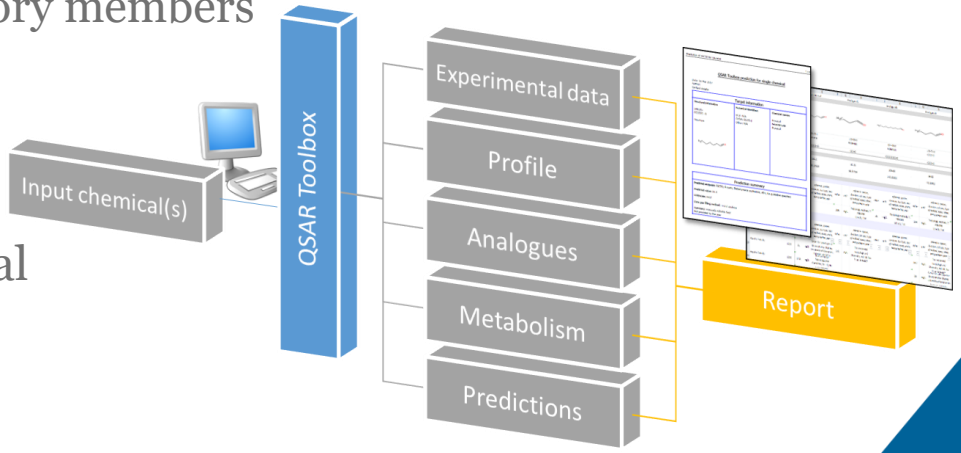
INTRODUCTION TO QAF

Patience Browne
November 9 2023

OECD QSAR Toolbox

- initiated in 2006
  - Developed with the goal of placing substances into chemical **categories** to predict apical outcome of regulatory interest
  - Using data from tested category members [**analogues**] to aid in filling data gaps for untested category members
- Now, that and so much more
  - Experimental data
  - Profilers for properties of chemical
  - Metabolism simulators



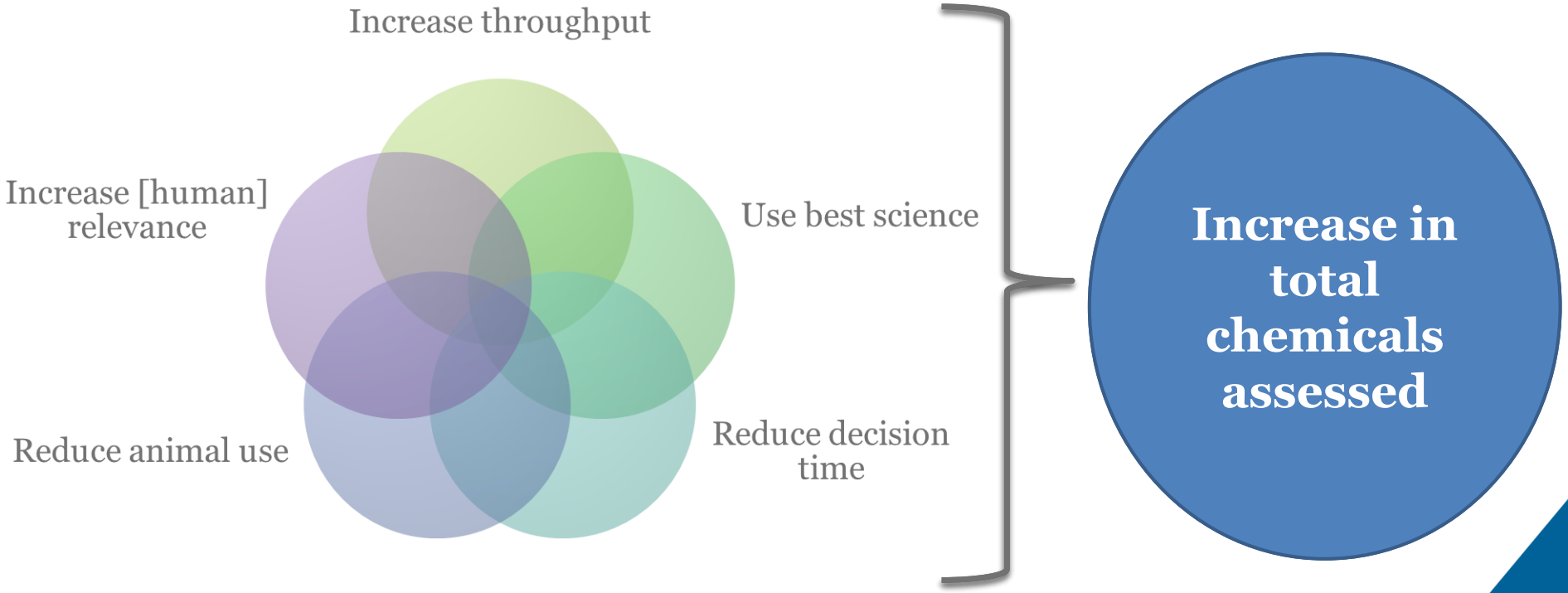
QSAR Toolbox supports alternatives to animal testing

- **Inform testing strategies** - by forming categories and identifying data gaps, intelligent testing strategies can be designed to reduce costs and number of animals required

- **Predict properties** - predictions can replace information requirements (e.g. test data) or be used to support prioritisation, substance evaluation

- **Sustainable development and green chemistry** - the toxicity of substances can be predicted even before they are produced

Global drivers to use NAMs in chemical risk assessment



OECD QSAR Assessment Framework (QAF)

Project added to OECD Hazard Assessment Work Programme: Q1 2021

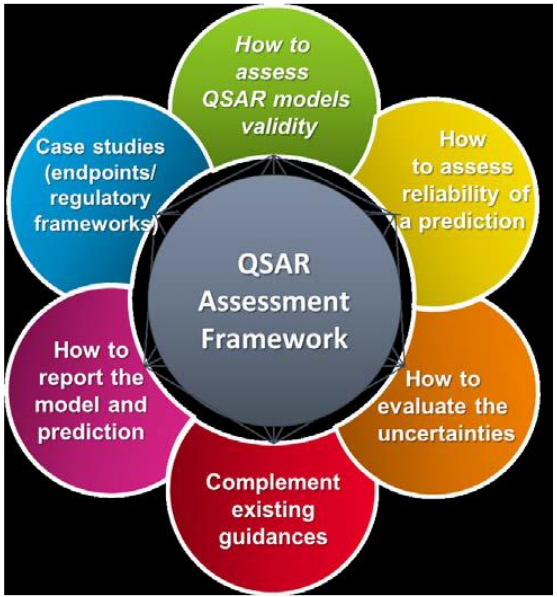
- Co-led by Instituto Superiore di Sanità (ISS) Italy and the European Chemicals Agency (ECHA)
- Supported by QAF Expert Group
  - met through a series of teleconferences in 2021 - 2023
  - drafting subgroups contribute to writing/review
  - face-to-face meeting of the QAF Expert Group Q4 2022 to help finalise the draft document
- Written commenting round to Working Party on Hazard Assessment Q2 2023
- Declassified in Q3 2023

QSAR Assessment Framework: overview

- Objective
  - develop a systematic and harmonised framework for the regulatory assessment
- Scope
  - (Q)SAR models
  - (Q)SAR predictions and results based on multiple predictions
- Relevance/applicability
  - irrespective of the technique used to build the model, the predicted endpoint, and the intended regulatory purpose
- Audience
  - primarily, regulatory authorities
  - as reference for other stakeholders using (Q)SARs for regulatory purposes

QSAR Assessment Framework

- Based on
  - GD 49: Principles for the validation of QSARs (2004)
  - GD 69: Guidance for validation of (Quantitative) Structure-Activity Relationship [(Q)SAR] models (2007)
- Sections on
  - Principles for assessing models
  - Principles for assessing predictions
  - Principles for assessing results from multiple predictions
- For each, development of assessment elements and a checklist of criteria
  - Guidance on how to determine if criteria are met
  - Examples illustrating how to evaluate criteria



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OECD Home > Chemical safety and biosafety > Assessment of chemicals > The OECD QSAR Toolbox

The OECD QSAR Toolbox

To increase the regulatory acceptance of (Q)SAR methods, the OECD is developing a QSAR Toolbox to make (Q)SAR technology readily accessible, transparent, and less demanding in terms of infrastructure costs.

Download the Toolbox | Guidance Documents and Training Materials | Webinar | Help Desk | Public Discussion Forum

WEBINAR ON THE NEW OECD (Q)SAR ASSESSMENT FRAMEWORK: GUIDANCE FOR ASSESSING (Q)SAR MODELS AND PREDICTIONS

WHEN: 9 November 2023 at 13:00 - 14:30 CET / 07:00 - 08:30 EST

The webinar will provide an overview of the new OECD (Q)SAR Assessment Framework for evaluating the scientific validity of (Q)SAR models and introduce new principles for evaluating (Q)SAR predictions: input, applicability domain, reliability, and fitness for purpose.

his new Framework provides regulators with a consistent and transparent approach for reviewing the use of (Q)SAR predictions in a regulatory context and increases the confidence to accept alternative methods for evaluating chemical hazards. The OECD worked closely together with the Istituto Superiore di Sanità (Italy) and the European Chemicals Agency (ECHA), supported by a variety of international experts to develop a checklist of criteria and guidance for evaluating each criterion. The aim of the QAF is to help establish confidence in the use of (Q)SARs in evaluating chemical safety, and was designed to be applicable irrespective of the modelling technique used to build the model, the predicted endpoint, and the intended regulatory purpose. The webinar will begin with an overview of the project and walk through the main aspects of the framework for assessing models and results based on individual or multiple predictions, and provide an opportunity for Q&A.

Agenda:

- Overview of the Project: Patience Browne, OECD Environment Directorate (10 minutes)
- (Q)SAR Assessment Framework for models: Olga Tcheremenskaia, ISS (25 minutes)
- (Q)SAR Assessment Framework for predictions and results from multiple predictions: Andrea Gissi – ECHA (25 minutes)
- Q&A (30 minutes)

REGISTER HERE.

OECD QSAR TOOLBOX 4.6 TUTORIALS

Do you need help with the QSAR Toolbox? Take a look at the video tutorials on ECHA's YouTube channel. They help you navigate through the different functionalities of the tool.

The tutorials were developed to respond to stakeholders' interest in learning to use the tool better. ECHA plans to develop more tutorials during the next year.

- Links to QAF and background documents
- Links to Webinar presentations + how to use the QAF
  - Coming soon
- Links to QSAR tutorials

Find out more

Thank You For Listening

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WEBINAR on THE NEW OECD (Q)SAR Assessment Framework: guidance for assessing (Q)SAR models and predictions

Part1

Presenter:
Olga Tcheremenskaia
Department of Environment and Health, Istituto Superiore di Sanità (ISS), Italy

(Q)SAR Assessment Framework for models

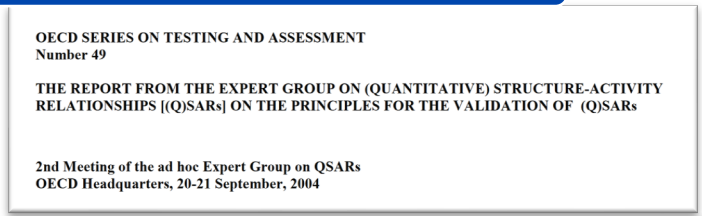
(Q)SAR Assessment Framework

Table of contents

Principles for assessment of (Q)SAR models

- Defined endpoint
- Unambiguous algorithm
- Defined domain of applicability
- Appropriate measures of goodness-of-fit, robustness and predictivity
- Mechanistic interpretation, if possible

Principles for QSAR model evaluation were established almost twenty years ago and extensively used so far by the scientific and regulatory communities:
https://one.oecd.org/document/env/jm/mono(2004)24/en/pdf

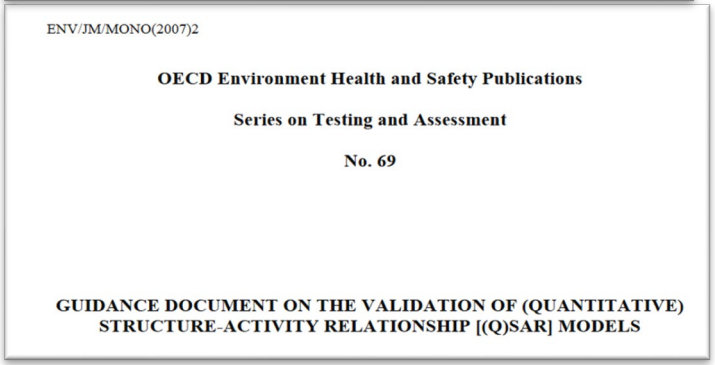


OECD SERIES ON TESTING AND ASSESSMENT
Number 49

THE REPORT FROM THE EXPERT GROUP ON (QUANTITATIVE) STRUCTURE-ACTIVITY RELATIONSHIPS [(Q)SARs] ON THE PRINCIPLES FOR THE VALIDATION OF (Q)SARs

2nd Meeting of the ad hoc Expert Group on QSARs
OECD Headquarters, 20-21 September, 2004

Guidance Document on the Validation of (Q)SAR Models was published in 2007 with the aim of providing guidance on how specific (Q)SAR models can be evaluated with respect to the OECD principles
https://one.oecd.org/document/env/jm/mono%282007%292/en/pdf



ENV/JM/MONO(2007)2

OECD Environment Health and Safety Publications

Series on Testing and Assessment

No. 69

GUIDANCE DOCUMENT ON THE VALIDATION OF (QUANTITATIVE) STRUCTURE-ACTIVITY RELATIONSHIP [(Q)SAR] MODELS

Assessment elements for (Q)SAR models in the guidance and in the checklist

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.

Principle	Assessment element	Practical advice	Examples
Unambiguous algorithm			
2.1	Description of the algorithm and/or software	An exact description of the algorithm might not be publicly available for commercial models. In such cases, any available relevant information should still be assessed. When the model is implemented in a computer 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, and assessors may decide that this is acceptable for some regulatory uses.	User manuals, publications, help files, such as EPISuite help file
2.2	Inputs and other options	The extent of this description depends on the complexity of the computer program. Simple programs with no customisable options require less explanations than programs that allow editing of the settings of the algorithm.	Instructions on the preparation of the input may include instructions how to pre-process salts and tautomers.
2.3	Model accessibility	When a different model version is available to the assessor, consider using it and compare the results.	"In vitro mutagenicity (Ames test) alerts" fragment-based model implemented in Toxtree 3.1.0 software available at https://toxtree.sourceforge.net/ has been used for generate a prediction.

Each principle is broken down to assessment elements (AEs)

The Guidance gives more details for each AE, the Checklist – more practical examples and advice

Glossary of selected terms

- **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.
- **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.

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

Checklist for the regulatory assessment of (Q)SAR models

Annex C. (Q)SAR Model, Prediction and Result Checklists

The checklist (EXCEL version) is available at the following link:
https://www.oecd.org/chemicalsafety/testing/QAF-Checklist.xlsx

Model name and version:
Software name and version (if applicable):
Predicted property:
Intended purpose of use of the model:
QMRF availability:
Assessor name and date of the assessment:

Model 1

when more than one model is considered, add a comment here to identify to which model the checklist refers to (e.g. model name)

Principle	Assessment element	Outcome	Comments
Defined endpoint			
1.1	Clear scientific and regulatory purpose		
1.2	Transparency of the underlying experimental data		
1.3	Quality of the underlying experimental data		
Unambiguous algorithm			
2.1	Description of the algorithm and/or software		
2.2	Inputs and other options		
2.3	Model accessibility		
Defined domain of applicability			
3.1	Clear definition of the applicability domain and limitations of the model		
Appropriate measures of goodness-of-fit, robustness and predictivity			
4.1	Goodness-of-fit, robustness		
4.2	Predictivity		
Mechanistic interpretation			
5.1	Plausibility of the mechanistic interpretation		
Conclusion on the model		The conclusion is based on the outcome of the assessment elements as decided by i	
Comments			

A list of critical elements to which the assessor should assign a predefined value (**i.e., fulfilled, not fulfilled, not applicable/assessed, not documented**).

The analysis of each element supports the **overall decision** on whether the model is suitable for the intended regulatory purpose.

Model criteria and QMRF mapping

- Checklist provides details, practical advice, examples and mapping to the (Q)SAR model reporting format (QMRF) for each AE

Checklist for the regulatory assessment of (Q)SAR models
Details on the assessment elements

Principle	Assessment element	Objective	What to check and how	Practical advice	Examples	Mapping to the most relevant QMRF field(s)
Defined endpoint						
1.1	Clear scientific and regulatory purpose	The predicted endpoint is clearly defined in relation to a scientific and/or regulatory purpose.	The predicted endpoint is clearly defined andis consistent with the data used to build the model. For a clear scientific purpose: the predicted endpoint refers to physicochemical, biological or environmental effects o that can be measured and therefore modelled. For a clear regulatory purpose: the predicted endpoint refers to a specific regulatory requirement or test method or test guideline.	The description of the predicted endpoint should be as detailed as possible by including all elements that have been taken into account (e.g. the unit of measurement, timescale, observations such as growth, mortality, etc.).	Clear scientific (and regulatory) purpose: predicted endpoint = "Fish-short term toxicity (96 hours) as LC50 according to the OECD Test Guideline 203". Clear regulatory purpose: Predicted endpoint = "Classification for skin sensitisation according to GHS criteria".	3.2 Endpoint 3.3 Comment on endpoint 3.5. Dependent variable 3.6. Experimental protocol
1.2	Transparency of the underlying experimental data	The documentation is sufficient to independently assess the quality of the experimental data used to build the model for the next assessment element.	Check to what extent the following information is available : - Clear identification of the substances tested (name, structures, SMILES numerical identifiers, etc.); -A (primary) reference to the original studies; - Description of relevant experimental conditions that could affect the prediction (e.g. sex, species, temperature, exposure period, protocol, measurements units); -The original value in the case of data processing before modelling, information on data processing, unit or scale conversion; - Availability of the description of the data aggregation procedure and individual values for datasets where multiple data for the same substance are aggregated for modelling; - Information in the experimental data selection and curation procedure.	It is rare to have full details on each data point used to build the model, but a general description about the experimental data selection and curation procedure can be expected.	Example 1: The model documentation includes the list of substances part of the training set, the experimental values for the predicted property and details or reference for each data point. This assessment element is fulfilled. Example 2: The predicted endpoint is "Bacterial mutagenicity according to OECD TG 471", but the information on the underlying data does include information on the strains tested or presence of metabolic activation. This assessment element is not fulfilled.	3.1 Species 3.4 Endpoints units 3.5 Dependent variable 3.6 Experimental protocol 6.2 Available information for the training set 6.3 Data for each descriptor variable for the training set 6.4 Data for the dependent variable for the training set 6.5 Other information about the training set
1.3	Quality of the underlying experimental data	Ensure that the model is built on data of sufficient quality to obtain acceptable predictions.	- Assess the experimental data curation procedure; - Assess the quality of the data point individually, if possible;	Ideally data points should be evaluated individually. However, especially for large training sets, this may be not possible. In these cases, assessors can verify how the relevant experimental conditions that could affect the results of experimental studies (e.g., sex, species, temperature, exposure period, protocol) have been considered when selecting data to build the model. For models with large training sets, spot check some data points. In some cases, lower data quality can be compensated by large number of data points fitting the same trend.	The model documentation indicates that the predicted endpoint is fish long-term toxicity. The assessment of the data used to build the model shows that the duration of the exposure was not taken into account when selecting data to build the model. It is suspected that some of the data used to build the model refer to results from fish short-term toxicity studies. Outcome: This assessment element is not fulfilled and the model not considered valid for predicting fish long-term toxicity.	3.7 Endpoint data quality and variability 6.6 Pre-processing of data before modelling
Unambiguous algorithm						
2.1	Description of the algorithm and/or software	Ensure that it is clear how the prediction is obtained and that it can be reproduced by others	- Check if a sufficient description of all descriptors and of approach used for their selection and calculation is provided; - Check the availability of a transparent description of the algorithm and/or software, explaining how the predictions were produced. - For fragment/alert based models, the list of the fragments (active, inactive, masks, etc. as relevant) together with information of all substructures and identification of its substituents should be provided. - For equation based models, a description of the equation and all data/descriptors and approach used for their selection should be provided.	An exact description of the algorithm might not be publicly available for commercial models. In such cases, any available relevant information should still be assessed. When the model is implemented in a computer 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, and assessors may decide that this is acceptable for some regulatory uses.	User manuals, publications, help files, such as EPISuite help file	4.1 Type of model 4.2 Explicit algorithm 4.3 Descriptors in the model 4.4 Descriptor selection 4.5 Algorithm and descriptor generation 4.6 Software name and version for descriptor generation 4.7 Chemicals/Descriptors ratio 6.1 Availability of the training set
2.2	Inputs and other options	Allowed input formats, pre-processing procedure for the input structures and customisable options/settings are explained.	- Availability of instructions to prepare the input. - Availability of information on the editable options/settings (if any).	The extent of this description depends on the complexity of the computer program. Simple programs with no customisable options require less explanations than programs that allow editing of the settings of the algorithm.	Instructions on the preparation of the input may include instructions how to pre-process salts and tautomers.	1.3 Software coding the model 2.8 Availability of information about the model 6.6 Pre-processing of data before modelling
2.3	Model accessibility	Assess if the model or computer program is or can be available to the assessor.	- Availability of the same model and version described in the documentation	When a different model version is available to the assessor, consider using it and compare the results.	"In vitro mutagenicity (Ames test) alerts" fragment-based model implemented in Toxtree 3.1.0 software available at https://toxtree.sourceforge.net/ has been used for generate a prediction.	1.3 Software coding the model 2.5 Model developer(s) and contact details 2.6 Date of model development and/or publication 2.7 Reference(s) to main scientific papers and/or software package 2.8 Availability of information about the model

1. Defined endpoint

- 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.
- The AEs to verify that the endpoint is clearly defined:
    - **Clear scientific and regulatory purposes**
    - **Transparency of the underlying experimental data**
    - **Quality of the underlying experimental data**

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

Objective

The predicted endpoint is **clearly defined in relation to a scientific and/or regulatory purpose**.

What to check and how

- The predicted endpoint is clearly defined and is consistent with the data used to build the model.
- For a clear scientific purpose: the predicted endpoint refers to physicochemical, biological or environmental effects, can be measured and therefore modelled.
- For a clear regulatory purpose: the predicted endpoint refers to a specific regulatory requirement or test method or test guideline.

Example

Clear scientific (and regulatory) purpose:

Predicted endpoint = “Fish-short term toxicity (96 hours) as LC50 according to the OECD TG 203”

The AE is fulfilled.

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

Objective

The documentation is sufficient to independently **assess the quality of the experimental data used to build the model**.

What to check and how

Check to what extent the following information is available :

- Clear **identification of the substances** tested (name, structures, SMILES numerical identifiers, etc.)
- Reference to the **original studies**
- Description of **relevant experimental conditions** that could affect the prediction (e.g., sex, species, temperature, exposure period, protocol, measurements units)
- The **original value in the case of data processing** before modelling, information on data processing, unit or scale
- Availability of the **description of the data aggregation** procedure where multiple data for the same substance were aggregated for modelling
- Information in the experimental data **selection and curation procedure**

Example

The predicted endpoint is "Bacterial mutagenicity according to OECD TG 471",

The information on the underlying data does include information on the strains tested or presence of metabolic activation.

The AS is not fulfilled (REACH)

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

Objective

Ensure that the model is built on **data of sufficient quality** to obtain acceptable predictions.

Example

The predicted endpoint is fish long-term toxicity.
Duration of the exposure was not considered when selecting data to build the model.
Some data used to build the model may refer to results from fish short-term toxicity studies.
The AS is not fulfilled, and the model not considered valid for predicting fish long-term toxicity.

What to check and how

- Assess the experimental data curation procedure
- Assess the quality of the data point individually, if possible

2. Unambiguous algorithm

- A (Q)SAR model should be expressed in the form of an unambiguous algorithm (intended as unambiguous description of the algorithm). **The intentof this principle is to ensure transparency in the description of the model algorithm to allow an independentreproducibility of its predictions.**
- The Model Checklist includes the following AEs to verify the principle of an unambiguous algorithm:
    - **Description of the algorithm and/or software**
    - **Inputs and other options**
    - **Model accessibility**

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

Example

Availability of user manuals, publications, help files, such as EPISuite help file

The AE is fulfilled.

Objective

Ensure that it is clear how the **prediction is obtained and that it can be reproduced** by others

What to check and how

- Check if a sufficient description of all descriptors and of approach used for their selection and calculation is provided;
- Check the availability of a transparent description of the algorithm and/or software, explaining how the predictions were produced.
- For fragment/alert-based models, the list of the fragments (active, inactive, masks, etc. as relevant) together with information of all substructures and identification of its substituents should be provided.
- For equation-based models, a description of the equation and all data/descriptors and approach used for their selection should be provided.

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

Objective

To assess the allowed input formats, pre-processing procedure for the input structures and customisable options/settings are explained.

Example

Instructions on the preparation of the input (target substance is a salt) include instructions how to pre-process salts.

AE is fulfilled

What to check and how

- Availability of instructions to prepare the input.
- Availability of information on the editable options/settings (if any).

Model accessibility (AE 2.3 in the Model Checklist)

Objective

Assess if the model or computer program is or can be available to the assessor.

Example

"In vitro mutagenicity (Ames test) alerts" fragment-based model implemented in Toxtree 3.1.0 software available at https://toxtree.sourceforge.net/ has been used for generate a prediction.

The AE si fulfilled

What to check and how

- Availability of the same model and version described in the documentation

3. A defined domain of applicability

- The AD of a (Q)SAR model, as described in the Guidance (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.**
- The QAF does not prescribe a specific way to define the AD of a model because multiple valid methodologies can be used but 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)

Objective

Ensure that the **AD definition is sufficiently detailed** to allow the assessment of how a given substance relates to the AD of the model (is the substance within the AD of the model?)

Example

The prediction report obtained using a model includes the information on the applicability of the model.

The input substance is within the AD.

The availability of an explainination how the assessment is done.

AE is fulfilled

What to check and how

- Check that the AD definition has sufficient details to decide if a substance is within AD

4. Appropriate measures of goodness-of-fit, robustness and predictivity

- 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 performance should be measured within the applicability domain defined by its developers.
- 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 (AEs 4.1 in the Model Checklist)

Predictivity (AEs 4.2 in the Model Checklist)

Example

For a model predicting categorical endpoints, the information on accuracy, sensitivity and specificity on the training set and on the external set is provided and considered good enough for the intended regulatory purpose.

The AE is fulfilled

Objective

Measures of performance for goodness-of-fit and robustness are provided and considered adequate.

Measures of performance for predictivity are provided and considered adequate.

What to check and how

Check the available information on the statistical method(s) used for internal/external validation of the model :

- For models predicting continuous endpoints, availability of at least basic statistics such as r2 value and standard error;
- For models predicting categorical endpoints, availability of at least basic statistics such as accuracy, sensitivity and specificity;
- If the regulatory context sets some reference values, compare the performance of the model to the reference values.
- An indication whether cross-validation or resampling was performed, if yes, by which method.

5. Mechanistic interpretation

- A (Q)SAR “should be associated with a mechanistic interpretation, if possible”.

- Assessors may require that the model documentation includes considerations on how the rationale behind a (Q)SAR model is consistent with 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)

Objective

To assess if the provided mechanistic interpretation is scientifically sound.

What to check and how

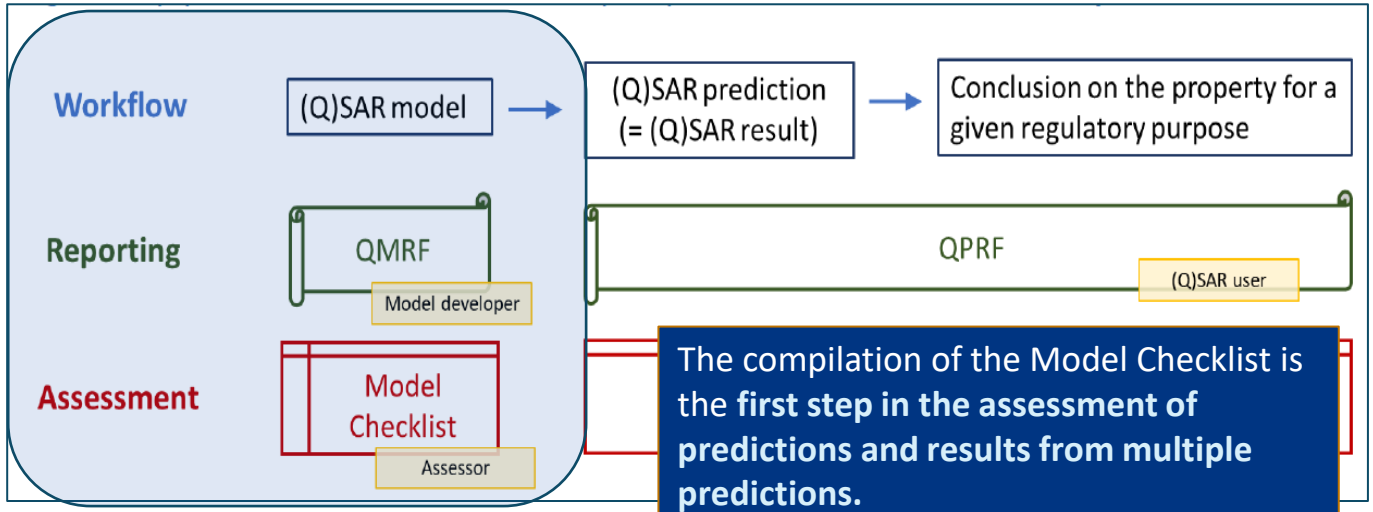
- Scientific plausibility of the proposed mechanistic interpretation (e.g., reference to scientific literature), when available.
- Check if a sufficient explanation and interpretation of the descriptors that is consistent with a known mechanism of (biological) action are provided.
- Check at what stage of modelling the mechanistic basis of the model was determined is provided.
- If relevant, an explanation and interpretation of the molecular events that underlie the properties of molecules containing the substructure should be provided.
- Consider that a mechanistic interpretation is optional in the OECD document on model validity ("if possible")

Example

The documentation of a model predicting skin sensitisation based on structural-alerts includes an explanation on how the structural-alerts are supposed to bind to proteins causing skin sensitization

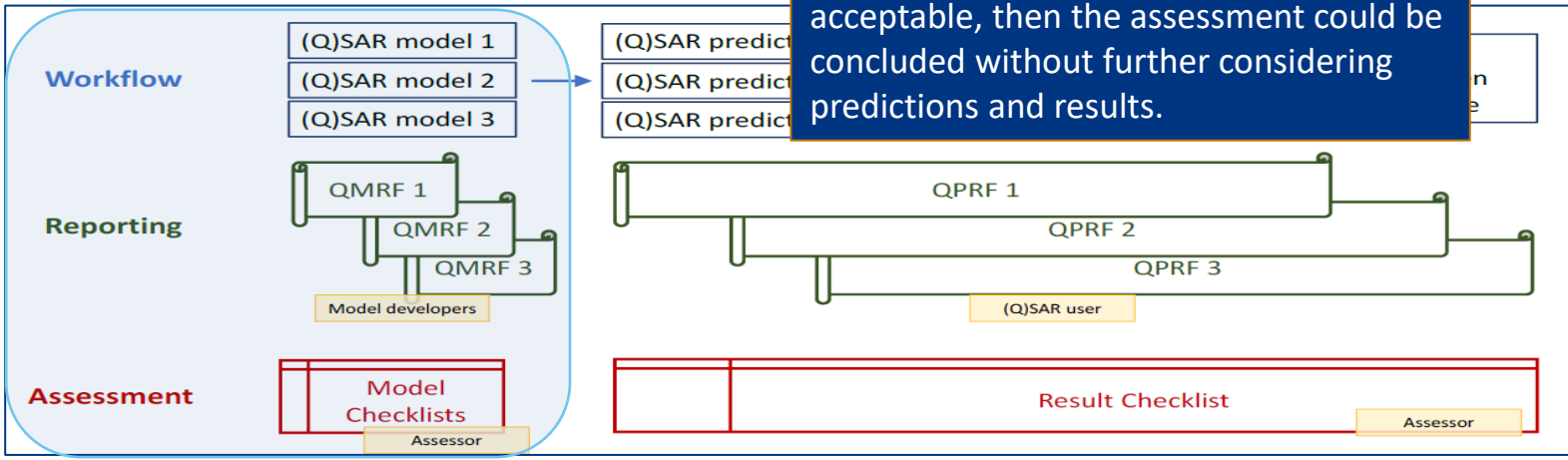
The AE is fulfilled.

Model Checklist in the QAF workflow for assessing predictions and results based on multiple predictions



The compilation of the Model Checklist is the **first step in the assessment of predictions and results from multiple predictions.**

When a model is considered not acceptable, then the assessment could be concluded without further considering predictions and results.



Final remarks on the (Q)SAR model checklist

- Our expectation is that the application of the QAF for model assessment will **improve the clarity and transparency** of the models' evaluations.
- The evaluation of AS will guide the assessors in assessment of the model regarding its **suitability for the specific regulatory purpose**.
- Assessment of individual predictions may not be feasible when running prediction of a large number of substances, e.g., for **screening of databases**
  - In this case, assessors may need to rely solely on the assessment of the model/model checklist
- The assessment of a model is **specific for the regulatory purpose**
  - It should be repeated when assessing the use of same model for a different purpose
  - If the regulatory purpose is the same, assessors do not need to repeat the evaluation of the model for each prediction
- The model checklist can be used to verify that a **QMRF contains all necessary information**
  - Models' developers could use it when preparing the model documentation

Thank you very much!

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Assessment of (Q)SAR predictions and results

The OECD (Q)SAR Assessment Framework

OECD Webinar, 9 November 2023

Andrea Gissi, PhD
Scientific Officer
European Chemicals Agency

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(Q)SAR Assessment Framework

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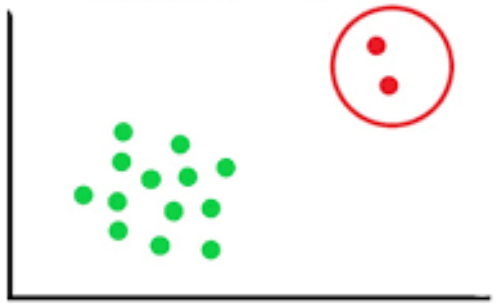
Assessment of individual predictions

Valid (Q)SAR model ≠ Valid (Q)SAR result

- → The use of (Q)SARs is allowed in many chemical regulations
- → OECD (Q)SAR principles from 2004 cover the scientific validity of **(Q)SAR models**
- → The use of a valid (Q)SAR model does not guarantee the validity of each of its results
- → Need to establish **principles to assess individual results** and a systematic and harmonised **assessment framework** for (Q)SAR models and predictions

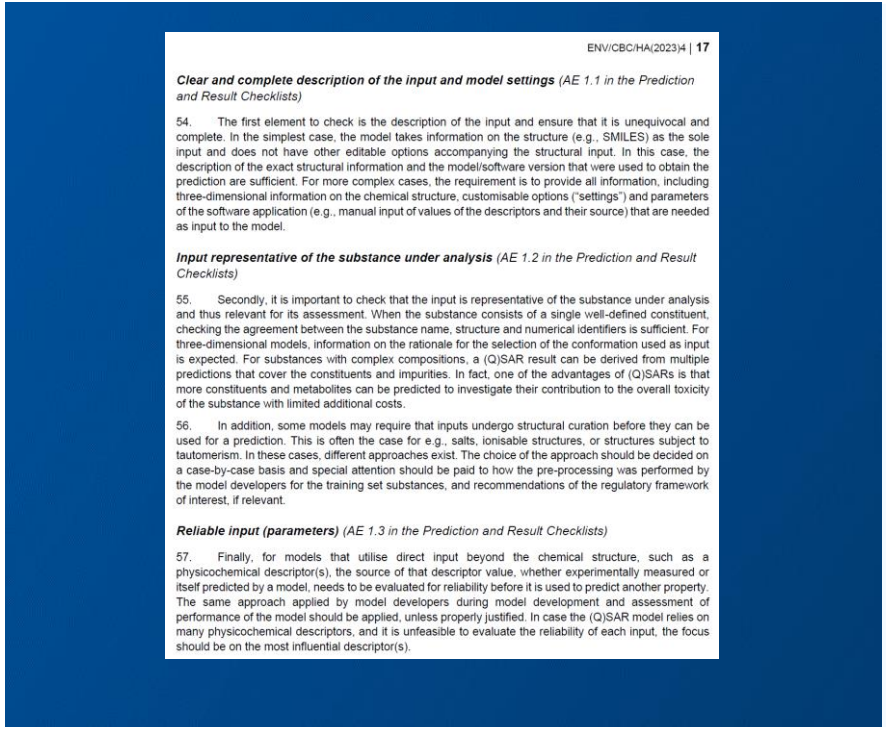


Principles for the assessment of (Q)SAR predictions

- Four new OECD principles for evaluating (Q)SAR predictions and results based on multiple predictions:
  1. **Correct input**
  2. **Substance within applicability domain**
  3. **Reliable prediction**
  4. **Outcome fit for purpose**

- For a result based on multiple predictions:
  - each prediction is assessed individually +
  - an additional evaluation step is dedicated to the final result

Guidance for the assessment of (Q)SAR predictions



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

54. 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)*

55. 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.

56. 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)*

57. 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).

- Each principle is broken down to assessment elements (AEs)
- AEs are further explained in the Guidance and Checklist
- The Guidance also explains the conditions for acceptable predictions

Figure: Guidance text with explanation of the AEs for assessing QSAR Predictions Principle 1: a correct input

Prediction Checklist

Prediction 1

when more than one prediction is considered, add a comment here to identify to which prediciton the checklist refers to (e.g. model name and/or predicted structure)

Principle	Assessment element	Weight	Outcome	Uncertainty Comments
		Default values		Only for elements that are fulfilled
Correct input(s) to the model				
1.1	Clear and complete description of the input and model settings	High		
1.2*	Input representative of the substance under analysis	High		
1.3	Reliable input (parameters)	Medium		
Substance within the applicability domain of a valid model				
2.1	Substance within the applicability domain	High		
2.2	Any other limitation of the model is considered	High		
Reliable prediction				
3.1	Reproducibility	High		
3.2	Overall performance of the model	Medium		
3.3	Relationship of the substance with the physicochemical, structural and response spaces of the training set of the model	Medium		
3.4	Performance of the model for similar substances	High		
3.5*	Mechanistic and/or metabolic considerations	High		
3.6*	Consistency of information	High		
Outcome is fit for the regulatory purpose				
4.1*	Compliance with additional requirements	High		
4.2*	Correspondence between predicted property and property required by the regulation	High		
4.3*	Decidability within the specific framework	High		
Conclusion on the individual prediciton				
Uncertainty				
Outcome of the assessment (individual prediction)				
Comments				

For each assessment element (AE):

→ **Weight** - how important is the AE in the context of use of the prediction. It depends on the purpose of use of the prediction

- Low; Medium; High

→ **Outcome:**

- Fulfilled; Not fulfilled; Not applicable/assessed; Not documented

→ **Uncertainty -** how confident is the assessor with the outcome

- Low; Medium; High

By default, high uncertainty to AEs that are not fulfilled or not documented

Prediction Checklist

Prediction 1				
when more than one prediction is considered, add a comment here to identify to which prediciton the checklist refers to (e.g. model name and/or predicted structure)				
Principle	**Assessment element**	**Weight**	**Outcome**	**Uncertainty Comments**
		Default values		Only for elements that are fulfilled
Correct input(s) to the model				
1.1	Clear and complete description of the input and model settings	High		
1.2*	Input representative of the substance under analysis	High		
1.3	Reliable input (parameters)	Medium		
Substance within the applicability domain of a valid model				
2.1	Substance within the applicability domain	High		
2.2	Any other limitation of the model is considered	High		
Reliable prediction				
3.1	Reproducibility	High		
3.2	Overall performance of the model	Medium		
3.3	Relationship of the substance with the physicochemical, structural and response spaces of the training set of the model	Medium		
3.4	Performance of the model for similar substances	High		
3.5*	Mechanistic and/or metabolic considerations	High		
3.6*	Consistency of information	High		
Outcome is fit for the regulatory purpose				
4.1*	Compliance with additional requirements	High		
4.2*	Correspondence between predicted property and property required by the regulation	High		
4.3*	Decidability within the specific framework	High		
Conclusion on the individual prediciton				
Uncertainty				
Outcome of the assessment (individual prediction)				
Comments				

Conclusion

→ **Uncertainty of the prediction**

- Low; medium; High

Based on the highest uncertainty of high weight AEs.

→ **Outcome of the assessment**

- Acceptable for the intended purpose;
- Not acceptable for the intended purpose;
- Documentation insufficient to decide on the acceptance for the intended purpose.

The document suggests to accept predictions with low or medium uncertainty

“Prediction Criteria and uncertainty” spreadsheet

→ Also for predictions and results, a separate spreadsheet of the Checklist provides details, practical advice, examples and mapping to the QPRF for each AE

→ In addition, there is a section dedicated to how to assign the uncertainty level

Principle	Practical advice	Examples	Uncertainty		Mapping to mos
			This table offers guidance on how to assign the uncertainty level of each assessment element. *To assign the uncertainty for elements that are fulfilled, refer to the explanation in the column.* *For elements that are not fulfilled or not documented, high uncertainty should be assigned by default unless a valid justification is provided.* *For elements that are not applicable/assessed, leave empty* *NOTE: some examples include numeric values to explain more concretely how to proceed with the assessment . However, acceptable values depend on the predicted property and purpose of use of the prediction. The values used as examples should not be intended as thresholds established by the project.*		
Correct input(s) to			**Explanation of the uncertainty level**	**Examples**	
1.1	If the input is incomplete but the assessors are still able to reproduce the prediction, then the weight of this element in the overall assessment is lower.	Example 1: in case the model accepts as input the structure in form of SMILES, it is not sufficient to indicate as input the substance name and/or its numerical identifiers (such as CAS or EC numbers). Names and numerical identifiers may not unequivocally identify the SMILES that has been used as input. The exact SMILES used as input needs to be specified. Example 2: in case the model accepts as input three-dimensional structures, it is not sufficient to indicate as input the SMILES of the structure. Information on the three-dimensional structure, such a .mol file or equivalent, is needed.	**Low:** input structure(s) and model settings are fully described **Medium:** some minor aspects of the input structure(s) and model settings are not clearly described **High:** some important aspects of the input structure(s) and model settings are not clearly described	A model requires SMILES and optionally logKow as input to generate a prediction. Low: SMILES and logKow provided Medium: SMILES provided, logKow not provided High: only CAS number provided, but CAS/SMILES association is ambiguous. **NOTE:** the reliability of logKow is assessed under AE 1.3	5 Input (all fields
1.2	The comparison can be done using expert judgment or by using publicly available information and tools that associate structures with names or other identifiers. If the model distinguishes the different tautomeric forms and generates different predictions, then it is important to indicate which form was used as input and justify the selection. If different tautomeric forms are investigated and produce the same prediction, this should also be indicated. If the model documentation indicates how to pre-process the input structure, possibly including how to represent tautomeric groups, these indications should be followed. Alternatively, the user should (if possible) use as input the structure in the tautomeric form that would be predominant if the corresponding experimental test were performed to measure the property of interest. Another option is to predict different forms and to calculate either a reasonable worst-case or an average, eventually weighted according to the abundance of the different forms.	Example 1: the substance under analysis is "formhaldeyde". The SMILES "C=O" is used as input. Using available resources, the correspondence between the name and the SMILES is verified. Example 2: the substance under analyis is a salt formed by an inorganic cation and an organic anion. The model does not accept the SMILES that includes both ions. The model documentation indicates that for salts, only the neutralised organic part should be used as input. The assessment consists in checking that the correct pre-processing has been followed. *Example 3 (for multiple predictions): the substance is formed by two major constituents. If two separate predictions are provided for the constituents, then the assessment element is fulfilled	**Low:** the composition of the substance under analysis is well covered by the input structure(s) **Medium:** the composition of the substance under analysis is mostly covered by the input structure(s) **High:** some constituents of the substance under analysis are not covered by the input structure(s)	The prediction refers to a substance that includes three constituents (one major constituent, one minor constituent and one impurity) in its composition. Low: predictions for all three constituents are provided Medim: predictions for two constituents are provided, impurity not considered High: only the prediction for the major constituent is provided	5 Input (all fields 2 Substance (all
1.3	Parameters that are automatically calculated by the model or software do not need to be evaluated at this stage.	An aquatic toxicity prediction is obtained from a model based on logKow. The prediction is generated by using as input an logKow defined by the user. The reliability of the user defined logKow needs to be verified.	**Low:** the values of the additional input parameters are associated with low uncertainty **Medium:** the values of additional input parameters are associated with medium uncertainty **High:** the values of additional input parameters are associated with high uncertainty	A model that requires manual input of logKow is used to generate a prediction. Low: the logKow value used as input is the result of a reliable experimental study Medium: the logKow value used as input is predicted by a QSAR model. No details are provided to assess its reliability. High: the logKow value used as input is predicted by a QSAR model. The prediction is unreliable, but it is the only available estimate.	5.2 Descriptors

ECHA EUROPEAN CHEMICALS AGENCY

Correct input – Assessment Elements (AEs)

→ AE 1.1: Clear and complete description of the input and model settings

- All information (input structure and/or parameters, model settings) is available to the assessors, thus making the prediction reproducible

→ AE 1.2: Input representative of the substance under analysis

- The structure(s) modelled represent the substance subject to regulatory assessment

→ AE 1.3: Reliable input (parameters)

- Parameters that are input manually (other than the chemical structure) are reliable

Correct input – example of assessment

→ AE 1.1: Clear and complete description of the input and model settings

What to check and how:

- It is clear whether the structure is input by using SMILES or other identifiers. If other parameters are also used as input, they are described

- If relevant, conformational (tri-dimensional) information is also given.

- In case of editable options, check if default settings are applied and, if not, if a justification is provided.

Example

A model requires SMILES and optionally logKow as input to generate a prediction.

Assessment:

→ Is the AE fulfilled? If yes, assign uncertainty:

- **Low** uncertainty: SMILES and logKow provided
- **Medium** uncertainty: SMILES provided, logKow not provided
- **High** uncertainty: only CAS number provided, but CAS/SMILES association is ambiguous.

Substance within the applicability domain of a valid model – AEs

→ AE 2.1: Substance within the applicability domain

- The substance meets the applicability domain (AD) requirements specified by model developers

→ AE 2.2: Any other limitation of the model is considered

- The substance does not meet any of the criteria for which the model should not be used

Reliable prediction – AEs

- → AE 3.1 Reproducibility
- → AE 3.2 Overall performance of the model
- → AE 3.3 Fit within the physicochemical, structural and response spaces of the training set of the model
- → AE 3.4 Performance of the model for similar substances
- → AE 3.5 Mechanistic and/or metabolic considerations
- → AE 3.6 Consistency of information

Outcome is fit for the regulatory purpose – AEs

→ AE 4.1: Compliance with additional requirements

→ AE 4.2: Correspondence between predicted property and property required by the regulation

→ AE 4.3: Decidability within the specific framework

Assessment of results based on multiple predictions

(Q)SAR results based on multiple predictions

Results that consider multiple predictions:

→ Predictions from different models for the same structure;

→ 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);

→ A combination of the above.

Assessment workflow for results from multiple predictions

1. Complete a checklist for each prediction individually (in the result checklist)
   - for complex cases, start by addressing multiple predictions associated with the same structure, and then consider the predictions for different structures

2. Assess the additional AE:
   - correct determination of the final result from individual predictions

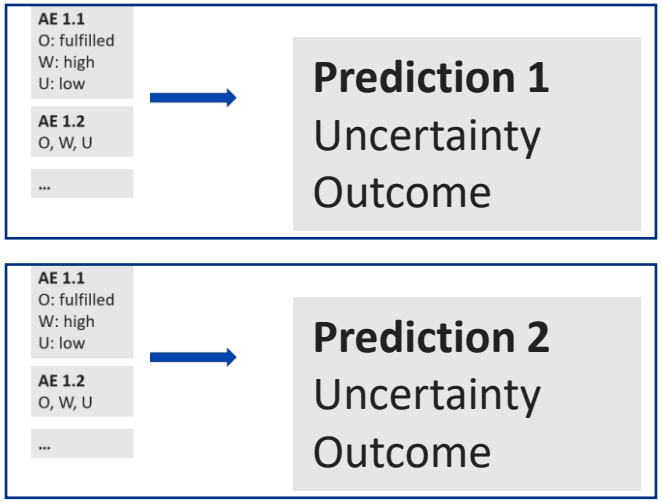
3. Determine the uncertainty of the final result
   - by weighing the uncertainty of individual predictions (e.g. consistent independent predictions lower uncertainty)

4. Decide on the acceptability of the result
   - the document suggests to accept results with low or medium uncertainty

Workflow for assessing results from multiple predictions

Assessment element (AE)
Outcome (O): fulfilled, not fulfilled, not documented, not applicable
Weight (W): low, medium, high
Uncertainty (U): low, medium, high
Conclusion: results acceptable, not acceptable, insufficient documentation

1. Assess predictions individually



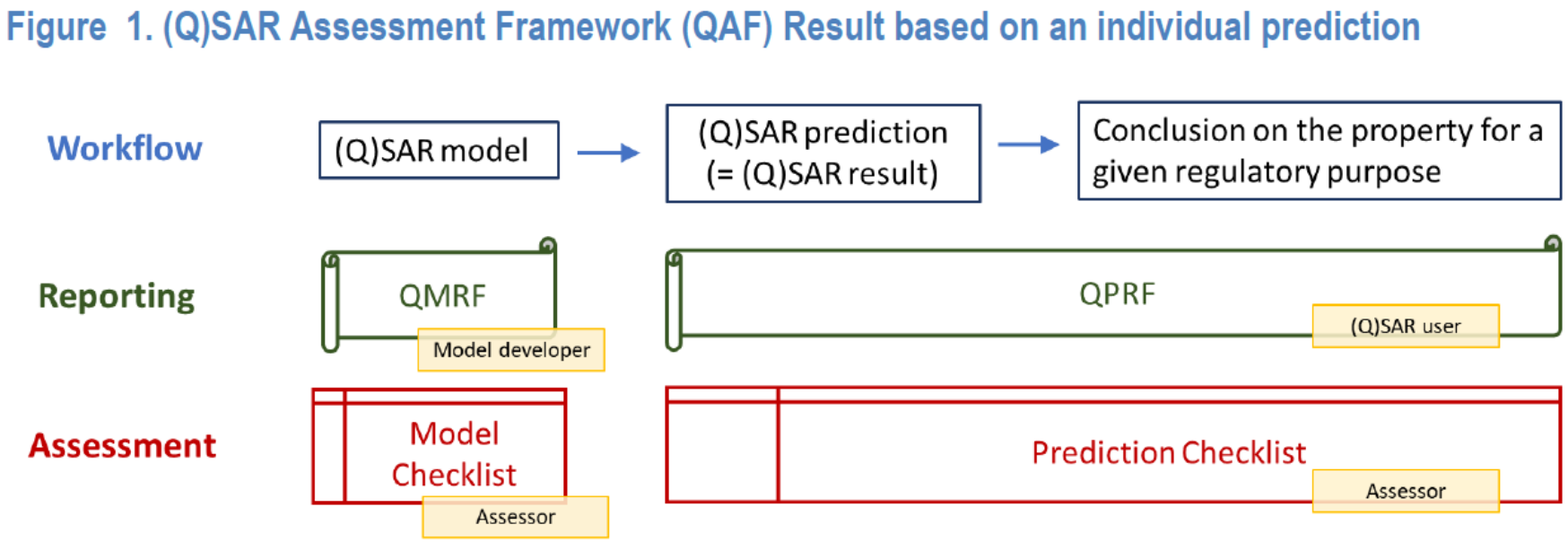
2. Check how the final result is determined (AE 5.1)

(Q)SAR result

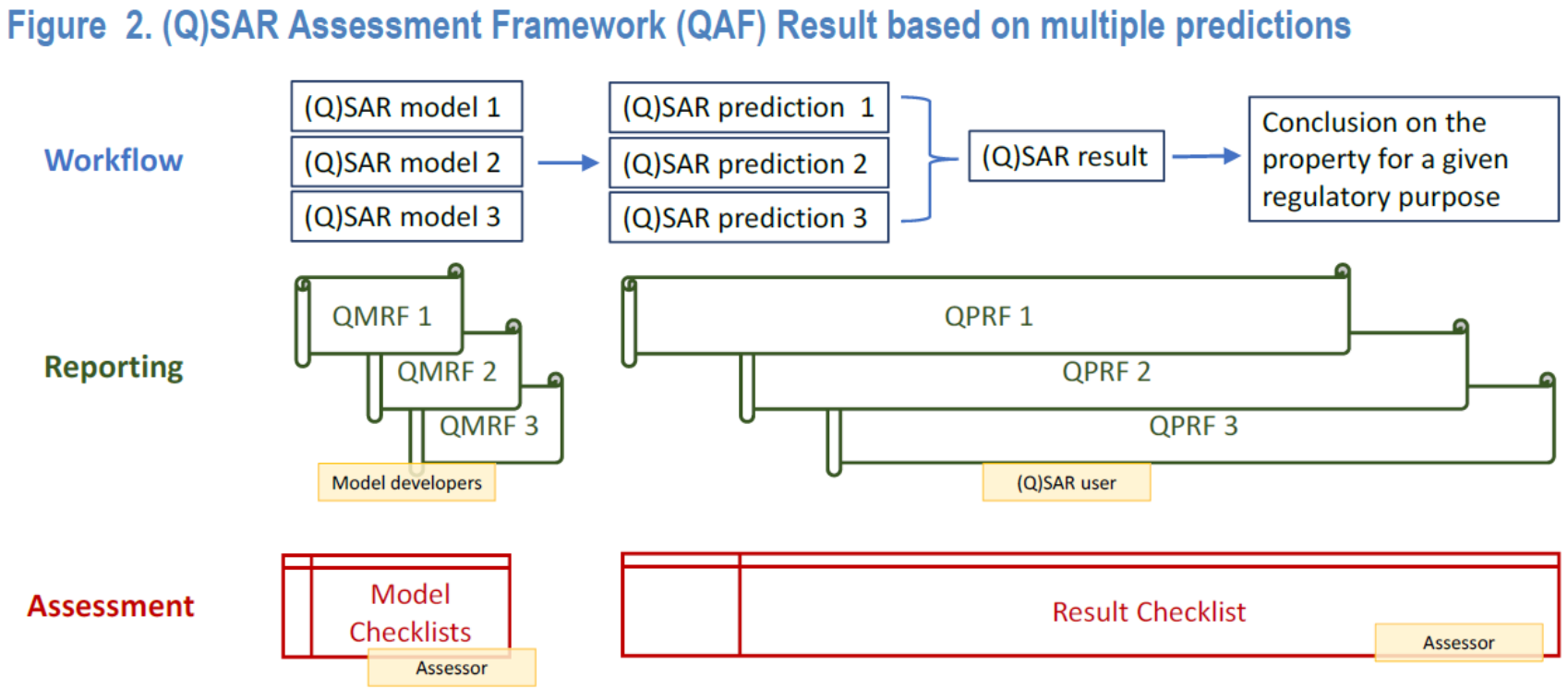
3. Conclusion based on the level of uncertainty and purpose of use

Conclusion on the result
Uncertainty
Outcome

Visual abstract 1/2



Visual abstract 2/2



QAF Annexes – Updated QPRF and QMRF

Annexes:

- Updated **QSAR Prediction Reporting Format (QPRF v2.0)**: Major update to reflect the QSAR Assessment Framework Guidance. 8 main sections:

    1. General information
    2. Substance
    3. Model and software
    4. Prediction
    5. Input
    6. Applicability domain and limitations
    7. Reliability assessment
    8. Purpose of use (for regulatory applications)

- Updated **QSAR Model Reporting Format (QMRF v2.1)**: minor update because the OECD principles for the validity of models have not been changed

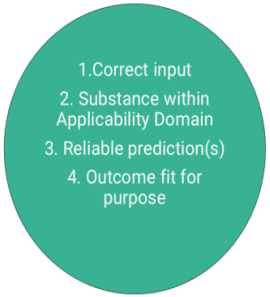
EFSA-ECHA project on the extension of OECD Harmonised Templates (OHTs) for structuring and reporting QSAR-based data in IUCLID 6

(Adapted from slides by Edoardo CARNESECCHI, EFSA)

(Q)SARs IN IUCLID

- Regulatory agencies store data on chemicals in IUCLID databases
- IUCLID data format follows OECD harmonised templates (OHTs)
- Currently, QSAR specific fields (e.g., applicability domain) are NOT available in OHTs
- Relevant information (e.g. QPRF) can only be included as attachments
- This project proposes an **extension of OHTs to include QSAR specific fields** for all endpoints
- The new fields will be implemented in IUCLID as conditional fields **appearing only if QSAR is selected as "study type"**

PRINCIPLES FOR THE ASSESSMENT OF (Q)SAR PREDICTIONS AND RESULTS



QPRF version 2.0

Reliability assessment
Reproducibility
Comments on reproducibility
Descriptor space
Structural space
Response space
Mechanistic considerations
Metabolic considerations
Comments on additional reliability
Analogues: identity information
Analogues: source
Analogues: predicted and experimental data
Analogues: reference experimental data
Analogues: comments on similarity
Considerations on structural analogues
Comments on analogues
Other information on the endpoint available
Conclusion on reliability

EXTENDED OHT

Field name	Field Display type and Picklist Freetext template	Help text
Additional information about applicability domain and reliability of (Q)SAR predictions	Header 2	
Fit within applicability domain	Picklist values: - In applicability domain - Outside applicability domain - Undefined applicability domain - Applicability not assessed - other	Indicate if the substance fits within the applicability domain of the model defined by the model developers.
Applicability domain methodology	Free text	Describe how the fit within the applicability domain was determined.
Any other limitations	Free text	Indicate if there is any additional known limitation of the applied model, not included in the applicability domain definition, that may influence the reliability of the prediction.
Reproducibility	Picklist values: - Yes - No - other	Indicate if the prediction can be reproduced by others. This is usually the case for publicly available free and commercial models.
Fit within the space defined by the training set of the model	Picklist values: - Yes - No - Not assessed - other	Indicate if the substance fits within the physicochemical, structural and response spaces defined by the training set of the model
Mechanistic and metabolic considerations	Free text	Indicate mechanistic and metabolic considerations relevant for the predictions, if applicable.
Similar substances with data	Block of fields (repeatable) Start	List experimental and predicted data for substances similar to the test material. This information is used to assess the performance of the model for similar substance, reported in the next field.

TIMELINE - NEXT STEPS

Conclusions

What is next

→ The OECD QAF expert group identified the following areas for further work:

- **Endpoint specific case studies** can be proposed under OECD IATA Case Study Project
- **Reporting** (extension of OECD Harmonised Templates to report QSAR information; a new report for results from multiple predictions)
- **Other** (update of the QMRF, technical annex on "external predictivity" of QSAR models)

Take home messages

Establishes new OECD principles for the assessment of (Q)SAR predictions and results from multiple predictions

Provides guidance and checklists for the assessment of (Q)SAR models and results

With a systematic and harmonised assessment framework, the QAF benefits regulators first, but also (Q)SAR model developers and users

The QAF will facilitate the assessment of (Q)SAR parts of IATA case studies and may be adapted for the assessment of other NAMs too

Acknowledgments

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- Cecilia Bossa
- Chiara Battistelli

→ **Co-lead from ECHA**
- Andrea Gissi

→ **OECD secretariat**
- Patience Browne
- Tomoko Aoyagi

→ **QAF Group Members**

If you want to go fast go alone.
If you want to go far go together.
(African Proverb)

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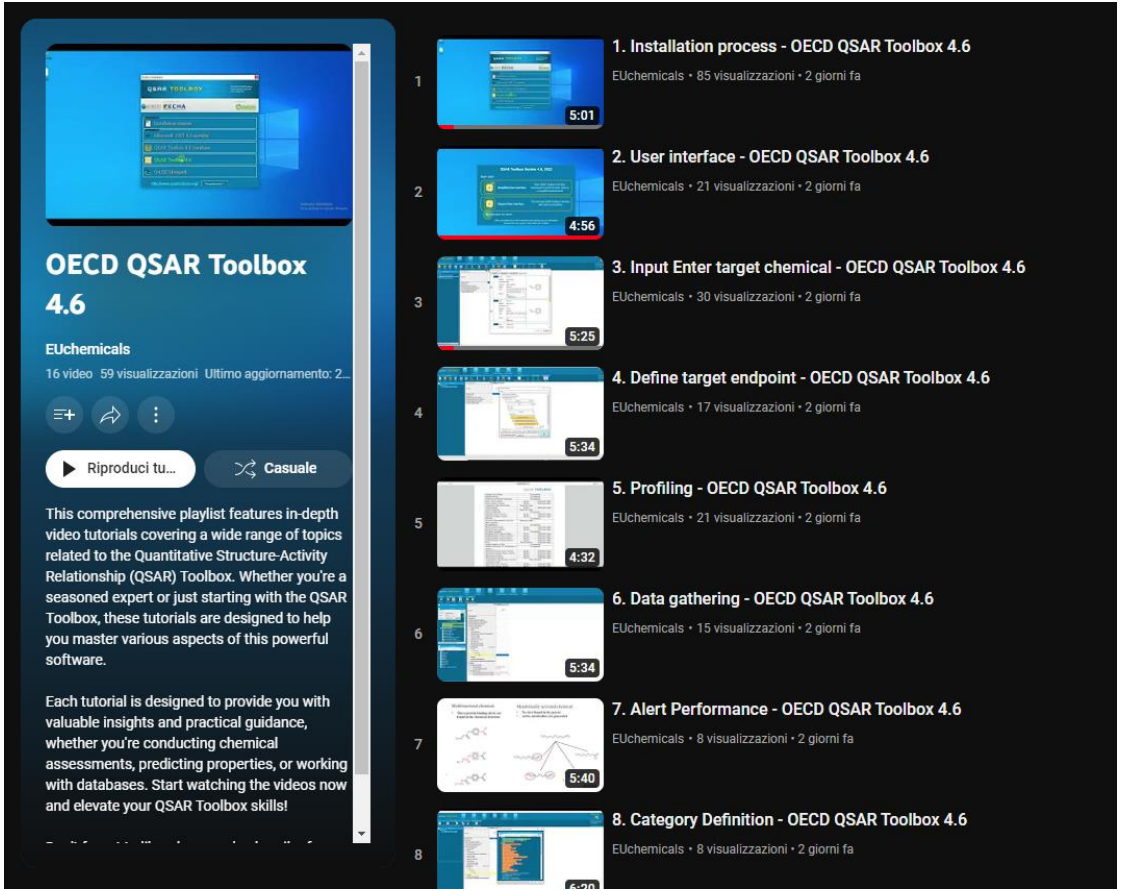
QSAR Toolbox video tutorials now available on ECHA's YouTube Channel



[OECD QSAR Toolbox 4.6 - YouTube]

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