | Assessment of significant impurities or mixtures |  | Impurities/mixtures defined and removed |
|  |  |  |  |
| *1.2* *Biological Data* | | | |
|  |  |  |  |
| 1.2a | Quality of individual studies in the data set |  | Quality of the individual studies are not known |
| 1.2b | Consistency of the data set including comparability of data |  | Assays used or laboratories not mentioned |
| 1.2c | Checking of toxicological data |  | Data quality reported to be verified |
| 1.2d | Error associated with biological data |  |  |
| 1.2e | (if required) Units of concentration known, stated and appropriate for use | N/A |  |
| 1.2f | (If appropriate) Nominal or measured concentrations | N/A |  |
| 1.2g | Internal exposure known | N/A |  |
|  |  |  |  |
| *1.3 Measurement and / or Estimation of Physico-Chemical Properties and Structural Descriptors* | | | |
|  |  |  |  |
| 1.3a | Measurement of physico-chemical properties | N/A |  |
| 1.3b | Calculation of properties and 2-D descriptors | N/A |  |
| 1.3c | Calculation of 3-D descriptors | N/A |  |
| 1.3d | Software utilised |  | Software is known but version number and parameters not fully described |
| 1.3e | Definition of molecular fragments |  | Correct fragments used, definition of the fragment and its domain defined |
|  |  |  |  |
| *1.4 Creation of the Data Set for QSAR Modelling* | | | |
|  |  |  |  |
| 1.4a | Data set is complete |  |  |
| 1.4b | Data set has appropriate variation in potency (quantitative) or balance of actives vs inactives (qualitative) |  | Well balanced data set of actives and inactives |
| 1.4c | Selection of training set data |  | Data selection reported to be without bias |
| 1.4d | Training set homogeneity |  | Chemicals are homogenous across chemical space |
| 1.4e | Suitable training and test sets defined and utilised |  | Appropriate training and test sets |
|  |  |  |  |
| *1.5 Modelling Approach* | | | |
|  |  |  |  |
| 1.5a | How appropriate is the modelling approach for the endpoint and to deal with the complexity / non-linearity of the data |  | Some modelling approaches likely, but unproven, to be appropriate for the reproductive endpoint |
|  |  |  |  |
| Description of the QSAR Model | | | |
|  |  |  |  |
| *2.1 Description of Model* | | | |
|  |  |  |  |
| 2.1a | Documentation and reporting |  | Model non-defined |
| 2.1b | Data set is complete and described |  | The dataset is provided, but not fully described |
| 2.1c | Transparency of the model |  | Models are described, but not provided |
|  |  |  |  |
| *2.2 Statistical Performance* | | | |
|  |  |  |  |
| 2.2a | Statement of statistical fit, performance and predictivity |  | Full description of model performance |
| 2.2b | Interpretation of statistical fit etc with respect to biological error (see Criterion 1.2d) | N/A |  |
|  |  |  |  |
| *2.3 Applicability Domains* | | | |
|  |  |  |  |
| 2.3a | Chemical applicability domain of model |  | Domain defined but not in terms of all key aspects |
| 2.3b | Mechanistic applicability domain of model |  | Not defined |
| 2.3c | Biological applicability domain of model |  | Not defined |
|  |  |  |  |
| *2.4 Mechanistic Relevance, Interpretability and Transparency* | | | |
|  |  |  |  |
| 2.4a | Mechanistic justification |  | No mechanistic basis |
| 2.4b | Presence / availability of other and supporting information |  | No supporting information |
| 2.4c | Relevance to descriptors to mechanism of action / AOP |  | Mechanistic basis for structural alerts clearly related to mechanism |
|  |  |  |  |
| *2.5 Adequate coverage of ADME effects* | | | |
|  |  |  |  |
| 2.5a | Metabolism and / or effect of significant metabolites have been considered |  | Metabolism is discussed but not able to be predicted by the model |
| 2.5b | Toxicokinetics have been addressed in the model |  | No reference to toxicokinetics |
|  |  |  |  |
| Application of the QSAR Model | | | |
|  |  |  |  |
| *3.1 Documentation and Reproducibility* | | | |
|  |  |  |  |
| 3.1a | Reproducibility of the models |  | Software used to gather descriptors and produce the models are not provided |
| 3.1b | Reproducibility of the prediction |  | Models are not provided |
|  |  |  |  |
| *3.2 Usability* | | | |
|  |  |  |  |
| 3.2a | Implementation of the model |  | Model has the potential to be implemented but this has not been undertaken |
| 3.2b | Software accessibility |  | Software is publicly and freely available |
| 3.2c | Software transparency | N/A |  |
| 3.2d | Relative cost |  | Cheap to use compared to that of a standard test |
| 3.2e | Sustainability |  | Published model |
| 3.2f | Maintenance and support | N/A |  |
| 3.2g | Intellectual Property |  | No IP considerations i.e. open access |
| 3.2h | Ownership |  | Model in public domain |
| 3.21 | Ethics |  | No ethical concerns |
|  |  |  |  |
| *3.3 Relevance* | | | |
|  |  |  |  |
| 3.3a | Heterogeneity and density of chemical space |  | Well populated and distributed chemical space |
| 3.3b | Relevance of the predicted endpoint for the regulatory risk assessment purpose/protection goal |  | Not a regulatory endpoint in terms of an OECD Test Guideline, however may provide some information as a weight of evidence |
| 3.3c | Adequacy |  | Adequate for stated purpose |
| 3.3d | Extrapolation and relevance to humans |  | Relevant to humans |
| 3.3e | Extrapolation and relevance to environmental biota | N/A |  |
|  |  |  |  |

Table S2i. QSAR Study #9. Gupta and Rana

|  |  |  |  |
| --- | --- | --- | --- |
| ID | Area of Uncertainty, Variability, Bias or Influence | Assignment of Uncertainty, Variability, Bias or Influence | Reason |
|  |  |  |  |
| Model Creation | | | |
|  |  |  |  |
| *1.1 Definition of Chemical Structures* | | | |
|  |  |  |  |
| 1.1a | Accuracy of chemical structure |  | Structures not defined |
| 1.1b | Assessment of significant impurities or mixtures |  | Impurities/mixtures not stated |
|  |  |  |  |
| *1.2* *Biological Data* | | | |
|  |  |  |  |
| 1.2a | Quality of individual studies in the data set |  | Quality of the individual studies are not known |
| 1.2b | Consistency of the data set including comparability of data |  | Assays used or laboratories not mentioned |
| 1.2c | Checking of toxicological data |  | No checking |
| 1.2d | Error associated with biological data |  |  |
| 1.2e | (if required) Units of concentration known, stated and appropriate for use |  |  |
| 1.2f | (If appropriate) Nominal or measured concentrations | N/A |  |
| 1.2g | Internal exposure known | N/A |  |
|  |  |  |  |
| *1.3 Measurement and / or Estimation of Physico-Chemical Properties and Structural Descriptors* | | | |
|  |  |  |  |
| 1.3a | Measurement of physico-chemical properties | N/A |  |
| 1.3b | Calculation of properties and 2-D descriptors |  | Well characterised software proving unambiguous properties |
| 1.3c | Calculation of 3-D descriptors | N/A |  |
| 1.3d | Software utilised |  | Software is known and fully described |
| 1.3e | Definition of molecular fragments |  |  |
|  |  |  |  |
| *1.4 Creation of the Data Set for QSAR Modelling* | | | |
|  |  |  |  |
| 1.4a | Data set is complete |  | Data set used is not provided |
| 1.4b | Data set has appropriate variation in potency (quantitative) or balance of actives vs inactives (qualitative) |  | Data set is highly imbalanced |
| 1.4c | Selection of training set data |  | Data selection assumed to be without bias, although not stated |
| 1.4d | Training set homogeneity |  | Chemicals are reported to be well distributed across the chemical space, although this can not be confirmed |
| 1.4e | Suitable training and test sets defined and utilised |  | As required, appropriate |
|  |  |  |  |
| *1.5 Modelling Approach* | | | |
|  |  |  |  |
| 1.5a | How appropriate is the modelling approach for the endpoint and to deal with the complexity / non-linearity of the data |  | Modelling approach likely to be too complex, with a large quantity of descriptors being selected |
|  |  |  |  |
| Description of the QSAR Model | | | |
|  |  |  |  |
| *2.1 Description of Model* | | | |
|  |  |  |  |
| 2.1a | Documentation and reporting |  | Model fully defined |
| 2.1b | Data set is complete and described |  | Data set is not provided |
| 2.1c | Transparency of the model |  | Model is fairly transparent, however machine learning methods may be difficult to interpret |
|  |  |  |  |
| *2.2 Statistical Performance* | | | |
|  |  |  |  |
| 2.2a | Statement of statistical fit, performance and predictivity |  | Full description of model performance |
| 2.2b | Interpretation of statistical fit etc with respect to biological error (see Criterion 1.2d) | N/A |  |
|  |  |  |  |
| *2.3 Applicability Domains* | | | |
|  |  |  |  |
| 2.3a | Chemical applicability domain of model |  | Not defined |
| 2.3b | Mechanistic applicability domain of model |  | Not defined |
| 2.3c | Biological applicability domain of model |  | Not defined |
|  |  |  |  |
| *2.4 Mechanistic Relevance, Interpretability and Transparency* | | | |
|  |  |  |  |
| 2.4a | Mechanistic justification |  | No mechanistic basis |
| 2.4b | Presence / availability of other and supporting information |  | No supporting information |
| 2.4c | Relevance to descriptors to mechanism of action / AOP |  | No mechanistic basis of descriptors |
|  |  |  |  |
| *2.5 Adequate coverage of ADME effects* | | | |
|  |  |  |  |
| 2.5a | Metabolism and / or effect of significant metabolites have been considered |  | No reference to metabolism |
| 2.5b | Toxicokinetics have been addressed in the model |  | No reference to toxicokinetics |
|  |  |  |  |
| Application of the QSAR Model | | | |
|  |  |  |  |
| *3.1 Documentation and Reproducibility* | | | |
|  |  |  |  |
| 3.1a | Reproducibility of the models |  | Methodology is detailed well, however no data set is provided therefore the models cannot be reproduced |
| 3.1b | Reproducibility of the prediction |  | Data set is not provided, therefore the predictions cannot be reproduced |
|  |  |  |  |
| *3.2 Usability* | | | |
|  |  |  |  |
| 3.2a | Implementation of the model |  | Model has the potential to be implemented, but this has not been undertaken |
| 3.2b | Software accessibility |  | Software is publicly and freely available |
| 3.2c | Software transparency | N/A |  |
| 3.2d | Relative cost |  | Cheap to use compared to that of a standard test |
| 3.2e | Sustainability |  | Published model |
| 3.2f | Maintenance and support | N/A |  |
| 3.2g | Intellectual Property |  | No IP considerations i.e. open access |
| 3.2h | Ownership |  | Model in public domain |
| 3.21 | Ethics |  | No ethical concerns |
|  |  |  |  |
| *3.3 Relevance* | | | |
|  |  |  |  |
| 3.3a | Heterogeneity and density of chemical space |  | Well populated and distributed chemical space |
| 3.3b | Relevance of the predicted endpoint for the regulatory risk assessment purpose/protection goal |  | Not a regulatory endpoint, though may be useful as part of a weight of evidence |
| 3.3c | Adequacy |  | Adequate for stated purpose |
| 3.3d | Extrapolation and relevance to humans |  | Relevant to humans |
| 3.3.e | Extrapolation and relevance to environmental biota | N/A |  |
|  |  |  |  |

Table S2j. QSAR Study #10. Ibrahim *et al*.

|  |  |  |  |
| --- | --- | --- | --- |
| ID | Area of Uncertainty, Variability, Bias or Influence | Assignment of Uncertainty, Variability, Bias or Influence | Reason |
|  |  |  |  |
| Model Creation | | | |
|  |  |  |  |
| *1.1 Definition of Chemical Structures* | | | |
|  |  |  |  |
| 1.1a | Accuracy of chemical structure |  | Structures unambiguously defined including any isomerism |
| 1.1b | Assessment of significant impurities or mixtures |  | Impurities/mixtures not known |
|  |  |  |  |
| *1.2* *Biological Data* | | | |
|  |  |  |  |
| 1.2a | Quality of individual studies in the data set |  | Quality of studies not stated |
| 1.2b | Consistency of the data set including comparability of data |  | Assays used or laboratories not mentioned |
| 1.2c | Checking of toxicological data |  | No checking |
| 1.2d | Error associated with biological data |  | Unknown error |
| 1.2e | (if required) Units of concentration known, stated and appropriate for use |  | Not known or stated |
| 1.2f | (If appropriate) Nominal or measured concentrations |  | Neither stated |
| 1.2g | Internal exposure known |  | Internal exposure not known |
|  |  |  |  |
| *1.3 Measurement and / or Estimation of Physico-Chemical Properties and Structural Descriptors* | | | |
|  |  |  |  |
| 1.3a | Measurement of physico-chemical properties | N/A |  |
| 1.3b | Calculation of properties and 2-D descriptors |  | Descriptor calculation not explicit |
| 1.3c | Calculation of 3-D descriptors | N/A |  |
| 1.3d | Software utilised |  | Mostly well described and reported, however gaps are present |
| 1.3e | Definition of molecular fragments | N/A |  |
|  |  |  |  |
| *1.4 Creation of the Data Set for QSAR Modelling* | | | |
|  |  |  |  |
| 1.4a | Data set is complete |  | A complete data set has not been provided, specifically the descriptors values are not provided |
| 1.4b | Data set has appropriate variation in potency (quantitative) or balance of actives vs inactives (qualitative) |  | Good range of potencies, although the compounds are not evenly distributed with regard to potency |
| 1.4c | Selection of training set data |  | Assumed to be without bias, although not reported |
| 1.4d | Training set homogeneity |  | Training set is homogeneous |
| 1.4e | Suitable training and test sets defined and utilised |  | Details of training and test sets not provided |
|  |  |  |  |
| *1.5 Modelling Approach* | | | |
|  |  |  |  |
| 1.5a | How appropriate is the modelling approach for the endpoint and to deal with the complexity / non-linearity of the data |  | Appropriate modelling approach for the endpoint used |
|  |  |  |  |
| Description of the QSAR Model | | | |
|  |  |  |  |
| *2.1 Description of Model* | | | |
|  |  |  |  |
| 2.1a | Documentation and reporting |  | Model fully defined |
| 2.1b | Data set is complete and described |  | Descriptor values are not provided |
| 2.1c | Transparency of the model |  | Model is transparent in terms of the algorithm |
|  |  |  |  |
| *2.2 Statistical Performance* | | | |
|  |  |  |  |
| 2.2a | Statement of statistical fit, performance and predictivity |  | Full description of model performance |
| 2.2b | Interpretation of statistical fit etc with respect to biological error (see Criterion 1.2d) |  | No interpretation is provided, although the standard errors of models are possibly consistent with experimental error |
|  |  |  |  |
| *2.3 Applicability Domains* | | | |
|  |  |  |  |
| 2.3a | Chemical applicability domain of model |  | Defined as persistent organic pollutants, however aspects are missing |
| 2.3b | Mechanistic applicability domain of model |  | Fully defined in terms of relevant mechanism(s) of action |
| 2.3c | Biological applicability domain of model |  | Not defined |
|  |  |  |  |
| *2.4 Mechanistic Relevance, Interpretability and Transparency* | | | |
|  |  |  |  |
| 2.4a | Mechanistic justification |  | Definition of endocrine disrupting mechanism of action |
| 2.4b | Presence / availability of other and supporting information |  | No supporting information |
| 2.4c | Relevance to descriptors to mechanism of action / AOP |  | No mechanistic basis of descriptors |
|  |  |  |  |
| *2.5 Adequate coverage of ADME effects* | | | |
|  |  |  |  |
| 2.5a | Metabolism and / or effect of significant metabolites have been considered |  | No reference to metabolism |
| 2.5b | Toxicokinetics have been addressed in the model |  | No reference to toxicokinetics |
|  |  |  |  |
| Application of the QSAR Model | | | |
|  |  |  |  |
| *3.1 Documentation and Reproducibility* | | | |
|  |  |  |  |
| 3.1a | Reproducibility of the models |  | Descriptor values are not available, therefore the model cannot be reproduced |
| 3.1b | Reproducibility of the prediction |  | Descriptor values are not available, therefore the predictions cannot be reproduced |
|  |  |  |  |
| *3.2 Usability* | | | |
|  |  |  |  |
| 3.2a | Implementation of the model |  | Model has the potential to be implemented but this has not been undertaken |
| 3.2b | Software accessibility |  | Software may be obtained on a specific licence |
| 3.2c | Software transparency | N/A |  |
| 3.2d | Relative cost |  | Cheap to use compared to a standard test |
| 3.2e | Sustainability | N/A |  |
| 3.2f | Maintenance and support |  | Need for licencing of software |
| 3.2g | Intellectual Property |  | No IP considerations i.e. open access |
| 3.2h | Ownership |  | Model in public domain |
| 3.21 | Ethics |  | No ethical concerns |
|  |  |  |  |
| *3.3 Relevance* | | | |
|  |  |  |  |
| 3.3a | Heterogeneity and density of chemical space |  | Well populated and distributed chemical space |
| 3.3b | Relevance of the predicted endpoint for the regulatory risk assessment purpose/protection goal |  | Not a regulatory endpoint, though may be useful as part of a weight of evidence |
| 3.3c | Adequacy |  | Adequate for stated purpose |
| 3.3d | Extrapolation and relevance to humans |  | Relevant to humans |
| 3.3.e | Extrapolation and relevance to environmental biota |  | Relevant to environmental biota |
|  |  |  |  |

Table S2k. QSAR Study #11. Hao *et al*.

|  |  |  |  |
| --- | --- | --- | --- |
| ID | Area of Uncertainty, Variability, Bias or Influence | Assignment of Uncertainty, Variability, Bias or Influence | Reason |
|  |  |  |  |
| Model Creation | | | |
|  |  |  |  |
| *1.1 Definition of Chemical Structures* | | | |
|  |  |  |  |
| 1.1a | Accuracy of chemical structure |  | Structures are fully defined |
| 1.1b | Assessment of significant impurities or mixtures |  | No mention of impurities or mixtures |
|  |  |  |  |
| *1.2* *Biological Data* | | | |
|  |  |  |  |
| 1.2a | Quality of individual studies in the data set |  | Tests are preformed to OECD guidelines |
| 1.2b | Consistency of the data set including comparability of data |  | Consistent set in terms of assay, same laboratory |
| 1.2c | Checking of toxicological data |  | Checking undertaken |
| 1.2d | Error associated with biological data | N/A |  |
| 1.2e | (if required) Units of concentration known, stated and appropriate for use |  | Units are not stated |
| 1.2f | (If appropriate) Nominal or measured concentrations |  | Nominal concentrations used |
| 1.2g | Internal exposure known |  | Internal exposure is not known |
|  |  |  |  |
| *1.3 Measurement and / or Estimation of Physico-Chemical Properties and Structural Descriptors* | | | |
|  |  |  |  |
| 1.3a | Measurement of physico-chemical properties | N/A |  |
| 1.3b | Calculation of properties and 2-D descriptors |  | Well characterised software providing unambiguous properties |
| 1.3c | Calculation of 3-D descriptors |  | Full structure optimisation without the need for conformational analysis |
| 1.3d | Software utilised |  | Full details and parameters of the software are provided |
| 1.3e | Definition of molecular fragments |  | Fragments are well defined |
|  |  |  |  |
| *1.4 Creation of the Data Set for QSAR Modelling* | | | |
|  |  |  |  |
| 1.4a | Data set is complete |  | Descriptor values are not provided |
| 1.4b | Data set has appropriate variation in potency (quantitative) or balance of actives vs inactives (qualitative) |  | Good variations in potency |
| 1.4c | Selection of training set data |  | Data selection assumed to be without bias although not stated |
| 1.4d | Training set homogeneity |  | Training set is homogenous |
| 1.4e | Suitable training and test sets defined and utilised |  | Appropriate training and test sets |
|  |  |  |  |
| *1.5 Modelling Approach* | | | |
|  |  |  |  |
| 1.5a | How appropriate is the modelling approach for the endpoint and to deal with the complexity / non-linearity of the data |  | Regression analysis is appropriate modelling approach for the endpoint |
|  |  |  |  |
| Description of the QSAR Model | | | |
|  |  |  |  |
| *2.1 Description of Model* | | | |
|  |  |  |  |
| 2.1a | Documentation and reporting |  | Model fully defined |
| 2.1b | Data set is complete and described |  | The data set is described/provided partially, descriptor values are not reported |
| 2.1c | Transparency of the model |  | Model is transparent in terms of the algorithm |
|  |  |  |  |
| *2.2 Statistical Performance* | | | |
|  |  |  |  |
| 2.2a | Statement of statistical fit, performance and predictivity |  | Full description of the models performance |
| 2.2b | Interpretation of statistical fit etc with respect to biological error (see Criterion 1.2d) |  |  |
|  |  |  |  |
| *2.3 Applicability Domains* | | | |
|  |  |  |  |
| 2.3a | Chemical applicability domain of model |  | Defined structurally, but not with regards to physico-chemical properties |
| 2.3b | Mechanistic applicability domain of model |  | Fully defined in terms of relevant mechanisms of action |
| 2.3c | Biological applicability domain of model |  | Not defined |
|  |  |  |  |
| *2.4 Mechanistic Relevance, Interpretability and Transparency* | | | |
|  |  |  |  |
| 2.4a | Mechanistic justification |  |  |
| 2.4b | Presence / availability of other and supporting information |  | Use of evidence relating to mechanistic basis |
| 2.4c | Relevance to descriptors to mechanism of action / AOP |  | Descriptors or properties clearly related to mechanism |
|  |  |  |  |
| *2.5 Adequate coverage of ADME effects* | | | |
|  |  |  |  |
| 2.5a | Metabolism and / or effect of significant metabolites have been considered |  |  |
| 2.5b | Toxicokinetics have been addressed in the model |  |  |
|  |  |  |  |
| Application of the QSAR Model | | | |
|  |  |  |  |
| *3.1 Documentation and Reproducibility* | | | |
|  |  |  |  |
| 3.1a | Reproducibility of the models |  | Descriptor values are not available, therefore the model cannot be reproduced |
| 3.1b | Reproducibility of the prediction |  | Descriptor values are not available, therefore the predictions cannot be reproduced |
|  |  |  |  |
| *3.2 Usability* | | | |
|  |  |  |  |
| 3.2a | Implementation of the model |  | Model has potential to be implemented but this has not been undertaken |
| 3.2b | Software accessibility |  | Software may be obtained on a specific licence |
| 3.2c | Software transparency | N/A |  |
| 3.2d | Relative cost |  | Cheap to use compared to that of a standard test |
| 3.2e | Sustainability |  | Need for licencing of software |
| 3.2f | Maintenance and support | N/A |  |
| 3.2g | Intellectual Property |  | No IP considerations i.e. open access |
| 3.2h | Ownership |  | Model in public domain |
| 3.21 | Ethics |  | No ethical concerns |
|  |  |  |  |
| *3.3 Relevance* | | | |
|  |  |  |  |
| 3.3a | Heterogeneity and density of chemical space |  | Well populated and distributed chemical space |
| 3.3b | Relevance of the predicted endpoint for the regulatory risk assessment purpose/protection goal |  | Endpoint sufficient for purpose, can be used as an estimation in hazard identification for this single strain of *S. typhimurium.* |
| 3.3c | Adequacy |  | Adequate for stated purpose |
| 3.3d | Extrapolation and relevance to humans |  |  |
| 3.3e | Extrapolation and relevance to environmental biota |  | Relevant to environmental biota |
|  |  |  |  |

Table S2l. QSAR Study #12. Ahmadi

|  |  |  |  |
| --- | --- | --- | --- |
| ID | Area of Uncertainty, Variability, Bias or Influence | Assignment of Uncertainty, Variability, Bias or Influence | Reason |
|  |  |  |  |
| Model Creation | | | |
|  |  |  |  |
| *1.1 Definition of Chemical Structures* | | | |
|  |  |  |  |
| 1.1a | Accuracy of chemical structure |  | Nanoparticles require chemical composition, size, shape and aspect ratio, and surface chemistry to be provided |
| 1.1b | Assessment of significant impurities or mixtures |  | Impurities or mixtures not stated |
|  |  |  |  |
| *1.2* *Biological Data* | | | |
|  |  |  |  |
| 1.2a | Quality of individual studies in the data set |  | Quality of tests are not known |
| 1.2b | Consistency of the data set including comparability of data |  | Various different cell line tests are used and combined into a single data set |
| 1.2c | Checking of toxicological data |  | No checking |
| 1.2d | Error associated with biological data |  | Error not stated |
| 1.2e | (if required) Units of concentration known, stated and appropriate for use |  | Units are stated but they may not be entirely appropriate |
| 1.2f | (If appropriate) Nominal or measured concentrations |  |  |
| 1.2g | Internal exposure known |  |  |
|  |  |  |  |
| *1.3 Measurement and / or Estimation of Physico-Chemical Properties and Structural Descriptors* | | | |
|  |  |  |  |
| 1.3a | Measurement of physico-chemical properties | N/A |  |
| 1.3b | Calculation of properties and 2-D descriptors |  | Well characterised software providing unambiguous properties |
| 1.3c | Calculation of 3-D descriptors | N/A |  |
| 1.3d | Software utilised |  | Full details provided |
| 1.3e | Definition of molecular fragments | N/A |  |
|  |  |  |  |
| *1.4 Creation of the Data Set for QSAR Modelling* | | | |
|  |  |  |  |
| 1.4a | Data set is complete |  | Data gaps are present within the descriptor values, only presented for the validation set |
| 1.4b | Data set has appropriate variation in potency (quantitative) or balance of actives vs inactives (qualitative) |  | Good variation in cell viabilities |
| 1.4c | Selection of training set data |  | Training set selected without bias |
| 1.4d | Training set homogeneity |  | Training set is homogeneous |
| 1.4e | Suitable training and test sets defined and utilised |  | As required, appropriate training and test sets |
|  |  |  |  |
| *1.5 Modelling Approach* | | | |
|  |  |  |  |
| 1.5a | How appropriate is the modelling approach for the endpoint and to deal with the complexity / non-linearity of the data |  | Target functions are likely to be too complex for the endpoint |
|  |  |  |  |
| Description of the QSAR Model | | | |
|  |  |  |  |
| *2.1 Description of Model* | | | |
|  |  |  |  |
| 2.1a | Documentation and reporting |  | Model fully defined |
| 2.1b | Data set is complete and described |  | Data set is well presented, although gaps emerge in regards to the descriptor values for all the different sets used |
| 2.1c | Transparency of the model |  | Model is transparent in terms of the algorithm |
|  |  |  |  |
| *2.2 Statistical Performance* | | | |
|  |  |  |  |
| 2.2a | Statement of statistical fit, performance and predictivity |  | Full description of model performance |
| 2.2b | Interpretation of statistical fit etc with respect to biological error (see Criterion 1.2d) |  | Statistical performance is significant, invisible set employed to prevent overtraining |
|  |  |  |  |
| *2.3 Applicability Domains* | | | |
|  |  |  |  |
| 2.3a | Chemical applicability domain of model |  | Structurally defined, although not with respect to physic-chemical properties |
| 2.3b | Mechanistic applicability domain of model |  | Not defined |
| 2.3c | Biological applicability domain of model |  | Not defined |
|  |  |  |  |
| *2.4 Mechanistic Relevance, Interpretability and Transparency* | | | |
|  |  |  |  |
| 2.4a | Mechanistic justification |  | No mechanistic basis |
| 2.4b | Presence / availability of other and supporting information |  | No supporting information |
| 2.4c | Relevance to descriptors to mechanism of action / AOP |  | Partial or correlated relationship to mechanism |
|  |  |  |  |
| *2.5 Adequate coverage of ADME effects* | | | |
|  |  |  |  |
| 2.5a | Metabolism and / or effect of significant metabolites have been considered |  | No reference to metabolism |
| 2.5b | Toxicokinetics have been addressed in the model |  | No reference to toxicokinetics |
|  |  |  |  |
| Application of the QSAR Model | | | |
|  |  |  |  |
| *3.1 Documentation and Reproducibility* | | | |
|  |  |  |  |
| 3.1a | Reproducibility of the models |  | Descriptor values are only provided for the validation set, therefore the models can not be reproduced |
| 3.1b | Reproducibility of the prediction |  | Descriptor values are only provided within the validation set, therefore the predictions can not be reproduced |
|  |  |  |  |
| *3.2 Usability* | | | |
|  |  |  |  |
| 3.2a | Implementation of the model |  | Model not implemented into software but this is possible |
| 3.2b | Software accessibility |  | Software used is freely available |
| 3.2c | Software transparency | N/A |  |
| 3.2d | Relative cost |  | Cheap to use compared to a standard test |
| 3.2e | Sustainability |  | Published QSAR |
| 3.2f | Maintenance and support |  |  |
| 3.2g | Intellectual Property |  | No IP considerations i.e. open access |
| 3.2h | Ownership |  | Model in public domain |
| 3.21 | Ethics |  | No ethical concerns |
|  |  |  |  |
| *3.3 Relevance* | | | |
|  |  |  |  |
| 3.3a | Heterogeneity and density of chemical space |  | Well populated and distributed chemical space |
| 3.3b | Relevance of the predicted endpoint for the regulatory risk assessment purpose/protection goal |  | Endpoint not currently relevant for regulatory purposes |
| 3.3c | Adequacy |  | Adequate for stated purpose |
| 3.3d | Extrapolation and relevance to humans |  | Relevant to humans |
| 3.3.e | Extrapolation and relevance to environmental biota | N/A |  |
|  |  |  |  |