(Q)SAR Assessment Framework: Guidance for the regulatory assessment of (Quantitative) Structure Activity Relationship models and predictions, Second Edition

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The Inter-Organisation Programme for the Sound Management of Chemicals (IOMC) was established in 1995 following recommendations made by the 1992 UN Conference on Environment and Development to strengthen co-operation and increase international co-ordination in the field of chemical safety. The Participating Organisations are FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank, Basel, Rotterdam and Stockholm Conventions and OECD. The purpose of the IOMC is to promote co-ordination of the policies and activities pursued by the Participating Organisations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

Foreword

In November 2004, the 37th OECD Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology (Joint Meeting) agreed on the "OECD Principles for the Validation, for Regulatory Purposes, of (Q)SAR Models".

In 2007, the same OECD Working Party published the "Guidance document on the validation of (Quantitative) Structure-Activity Relationships [(Q)SAR] models" for the use of (Q)SARs in regulatory applications (OECD, 2007).

Since then, the possibility to use (Q)SARs was included within various regulations related to chemical substances. This has allowed different stakeholders to gain practical experience in assessing (Q)SARs for different regulatory purposes.

This experience has highlighted that not all predictions produced by a valid model are acceptable for all regulatory purposes. When a (Q)SAR prediction or a result generated from multiple predictions is used for a given regulatory purpose, it needs to be verified in the context of the specific application. While there was agreement on the principles for the assessment of models, there was a need to establish a set of commonly agreed principles for the regulatory assessment of (Q)SAR predictions, and results from multiple predictions.

In late 2020, a project led by the Istituto Superiore di Sanità (ISS) to develop a (Q)SAR Assessment Framework (QAF) was proposed to the OECD Working Party on Hazard Assessment (WPHA) and was added to the work plan in early 2021. The project includes the principles for assessing (Q)SAR models and predictions in the form of a checklist and criteria for evaluating the element in the checklist. In addition, the European Chemical Agency (ECHA) joined ISS as a project co-lead.

A request for the nomination of experts was sent to delegates of the Working Party on Hazard Assessment (WPHA) and the group of more than 40 experts was convened to provide input and review on the QAF. The QAF Expert Group met through a series of teleconferences in 2021 - 2023 and smaller subgroups contributed to the drafting. A face-to-face meeting of the QAF Expert Group was convened in November 2022 to help finalise the draft document.

The first edition of the QAF was published in August 2023. With this document, the OECD QAF expert group has established OECD principles for the assessment of (Q)SAR predictions and results based on multiple predictions and agreed on checklists to perform the assessment of models, predictions, and results from multiple predictions in practice.

In 2024, the OECD QSAR Result Reporting format (QRRF) Expert Group (led by ECHA and European Food Safety Authority (EFSA)) was convened and developed the OECD QRRF (Annex III) for inclusion in the second edition of the QAF Guidance Document.

This document is published under the responsibility of the Chemicals and Biotechnology Committee of the OECD.

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Executive summary

The aim of the (Quantitative) Structure-Activity Relationship ((Q)SAR) Assessment Framework (QAF) is to develop a systematic and harmonised framework for the regulatory assessment of (Q)SAR models, predictions, and results based on multiple predictions. The proposed assessment is meant to be applicable irrespective of the modelling technique used to build the model, the predicted endpoint, and the intended regulatory purpose. The primary audience of this document is regulatory authorities and their stakeholders. In addition, any other (Q)SAR user is encouraged to refer to the QAF when using (Q)SARs for regulatory purposes.

The assessment of (Q)SARs for regulatory purposes should not be limited to checking the validity of the model used because even a valid model can produce unacceptable predictions in certain conditions. Therefore, individual predictions and results from multiple predictions need dedicated assessments. To this purpose, the QAF is based on the OECD principles for the model validation (OECD, 2007[1], referred as OECD (Q)SAR Model Principles in the rest of the document), and newly defines the principles for the assessment of (Q)SAR predictions and results based on multiple predictions. Four principles have been established (referred as OECD (Q)SAR Prediction Principles in the rest of the document) related to 1) the correct input, 2) the fit of the substance within the applicability domain of the model, 3) the reliability of the prediction, and 4) the outcome's fitness for the identified purpose. To streamline the evaluation, each principle has been subdivided in elements that should be considered in the assessment (Assessment Elements, AEs). AEs are included in three checklists (Model Checklist, Prediction Checklist, and Result Checklist, provided as a separate document) that can be used to evaluate the acceptability of the use of (Q)SARs in practice. Each AE can either be fulfilled or not, not documented, or not applicable. The Checklists also provide further details and examples for each AE.

The Model Checklist consists of a list of AEs to evaluate a model according to the OECD (Q)SAR Model Principles (OECD, 2007). The Model Checklist should be used together with the other Checklists when assessing predictions and results based on multiple predictions. In this case, the use of an acceptable model can be considered the first step of the assessment. If the model is considered acceptable, then the assessment needs to further consider the other Checklists. When a model is considered not acceptable, then the assessment could be concluded without further considering predictions and results. Alternatively, the Model Checklist

[1]OECD principles for the Validation, for Regulatory Purposes, of (Q)SAR Models, ENV/JM/MONO(2007)2 https://www.oecd.org/content/dam/oecd/en/topics/policy-sub-issues/assessment-of-chemicals/oecd-principles-for-the-validation-for-regulatory-purposes-of-quantitative-structure-activity-relationship-models.pdf (OECD, 2007)

can be used as a standalone tool when e.g., (Q)SARs are used for screening databases without the possibility to assess predictions individually, or to keep a separate record for the assessment of a model that could be reused in future. The assessment of a model is specific for the regulatory purpose and should be repeated when assessing the same model for other purposes.

The Prediction and Result Checklists are used to evaluate individual (Q)SAR predictions and results based on multiple predictions, respectively. They consist of AEs based on the OECD (Q)SAR Prediction Principles, which have different weight depending on how critical they are for the assessment. Suggested default values for the weights are given in the Prediction and Result Checklists, but assessors can modify the weights to fit their own regulatory framework or paradigm. Moreover, assessors can assign a semi-quantitative uncertainty value (low, medium, high) to each assessment element, following this guidance and the examples in the Checklists. Finally, the overall uncertainty of the prediction is determined by considering the uncertainty associated with each AE and its weight in the assessment. Based on the purpose of use and the level of uncertainty of the individual prediction, the assessor can conclude on the outcome of the assessment (i.e., if the prediction is acceptable for the intended purpose of use).

In case of results based on multiple predictions, in addition to the individual assessment of each prediction, the Result Checklist considers one additional AE to evaluate if the predictions are integrated correctly for the determination of the final result. The level of uncertainty of the final result is assigned by weighting the uncertainty of the individual predictions and the additional AE. Finally, also in this case the assessor concludes on the outcome of the assessment depending on the purpose of use of the result, which determines the level of acceptable uncertainty (i.e., if the result is acceptable for the intended purpose of use).

Complementing the QAF, updates for the (Q)SAR model reporting format (QMRF) and (Q)SAR prediction reporting format (QPRF) have been developed. While the update of the QMRF only concerns the description of the expected information in each field, without changes in the field names and order, the QPRF was more extensively updated, to reflect the newly established OECD (Q)SAR Prediction Principles. In the OECD QRRF project, experts developed a reporting format for (Q)SAR results derived from multiple predictions. The updated QMRF and QPRF, and the QRRF templates are provided as Annexes of this document.

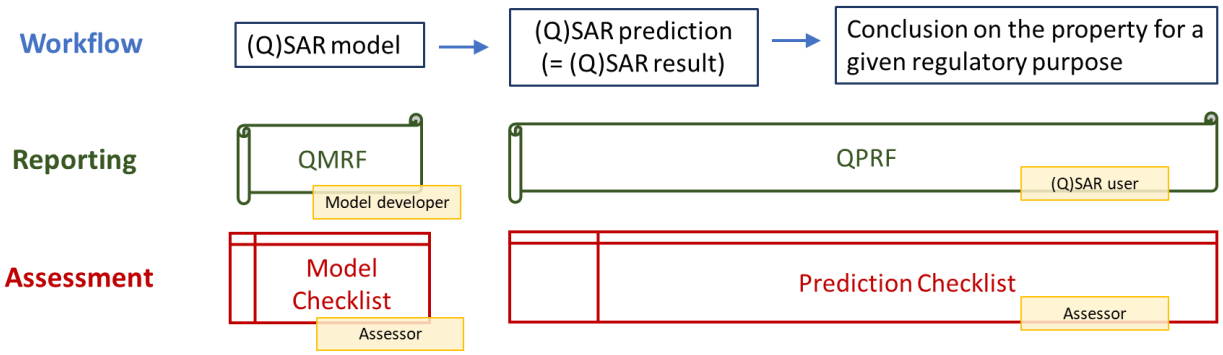
Furthermore, examples that illustrate the use of the Checklists have also been developed and will be provided as separate documents. The expert group recommends the further usage and application of the QAF principles under OECD IATA case studies project for the case studies including (Q)SAR approaches.

Finally, some experts in the group have identified the need for further guidance on how to measure external predictivity of (Q)SAR models and a discussion was initiated towards the end of the QAF project. However, the topic was not elaborated in the final version of the QAF because there is no scientific consensus on how to measure external predictivity, and thus, this topic would require extensive review of the literature which is outside of the scope of this project. Further, model validation is a task for model developers and as such beyond the scope of the QAF, which aims primarily at providing instructions for regulators assessing pre-existing models.

The assessment checklists, QMRF, QPRF, and QRRF are available for download in the ***Supporting Materials*** tab of associated with the QAF.

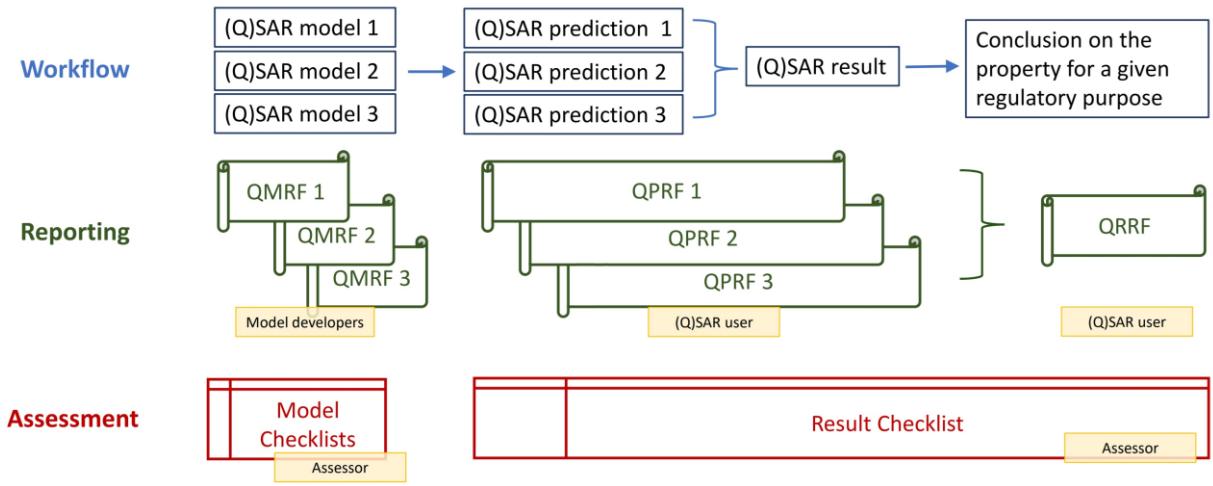
Visual Abstracts

Figure 1. (Q)SAR Assessment Framework (QAF) Result based on an individual prediction



Note: Workflow of (Q)SAR information for a result based on an individual prediction according to the OECD (Q)SAR assessment framework (QAF). The information about the model is reported in the (Q)SAR Model Reporting Format (QMRF) document prepared by the model developer and assessed by regulators using the QAF Model Checklist. The information about the (Q)SAR prediction is reported in the (Q)SAR Prediction Reporting Format (QPRF) document by the (Q)SAR user and assessed by regulators using the QAF Prediction Checklist. Checklists could also be pre-compiled by the (Q)SAR user to facilitate the work of the assessor.

Figure 2. (Q)SAR Assessment Framework (QAF) Result based on multiple predictions



Note: Workflow of (Q)SAR information for a result based on multiple predictions according to the OECD (Q)SAR assessment framework (QAF). The information about the models is reported in the (Q)SAR Model Reporting Format (QMRF) documents prepared by the model developers and assessed by regulators using the QAF Model Checklist. The information about the (Q)SAR predictions and result are reported in the (Q)SAR Prediction Reporting Format (QPRF) and (Q)SAR Results Reporting Format (QRRF) document by the (Q)SAR user, and assessed by regulators using the QAF Result Checklist.

1 Assessment of (Q)SAR Models (Model Checklist)

This section of the document provides practical advice for completing the Model Checklist. It is based on and complements the more theoretical OECD guidance on model validation (OECD, 2007).

The OECD Principles for (Q)SAR validation state that "to facilitate the consideration of a (Q)SAR model for regulatory purposes, it should be associated with the following information:

1. a defined endpoint
2. an unambiguous algorithm
3. a defined domain of applicability
4. appropriate measures of goodness-of-fit, robustness and predictivity
5. a mechanistic interpretation, if possible."

The following chapters and the Model Checklist provide more details on these principles and how to verify that a (Q)SAR model is compliant with them. The assessment should be based on the information provided in the QSAR Model Reporting Format (QMRF). A map of the AEs in the Model Checklist to the QMRF fields is also provided in the Model Checklist to facilitate the retrieval of the information relevant for the assessment. Each OECD (Q)SAR Validation Principle is also further considered in one or more AEs of the Prediction and Result Checklists, as indicated at the end of each sub-chapter below.

1.1 Defined endpoint[2]

According to OECD (Q)SAR Model Principle 1 (OECD, 2007), a (Q)SAR should be associated with a "defined endpoint", where endpoint refers to any physicochemical, biological, or environmental property that can be measured and therefore modelled. The intent of this principle is to ensure transparency in the endpoint being predicted by a given model, since an endpoint could be determined by different experimental protocols and under different experimental conditions.

[2] As explained in the glossary, this document uses the term "property" to refer to the endpoint predicted by the model. However, the original term "endpoint" has been preserved in the title and first paragraph of this is chapter to avoid confusion for the readers familiar with "OECD (Q)SAR Validation Principle 1: Defined Endpoint"

The Model Checklist includes the following AEs to verify that the endpoint is clearly defined:

1. Clear scientific and regulatory purposes
2. Transparency of the underlying experimental data
3. Quality of the underlying experimental data

Clear scientific and regulatory purposes *(AE 1.1 in the Model Checklist)*

To have a clear scientific purpose, the predicted property has to be precisely described. To have a clear regulatory purpose, a model should address a specific regulatory requirement, which is often associated with a specific test method or test guideline, or it should provide supporting information to such requirement (e.g., mechanistic information). The description of the predicted property should be as detailed as possible by including all elements that have been considered (e.g., the unit of measurement, timescale, observations such as growth, mortality, etc.). The complexity of the predicted property influences the extent of documentation required (i.e., models predicting more complex properties such as developmental toxicity require more details in the definition of the property compared to models predicting simpler properties such as *in vitro* mutagenicity in Ames test).

Transparency of the underlying experimental data *(AE 1.2 in the Model Checklist)*

This AE concerns the transparency of the underlying experimental data and of the related data selection and curation procedure. The sources of the experimental data should be adequately reported, as well as information on experimental data selection criteria, data processing and information on chemical identifiers (including at least one identifier that codifies the chemical structure, such as InChi/InChIKey or (canonical) SMILES, and other commonly reported information such as CAS registry numbers) of tested substances. Potential biases in the data selection should also be investigated (e.g., systematic inclusion in the training set of data measured according to test guidelines not related to the predicted endpoint). The original studies (or an accessible reference) represent the highest level of transparency, but they are rarely available. On the contrary, the underlying studies may not be available at all for some models due to confidentiality or insufficient documentation. For many existing (Q)SAR models, the level of transparency is between these two extremes, with some but not all details available for the experimental studies used to build the models.

Authorities responsible for the assessment can decide the minimum acceptable level of transparency needed for specific purposes, with the understanding that for some models the available information might be limited for e.g., commercial reasons. In general, there should be sufficient information on the underlying data or on the data curation procedure to be able to assess data quality.

Quality of the underlying experimental data *(AE 1.3 in the Model Checklist)*

The (Q)SAR model should be built on data of sufficient quality. However, the individual assessment of the quality of each data point is often not feasible. In these cases, the quality of the underlying data can be assessed based on the description of the data curation procedure. For instance, assessors can verify how the relevant experimental parameters (e.g., sex,

species, temperature, exposure period, protocol) that could affect the results of experimental studies have been considered when selecting data to build the model. Assessors may also consider whether all data points applied to develop and validate a model are generated by use of 1) the same assay protocol; and 2) the most updated assay protocol – and what are the consequences for the reliability. The quality of individual data should also be assessed to the extent possible.

OECD (Q)SAR Validation Principle 1 is further considered in the Prediction and Result Checklists under the element "Correspondence between predicted property and property required by the regulation".

1.2 Unambiguous algorithm

According to OECD (Q)SAR Model Principle 2 (OECD, 2007), a (Q)SAR model should be expressed in the form of an unambiguous algorithm (intended as unambiguous description of the algorithm). The intent of this principle is to ensure transparency in the description of the model algorithm to allow an independent reproducibility of its predictions.

The Model Checklist includes the following AEs to verify the principle of an unambiguous algorithm:

1. Description of the algorithm and/or software
2. Inputs and other options
3. Model accessibility

Description of the algorithm and/or software *(AE 2.1 in the Model Checklist)*

The first element to be checked is the availability of a transparent description of the algorithm. The model equation, if applicable, including all descriptors and approach used for their selection, should be detailed. Furthermore, if applicable, a list of fragments/structure alerts (e.g., active, inactive, masks) and their description should be provided. The rationale that guided their identification could also be included. Calculated descriptors should be denoted with the software name and version used for their calculation. Furthermore, the version, developers' contact information and any available description of the software for the (Q)SAR model should also be provided. When an exact description of the algorithm is not publicly available (e.g., for commercial models), any available relevant information should still be assessed.

Inputs and other options *(AE 2.2 in the Model Checklist)*

Secondly, assessors should check if the documentation includes a description of inputs and settings of the model software. The allowed (or preferred) input formats for the chemical structure and its descriptors, including applicable pre-processing procedures (e.g., for salts and tautomers) should be documented. Further, customisable options/settings on the software should be reported and explained. Unless justified otherwise, the recommended input formats and options are expected to be the same as those used by model developers when developing the model and assessing its performance.

Model accessibility *(AE 2.3 in the Model Checklist)*

Finally, it should be checked if the model version under assessment is publicly accessible. A working link to access or download the model is expected in the QMRF documentation. When assessors have access to a different version of the model under assessment (e.g. a newer version), any differences in the outputs should be investigated.

OECD (Q)SAR Model Principle 2 is further considered in the Prediction and Result Checklists under the element "Reproducibility". Note that when the model is implemented in a software program that is accessible to the assessor, the reproducibility of the results should be possible even for cases when the description of the algorithm is not fully disclosed. Assessors may decide that this is acceptable for some regulatory purposes.

1.3 A defined domain of applicability

According to OECD (Q)SAR Model Principle 3 (OECD, 2007), a valid model is associated with a defined applicability domain (AD). The AD of a (Q)SAR model, as described in the Guidance Document (OECD, 2007), is *the response and chemical structure space in which the model makes predictions with a given reliability*. Elaborating on the AD definition given above, the AD should therefore consider the parametric, structural, mechanistic, metabolic and response space of the model. Nevertheless, the QAF does not prescribe a specific way to define the AD of a model because multiple valid methodologies can be used. These are described in the Guidance Document (OECD, 2007), which can be consulted for further scientific aspects concerning the AD, while this paragraph focuses on practical aspects of the assessment within the QAF.

The Model Checklist includes one AE related to the applicability domain:

- Clear definition of the applicability domain and limitations of the model

Clear definition of the applicability domain and limitations of the model *(AE 3.1 in the Model Checklist)*

Assessors should verify that the definition proposed by model developers is sufficiently detailed to allow the assessment of how a given substance relates to the AD of the model in the Prediction and Result Checklists (e.g. is the substance within the AD of the model etc.?). To facilitate the assessment, developers of new models are encouraged to implement functionalities to automatically include in the prediction report information on how the input substance relates to the AD. In addition, the Prediction and Result Checklists include a separate reliability assessment that considers crucial aspects that may influence the reliability of the result, irrespective of whether they are included in the AD definition, as described in Chapter 2.3 below.

The model documentation may include a list of limitations of the model in addition to the AD definition, such as substance classes for which the use of the model is not recommended. The QAF is not prescriptive in terms of how to define such limitations, but it should be verified that the description of potential additional limitations is sufficiently detailed for assessing how a given input substance relates to them.

Principle 3 is further considered in the Prediction and Result Checklists under the elements "Substance within the applicability domain" and "Any other limitation of the model is considered".

1.4 Appropriate measures of goodness-of-fit, robustness and predictivity

According to Principle 4 (OECD, 2007), a (Q)SAR should be associated with "appropriate measures of goodness-of–fit, robustness and predictivity." This principle expresses the need to provide information on the goodness-of-fit and robustness of a model (as determined by internal validation) and the predictivity of a model (as determined by external validation). The AD and the performance of a model are connected. The performance should be measured within the applicability domain defined by its developers. An enhanced model performance can generally be obtained with a narrower AD. The Guidance Document (OECD, 2007) can be consulted for further scientific aspects concerning Principle 4.

The Model Checklist includes the following AEs to verify the appropriateness of measures of goodness-of-fit, robustness and predictivity of the model:

- Goodness-of-fit, robustness
- Predictivity

Goodness-of-fit, robustness and predictivity *(AEs 4.1 and 4.2 in the Model Checklist)*

Assessors should verify that the information available on the model's internal and external performance can be used as an indication of the expected accuracy of the model when predicting new substances. Size of the training, test and external sets, statistical methods and metrics used, values of the statistical metrics, and transparency of the procedure to measure performance are some of the important aspects to consider when assessing the performance of the model. Training, test, and external sets should be independent. The information describing how the QSAR model under scrutiny was selected, and its predictive performance estimated, has to be assessed in order to check if the model was correctly trained without accounting for the information to be used to estimate the model's external predictivity. For instance, the use of information from an external test set of chemicals (originally devised for the exclusive assessment of external predictivity) during the development of the model (i.e., "data leakage" from test set for model calibration or selection), is very likely to result into an overestimation of the model's external predictivity.

OECD (Q)SAR Model Principle 4 is further considered in the Prediction and Result Checklists under the element "Overall performance of the model".

1.5 Mechanistic interpretation

According to Principle 5 (OECD, 2007), a (Q)SAR "should be associated with a mechanistic interpretation, if possible". Statistical methods used to describe relationships between chemical structure and activity are not intended to replace other knowledge from chemistry and toxicology when such knowledge exists. Assessors may require that the model documentation includes considerations on how the rationale behind a (Q)SAR model is consistent with or accounts for the knowledge related to the predicted property (such as known Adverse Outcome Pathways,

AOPs, relevant for the predicted property), namely a mechanistic interpretation. Toxicokinetic considerations are also part of the mechanistic interpretation, if relevant for the property of interest.

The Model Checklist includes the following AE related to mechanistic interpretation:

- Plausibility of the mechanistic interpretation

Plausibility of the mechanistic interpretation *(AE 5.1 in the Model Checklist)*

For fragment-/alert- based models, the mechanistic interpretation can be based on the explanation of the chemical reactivity or molecular interaction caused or inhibited by the fragments associated with the alerts. For equation-based models, the mechanistic interpretation can be based on the physicochemical interpretation of each descriptor and its association with a mode or mechanism of action. An indication whether the mechanistic basis of the model was determined *a priori* (e.g., by pre-selecting descriptors or fragments to fit a specific mechanism of action) or *a posteriori* (e.g., after the modelling, by interpretation of the final set of training structures and/or descriptors) is also expected.

OECD (Q)SAR Model Principle 5 is further considered in the Prediction and Result Checklists under the element “Mechanistic and/or metabolic considerations”.

1.6 Outcome of the assessment of the model

The assessment of each AE and of the model in general depends on (and is specific for) a given regulatory purpose.

A model should be considered as acceptable when the outcome of each AE is “fulfilled”, or, alternatively, when sufficient information about the model is available for assessing the AEs related to the model in the Prediction and Result Checklists. For some regulatory purposes and with a valid justification, models that do not fulfil all AEs can also be accepted.

1.7 Conclusions on the assessment of the model

The compilation of the Model Checklist is the first step in the assessment of predictions and results from multiple predictions. It also supports the evaluation of AEs related to the validity of the model in the Prediction and Result Checklists. Once completed, the Model Checklist can be reused, i.e. assessors do not need to re-evaluate the model each time that a new prediction is submitted. Furthermore, the Model Checklist can serve as a standalone tool to assess models used for screening of databases for which predictions are not meant to be assessed individually.

Finally, the Model checklist includes a mapping between the Model Checklist and the QMRF. This mapping, together with the outcome of the assessment of the Model Checklist, when disclosed, can serve as feedback to model developers for further improvement of their models and related documentation.

2 Assessment of (Q)SAR Predictions (Prediction Checklist)

In order to assess (Q)SAR predictions and results from multiple predictions, principles for their regulatory assessment needed to be established, in addition to the (Q)SAR Model Principles. The QAF establishes four principles for the assessment of (Q)SAR predictions and results from multiple predictions for regulatory purposes:

1. the model input(s) should be correct;
2. the substance should be within the applicability domain of the model;
3. the prediction(s) should be reliable;
4. the outcome should be fit for the regulatory purpose.

The same principles are included in the Prediction and Result Checklists. This chapter and the Prediction and Result Checklists provide more details on these principles and how to verify that an individual prediction or a result from multiple predictions is compliant with them. The assessment should be based on the information provided in the QMRF and QPRF. This chapter describes the AEs common to the Prediction and Result Checklists, while the next chapter focuses on the additional elements to consider in the Result Checklist.

2.1 Correct input(s) to the model

(Q)SAR models require one or more inputs to generate a prediction. Depending on the model, the input may be limited to information on the structure of the substance or also include some of its descriptors. Some models also have customisable settings in the software.

The input is correct when it is clearly and completely described, is representative of the substance being analysed, and uses reliable parameters (e.g. values for descriptors to be used in the prediction). The documentation needed to ensure that an input is correct depends on the complexity of the model (or of the software implementing it) and of the substance under analysis. In general, the input should be prepared by carefully following the instructions of the model or software developers, if available.

The Prediction Checklist includes the following AEs to verify that the input is correct:

- Clear and complete description of the input and model settings
- Input representative of the substance under analysis
- Reliable input (parameters)

Clear and complete description of the input and model settings *(AE 1.1 in the Prediction and Result Checklists)*

The first element to check is the description of the input and ensure that it is unequivocal and complete. In the simplest case, the model takes information on the structure (e.g., SMILES) as the sole input and does not have other editable options accompanying the structural input. In this case, the description of the exact structural information and the model/software version that were used to obtain the prediction are sufficient. For more complex cases, the requirement is to provide all information, including three-dimensional information on the chemical structure, customisable options ("settings") and parameters of the software application (e.g., manual input of values of the descriptors and their source) that are needed as input to the model.

Input representative of the substance under analysis *(AE 1.2 in the Prediction and Result Checklists)*

Secondly, it is important to check that the input is representative of the substance under analysis and thus relevant for its assessment. When the substance consists of a single well-defined constituent, checking the agreement between the substance name, structure and numerical identifiers is sufficient. For three-dimensional models, information on the rationale for the selection of the conformation used as input is expected. For substances with complex compositions, a (Q)SAR result can be derived from multiple predictions that cover the constituents and impurities. In fact, one of the advantages of (Q)SARs is that more constituents and metabolites can be predicted to investigate their contribution to the overall toxicity of the substance with limited additional costs.

In addition, some models may require that inputs undergo structural curation before they can be used for a prediction. This is often the case for e.g., salts, ionisable structures, or structures subject to tautomerism. In these cases, different approaches exist. The choice of the approach should be decided on a case-by-case basis and special attention should be paid to how the pre-processing was performed by the model developers for the training set substances, and recommendations of the regulatory framework of interest, if relevant.

Reliable input (parameters) *(AE 1.3 in the Prediction and Result Checklists)*

Finally, for models that utilise direct input beyond the chemical structure, such as a physicochemical descriptor(s), the source of that descriptor value, whether experimentally measured or itself predicted by a model, needs to be evaluated for reliability before it is used to predict another property. The same approach applied by model developers during model development and assessment of performance of the model should be applied, unless properly justified. In case the (Q)SAR model relies on many physicochemical descriptors, and it is unfeasible to evaluate the reliability of each input, the focus should be on the most influential descriptor(s).

2.2 Substance within the applicability domain

The second principle requires that the model is applicable to the substance under analysis. The assessment of the applicability of the model to the substance relies on the verification of how the substance under analysis relates to the applicability domain (AD) and to the limitations of

the model as defined by the model developers. If there are aspects potentially influencing the reliability of the prediction that have not been considered by the model developers when defining the applicability domain, these can be evaluated when assessing the next principle “Reliable prediction(s)”. Applicability domain informs the reliability of the prediction. In this document, AD and reliability are evaluated separately to streamline the assessment procedure.

The Prediction Checklist includes the following AEs to verify that the substance is within the applicability domain of the model:

- Substance within the applicability domain
- Any other limitation of the model is considered

Substance within applicability domain, and any other limitation is considered *(AEs 2.1 and 2.2 in the Prediction and Result Checklists)*

In general, the AD definition should include criteria for assessing whether the substance under analysis falls within the AD. In some cases, model developers also provide a description of the known limitations of the model and of cases when the model should not be used (e.g., a list of chemical classes or descriptor ranges for which the model is known to make inaccurate predictions). Such descriptions may be provided separately from the given definition of AD but are of similar importance. Many recent software tools provide an automatic assessment of the applicability of the model to the substance along with the prediction result. In this case, it is important that the automatic assessment can be verified independently.

In the preferable scenario, the substance falls within the applicability domain of the model and model specific limitations do not apply to the substance.

On the contrary, in some cases it is clear that the substance is outside the AD of the model, or model specific limitations apply. In these cases, the prediction should not be considered further, (unless a valid justification is provided, e.g., it is not technically possible to perform an experimental test, but a numerical value is still needed). An example is a model for which the applicability domain is defined as range of physicochemical properties, and in addition the description of the model clarifies that the model has been developed to predict organic chemicals within certain chemical classes. In this case, predictions of organic substances outside these classes should not be considered further, irrespective of whether the physicochemical values are within AD.

Between these two clear-cut scenarios there are intermediate cases. An example of such cases are substances for which their relation to the applicability domain cannot be unequivocally established but at the same time do not meet the exclusion criteria for which the model should not be used. For these substances the accuracy of the model prediction may be unknown but not necessarily unacceptable for all regulatory purposes. Another example are predictions for chemicals that are located near the boundaries of the applicability domain and therefore may be associated with higher uncertainty. For these cases, the assessment of the reliability of the prediction, as described in the next section, is decisive for its overall acceptance for a given regulatory purpose.

2.3 Reliability of the prediction(s)

In addition to the AD, several other aspects can be considered when assessing the reliability of a prediction. If these aspects are already included in the AD definition, the assessment does not need to be repeated.

The Prediction Checklist includes the following AEs to verify that a prediction is reliable:

- Reproducibility
- Overall performance of the model
- Fit within the physicochemical, structural and response spaces of the training set of the model
- Performance of the model for similar substances
- Mechanistic and/or metabolic considerations
- Consistency of information

Reproducibility *(AE 3.1 in the Prediction and Result Checklists)*

First, it should be verified that it is possible to reproduce the prediction (i.e., to obtain the same result) using the documented input and model. When assessors have access to the same model and version used to generate the prediction, they can repeat the prediction to confirm that the same prediction is obtained. If a different prediction is obtained without a valid explanation (e.g. different model version), is symptomatic of lower reliability.

Overall performance of the model *(AE 3.2 in the Prediction and Result Checklists)*

Second, the overall model performance should be considered. It represents the baseline for the reliability assessment and is expected in the model documentation (c.f. QMRF). As an example, a similar standard error for models predicting continuous outcomes (or the accuracy of models predicting categorical outcomes) can be expected for the prediction of the substance under analysis. For this reason, a prediction generated by a model with better performance should be considered more reliable than a prediction generated by a model with lower performance.

Fit within the physicochemical, structural and response spaces of the training set of the model *(AE 3.3 in the Prediction and Result Checklists)*

The substances in the training set have defined values for the descriptors (such as physicochemical descriptors, molecular descriptors, etc.) and for the property of interest (response values). These values can be used to define descriptor and response spaces based on ranges or distributions. The assessors shall compare descriptor and response values of the substance under analysis with the ranges defined by the training set.

Likewise, the substances in the training set can be used to define a structural space in terms of functional groups or structural fragments. When all structural characteristics of the substance are known by the model, the prediction is considered more reliable. Structural characteristics not known by the model may have an impact on the reliability of the prediction. This aspect is of particular importance for predictions indicating a lack of biological activity by fragment/alert based models, where the lack of effect may be due to lack of knowledge by the model, which might have not been trained to predict the effect of certain fragments.

The reliability of the prediction is lower when the substance under analysis falls in regions of the training set spaces that are scarcely populated or associated with lower model performance. Special attention should be paid in such cases.

Performance of the model for similar substances *(AE 3.4 in the Prediction and Result Checklists)*

An assessment of local performance of the model requires the identification of similar substances with reliable experimental data for the property of interest. If not executed automatically by the software, this work should be performed by (Q)SAR users, and then verified by the assessors. Similar substances can be defined by considering multiple aspects, such as structural, physicochemical, and/or mechanistic similarity. Similar substances may be identified manually by the users using expert judgment, with or without the help of computational tools for analogue identification such as the OECD QSAR Toolbox[3]. Some (Q)SAR models automatically provide with the prediction a list of substances similar to the input, their experimental values, and the accuracy of their predictions.

However, molecular similarity indices alone are not necessarily sufficient to define similarity, as some molecular fragments may be very important for one property but not for another property, and in some cases co-occurrence of multiple fragments can be very important (e.g. cross-linking agents).

If reliable experimental data are available for substances similar to the one under analysis, the performance of the model when predicting these can be used to better characterize the reliability of the prediction. The support is higher when the similar substances used for this assessment are not part of the training set of the model, as this case mimics more objectively the real-life application of the model when predicting new substances. The more similar the substances are to the substance under analysis, especially in terms of the descriptors, fragments, or other properties most relevant to the prediction, the more informative is the accuracy of their predictions to estimate the accuracy for the prediction of substance under analysis. In some cases, the reliability improvement is applicable even when the substance under analysis or similar substances are formally outside the AD of the model. The substance under analysis may be out of AD due to lack of experimental data in its chemical space at the time of model development. If new data for similar substances shows good performance of the model in that chemical space, then there is a concomitant improvement in the reliability of the prediction of the substance under analysis.

For fragment/alert- based models, the performance of the identified positive/negative alerts (expressed as, e.g., Cooper statistics (OECD, 2007)) can also provide information on the local performance of the model.

In absence of data for similar substances or when their identification is not possible or feasible, then the outcome for this AE should be marked “not applicable/assessed”.

[3] More information about this software, which is freely available and co-developed by OECD and the European Chemicals Agency (ECHA), is available at www.qsartoolbox.org

Mechanistic and/or metabolic considerations *(AE 3.5 in the Prediction and Result Checklists)*

This assessment element covers toxicokinetic and toxicodynamic considerations relevant for the property under analysis. A discussion on how considerations on mechanistic aspects (such as Adverse Outcome Pathways, AOPs) and ADME[3] properties (such as (bio)transformations, i.e., metabolism and other biotic or abiotic transformations such as hydrolysis, autooxidation, and photolysis) fit the prediction can contribute to the reliability assessment and should therefore be provided when possible. If the structure is known or predicted to have a certain mechanism of action relevant for the property under analysis, or the formation of certain metabolites or other transformation products is expected, then their relation to the prediction and how the model takes them into account are expected to be described. One example is the prediction of a property for which modes of action are known, such as skin sensitisation due to protein binding. If the model provides a "non-sensitiser" prediction, but the substance under analysis is known or predicted to bind to proteins, then additional explanations are necessary to support the reliability of the negative prediction. Similarly, if the substance under analysis is known to undergo metabolism leading to the formation of hazardous metabolites, a prediction of lack of hazard would need additional justification to discuss how the model prediction considers the effects of metabolism and its products.

Consistency of information *(AE 3.6 in the Prediction and Result Checklists)*

Finally, it is often the case that predictions from more than one model are used to predict the property of interest, and/or additional information (measured or calculated values) for the same or related property is available. The consistency between (Q)SAR predictions and/or with other reliable information, if available, needs to be considered. Predictions consistent (i.e., in agreement) with each other are considered more reliable when generated by independent models (in terms of training sets, modelling techniques and/or descriptors/alerts used). Contradicting information, in the absence of some explanation, tends to decrease the reliability of the prediction. The Result Checklist should be used when a (Q)SAR result is based on multiple predictions (see Chapter 3). Further weight of evidence considerations are out of the scope of this document.

The reliability assessment is anticipated to be the most complex part of the assessment. It requires an in-depth analysis and expert judgment, even when facilitated by the comprehensive reports of modern (Q)SAR software. However, when a prediction-specific reliability assessment is thoroughly performed, it may offer more insight than the more generic information on the applicability domain of the model.

2.4 Outcome fit for the regulatory purpose

This principle describes the assessment of the usefulness of the (Q)SAR prediction to answer a specific regulatory question. Even if very reliable, a prediction or a result from multiple predictions can be used for a specific regulatory purpose only if it is fit for that purpose. The elements to consider when evaluating the fitness for purpose depend on the regulatory

[3] Absorption, Distribution, Metabolism, Elimination

framework. The final decision on the fitness for the purpose (and on the acceptability in general) lies with the authority responsible for the regulatory framework.

The Prediction Checklist includes the following AEs to verify that an outcome is fit for the regulatory purpose:

- Compliance with additional requirements
- Correspondence between predicted property and property required by the regulation
- Decidability within the specific framework

Compliance with additional requirements *(AE 4.1 in the Prediction and Result Checklists)*

A regulatory framework may directly indicate specific criteria for the acceptable use of (Q)SARs. If the criteria include elements not covered in this document, then the compliance of the prediction with these additional criteria is expected for considering the use as acceptable. As an example, in case of regulations that address substances with complex compositions or mixtures, a crucial element to assess is the consideration of the whole composition of the substance or components of the mixture following the criteria specified by the regulation (e.g. by taking into account all components present at a concentration above a given threshold, using a concentration or dose addition approach or selecting a reasonable worst case). In some cases, the consideration of potential antagonistic and synergic effects of the different components may also be required. Another example are regulations that require the use in combination of two different types of models to produce a result (such as the ICH guideline M7 assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk[4], which requires the use of one expert rule-based and one statistical-based model). In this case, the use of an individual prediction will not be fit for purpose.

Correspondence between predicted property and property required by the regulation *(AE 4.2 in the Prediction and Result Checklists)*

It is important that the property predicted by the (Q)SAR model matches the property required by the regulation. The property predicted by a (Q)SAR model depends on the experimental data applied as training set and the data curation performed on the data prior to (Q)SAR modelling (e.g. inclusion/exclusion criteria, transparency of manual evaluations and removal of outliers, thresholds applied for defining positives and negatives, etc.). As an example, specific bacterial strains and presence of metabolic activation may need to be explicitly considered by the model if required by the regulation when evaluating in vitro mutagenicity in a bacterial reverse mutation assay. If the regulation refers to a specific test guideline, the model should include the experimental results obtained following the specified test guideline in its training set. However, this may not always be necessary, e.g. models for Ames mutagenicity may include historical data not performed by use of all currently required strains, but positive predictions from the model may still be adequate. Another example is degradation half-life, where predictions from

[4] https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-m7r1-assessment-control-dna-reactive-mutagenic-impurities-pharmaceuticals-limit_en.pdf

models trained with data on primary degradation half-life are not fit for the purpose of assessing ultimate degradation half-life.

Decidability within the specific framework *(AE 4.3 in the Prediction and Result Checklists)*

A prediction is fit for purpose when it allows to take a regulatory decision in the framework of use. In presence of a regulatory threshold, the prediction will be decidable when it is comparable to the threshold (i.e., expressed in the same or convertible unit) and provides a sufficient level of confidence that the prediction lies on one side of the threshold or is close enough that a concern cannot be ruled out. As an example, if a model predicts a water solubility of 0.09 mg/L with high uncertainty and the regulatory decision depends on whether the substance has a solubility above or below 0.10 mg/L, then the prediction will not be decidable. The level of confidence required, as well as the way to establish it, will depend on the intended regulatory purpose.

2.5. Conclusion on the assessment of an individual prediction

The conclusion of the Prediction Checklist consists of an uncertainty value for the assessment and an outcome based on this uncertainty.

2.5.1. Uncertainty

When using the Prediction Checklist, assessors need to decide if each AE is fulfilled or not. In most cases, this decision will include a certain level of uncertainty[4].

The uncertainty of each applicable AE can be described using semi-quantitative values (low, medium, or high), while AEs that are not applicable/assessed are not given an uncertainty score. For AEs that are fulfilled, the explanation of how to assign the uncertainty level for each AE is provided in a separate table of the Prediction Checklist. In addition, a default high uncertainty is assigned to AEs that are not fulfilled or not documented, unless a valid justification is provided. Then, the uncertainty associated with each AE can be used to decide on the overall uncertainty of the prediction.

The overall Prediction Checklist uncertainty is considered “Low” when:

- the prediction fulfils all elements with low uncertainty, OR
- most elements have low uncertainty and the elements with greater uncertainty (including elements not documented or not fulfilled, if any) are not considered of high weight in the overall assessment, and a convincing justification of this consideration is provided.

The overall Prediction Checklist uncertainty is considered “Medium” when:

[4] The uncertainty refers to the assessment itself, irrespective of whether the prediction is expressed as a point value, a range, or a probability estimate. For a definition of uncertainty, see the Glossary.

- the prediction fulfils all or most elements with medium uncertainty. Elements with greater uncertainty (if any) are not considered of high weight in the overall assessment, OR
- the prediction fulfils most elements with low uncertainty, but some elements of high weight in the overall assessment have medium uncertainty.

The overall Prediction Checklist uncertainty is considered “High” when:

- the prediction fulfils all or most elements with high uncertainty, OR
- the prediction fulfils most elements with low or medium uncertainty, but some elements of high weight in the overall assessment have high uncertainty.

2.5.2. Outcome

The outcome of the assessment of the prediction is based on an integration of the outcome and uncertainty of the AEs in the Prediction Checklist. In general, AEs with high weight are the most critical for the assessment, and an acceptable prediction should fulfil all of them with low or medium uncertainty. AEs with lower weight are also important, but predictions that fulfil some of them with high uncertainty or do not fulfil them can also be acceptable for some applications. When applying the logic described in Chapter 2.5.1., this approach corresponds to considering predictions with Low or Medium uncertainty to be acceptable.

This document provides general advice on the assessment and suggests the “weight” that can be used for each AE, but each authority could establish (and communicate) different requirements for acceptable results for their applications.

For an individual prediction, the assessment is concluded at this stage.

3 Assessment of a (Q)SAR Result derived from multiple predictions (Result Checklist)

3.1 When to use the Result Checklist

The Result Checklist should be used when assessing a result derived from multiple predictions for the same or related properties. Cases that consider multiple predictions include:

a. Predictions from different models for the same structure;

b. Predictions from the same models for different structures (such as the multiple constituents of a substance or for the substance under analysis and its metabolites or transformation products);

c. A combination of the above.

First, each prediction needs to be evaluated using the individual prediction checklists within the Result Checklist. For complex cases (point c), it is advised to start by addressing multiple predictions associated with the same structure, and then consider the predictions for different structures.

A checklist for each prediction (within the Result Checklist) needs to be completed. The assessment of each prediction can be carried out independently, except for the AEs listed below. For these AEs, the outcome needs to consider the information from all predictions:

- Input representative of the substance under analysis;
- Mechanistic and/or metabolic considerations;
- Consistency of information;
- All AEs referring to the principle “Outcome is fit for the regulatory purpose”.

This situation can be exemplified with a case where two constituents of the same substance are predicted individually. Two checklists should be compiled within the Result Checklist, one for each prediction. When evaluating the AE on the representativeness of the input, both constituents shall be considered, and the same outcome can be recorded in the checklists for each prediction within the Result Checklist.

There is one additional AE to consider when evaluating a result from multiple predictions:

- Correct determination of the final result from individual predictions

The assessment of (Q)SAR results derived from multiple predictions should be based on the information provided in the QMRF, QPRF, and the (Q)SAR Results Reporting Format (QRRF).

Assessors should verify that the final result, derived from the individual predicted values, has been correctly determined. Depending on the type of endpoint and regulatory requirement, the final result can be determined by majority consensus, worst case, average value, or more complex techniques. In this calculation, different weights may be given to predictions depending on e.g., their reliability. In any case, assessors should verify that the determination is documented and adequately justified.

3.2 Uncertainty and outcome of the (Q)SAR Result

3.2.1. Uncertainty

Finally, there is an additional step aimed at weighing each prediction in order to reach a conclusion, i.e., to decide on the acceptability of the final result. The logic for the estimation of the uncertainty of the result derived from multiple predictions is as follows:

- When the final result is generated by integrating consistent (i.e., in agreement) predictions for the same structure from different independent models, then the uncertainty of the final result can be equal or lower than the uncertainty of the individual predictions. The uncertainty of a result from multiple predictions can be lower when the AEs with higher uncertainty are different for the predictions, and they can therefore support each other on their elements of uncertainty. This is not the case when higher uncertainty comes from the same AEs;
- When the final result is generated by integrating inconsistent predictions for the same structure from independent models, then the uncertainty of the final result will be equal or higher than the uncertainty of the individual predictions. Normally, results derived from inconsistent predictions will be acceptable only if one or more predictions in agreement outweigh the inconsistencies due to better fit to the applicability domain, higher reliability, or lower uncertainty. A justification on the rationale of the integration is expected from the (Q)SAR user, while the (Q)SAR assessor can comment on this aspect under the AE “Consistency of information”;
- When the final result depends on predictions for different structures (e.g., different constituents of the same substance, and/or a parent and its metabolites, etc.), then its uncertainty should take into account the uncertainty of the individual predictions and the composition of the substance under analysis. As an example, when predicting water solubility, the uncertainty of the prediction for the main constituent could have a higher influence on the uncertainty of the final result compared to the uncertainty of the prediction for a minor impurity. In this example, if the uncertainty of the prediction for the main constituent is “Medium”, and the uncertainty for the prediction of the minor impurity is “High”, then the uncertainty of the final result could be “Medium”. While if the uncertainty of the prediction for the main constituent is “High”, while for the minor impurity is “Medium”, then the uncertainty of the final result could be “High”. For other properties such as mutagenicity, where a mutagenic impurity can make the whole substance mutagenic, the concentration of a constituent or impurity in the composition

will have a smaller role or no role in weighing the individual predictions to decide on the uncertainty of the overall result.

3.2.2. Outcome

The uncertainty of the result can then be used to determine the outcome of the assessment. Consistently with the approach for individual predictions described in 2.5.2, results with Low or Medium uncertainty could be considered as acceptable. The decision of the outcome for the final result completes the assessment.

4 Final considerations

This document aims at providing a comprehensive list of the elements needed for assessing (Q)SAR models, predictions, and results from multiple predictions. Depending on the specificities of the case and context of use, not all AEs may be applicable or required. Each regulatory authority should decide and communicate what elements need to be systematically considered for the assessment in a specific regulatory framework and context (e.g., the reliability requirements may be lower when the (Q)SARs are used for the purpose of screening a database compared to when they are used for assessing an individual substance). Thresholds to judge whether an AE is fulfilled may also be introduced by some authorities but are not included in this document for at least two reasons: 1. lack of generally agreed thresholds in the scientific community and 2. acceptable thresholds may vary depending on a multitude of factors including the property of interest and the regulatory purpose or context of use.

In general, the use of valid (Q)SAR models shall be expected. This can be verified using the Model Checklist.

A correct input should always be required, irrespective of the context of use. If the input is not correct, the (Q)SARs will not be useful for further regulatory considerations.

The relation of the substance with the AD of the model is also important. Ideally, the substance should clearly fall within the AD of the model. If this is not the case, other reliability aspects may still lead to the acceptance of the use of the prediction or result for a given purpose.

Finally, even if otherwise correct and reliable, a prediction or result can only be used if it is fit for purpose. Clear regulatory requirements for the use of (Q)SAR results facilitate the assessment of this principle.

When integrating multiple predictions into one result, a description of and a justification for the approach used to derive the overall result is essential.

This document includes a major update to the QPRF format. The need for a more comprehensive update of the QMRF has also been identified, and will be discussed as a future undertaking. In addition, the newly developed template to report results based on multiple predictions (QRRF) is included as Annex III of this document.

The QAF Checklists offer more explanations and examples useful to perform the assessment in practice. After the publication of this document, more regulation-specific guidance documents or case studies may be prepared to clarify prediction- and regulation-specific requirements.

Annex I (Q)SAR model reporting format (QMRF) v.2.1

Download an editable format in the **Support Materials** tab.

QMRF v.2.1 is a minor update of the version 2.0[5] QMRF template, as it only concerns the description of the QMRF fields. The only exception is Section 10, which has been entirely removed. This section refers to the JRC QSAR Model Database, which is no longer updated.

	Element	Explanation
1.	**QSAR identifier**	
1.1.	QSAR identifier (title)	Provide the title of the model. The title should include keywords such as: endpoint modelled (as detailed as possible and consistent with section 3 of the QMRF, recommended), name of the model, name of the modeller, and name of the software and version coding the model. Examples: "*EPI Suite™* BIOWIN *v4.10* for Biodegradation"; "TOPKAT Rabbit Skin Irritation (Draize test) for Acyclic compounds (Acids, Amines, Esters) Severe vs Non/Mild/Moderate skin irritation".
1.2	Other related models	If applicable, identify any model that is related to the model described in the present QMRF. Example: TOPKAT Rabbit Skin Irritation (Draize test) for Acyclics compounds (Acids, Amines, Esters) NEG/MLD v MOD/SEV Model Nonirritant vs. Mild/Moderate skin irritation" is related to the model mentioned in 1.1: "TOPKAT Skin Irritation Acyclics compounds (Acids, Amines, Esters) Severe vs. Non/Mild/Moderate skin irritation

[5] Triebe, J., Worth, A., Janusch Roi, A. and Coe, A., JRC QSAR Model Database: EURL ECVAM DataBase service on ALternative Methods to animal experimentation: To promote the development and uptake of alternative and advanced methods in toxicology and biomedical sciences: User Support & Tutorial, EUR 28713 EN, Publications Office of the European Union, Luxembourg, 2017, ISBN 978-92-79-71406-1, doi:10.2760/905519, JRC107491.

		MOD v SEV Model."
1.3.	Software coding the model	Specify the name and the version of the software that implements the model. Examples: "BIOWIN v. 4.2 (EPI Suite)"; "TOPKAT v. 6.2". If the model is implemented as a web service, please report link to the service. If no software implements the model, please state this.
2.	**General information**	
2.0	Abstract	A free text description of the context and background of the (Q)SAR model. In addition, a more comprehensive explanation should be added if there is no scientific article about the model or if the presented model is based on several scientific articles. If the model is adapted from a scientific article, or from data obtained from open (or closed) sources, it must be clearly stated, and the changes made during the adoption of the model must be described.
2.1.	Date of QMRF	Report the date of QMRF drafting (day/month/year). Example: "5 November 2023".
2.2.	QMRF author(s) and contact details	QMRF author(s) and contact details: Indicate the name and the contact details of the author(s) of the QMRF (first version of the QMRF).
2.3.	Date of QMRF update(s)	Date of QMRF update(s): Indicate the date (day/month/year) of any update of the QMRF. The QMRF can be updated for a number of reasons such as additions of new information (e.g. addition of new validation studies in section 7) and corrections of information. However, please note that if the (Q)SAR itself is being updated (i.e. changes in training set or modelling) this should be regarded as a new model which should have a new QMRF, rather than an update of the old QMRF.
2.4.	QMRF update(s)	QMRF update(s): Indicate the name and the contact details of the author(s) of the QMRF updates (see field 2.3) and list which sections and fields have been modified and why.

2.5.	Model developer(s) and contact details	Model developer(s) and contact details: Indicate the name of model developer(s)/author(s), and the corresponding contact details; possibly report the contact details of the corresponding author.
2.6.	Date of model development and/or publication	Date of model development and/or publication: Report the year of release/publication of the model described in this QMRF.
2.7.	Reference(s) to main scientific papers and/or software package	Reference(s) to main scientific papers and/or software package: List the main bibliographic references (if any) to original paper(s) explaining the model development and/or software implementation. Any other reference such as references to original experimental data and related models can be reported in field 9.2 “Bibliography”. Please note, that it should be clearly indicated if the scientific paper(s) refer to an earlier model version / model than the one addressed in the QMRF.
2.8.	Availability of information about the model	Availability of information about the model: Indicate whether the model is proprietary or non-proprietary and specify (if possible) what kind of information about the model cannot be disclosed or are not available (e.g., training and external validation sets, source code, and algorithm). Example: "The model is non-proprietary: full description of the model algorithm is available, training and test sets are available as supplementary material of original research article"; "The model is non-proprietary: training and test sets are available in model repository X; “The model is non- proprietary: but the training and test sets are not available”; “The model is proprietary and: the algorithm and the data sets are confidential”; "The model is proprietary: the algorithm and data sets and model development are confidential, however the model is implemented in a public web service";
2.9.	Availability of another QMRF for exactly the same model	Availability of another QMRF for exactly the same model: Indicate if you are aware or suspect that another QMRF is available for the current model you are describing. If possible, identify this other QMRF.

3	**Defining the endpoint - OECD Principle 1: "A DEFINED ENDPOINT"**	**PRINCIPLE 1: "A DEFINED ENDPOINT". ENDPOINT refers to any physicochemical, biological, or environmental property/activity/effect that can be measured and therefore modelled. The intent of PRINCIPLE 1 (a (Q)SAR should be associated with a defined endpoint) is to ensure clarity in the endpoint being predicted by a given model, since a given endpoint could be determined by different experimental protocols and under different experimental conditions. It is therefore important to identify the experimental system and test conditions that is being modelled by the Q)SAR.**
3.1.	Species	Species: if applicable, indicate the species for the endpoint being modelled. Taxon, species, strain, clone, type of organism, cell type, or other (e.g., *in chemico*) Example: Fathead minnow (*Pimephales promelas*)
3.2.	Endpoint	Endpoint: describe the endpoint that is modelled. The experimental protocol(s) and test conditions applied for the training set data together with the subsequent data curation for (Q)SAR modelling determine the endpoint predicted by the model.
3.3	Comment on endpoint	Comment on the endpoint: Include in this field any other information to define the endpoint being modelled. Specify the endpoint further if relevant, e.g. according to test organism such as species, strain, sex, age or life stage; according to test duration and protocol; according to the detailed nature of endpoint etc.
3.4.	Endpoint units	Endpoint units: Specify the units of the endpoint measured. For categorical endpoints, provide details on the scale and eventual conversions.
3.5.	Dependent variable	Dependent variable: Specify the relationship between the dependent variable being modelled and the endpoint measured since the two quantities may be different. Example: For modelling purposes all rate constants (i.e. Nitrate radical degradation rate constant (kNO3) were transformed to logarithmic units and multiplied by -1 to obtain positive values. The dependent variable is: -log(kNO3).
3.6.	Experimental protocol	Experimental protocol: Make any useful reference to a specific experimental protocol(s) (for example OECD Test Guideline number) followed in the collection and evaluation of the

		experimental data sets.
3.7.	Endpoint data quality and variability	Endpoint data quality and variability: provide available information about the experimental test data quality selection and evaluation and include a description of the data quality used to develop the model. This includes provision of information about in terms of the known variability of the test data, i.e. repeatability (variability over time) and reproducibility (variability between laboratories) and sources of error (confounding factors which may influence testing results) etc.. Please also as far as possible provide information about test chemical purity. Ideally, (Q)SARs should be based on experimental tests performed with test chemical of high purity to assure good correlation between structures and effect. Test chemical purity should preferably be provided for the individual substances used in the training and validation sets. The data curation procedure and its effect on data quality should also be described here.
4	**Defining the algorithm - OECD Principle 2 : "AN UNAMBIGUOUS ALGORITHM"**	**PRINCIPLE 2: "AN UNAMBIGUOUS ALGORITHM". The (Q)SAR estimate of an endpoint is the result of applying an ALGORITHM to a set of structural parameters which describe the chemical structure. The intent of PRINCIPLE 2 (a (Q)SAR should be associated with an unambiguous algorithm) is to ensure transparency in the model algorithm that generates predictions of an endpoint from information on chemical structure and/or physicochemical properties. In this context, algorithm refers to any mathematical equation, decision rule or output approach.**
4.1.	Type of model	Type of model: Describe the type of model, e.g., equation based, fragment/alert based (expert rule-based and/or statistical based), etc..
4.2.	Explicit algorithm	Explicit algorithm: Report the algorithm (only the algorithm) for generating predictions from the descriptors and/or structural fragments/alerts; more text information about the algorithm can be reported in the following fields of this section or as supporting information (see field 9.3). If the algorithm is too long and complicated, include in this field a reference to a scientific paper or another document where the algorithm and/or general modelling approach is described in detail. If possible, the algorithm should be made available in a machine-readable manner (e.g., PMML or some other model describing format).

		This material can be attached as supporting information or made available in an open access repository. This material can be attached as supporting information. If the algorithm cannot be disclosed or fully disclosed due to confidentiality, it should be explicitly stated.
4.3.	Descriptors in the model	Descriptors in the model: Identify the number and the name or identifier of the descriptors included in the model. In this context, descriptors refer to e.g. physicochemical parameters, structural fragments etc.
4.4.	Descriptor selection	Descriptor selection: Indicate the number and the type (name) of descriptors /decision rules initially screened, and explain the method used to select the descriptors and develop the model from them.
4.5.	Algorithm and descriptor generation	Algorithm and descriptor generation: Explain the approach used to derive the algorithm and the method (approach) used to generate each descriptor.
4.6.	Software name and version for descriptor generation	Software name and version for descriptor and algorithm generation: Specify the name and the version of the software used to generate the descriptors and the algorithm. If relevant, report the specific settings chosen in the software to generate a descriptor or the algorithm.
4.7.	Chemicals/Descriptors ratio	Chemicals/ Descriptors ratio: Report the following ratio: number of chemicals (chemicals from the training set) to number of descriptors, if applicable (if not, explain why). For some type of models, it may also be important to report the number of other parameters in the model (e.g., number of hidden neurons in artificial neural network models).

5	**Defining the applicability domain - OECD Principle 3: "A DEFINED DOMAIN OF APPLICABILITY"**	**PRINCIPLE 3: "A DEFINED DOMAIN OF APPLICABILITY". APPLICABILITY DOMAIN refers to the response and chemical structure space in which the model makes predictions with a given reliability. Ideally the applicability domain should express the structural, physicochemical and response space of the model. The CHEMICAL STRUCTURE (x variable) space can be expressed by information on physicochemical properties and/or structural fragments. The RESPONSE (y variable) can be any physicochemical, biological or environmental effect that is being predicted. According to PRINCIPLE 3 a (Q)SAR should be associated with a defined domain of applicability. Section 5 can be repeated (e.g., 5.a, 5.b, 5.c, etc) as many times as necessary if more than one method has been used to assess the applicability domain.**
5.1.	Description of the applicability domain of the model	Description of the applicability domain of the model: Define / describe the response and chemical structure and/or descriptor space in which the model makes predictions with a given reliability determined in the statistical validation. Describe the defined applicability domain in terms of the following, as relevant: a) fixed or probabilistic boundaries; b) structural features, a descriptor and/or a response space; c) in the case of (Q)SARs which applies substructures as descriptors, describe possible defined limits on applicability (inclusion and/or exclusion rules regarding the chemical classes to which the model is applicable); d) in the case of (Q)SARs applying substructures as descriptors, describe possible rules on the modularity effects of the substructure's molecular environment; e) possible defined inclusion and/or exclusion rules for the descriptor variable ranges for which the (Q)SAR is applicable; f) possible defined inclusion and/or exclusion rules that define the response variable ranges for which the QSAR is applicable; g) possible defined (graphical) expression of how the descriptor values of the chemicals in the training set are distributed in relation to the endpoint values predicted by the model.
5.2.	Method used to assess the applicability domain	Method used to assess the applicability domain: Describe the method used to assess the applicability domain of the model.

5.3.	Software name and version for applicability domain assessment	Software name and version for applicability domain assessment: Specify the name and the version of the software used to apply the applicability domain method, where applicable. If relevant, report the specific settings chosen in the software to apply the method.
5.4.	Limits of applicability	Limits of applicability: Describe for example the inclusion and/or exclusion rules (fixed or probabilistic boundaries, structural features, descriptor space, response space) that define the applicability domain.
6	**Defining goodness-of-fit and robustness (internal validation) – OECD Principle 4: "APPROPRIATE MEASURES OF GOODNESS-OF-FIT, ROBUSTENESS AND PREDICTIVITY"**	**PRINCIPLE 4: "APPROPRIATE MEASURES OF GOODNESS-OF-FIT, ROBUSTENESS AND PREDICTIVITY". PRINCIPLE 4 expresses the need to perform validation to establish the performance of the model. GOODNESS-OF-FIT and ROBUSTNESS refer to the internal model performance.**
6.1.	Availability of the training set	Availability of the training set: Indicate whether the training set is somehow available (e.g., published in a paper, embedded in the software implementing the model, stored in a database) and appended to the current QMRF as supporting information (field 9.3). If it is not available, explain why. Example: "It is available and attached" "It is available but not attached"; "It is not available because the data set is proprietary"; "The data set could not be retrieved".
6.2.	Available information for the training set	Available information for the training set: Indicate whether the following information for the training set is reported as supporting information (see field 9.3): a) Chemical names (common names and/or IUPAC names); b) CAS numbers; c) SMILES; d) InChI codes; e) MOL files; f) Structural formula; g) If the dataset contains nanomaterials; h) test chemical purity for individual substances; i) Any other structural information.
6.3.	Data for each descriptor variable for the training set	Data for each descriptor variable for the training set: Indicate whether the descriptor values of the training set are available and are attached as supporting information (see field 9.3).
6.4.	Data for the dependent variable for the training set	Data for the dependent variable (response) for the training set: Indicate whether dependent variable values of the training set are available and attached as supporting information (see field 9.3).

6.5.	Other information about the training set	Regardless of whether the training set is made available, other information about the training set: Indicate any other relevant information about the training set (e.g. number and type of compounds in the training set (e.g. for models predicting positive and negative results the number of positives and the number of negatives in the training set)). Also indicate the rationale on the selection of the different compounds of the training set here.
6.6.	Pre-processing of data before modelling	Pre-processing of data before modelling: Indicate whether raw data have been processed before modelling (e.g. averaging of replicate values); if yes, report whether both raw data and processed data are given.
6.7.	Statistics for goodness-of-fit	Statistics for goodness-of-fit: Report here goodness-of-fit statistics: in the case of models for continuous endpoints, report at least r2, r2 adjusted, RMSE; in the case of models for categorical endpoints, report at least sensitivity, specificity, true positives (TP), true negatives (TN), false negatives (FN), false positives (FP)
6.8.	Robustness - Statistics obtained by leave-one-out cross-validation	Robustness – Statistics obtained by leave-one-out cross-validation: Report here the corresponding statistics.
6.9.	Robustness - Statistics obtained by leave-many-out cross-validation	Robustness – Statistics obtained by leave-many-out cross-validation: Report here the corresponding statistics, the strategy for splitting the data set (e.g. random, stratified), the percentage of left out compounds and the number of cross-validations.
6.10.	Robustness - Statistics obtained by Y-scrambling	Robustness – Statistics obtained by Y-scrambling: Report here the corresponding statistics and the number of iterations.
6.11.	Robustness - Statistics obtained by bootstrap	Robustness – Statistics obtained by bootstrap: Report here the corresponding statistics and the number of iterations.
6.12.	Robustness - Statistics obtained by other methods	Robustness – Statistics obtained by other methods: Report here the corresponding statistics.
7	**Defining predictivity (external validation) – OECD Principle 4: "APPROPRIATE MEASURES OF GOODNESS-OF-FIT, ROBUSTENESS AND PREDICTIVITY"**	**PRINCIPLE 4: "APPROPRIATE MEASURES OF GOODNESS-OF-FIT, ROBUSTENESS AND PREDICTIVITY". PRINCIPLE 4 expresses the need to perform validation to establish the performance of the model. PREDICTIVITY refers to the external model validation. Section 7 can be repeated (e.g., 7.a, 7.b, 7.c, etc) as many times as necessary if more validation studies need to be reported in the QMRF.**

7.1.	Availability of the external validation set	Availability of the external validation set: Indicate whether an external validation set is available and appended to the current QMRF as supporting information (field 9.3). If it is not available, explain why.
7.2.	Available information for the external validation set	Available information for the external validation set: Indicate whether the following information for the external validation set is reported as supporting information (see field 9.3): a) Chemical names (common names and/or IUPAC names); b) CAS numbers; c) SMILES; d) InChI codes; e) MOL files; f) Structural formula; g) If the dataset contains nanomaterials; h) test chemical purity for individual substances; i) Any other structural information.
7.3.	Data for each descriptor variable for the external validation set	Data for each descriptor variable for the external validation set: Indicate whether descriptor values of the external validation set are somehow available and attached as supporting information (see field 9.3).
7.4.	Data for the dependent variable for the external validation set	Data for the dependent variable for the external validation set: Indicate whether dependent variable values of the external validation set are somehow available and attached as supporting information (see field 9.3).
7.5.	Other information about the external validation set	Other information about the external validation set: Indicate any other relevant information about the validation set. Example: “External validation set with 56 compounds appended”.
7.6.	Experimental design of test set	Experimental design of test set: Indicate any experimental design for getting the validation set (e.g. by randomly setting aside chemicals before modelling, by literature search after modelling, by prospective experimental testing after modelling, etc.).
7.7.	Predictivity - Statistics obtained by external validation	Predictivity – Statistics obtained by external validation: Report here the corresponding statistics. In the case of classification models, include false positive and negative rates.
7.8.	Predictivity - Assessment of the external validation set	Predictivity – Assessment of the external validation set: Discuss whether the external validation set is sufficiently large and representative of the applicability domain. Describe for example the descriptor and response range or space for the validation test set as compared with that for the training set. Here the descriptor values of the chemicals predicted by the model (training set) should be compared with the descriptor value range of the test set. In addition, the distribution of the response values of the chemicals in the training set should be compared to the distribution of the response values of the test set. Predictivity of certain (Q)SARs can be measured by a

		cross-validation procedure qualifying it to be a “n-fold external validation procedure” or “external cross-validation”
7.9.	Comments on the external validation of the model	Comments on the external validation of the model: Add any other useful comments about the external validation procedure.
8	**Providing a mechanistic interpretation - OECD Principle 5: “A MECHANISTIC INTERPRETATION, IF POSSIBLE”**	**PRINCIPLE 5: “A MECHANISTIC INTERPRETATION, IF POSSIBLE”. According to PRINCIPLE 5, a (Q)SAR should be associated with a mechanistic interpretation, if possible.**
8.1.	Mechanistic basis of the model	Mechanistic basis of the model: Provide information on the mechanistic basis of the model (if possible). In the case of (Q)SARs using structural features as descriptors, you may want to describe (if possible) the molecular features that underlie the properties of the molecules containing the substructure (e.g. a description of how sub-structural features could act as nucleophiles or electrophiles, or form part or all of a receptor-binding region). In the case of (Q)SARs using numeric descriptors, you may give (if possible) a physicochemical interpretation of the descriptors used (consistent with a known mechanism of biological action). If it is not possible to provide a mechanistic interpretation, try to explain why.
8.2.	A priori or a posteriori mechanistic interpretation	A priori or a posteriori mechanistic interpretation: Indicate whether the mechanistic basis of the model was determined a priori (i.e. before modelling, by ensuring that the initial set of training structures and/or descriptors were selected to fit pre-defined known mechanism of action) or a posteriori (i.e. after modelling, by interpretation of the final set of training structures and or descriptors).
8.3.	Other information about the mechanistic interpretation	Other information about the mechanistic interpretation: Report any other useful information about the (purported) mechanistic interpretation described in the previous fields (8.1 and 8.2) such as any reference supporting the mechanistic basis.
9	**Miscellaneous information**	

9.1.	Comments	Comments: Add here other relevant and useful comments (e.g. other related models, known applications of the model) that may facilitate regulatory considerations on the model described. Include if relevant experience obtained by use of model prediction for various types of regulatory decisions (incl. references as appropriate).
9.2.	Bibliography	Bibliography: Report useful references other than those directly associated with the model development (references describing the model development are reported in field 2.7).
9.3	Supporting information	Supporting information: Indicate whether supporting information is attached (e.g. external documents) to this QMRF and specify its content and possibly its utility. This should cover structures in the training, set, and validation sets, response variable value), descriptor values, whether the training and test sets are submitted in defined file formats (txt, csv, SDF, etc.), model (e.g., pmml), predictions for training and validation sets and other documents, as relevant.

Annex II (Q)SAR prediction reporting format (QPRF) v.2.0

Download an editable format in the **Support Materials** tab.

	Element	Explanation
1.	**General information**	*Information about the compilation of the current QPRF is provided in this section.*
1.1.	**Date of QPRF**	*Report the date of compilation of the QPRF. Example: 30th January 2023.*
1.2.	**QPRF author and contact details**	*Report the contact details of the author of the QPRF.*
2.	**Substance**	*Information about the substance under analysis. Some substances might be associated to more than one structure. The information on the structure(s) used as input is expected in Section 5.1.*
2.1.	**CAS number**	*Report the CAS number.*
2.2.	***EC number***	*Report the EC number.*
2.3.	**Other regulatory numerical identifiers**	*Report other numerical identifiers, e.g. METI number*
2.4.	**Chemical name**	*Report the chemical name (e.g., IUPAC and/or CAS names)*
2.5.	**Structural formula**	*Report the structural formula.*
2.6.	**Structural and composition information** ***a.*** **SMILES**	*Report the SMILES of the substance, if available.*
	b. **InChI**	*Report the InChI code of the substance, if available.*
	c. **Other structural representation**	*Indicate if another structural representation was used to generate the prediction. Indicate whether this information is included as supporting information. Example: "mol file used and included in the supporting information".*
	d. **Stereochemical features**	*Indicate whether the substance is a stereoisomer and consequently may have properties that depend on the orientation of its atoms in space.*
	e. **Composition information**	*Comment on whether there is more than one constituent, impurity or additive in the composition of the substance that should be considered for the assessment.*
	Comments on substance information	*Add any other information, as relevant*

3.	**Model and software**	*Information about the model and software used to make the prediction*
3.1	**Model** **a. Model or submodel name**	*Identify the model used to make the prediction*
	b. Model version	*Identify, where relevant, the version number and/or date of the model and submodel.*
	c. Reference to QMRF	*Provide relevant information about the QMRF that stores information about the model used to make the prediction.*
	Comments on model	*add any other information, as relevant*
3.2	**Software** **a. Software name**	*Identify the software used to make the prediction*
	b. Software version	*Identify the version number of the software.*
	c. Software reference	*Provide relevant information about the software*
	d. Software availability	*Provide information on the availability of the software (e.g. whether it is available for download, if it is commercial or free to use.)*
	Comments on software	*Add any other information, as relevant*
4.	**Prediction**	*Information about the prediction of the model*
4.1	**a. Predicted Property**	*Define the property for which the model provides predictions (this information should correspond to the information provided in the QMRF under fields 3.2 and 3.3). Information such as species, duration, should be included in the description of the property, where possible. Examples: 28 days repeated dose oral toxicity to rat. 96-hour toxicity to fish (fresh water). Provide information about the specifics of the data curation procedure, e.g. inclusion/exclusion rules, for binary endpoints the definitions of the positives and negatives etc.*
	b. Test guideline covered	*indicate if the data in the training set covers one or more specific test guidelines.*
	c. Dependent variable	*Report the dependent variable for which the model provides predictions including any transformations introduced for modelling purposes (note that this information should correspond to the information provided in the QMRF under field 3.5). Example: NOEL, LOAEL, LC_{50}*
	Comments on the predicted property	*Add any other information, as relevant*

4.2	**a. Predicted value**	*Report the predicted value (including units) obtained from the application of the model to the input structure. For alert-based expert models, report the alert triggered together with the reasoning. Example: "aromatic amine - mutagenicity, plausible".*
	b. Predicted value (comments)	*The predicted value is categorical (e.g. yes/no or low/medium/high), explain the cut-off values that were used as the basis for classification.*
	c. Unit	*Indicate the unit in which the predicted value is expressed*
	Comments on the predicted value	*Add any other information, as relevant*
5	**Input**	*Information about the input used to generate the prediction. It should be detailed enough to allow reproducibility of the prediction by others when using the same model and software.*
5.1	**a. Input structure**	*Specify what kind of input was used to represent the input structure (e.g., SMILES, CAS RN, mol file) and associated value*
	b. Stereochemical features	*indicate whether the substance is a stereoisomer and consequently may have properties that depend on the orientation of its atoms in space. Identify the stereochemical features that may affect the reliability of predictions for the substance, e.g. cis-trans isomerism, chiral centers. Are these features encoded in the structural representations mentioned above?*
	c. Tautomerism	*Indicate whether the substance is known to undergo tautomerism and what impact it may have on the prediction.*
	Comments on the input structure	*Add any other information, as relevant*
5.2	**Descriptors**	*Report, for each descriptor ((at least for descriptors manually input)* *a. The value and unit of the descriptor* *b. If the descriptor is measured experimentally or calculated* *c. Reference to the descriptor source* *d. A justification if different types of descriptors are used for the prediction compared to those that were used for model development and validation*
	Comments on descriptors	*Add any other information, as relevant*

5.3	**Model and/or software settings**	*For models or software that allow customization of their algorithm, indicate the custom settings used to generate the prediction*
	Comments on settings	*Add any other information, as relevant*
6	**Applicability domain (AD) and limitations**	*Information about how the substance relates to the AD as defined by the model developers and any other documented limitations. Any other reliability considerations can be reported in Section 7.*
6.1	**Applicability domain (AD) and limitations**	*In this section, the assessment of the AD is limited to the AD definition as intended by model developers. In the Reliability section, other AD considerations can be added.*
	a. AD assessment	*Indicate if the prediction is within or outside the defined AD of the model. Specify if the assessment was done manually by the user or automatically by the software. If the AD is not defined, indicate in this field "Not applicable".*
	b. AD assessment justification	*Describe why the substance is within or outside the AD assessment*
	c. Any other limitation	*Indicate if any other known limitation beyond those defined in the applicability domain are applicable to the prediction. Example: if the input structure is a perfluorinated substance and it has been documented that the model cannot predict these types of substances, the use of the model for this particular substance needs additional justification.*
	Comments on AD	*Add any other information, as relevant*
7	**Reliability assessment**	*Information about reliability of the prediction beyond the AD as defined by the model developers.*
7.1	**Reproducibility**	*Indicate if it is possible to reproduce the prediction. This requires e.g., public availability of the software implementing the model and/or a clear description of the model.*
	Comments on reproducibility	*Add any other information, as relevant*
7.2	**Overall performance of the model**	*With a reference to the predictive performance of the model reported in the QMRF, indicate why the performance is considered acceptable for the intended regulatory purpose*
7.3	**Additional reliability aspects based on the training set**	*Discuss whether the input structure is covered by the training set in terms of:*
	a. Descriptor space	*Discuss if the values of the descriptors used in the model of the chemical*

		are within the limits (i.e. highest and lowest values) of the descriptors associated with training set chemicals.
	b. Structural fragment space	*Discuss if the chemical contains fragments that are represented in the model training set, including stereoisomerism when relevant*
	c. Response space	*Discuss if the predicted value of the chemical falls within the response (i.e., predicted property) space of the model training set*
	d. Mechanism considerations	*Discuss if the mechanism of action of the chemical, if possible (where relevant), is covered by the model, i.e. that there are substances in the training set following (or expected to follow) the same mechanism as the input structure.*
	e. Metabolic considerations	*Discuss if the metabolism of the chemical, where relevant, is covered by model, i.e. if the training set of the model includes substances which have (or are expected to have) a similar metabolism compared to the input structure*
	Comments on additional reliability aspects	*Add any other information, as relevant*
7.4	**Analogues**	*List the structural and/or mechanistic analogues with associated experimental data that can be used to support the reliability of the prediction. For each analogue indicate:*
	a. Identifiers	*E.g. CAS number, the structural formula, the SMILES code*
	b. Source of the analogue	*From the training or test sets, or accessible from other sources (in this case it should be explained how the structural analogue was retrieved)*
	c. Experimental value for the property of interest	*Self-explanatory field name*
	d. Reference for experimental value	*To verify the validity of the experimental data*
	e. Predicted value for the property of interest	*Self-explanatory field name*
	f. Accuracy of the prediction	*Comparison between experimental and predicted value*
	g. Comments on similarity	*Justification about the reasons that qualify a structural analogue as relevant*
	Considerations on analogues	*Discuss how predicted and experimental data for structural analogues support the prediction of the chemical under consideration.*

	Comments on analogues	*Add any other information, as relevant*
7.5	**Other reliable information on the property**	*Indicate if any other information other than the prediction is available for the property. Additional information can be obtained from additional models or different type of information. Provide considerations on how the other information fit with the prediction.*
7.6	**Conclusion on reliability**	*Summary of reliability assessment*
8	**Purpose of use (for regulatory applications)**	*This information aims to facilitate considerations about the adequacy of the (Q)SAR prediction or the result derived from multiple predictions for a specific regulatory use*
8.1.	**Regulatory purpose**	*Explain the regulatory purpose for which the prediction is being used.*
8.2.	**Approach for regulatory interpretation of the prediction or result derived from multiple predictions**:	*Describe how the result is going to be interpreted in light of the specific regulatory purpose (e.g. by applying an algorithm or regulatory criteria). This may involve the need to convert the units of the dependent variable (e.g. from log molar units to mg/l). It may also involve the application of another algorithm, an assessment factor, or regulatory criteria, and the use or consideration of additional information in a weight-of-evidence assessment. For a result derived from multiple predictions, explain how the individual predictions were integrated to obtain the final result.*
8.3.	**Regulatory interpretation of the result**	*Report the interpretation of the model result in relation to the defined regulatory purpose.*
8.4	**Uncertainty**	*Estimate and comment on the uncertainty of the prediction for the input structure. The methodology proposed in the OECD (Q)SAR Assessment Framework can be used for this purpose.*
8.5.	**Conclusion**	*Provide an assessment of whether the final result is considered adequate for a regulatory conclusion, or whether additional information is required (if this is the case the content of additional information should be specified).*

Annex III (Q)SAR result reporting format version (QRRF) 1.0

Download an editable format in the **Support Materials** tab.

To help QSAR users further organise the information to document a (Q)SAR result, a (Q)SAR result reporting format (QRRF) has been prepared and added to the QAF.

The QRRF should be completed when users (and not a predefined algorithm) combine multiple predictions to determine a (Q)SAR result. The QRRF should be provided in addition to the individual QPRFs and QMRFs. Certain fields of the QPRF (section 2 – substance, and fields 8.1, 8.2, 8.3, 8.5 under "purpose of use") are repeated in the QRRF. These fields do not need to be completed by users within each QPRF when already included in the QRRF.

To facilitate the preparation of the reports by QSAR users, an Excel file with the QRRF also includes a copy of the QPRF, along with information on how to populate the format in the case of multiple predictions that will be combined to determine a (Q)SAR result. The fields are arranged in a practical format ready to be filled in by users.

	Element	Explanation
1	**General information**	*General information on the current QRRF is provided in this section.*
1.1.	**Date of QRRF**	*Report the date of compilation of the QRRF.*
1.2.	**QRRF author and contact details**	*Report the contact details of the author of the QRRF.*
1.3	**Reference to QPRFs and QMRFs**	*Provide references or links to the QPRFs and QMRF(s) associated to the (Q)SAR result, as relevant*
2	**Substance**	*Information about the substance under analysis. Some substances might be associated to more than one structure (e.g. multiple consitutents of the same substance of a parent substance and its transformation products). The information on the structure(s) used as input is expected in the individual QPRFs.*
2.1.	**CAS number**	*Report the CAS number.*
2.2.	**EC number**	*Report the EC number.*
2.3.	**Other regulatory numerical identifiers**	*Report other numerical identifiers, e.g. METI number*
2.4.	**Chemical name**	*Report the chemical name (e.g., IUPAC and/or CAS names)*
2.5.	**Structural formula**	*Report the structural formula.*

2.6. **Structural and composition information**	**a. SMILES**	*Report the SMILES of the substance, if available.*
	b. InChI	*Report the InChI code of the substance, if available.*
	c. Other structural representation	*Indicate if another structural representation was used to generate the prediction. Indicate whether this information is included as supporting information. Example: "mol file used and included in the supporting information".*
	d. Stereochemical features	*Indicate whether the substance is a stereoisomer and consequently may have properties that depend on the orientation of its atoms in space.*
	e. Composition information	*Comment on whether there is more than one constituent, impurity or additive in the composition of the substance, that should be considered for the assessment.*
	f. Comments on substance information	*Add any other information, as relevant*
3	**(Q)SAR Result**	*Detailed information on the (Q)SAR result*
3.1	**Scenario addressed by the result**	*Select one of the following scenarios:* *Multiple models:* *- One structure predicted with multiple models addressing exactly the same endpoint* *- One structure predicted with multiple models addressing different aspects of the same regulatory endpoint* *Multiple structures:* *- One model to predict multiple structures (different constituents of the same substance or product)* *- One model to predict multiple structures (a parent substance and its transformation products)* *Other:* *- Other combinations (please specify)* *Also specify the number of structures and models considered and justify the approach.*
3.2	**Model and input structure selection**	*Provide the rationale for model and input structure selection. To rule out bias, justify the intentional exclusion of other availabe models for the same property, if applicable.* *For scenarios that include transformation products, this field can be used provide additional information on the transformation products (e.g. if they are predicted or observed, information on their quantities and rate of formation, etc).*
3.3	**Result value and unit**	*Report the (Q)SAR result value (with unit, if applicable).*
3.4	**Calculation approach**	*Describe and justify the (statistical) approach followed to combine the individual predictions into the final (Q)SAR result. (e.g. by majority consensus, worst case, average value, or more complex techniques. In this calculation, different weights may be given to predictions depending on e.g., their reliability.)*
3.5	**Concordance of the (Q)SAR predictions**	*Provide considerations on the agreement of the individual predictions with each other and with the (Q)SAR result.*
3.6	**Independence of the (Q)SAR models**	*Provide considerations on the independence of the models in terms of training sets, modelling techniques and/or descriptors/alerts.* *Only applicable to scenarios that consider more than one model.*
3.7	**Complementarity of (Q)SAR predictions and models**	*Provide considerations on how the predictions and/or the models complement each other, i.e. the added value of the result compared to the individual predictions used for its determination*

4	**Purpose of use (for regulatory applications)**	*This information aims to facilitate considerations about the adequacy of the result derived from multiple predictions for a specific regulatory use.*
4.1.	**Regulatory purpose**	*Explain the regulatory purpose for which the result is being used. Make a link between the (regulatory) property addressed by the result and the property(ies) predicted by the individual models*
4.2.	**Approach for regulatory interpretation of the (Q)SAR result**	*Describe how the result is going to be interpreted in light of the specific regulatory purpose (e.g. by applying an algorithm or regulatory criteria). This may involve the need to convert the units of the dependent variable (e.g. from log molar units to mg/l).*
4.3.	**Regulatory interpretation of the (Q)SAR result**	*Report the interpretation of the (Q)SAR result in relation to the defined regulatory purpose.*
4.4.	**Uncertainty**	*Estimate and comment on the uncertainty of the (Q)SAR result. Include a justification based on the uncertainty of individual predictions which must be provided in each QPRF (section 8.4), as described in the OECD (Q)SAR Assessment Framework.*
4.5.	**Conclusion**	*Provide an assessment of whether the final result is considered adequate for a regulatory conclusion, or whether additional information is required (if this is the case the content of additional information should be specified).*

Glossary of selected terms

Assessment element (AE): a critical aspect to consider when assessing (Q)SAR models, predictions and overall results meet. AEs are associated with the OECD (Q)SAR principles for models and results.

Assessor: the person evaluating the acceptability of a model and/or prediction for the intended regulatory purpose.

Conclusion: the uncertainty and outcome of the assessment for an individual (Q)SAR prediction or a (Q)SAR result.

Model checklist: a separate document to facilitate the assessment of a (Q)SAR models according to QAF principles. It includes a list of assessment elements to consider, columns to record the outcome of the assessment, practical advice, and examples.

Outcome of the assessment: the decision if the (Q)SAR prediction or result is acceptable for the intended regulatory purpose.

Prediction checklist: a separate document to facilitate the assessment of a (Q)SAR prediction according to QAF principles. It includes a list of assessment elements to consider, columns to record the outcome of the assessment, practical advice, and examples.

Property: a physicochemical, toxicological, ecotoxicological, or fate property; chemical reactivity or biological interaction. In this document, the term “property” is preferred to “endpoint” because of the different understanding of the meaning of the term endpoint depending on the audience.

(Q)SAR model: a model that predicts the property of a substance using as input information on the structure.

(Q)SAR prediction: an individual output (i.e., the predicted value of a property) of a (Q)SAR model. It can be a continuous or a categorical (two or more categories) output.

(Q)SAR result: the assessment of a property of a substance based on multiple (Q)SAR predictions.

Regulatory framework: the specific guidelines, rules or mechanisms used to fulfil regulatory requirements.

Regulatory purpose/use/purpose: the specific application within a regulatory framework for which the (Q)SAR result is used.

Result checklist: a separate document to facilitate the assessment of a (Q)SAR result based on multiple predictions according to QAF principles. It includes a list of assessment elements to consider, columns to record the outcome of the assessment, practical advice, and examples.

Substance: the chemical substance under analysis. A substance can be formed by one or more constituents, and hence by associated to one or more structures.

Uncertainty: according to EFSA Guidance on Uncertainty Analysis in Scientific Assessments (2018)[6] "a general term referring to all types of limitations in available knowledge that affect the range and probability of possible answers to an assessment question". In the result checklist, uncertainty can be assigned a low, medium, or high value and it can refer to individual assessment elements, (Q)SAR predictions, or (Q)SAR results.

Internal and external validation of a (Q)SAR model: the statistical procedure to evaluate the performance of the model, based on the use of a training and (independent) test set.

Weight of the assessment element: the importance of an assessment element in the overall assessment of a (Q)SAR prediction. It depends on the regulatory purpose and can have a low, medium, or high value.

[6] EFSA (European Food Safety Authority) Scientific Committee, Benford, D, Halldorsson, T, Jeger, MJ, Knutsen, HK, More, S, Naegeli, H, Noteborn, H, Ockleford, C, Ricci, A, Rychen, G, Schlatter, JR, Silano, V, Solecki, R, Turck, D, Younes, M, Craig, P, Hart, A, Von Goetz, N, Koutsoumanis, K, Mortensen, A, Ossendorp, B, Martino, L, Merten, C, Mosbach-Schulz, O and Hardy, A, 2018. Guidance on Uncertainty Analysis in Scientific Assessments. EFSA Journal 2018;16(1):5123, 39 pp. https://doi.org/10.2903/j.efsa.2018.5123

The aim of the OECD (Quantitative) Structure-Activity Relationship ((Q)SAR) Assessment Framework (QAF) is to provide a systematic and harmonised framework for the regulatory assessment of (Q)SAR models, predictions and results based on multiple predictions. The QAF is meant to be applicable (Q)SARs, irrespective of the modelling technique used to build the model, the predicted endpoint, and the intended regulatory purpose. The updated second edition includes a reporting format for (Q)SAR results that rely on multiple predictions. The (Q)SAR Result Reporting Format (QRRF) was created to address an identified gap in the first edition of the QAF and is designed to increase confidence in using (Q)SAR results for regulatory application. The primary audience of this document is regulatory authorities and their stakeholders. In addition, any other (Q)SAR user is encouraged to refer to the QAF when using (Q)SARs for regulatory purposes.

https://www.oecd.org/en/data/tools/oecd-qsar-toolbox.html