Welcome

Webinar: OECD QSAR Assessment Framework in REACH dossier evaluation: what you need to know

21 March 2024

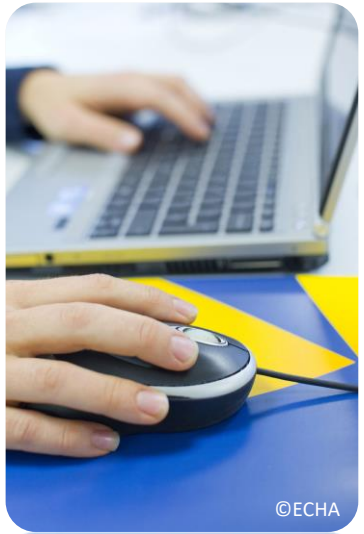
Adam Elwan
European Chemicals Agency

What you can expect today

Time	Topic	Speaker
11.00	Welcome	Adam Elwan – ECHA
11.05	ECHA efforts towards phasing out animal studies	Tomasz Sobanski – ECHA
11.15	Introduction of OECD QSAR Assessment Framework	Patience Browne – OECD
11.25	OECD QSAR Assessment Framework: ECHA perspective • QSAR Assessment Framework and related IUCLID updates • ECHA's current practice in assessing QSARs and comparison with QSAR Assessment Framework	Doris Hirmann - ECHA Andrea Gissi – ECHA
12.25	Conclusions	Adam Elwan – ECHA
12:30	BREAK 15 minutes	
12.45 – 14.00	Live Q&A panel	

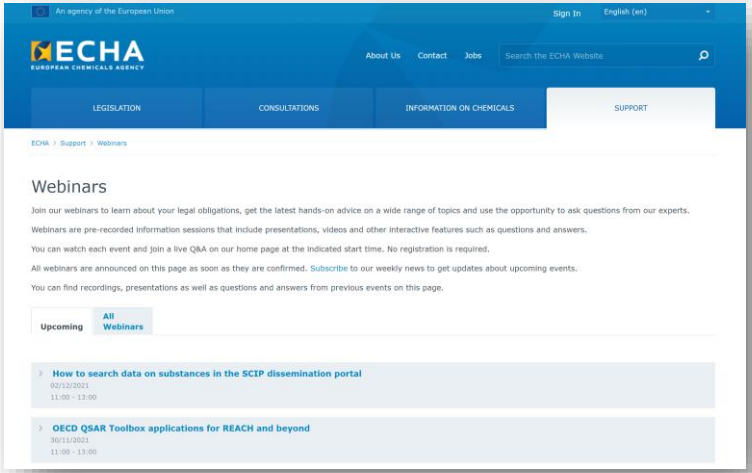
Live Q&A

- Join Q&A at: slido.com
  Event code: # qaf2024
- Send questions until 13:00 (EET, GMT +2)
- Only questions within scope
- Question not answered?
  Contact us: echa.europa.eu/contact



Material available

- Video recording
- Presentations
- Q&A transcript (soon after the event)
- Subscribe to our newsletter at echa.europa.eu/subscribe



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ECHA efforts towards phasing out animal studies

Webinar: OECD QSAR Assessment Framework in REACH dossier evaluation: what you need to know

21 March 2024

Tomasz Sobanski
European Chemicals Agency

ECHA's mandate and legal context

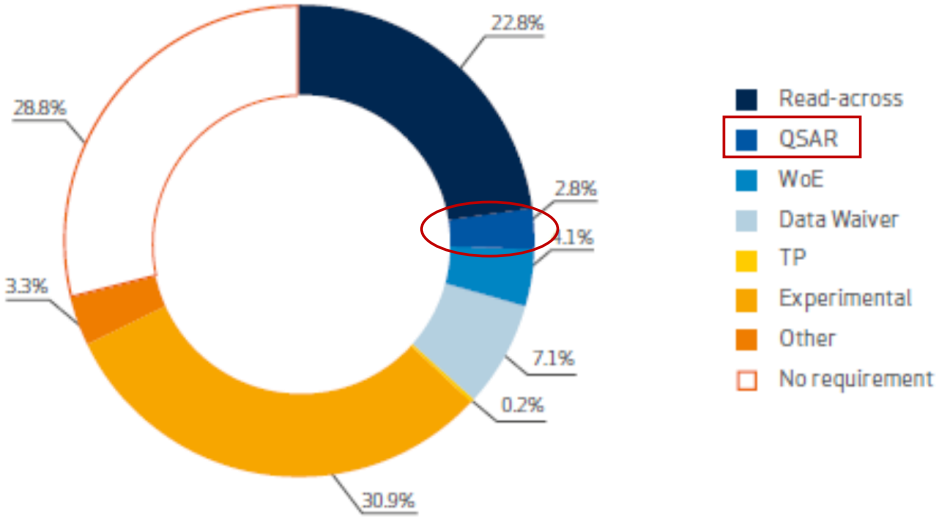
- → Promotion of alternative methods: part of aim and scope of REACH (Article 1)
- → To introduce substances to EU market, REACH registrants need to provide information about (eco)toxicological properties – part of standard information requirements
- → REACH registrants can adapt standard information requirements using alternative methods such as *in vitro*, read-across and (Q)SAR studies
- → Criteria for adaptations listed in Annex XI of REACH

ECHA’s mandate and legal context (2)

→ ECHA working on development and promotion of alternative methods by:

- Providing guidance
- Developing new ways of characterising hazard
- Contributing to discussion about future regulatory system

Alternatives used so far



→ Adaptations used more than experimental studies

→ Read-across most used adaptation

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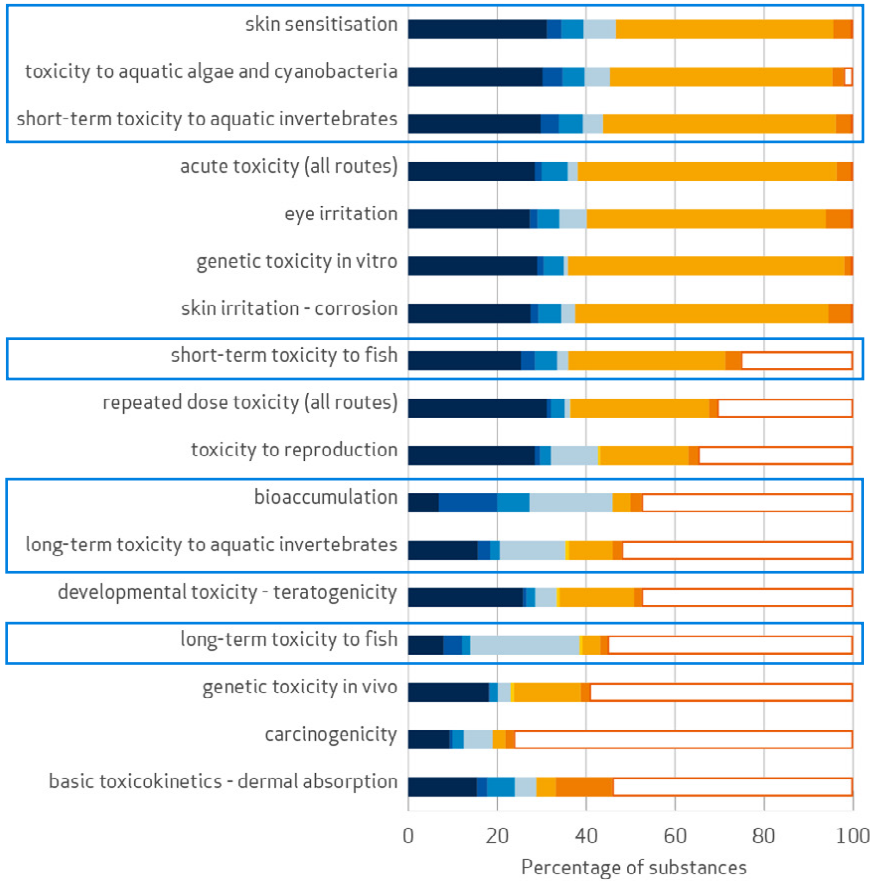
Use of adaptations in REACH information requirements



REACH information requirements where QSARs used the most:

- bioaccumulation,
- aquatic toxicity (all)
- skin sensitisation

Room for more effective use of QSARs under REACH

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Extrapolation from existing toxicological knowledge provide biggest reduction potential in short to medium term.

Reliable QSARs more suitable for less complex properties, while well justified read-across can be used for more complex ones.

To further eliminate need for animal testing, application of new approach methodologies needed.

ECHA approach towards animal-free hazard assessment in three steps:

Step 1. Define

Identify critical needs to transition to animal-free system to steer further development

Step 2. Demonstrate

Apply available tools under current system

Step 3. Re-design

Re-think overall system to enable new approach methodologies and **redefine** main elements

Step 2: Demonstrate

Apply already existing tools under current system to build experience and gain confidence

ECHA focusing on this step, using tools available in following areas:

→ Advancements in *in silico methods*:
- Enhanced predictive capacity and broader applicability from ECHA data efforts
- OECD QSAR Assessment Framework: explicit regulatory acceptance criteria

→ Use of molecular data for read-across and grouping with clear acceptance criteria

→ Establishment of in vitro PBK/TK measurements and modelling for industrial chemicals

→ Integration of 'omics in regulatory toxicological testing for molecular data in relevant biological systems

QAF: important part of ECHA approach

- Newly introduced criteria for prediction:
  - Provide **guidance** to QSAR developers on how to check if prediction is reliable
  - Allow users to **assess** validity of predictions for substances (even using existing tools)
  - Bring **transparency** on how QSAR predictions are assessed by authorities

QAF: important part of ECHA approach (2)

- → Clear and **transparent criteria** key **for wider acceptance** of QSAR models/predictions by users and authorities
- → **Wider acceptance** of QSARs lead to **new regulatory applications** (more adaptation possibilities, better use in risk management)
- → More **regulatory applications**, significant **reduction potential** for tests needed and costs

Thank you

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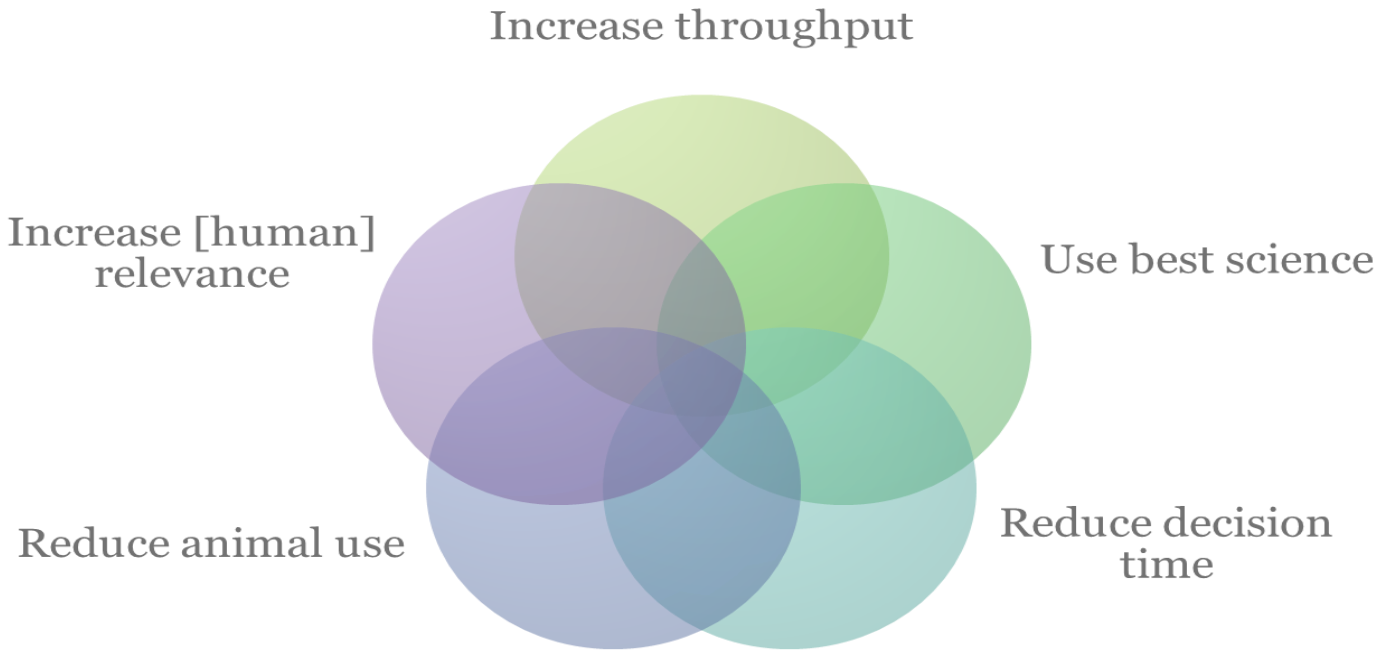
INTRODUCTION TO QAF

Patience Browne OECD
2024

BETTER POLICIES FOR BETTER LIVES

Global drivers to use NAMs in chemical risk assessment



OECD Test Guidelines & NAMs

- OECD Test Guidelines are **internationally harmonised methods for generating data** to evaluate chemical hazard
- include that NAMs (not exhaustive)

Acute Toxicity	OECD publications
Oral	GD 237 ; TG 420, 423, 425
Dermal	GD 237; TG 402
Inhalation	GD 237, GD 39; TG 403, 433, 436
Eye Irritation and damage	GD 263; TG 437, 438, 460, 491, 492, TG 467
Skin Irritation and corrosion	GD 203; TG 430, 431, 435, 439, 460
Skin sensitisation	GD 256; TG 442C, 442D, 442E, TG 497

- OECD TG are validated following principles described in Guidance Document 34 VALIDATION AND INTERNATIONAL ACCEPTANCE OF NEW OR UPDATED TEST METHODS
- Results of OECD TG covered by **MAD**

OECD Hazard Assessment & NAMs

Best approaches and practices for **integrating information to come to a regulatory decision** on chemical hazard

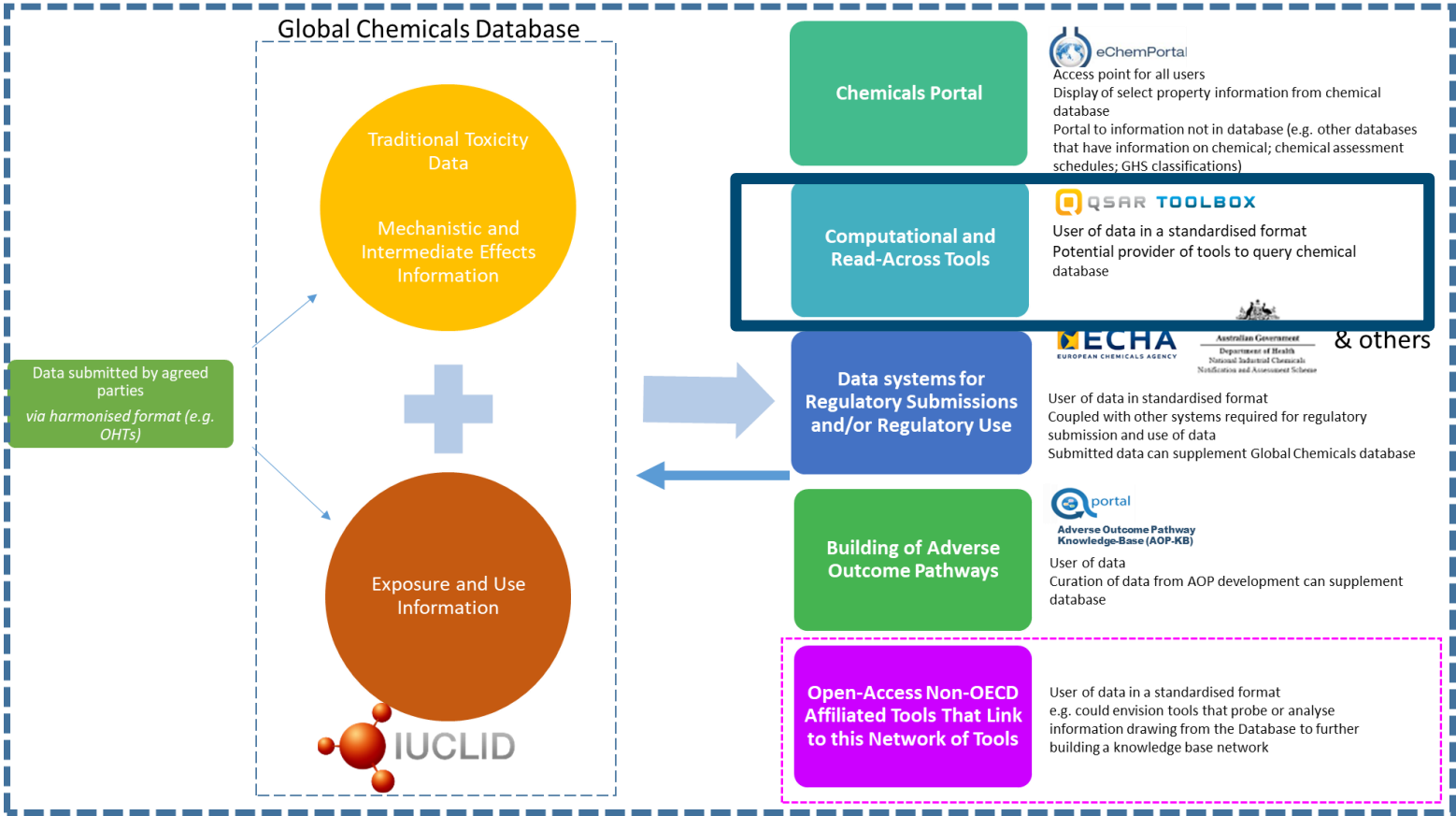
- Discussion of use of NAMs in a regulatory context
  - IATA Case Studies
  - Chemical grouping
  - Omics approaches
  - Various topic-specific guidance documents

- Forum to discuss how to **build confidence in NAMs**
  - **identification of aspects that can be harmonised**

OECD Ecosystem of Electronic Tool

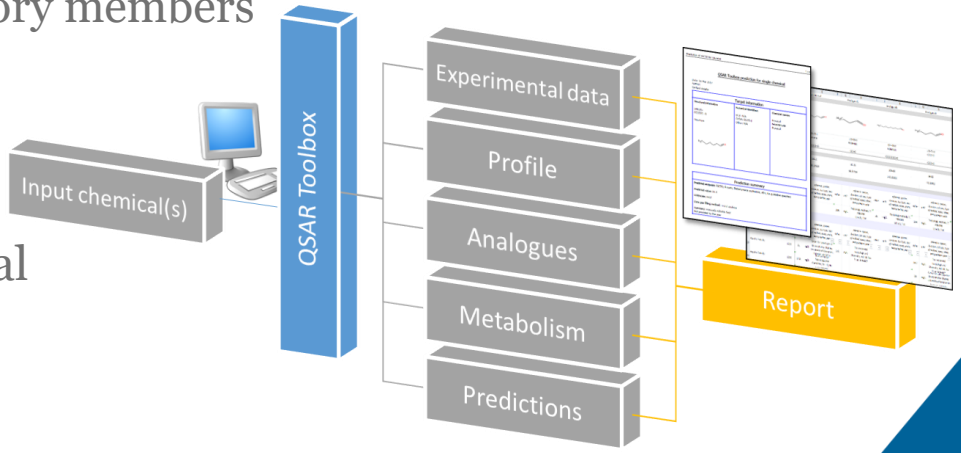
Promotes the **interlinkage** of tools to support regulatory decisions on chemicals

Encourages use of **OHTs** to increase the ability to share data.



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 (industry) or be used as input to support authorities e.g. prioritisation, substance evaluation

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

QSAR Assessment Framework: overview

- Objective
  - 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
- 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

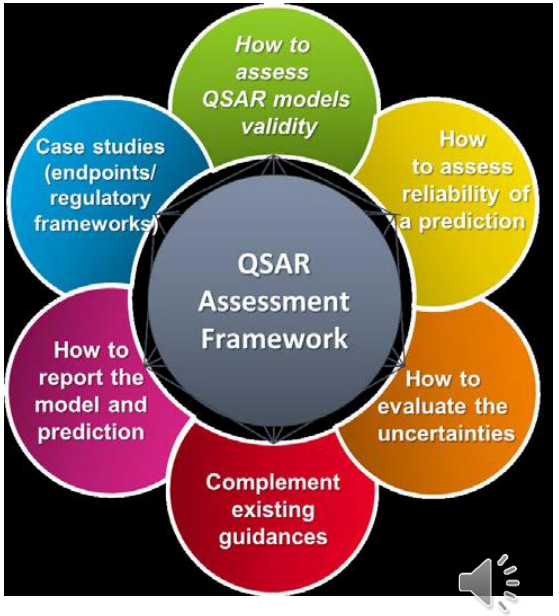
OECD QSAR Assessment Framework (QAF)

Project added to OECD Hazard Assessment Work Programme

- Co-led by Instituto Superiore di Sanità (ISS) Italy and the European Chemicals Agency (ECHA)
- Supported by QAF Expert Group
  - provided general input on project, feedback on proposed path forward, written comments on drafts
  - 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
  - request for written commenting round to Working Party on Hazard Assessment Q2 2023
  - declassified in Q3 2023

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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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

Find out more

Thank You For Listening

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OECD QSAR Assessment Framework: ECHA perspective

Webinar: OECD QSAR Assessment Framework in REACH dossier evaluation: what you need to know

21 March 2024

Doris Hirmann
European Chemicals Agency

OECD QSAR Assessment Framework
ECHA perspective

VIDEO

- → Part I: General aspects
- → Part II: ECHA’s current practice in assessing QSARs under dossier evaluation
- → Part III: Comparison of ECHA’s current evaluation practices with OECD QSAR Assessment Framework
- → Part IV: IUCLID changes

OECD QSAR Assessment Framework **ECHA perspective**

- **Part I: General aspects**
- Part II: ECHA's current practice in assessing QSARs under dossier evaluation
- Part III: Comparison of ECHA's current evaluation practices with the OECD QSAR Assessment Framework
- Part IV: IUCLID changes

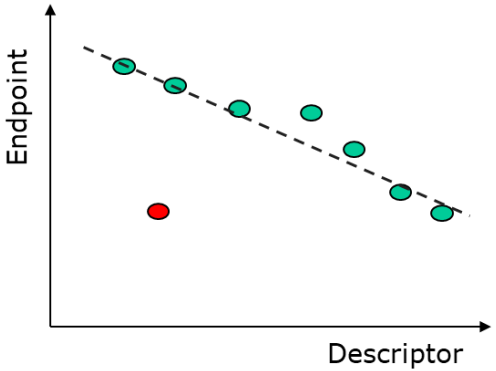
QSAR Assessment Framework
General aspects

OECD webinar on QSAR Assessment Framework

Starting point

Valid QSAR model ≠ Valid QSAR result

- → QSARs allowed in many chemical regulations
- → 2004 OECD QSAR principles cover scientific validity of **QSAR models**
- → Use of valid QSAR model does not guarantee validity of each result
- → Need to establish **principles to assess individual results** and a systematic and harmonised **assessment framework** for QSAR models and predictions



QSAR models
Principles for assessment

QSAR Assessment Framework Group: agree OECD principles for evaluating scientific validity of **QSAR models** remain relevant:

1. Defined endpoint
2. Unambiguous algorithm
3. Defined domain of applicability
4. Appropriate measures of goodness-of-fit, robustness and predictivity
5. Mechanistic interpretation, if possible

QSAR models
Principles for assessment

Four new OECD principles for evaluating QSAR predictions and results based on multiple predictions:

1. **Correct input**
2. **Substance within applicability domain**
3. **Reliable prediction**
4. **Outcome fit for purpose**

QAF guidance document

Text document establishing principles for assessment of QSAR results and explaining how to assess models and their results

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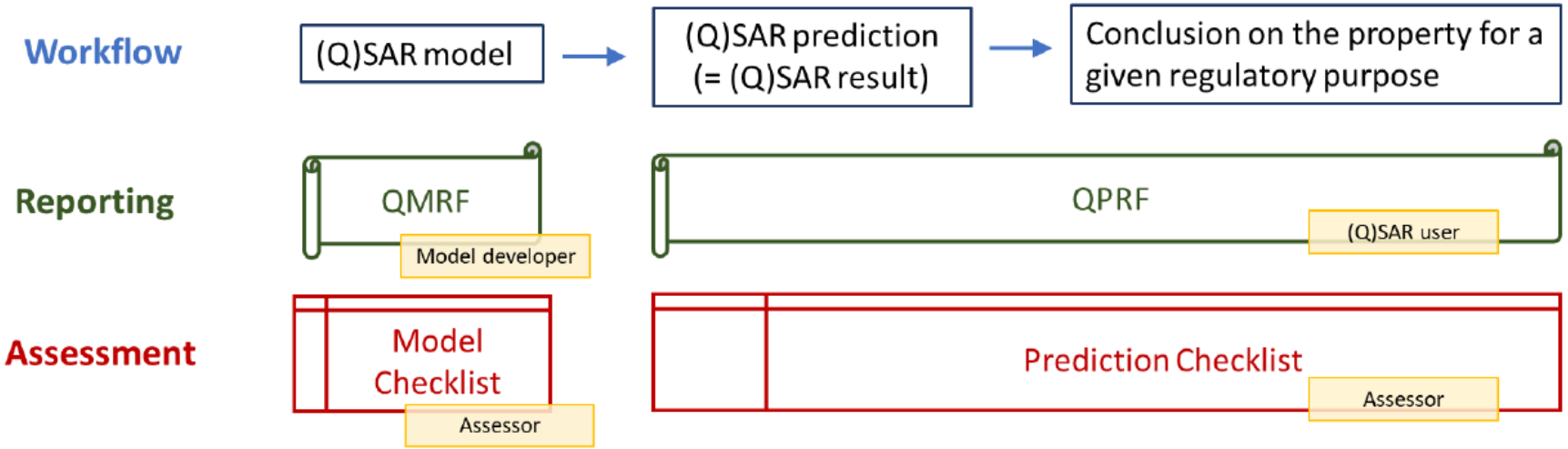
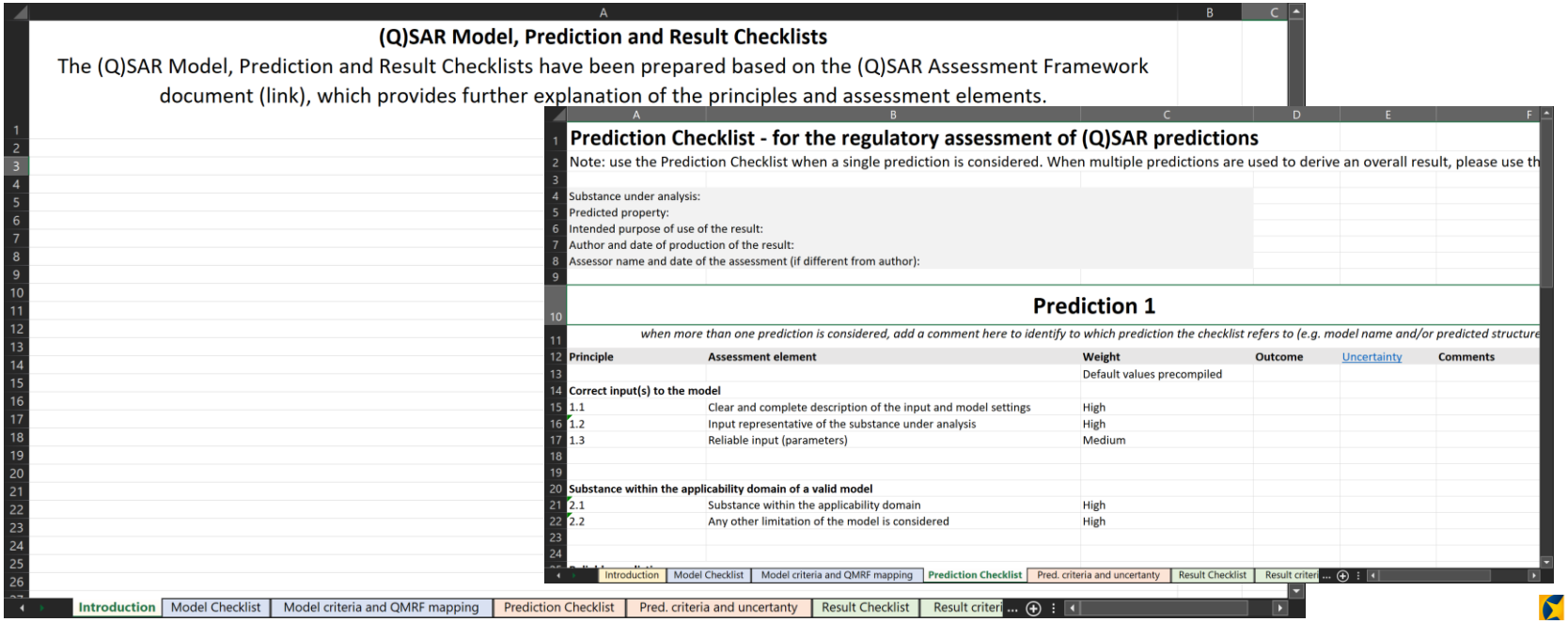
Roles
Visual abstract

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



QSAR Assessment Framework
Checklist

Excel document to perform assessment in practice. Includes Model Checklist, Prediction Checklist, Result Checklist + examples and explanations



Spreadsheets: more than just checklists

Tabs in excel:

- Model Checklist
- Model criteria and QMRF mapping
- Prediction Checklist
- Pred. criteria and uncertainty
- Result Checklist
- Result criteria and uncertainty

→ Separate spreadsheets provide
- details,
- practical advice,
- examples and
- mapping to QMRF/QPRF

for each Assessment Element

→ Section dedicated on how to assign uncertainty level for predictions and results

QSAR Assessment Framework documents

- **OECD Series on Testing and Assessment: publications by number**
- **No. 386** (Q)SAR Assessment Framework: Guidance for the regulatory assessment of (Quantitative) Structure – Activity Relationship models, predictions, and results based on multiple predictions
  Glossy - Mono, Annex 1 (Word file), Annex 2 (Word file), Checklist in Excel

QAF guidance for assessment of **models**

Figure: Guidance text with explanation of Assessment Element (AE) for assessing QSAR models principle 1: a defined endpoint

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

21. 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)*

22. 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,

Each principle is broken down to Assessment Elements (AEs)

Guidance gives more details for each AE

Ideally, acceptable model should fulfil all AEs. Depending on purpose of use, evaluators may accept models where not all AEs fulfilled

Guidance for assessment of **QSAR predictions**

Figure: Guidance text with explanation of AEs for assessing QSAR predictions principle 1: a correct input

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

Each principle broken down to assessment elements (AEs)

AEs further explained in guidance and checklist

Guidance also explains conditions for acceptable predictions

Guidance for assessment of **QSAR predictions**

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 AE in the context of use of the prediction. Depends on purpose of use of prediction (default given)

- High
- Medium
- Low

Outcome:

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

Uncertainty:

- Low
- Medium
- High

Comments

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Guidance for assessment of **QSAR predictions**

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)

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Conclusion on the individual prediciton				
Uncertainty				
Outcome of the assessment (individual prediction)				
Comments				

For each prediction:

Conclusion on individual prediction

Uncertainty of prediction

- Low
- Medium
- High

Based on highest uncertainty of high weight AEs.

Outcome of assessment

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

Document suggests to accept predictions with low or medium uncertainty

Comments

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Principles for assessment of **QSAR predictions**

- Four new OECD principles for evaluating QSAR predictions and results based on multiple predictions:
  1. **Correct input** - complete and representative of the substance being analysed, uses reliable parameters

Correct input
Assessment Elements (AEs)

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

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

→ AE 1.2: Input representative of the substance under analysis

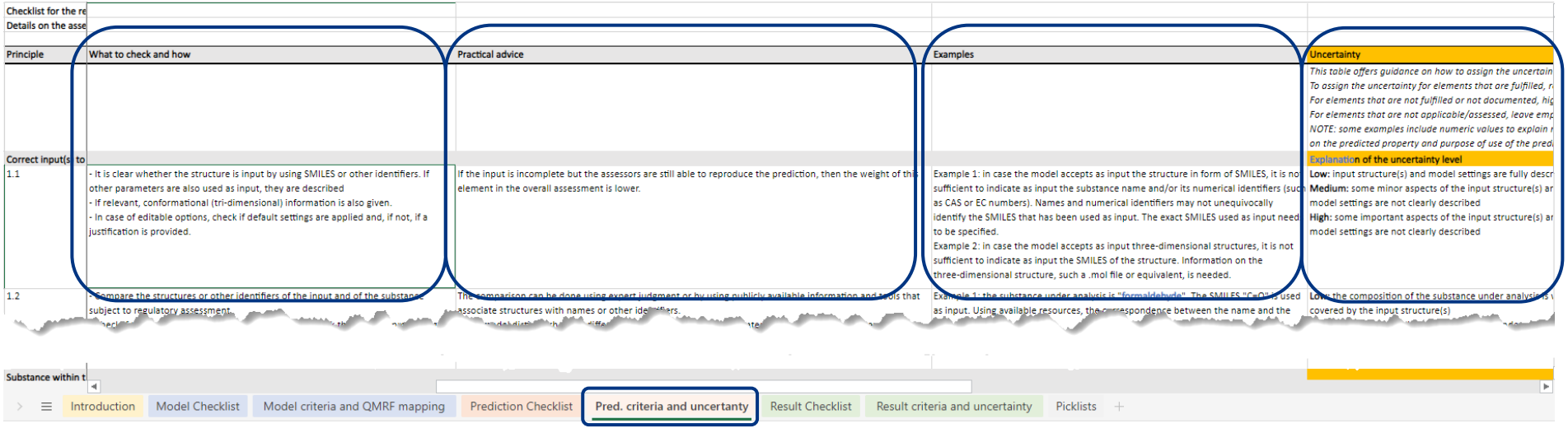
- Structure(s) modelled represent the substance subject to regulatory assessment

→ AE 1.3: Reliable input (parameters)

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

Example for assessment
Correct input

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



What to check and how Practical advice Examples Uncertainty

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Example for assessment
Correct input

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

What to check and how:

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

- If relevant, conformational (tri-dimensional) information 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 AE fulfilled? If yes, assign uncertainty:

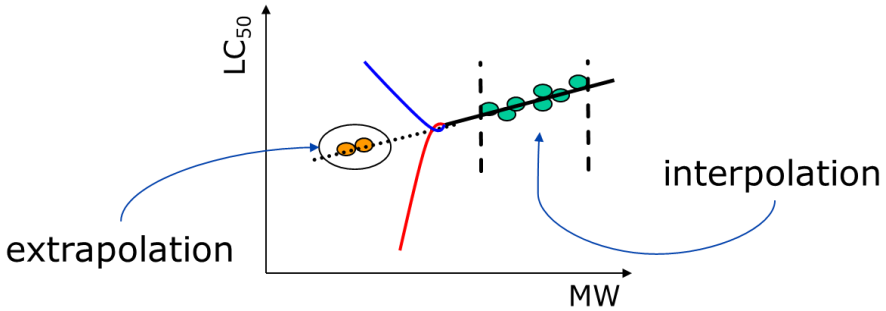
- **Low** uncertainty: SMILES and logKow provided
- **Medium** uncertainty: SMILES provided, logKow not provided
- **High** uncertainty: only CAS number provided, but CAS/SMILES association is ambiguous

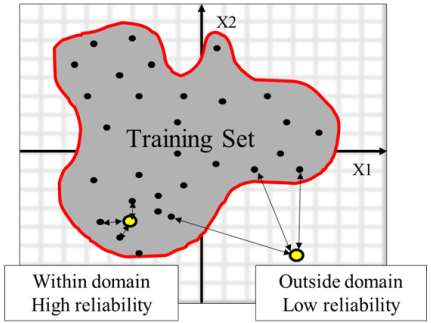
Principles for assessment of **QSAR predictions**

- Four new OECD principles for evaluating QSAR predictions and results based on multiple predictions:
  1. **Correct input** - complete and representative of the substance being analysed, uses reliable parameters
  2. **Substance within applicability domain** – assessment limited to domain as defined by model developers

Applicability domain

- → Applicability domain (AD) of a QSAR model is the physico-chemical, structural or biological space, knowledge or information on which the training set of the model has been developed
- → Predictions outside AD have **higher or unknown uncertainty** compared to predictions inside AD
- → Predictions within the applicability domain of the model are more reliable than predictions outside applicability domain





Substance within applicability domain of a valid model

→ AE 2.1: Substance within applicability domain

- Substance meets applicability domain (AD) requirements specified by model developers

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

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

Principles for assessment of **QSAR predictions**

- Four new OECD principles for evaluating QSAR predictions and results based on multiple predictions:
  1. **Correct input** - complete and representative of the substance being analysed, uses reliable parameters
  2. **Substance within applicability domain** – assessment limited to domain as defined by model developers
  3. **Reliable prediction** – to cover elements that may not be part of developers' definition of applicability domain

Reliable prediction

- → AE 3.1 Reproducibility
- → AE 3.2 Overall performance of the model
- → AE 3.3 Fit within 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

More details in the following presentation

Principles for assessment of **QSAR predictions**

- Four new OECD principles for evaluating QSAR predictions and results based on multiple predictions:
  1. **Correct input** - complete and representative of the substance being analysed, uses reliable parameters
  2. **Substance within applicability domain** – assessment limited to domain as defined by model developers
  3. **Reliable prediction** – to cover elements that may not be part of developers' definition of applicability domain
  4. **Outcome fit for purpose** - usefulness of computational prediction to answer specific regulatory question

Outcome fit for regulatory purpose

→ AE 4.1: Compliance with additional requirements

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

→ AE 4.3: Decidability within specific framework

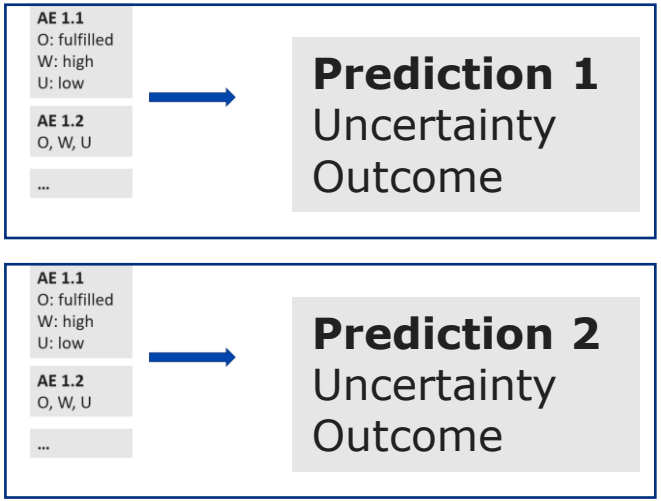
Assessment of results based on multiple predictions

(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.

Workflow for assessing results from multiple predictions

1. Assess predictions individually



2. Check how final result determined (AE 5.1)

QSAR result

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

Conclusion on the result
Uncertainty
Outcome

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- for intended purpose

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Take home messages

QSAR Assessment Framework (QAF) published in August 2023

Establishes new OECD principles for assessment of QSAR predictions and results from multiple predictions, and provides guidance and checklists for their assessment

QSAR Assessment Framework becomes reference point for regulatory assessment of QSARs

With a systematic and harmonised assessment framework, QAF will benefit regulators first, followed by model developers and QSAR users

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OECD QSAR Assessment Framework: ECHA perspective

Webinar: OECD QSAR Assessment Framework in REACH dossier evaluation: what you need to know

21 March 2024

Andrea Gissi
European Chemicals Agency

OECD QSAR Assessment Framework
ECHA perspective

- → Part I: General aspects
- → **Part II: ECHA's current practice in assessing QSARs under dossier evaluation**
- → Part III: Comparison of ECHA's current evaluation practices with OECD QSAR Assessment Framework
- → Part IV: IUCLID changes

Current practice in QSAR assessment

QSARs and their assessment under dossier evaluation

Webinar date

3 June 2021 11:00 - 12:30

Summary

The webinar covers the requirements for the use of QSAR results as adaptations to standard information in REACH registrations. It also shows how ECHA evaluates the compliance of QSAR information. Finally, it illustrates the most common issues found in QSAR studies included in REACH dossiers and how they are addressed in ECHA's decisions. The webinar is particularly addressed to REACH registrants, who may include QSAR results in their registration dossiers and to stakeholders interested in learning about ECHA's methods on evaluating QSAR results.

echa.europa.eu/-/qsars-and-their-assessment-under-dossier-evaluation

- Presented in detail previously, still relevant
- Summarised and compared to QAF in next slides

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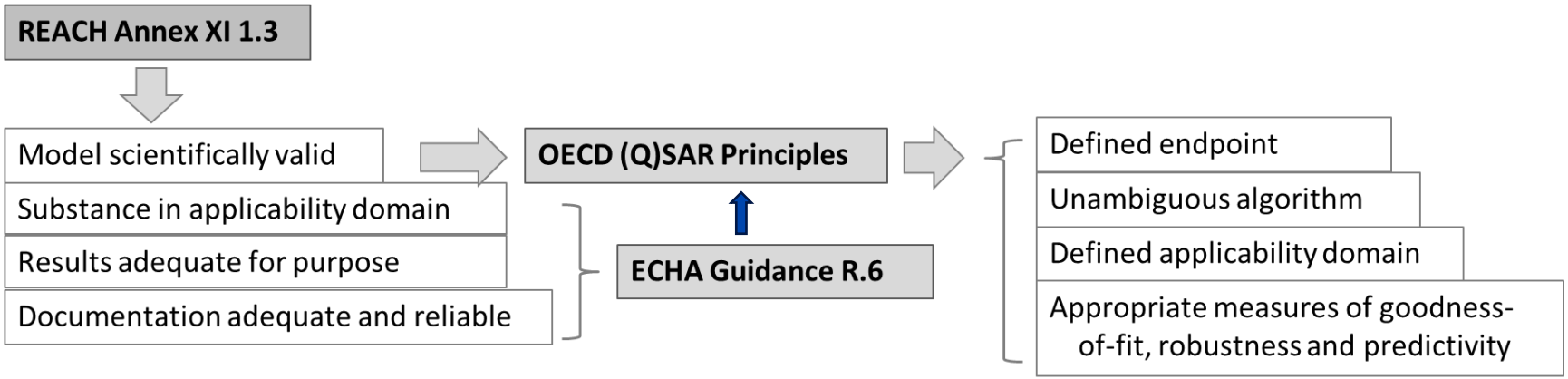
QSAR assessment in REACH dossier evaluation



- REACH requirements for using QSARs to adapt standard information requirements specified in Annex XI 1.3
- **ECHA Guidance R6** used as reference in our evaluation

GUIDANCE DOCUMENT ON THE VALIDATION OF (QUANTITATIVE)STRUCTURE-ACTIVITY RELATIONSHIPS [(Q)SAR] MODELS (OECD ENV/JM/MONO(2007)2)

Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of chemicals

Current practice

- → **Scientifically valid model** -> OECD QSAR principles (2007)
- → **Substance within applicability domain** -> Check applicability domain
  as defined by model developers + parametric, structural, mechanistic and metabolic domain, as relevant
- → **Results adequate for purpose** -> Check input structure and reliability of prediction
- → **Documentation** -> Check QSAR Prediction Reporting Format (QPRF) and QSAR Model Reporting Format (QMRF), or equivalent content

Is the model scientifically valid?

- → **Defined endpoint** -> Check data used to build the model (i.e. training set)
- → **Unambiguous algorithm** -> Check prediction is reproducible (same input and settings = same output)
- → **Defined domain of applicability** -> Check applicability domain is defined
- → **Appropriate measures of goodness of fit, robustness and predictivity** -> check availability of measures of performances
- → **Mechanistic interpretation, if possible** -> Not formally checked

Substance within domain?

Model developers' definition of applicability domain is the starting point for ECHA’s assessment.

ECHA also considers following aspects, as relevant:

→ Descriptor domain

→ Structural domain

→ Mechanistic domain

→ Metabolic domain

Adequate results?
(for adapting REACH information requirements)

Input structure

Choosing correct input structure(s) is not trivial in case of multi-constituents or substances with unknown or variable composition, complex reaction product or biological origin (UVCB).

Reliability of prediction

→ Reliability of input parameters

→ Presence of analogues in training/test sets and accuracy of their predictions

→ Consistency of prediction with other information available for substance

Adequate documentation?

QSAR Model Reporting Format (QMRF) must include information on:

- → Predicted endpoint, including information on experimental protocol and data quality for data used to develop model
- → Unambiguous definition of algorithm, descriptor(s) of the model and its applicability domain
- → Estimate of goodness-of-fit and of predictivity of the model, including information on training set and validation statistics

Adequate documentation? (2)

QSAR Prediction Reporting Format (QPRF) must include information on:

- → Model prediction(s), including endpoint
- → Precise identification of the substance modelled
- → Relationship between modelled substance and defined applicability domain
- → Identities of close analogues, including considerations on how predicted and experimental data for analogues support the prediction

OECD QSAR Assessment Framework **ECHA perspective**

- → Part I: General aspects
- → Part II: ECHA's current practice in assessing QSARs under dossier evaluation
- → **Part III: Comparison of ECHA's current evaluation practices with OECD QSAR Assessment Framework**
- → Part IV: IUCLID changes

Current evaluation practices vs QAF
1. Scientific validity of the model

→ When assessing models, ECHA refers to OECD QSAR principles from 2007

→ QAF expert group confirmed use of principles from 2007, with special attention to quality of data used to build the model

→ Data quality checked by ECHA under first OECD principle (defined endpoint), in line with AEs 1.2 and 1.3 in the QAF Model Checklist (transparency and quality of underlying experimental data)

Current evaluation practices vs QAF
2. Substance within applicability domain

→ ECHA refers to applicability domain (AD) as defined by model developers + parametric, structural, mechanistic and metabolic domain, as relevant

→ Under applicability domain (AD), QAF considers AD as defined by model developers only. However, under reliability, QAF checks:

- AE 3.3 - Fit within physicochemical, structural and response spaces of model training set
- AE 3.6 - Mechanistic and/or metabolic considerations

→ Overall, two approaches are aligned

Current evaluation practices vs QAF
3. Results adequate for purpose

- → For adequacy, ECHA refers to input structure and reliability of prediction
- → QAF checks that input is correct as first principle, and reliability as third principle
- → Let’s look at “Reliability” in more detail…

Current evaluation practices vs QAF
Results adequate for purpose: Reliability

Dossier evaluation	**(Q)SAR Assessment Framework** (AEs from Prediction Checklist)
Input structure	**AE 1.2** - Input representative of the substance under analysis
Reliability of input parameters	**AE 1.3** – Reliable input (parameters) [Under input]
Presence of analogues in training/test sets and accuracy of their predictions	**AE 3.4** – Performance of model for similar substances
Consistency of prediction with other information available for the substance	**AE 3.6** – Consistency of information
[Considered under validity of the model – Unambiguous algorithm]	**AE 3.1** – Reproducibility
[Considered under validity of the model]	**AE 3.2** – Overall performance of the model
[Considered under applicability domain]	**AE 3.3** - Fit within physicochemical, structural and response spaces of the training set of the model and **AE 3.5** - Mechanistic and/or metabolic considerations

Current evaluation practices vs QAF
4. Adequate documentation

→ ECHA requires information on model (QSAR Model Reporting Format (QMRF)) and on prediction (QSAR Prediction Reporting Format (QPRF))

→ QAF provides updated versions of QMRF and QPRF

What changes in ECHA's assessments with QAF publication?

→ **Scientific assessment will not change**
QAF fully aligned with current ECHA practice

→ In our decisions in compliance check:

- For now, we keep using reference to ECHA Guidance R6
- In future, we will refer to QAF assessment elements to be even clearer on identified issues

OECD QSAR Assessment Framework **ECHA perspective**

- → Part I: General aspects
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QAF publication
Changes in IUCLID

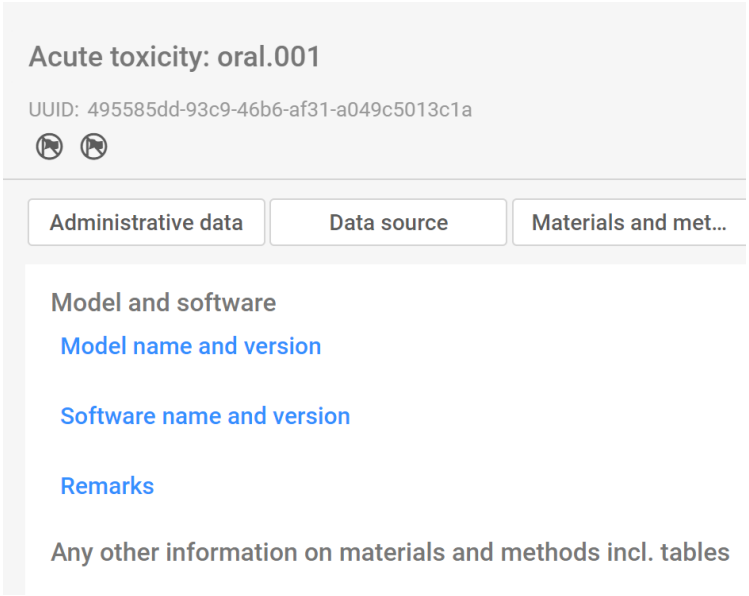
- → Based on updated QPRF in QAF
- → 17 new fields appear when “study type = QSAR” and reliability score is assigned
- → Benefits
  - Help QSAR users to report key information
  - Facilitate assessors in finding key information for evaluation
  - Structuring of information in IUCLID fields and not in attachments
- → Model information (QMRF) still expected as an attachment (especially if information is not easily publicly accessible)

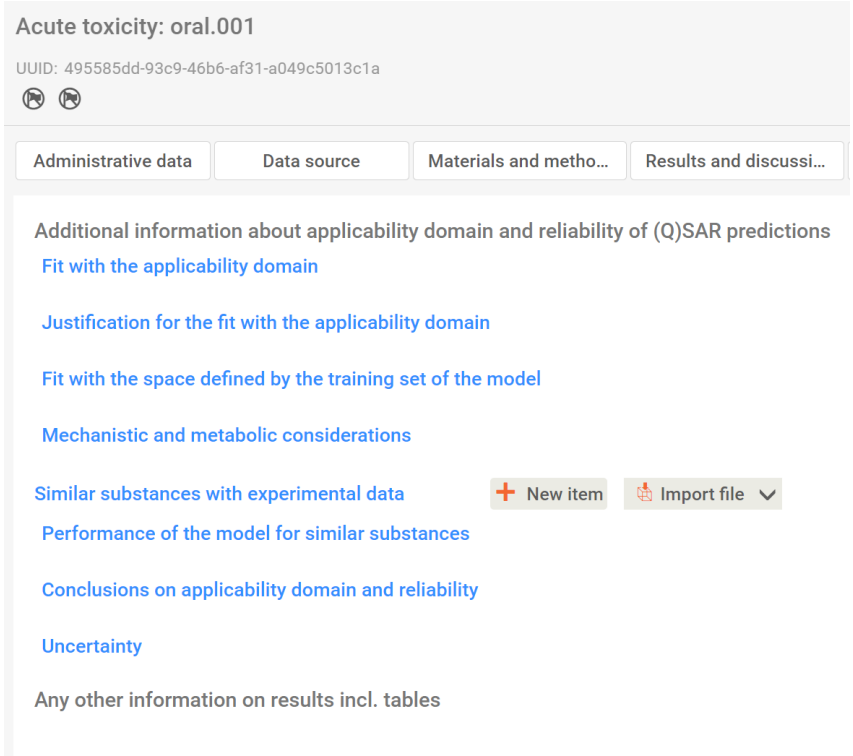
QAF Annexes
Updated QPRF and QMRF

Annexes:

- Updated **QSAR Prediction Reporting Format (QPRF v2.0)**: Major update to reflect QSAR Assessment Framework Guidance. Eight 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 OECD principles for validity of models have not changed

New QSAR fields in IUCLID





New QSAR fields in IUCLID

- → QAF-related fields available in IUCLID release planned for 29 April 2024
- → Expect registrants to fill-in new IUCLID fields for QSARs but they will not be mandatory (at least for now)
- → By completing new fields, easier for registrants to make sure relevant information is reported and considered during dossier evaluation

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Conclusions

Webinar: OECD QSAR Assessment Framework in REACH dossier evaluation: what you need to know

21 March 2024

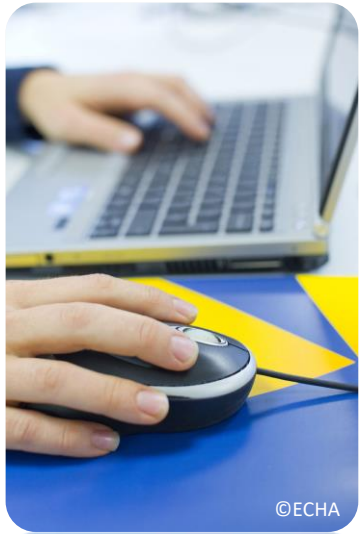
Adam Elwan
European Chemicals Agency

Conclusions

- → QAF guidance and checklist reflects ECHA's current practices
- → ECHA's scientific assessment of QSAR studies remains the same
- → Communication of incompliances: ECHA starts referring to QAF to be even clearer on reasons for rejecting a QSAR study
- → Guidance, new reporting formats, and IUCLID fields guide you in providing documentation needed for ECHA's assessment

Live Q&A

- Join Q&A at: slido.com
  Event code: # qaf2024
- Send questions until 13:00 (EET, GMT +2)
- Only questions within scope
- Question not answered?
  Contact us: echa.europa.eu/contact



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