OECD (Q)SAR Assessment Framework for REACH Dossier Evaluation

SETAC Europe 2024

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Doris Hirmann, Andrea Gissi
European Chemicals Agency

Overview

- → (Q)SAR Assessment Framework (QAF) – brief introduction
- → (Q)SAR assessment in REACH dossier evaluation
- → Current evaluation practices and QAF
- → Illustrative examples

(Q)SAR Assessment Framework (QAF)

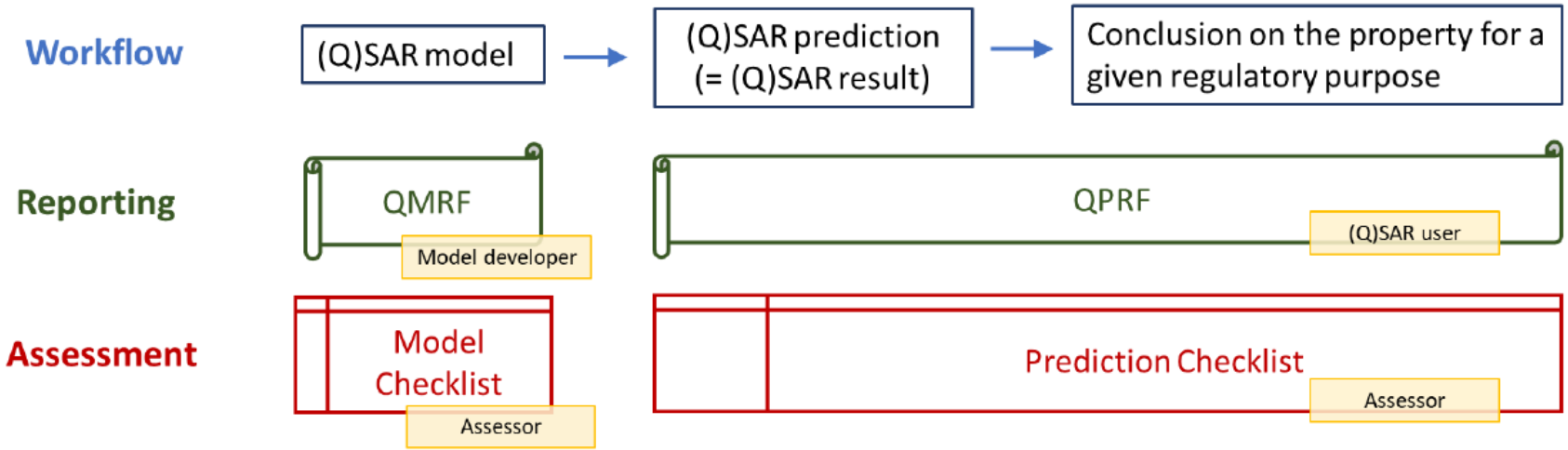
Published in August 2023

Aim	Provision of a systematic and harmonised framework for regulatory assessment of (Q)SAR models
Scope	→ QSAR models → QSAR predictions, → QSAR results based on multiple predictions
Applicability	(Q)SARs irrespective of → modelling technique, → predicted endpoint, → intended regulatory purpose
Audience	→ Primarily for regulatory authorities → As reference for QSAR model developers and users

Roles

Visual abstract:

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



QAF Guidance document content

Text document

- Assessment of (Q)SAR Models (Model Checklist),
- Assessment of (Q)SAR Predictions (Prediction Checklist) & Results derived from multiple predictions (Result Checklist)
- Annex I – (Q)SAR model reporting format (QMRF) v2.1 (minor update)
- Annex II – (Q)SAR prediction reporting format (QPRF) v2.0 (major update)

Excel document

- Model Checklist
- Prediction Checklist
- Result Checklist

+ examples and explanations

OECD principles for (Q)SAR assessment

Five existing OECD principles for evaluating scientific validity of **(Q)SAR models**:

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

Four new OECD principles for evaluating **(Q)SAR predictions** and results based on multiple predictions:

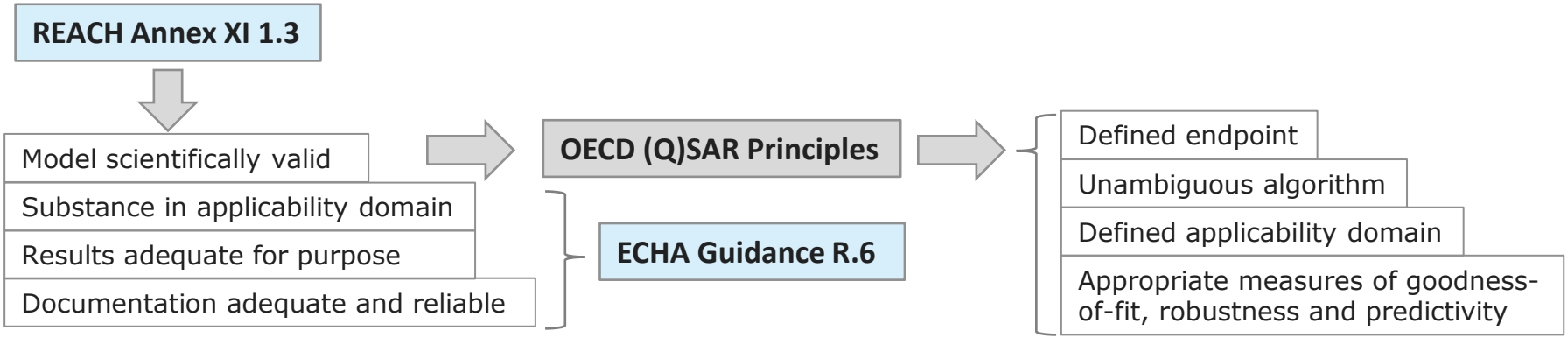
1. Correct input
2. Substance within applicability domain
3. Reliable prediction
4. Outcome fit for purpose

New principle for evaluating **(Q)SAR results**

5. Correct determination of the final result

(Q)SAR assessment in REACH dossier evaluation

QSAR assessment in REACH dossier evaluation



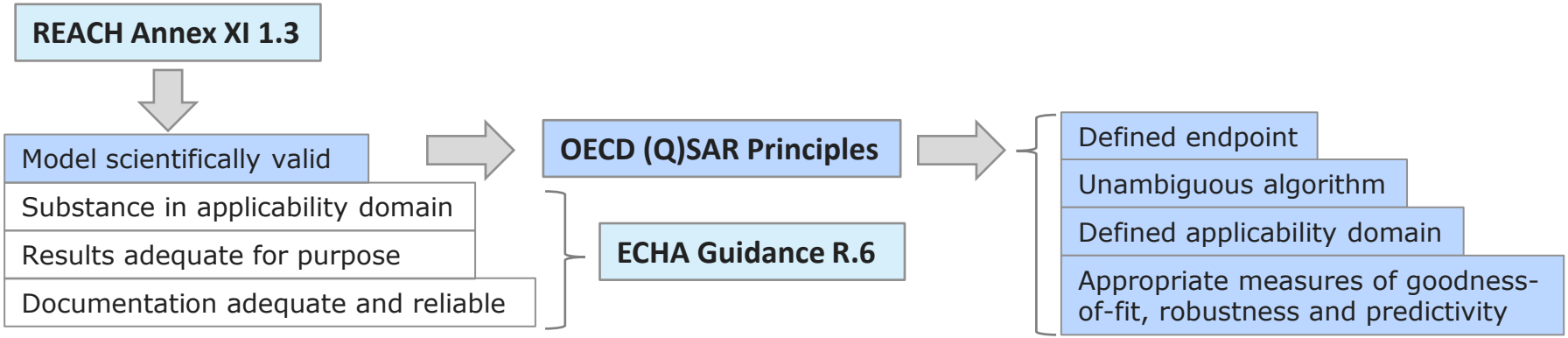
→ REACH requirements for using QSARs to adapt standard information requirements specified in Annex XI 1.3

→ **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)

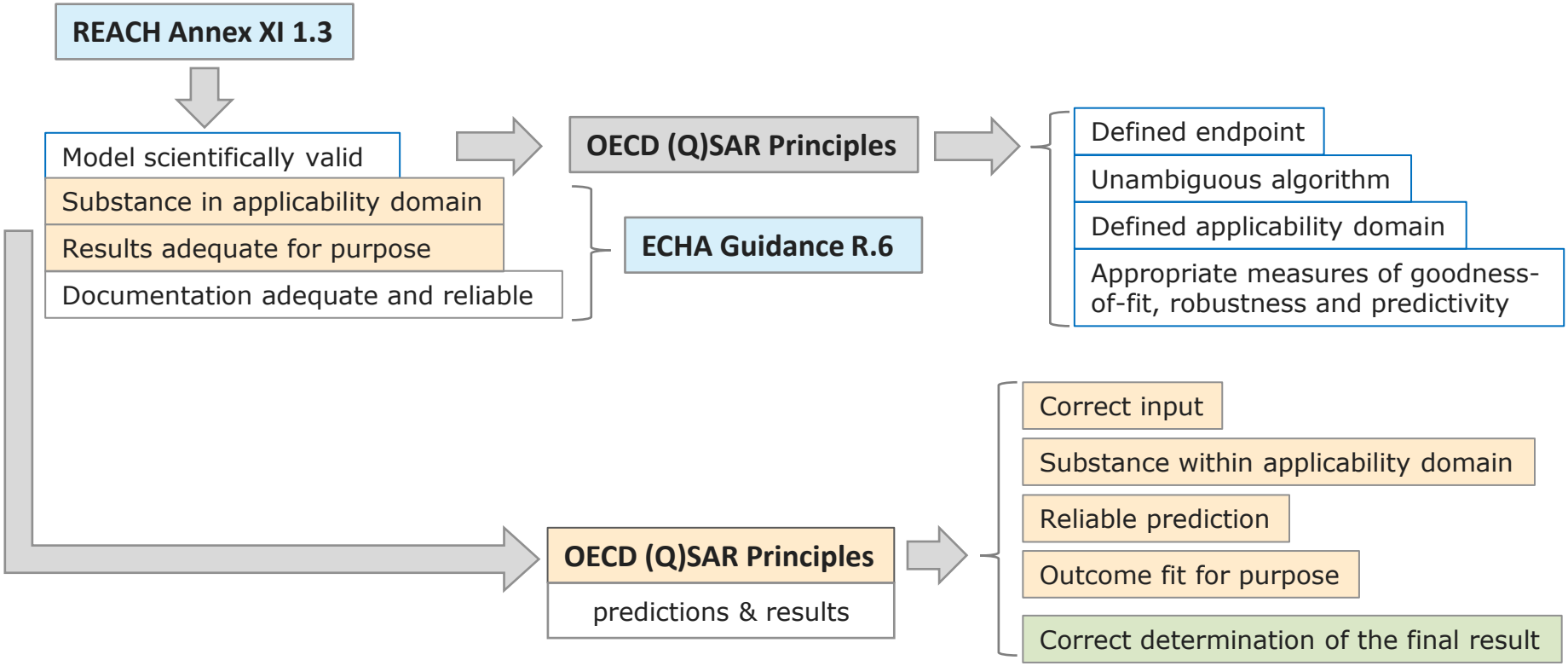
Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of chemicals

Current evaluation practices versus QAF



- → 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 will be checked under first OECD principle "Defined endpoint" - transparency and quality of underlying experimental data (Assessment elements 1.2 and 1.3)

Current evaluation practices versus QAF

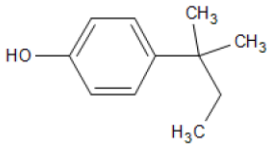


Illustrative examples

Principle 1: Correct input

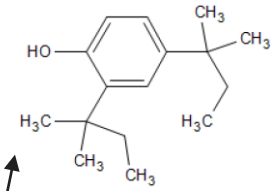
Illustrative examples

Assessment element (AE)	Objective
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
1.2 Input representative of the substance under	The structure(s) modelled represent the substance subject to regulatory assessment
1.3 Reliable input (parameters)	Parameters that are input manually (other than the chemical structure) are reliable



SMILES: CCC(C)(C)c1ccc(O)cc1
Additional input: exp log Kow 3.3

All information to reproduce the predictions are provided (AE 1.1)



Log Kow as input is reliable (AE 1.3)

SMILES: CCC(C)(C)c1ccc(O)c(c1)C(C)(C)CC
Additional input: exp log Kow: 5.8

All (representative) constituents of the multi-constituent substance are predicted (AE 1.2)

Impurities may also need to be considered!

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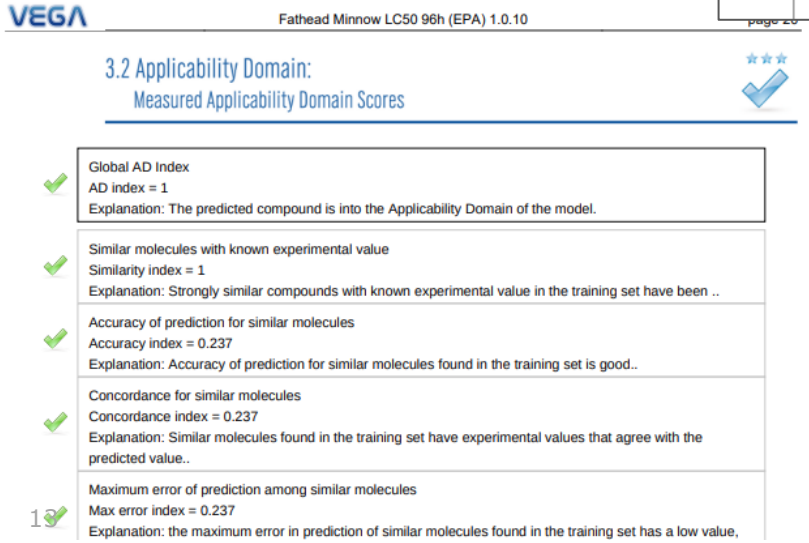
Principle 2: Substance within applicability domain

Illustrative examples

Assessment element (AE)	Objective
2.1	Substance within the applicability domain	The substance meets the applicability domain (AD) requirements specified by model developers
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

Automated domain check (AE 2.1)

Example: VEGA



Example: EPISuite

Manual check if substances falls within Applicability domain ranges (AE 2.1)

7.2.3. Estimation Domain

Training Set (421 Compounds):

Molecular Weight:
Minimum MW: 68.08 (Furan)
Maximum MW: 959.17 (Decabromodiphenyl ether)
Average MW: 259.75

Log Kow:
Minimum LogKow: 0.31 (Benzenesulfonamide)
Maximum LogKow: 8.70 (Decabromodiphenyl ether)

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Example:
EAWAG pathway prediction system:

Chemicals whose Biodegradation Should Not be Predicted

- Readily Degraded and Selected Other Compounds
- Inorganic Chemicals
- High Molecular Weight Compounds
- Chemicals with Unknown or Variable Composition
- Mixtures
- Highly Fluorinated Compounds

Model limitations (AE 2.2)

Principle 3: Reliable prediction

Illustrative examples

Assessment element (AE)		Objective
3.1	Reproducibility	The prediction can be reproduced using the same input and model version
3.2	Overall performance of the model	The model has an overall performance that is considered acceptable for the intended regulatory application
3.3	Fit within the physicochemical, structural and response spaces of the training set of the model	The prediction is result of interpolation in terms of physicochemical, structural and response space
3.4	Performance of the model for similar substances	The model predicts accurately substances similar to the one under analysis
3.5	Mechanistic and/or metabolic considerations	Mechanistic and metabolic considerations support the prediction
3.6	Consistency of information	Additional relevant and reliable information supports the prediction

Example: EPISuite

Model and software

Model name and version

BIOWIN v4.11

Software name and version

EPI Suite™ v4.11 (updated version 2017)

Reproducibility (AE 3.1)

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Example: KATE2020

Performance (AE 3.2)

Equation	Number of Chemicals used for Regression	Number of Support Chemicals	Applicable Range of log P	R^2	Q^2	RMSE
y = 0.86 * log P -1.78	22	15	[-1.75, 5.26]	0.92	0.90	0.44

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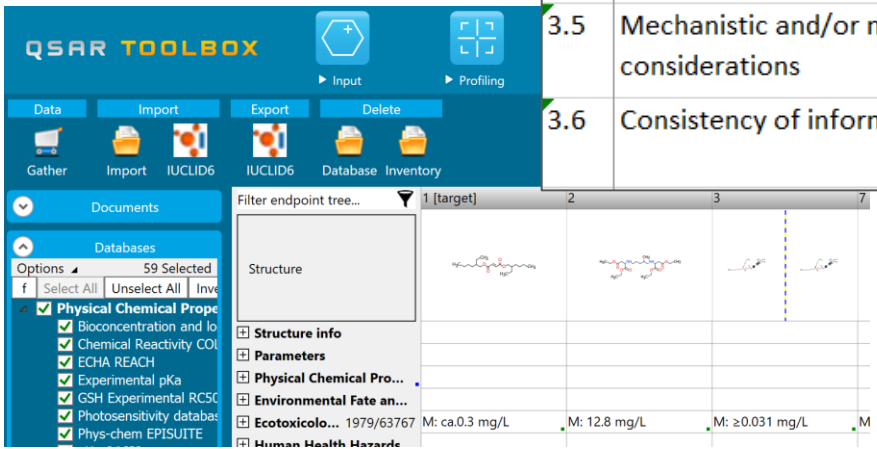

Performance for similar substances (AE 3.4):

- some software present this info as part of the results (e.g. VEGA);
- Use of other tools, e.g. OECD QSAR Toolbox can be useful

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Illustrative examples

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EAS-E SUITE

IFSQSAR QSARINS-Chem OPERA

Toxicokinetics:

- [x] biotransformation half-life in fish
- [ ] biotransformation half-life in humans
- [ ] total elimination half-life in humans

Metabolic considerations for bioaccumulation assessment:
e.g., biotransformation prediction models in EAS-E Suite (AE 3.5)

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Principle 4: Outcome fit for regulatory purpose

Illustrative examples

Outcome is fit for the regulatory purpose		
4.1	Compliance with additional requirements	Regulation specific requirements for the use of computational results are met
4.2	Correspondence between predicted and required property	The modelled property corresponds to the property required by the regulation
4.3	Decidability within the specific framework	The outcome allows to take a regulatory decision in the framework of use

R.7.1.6 Surface tension

The surface tension of an aqueous solution of a substance can be used to determine whether the substance is surface active.

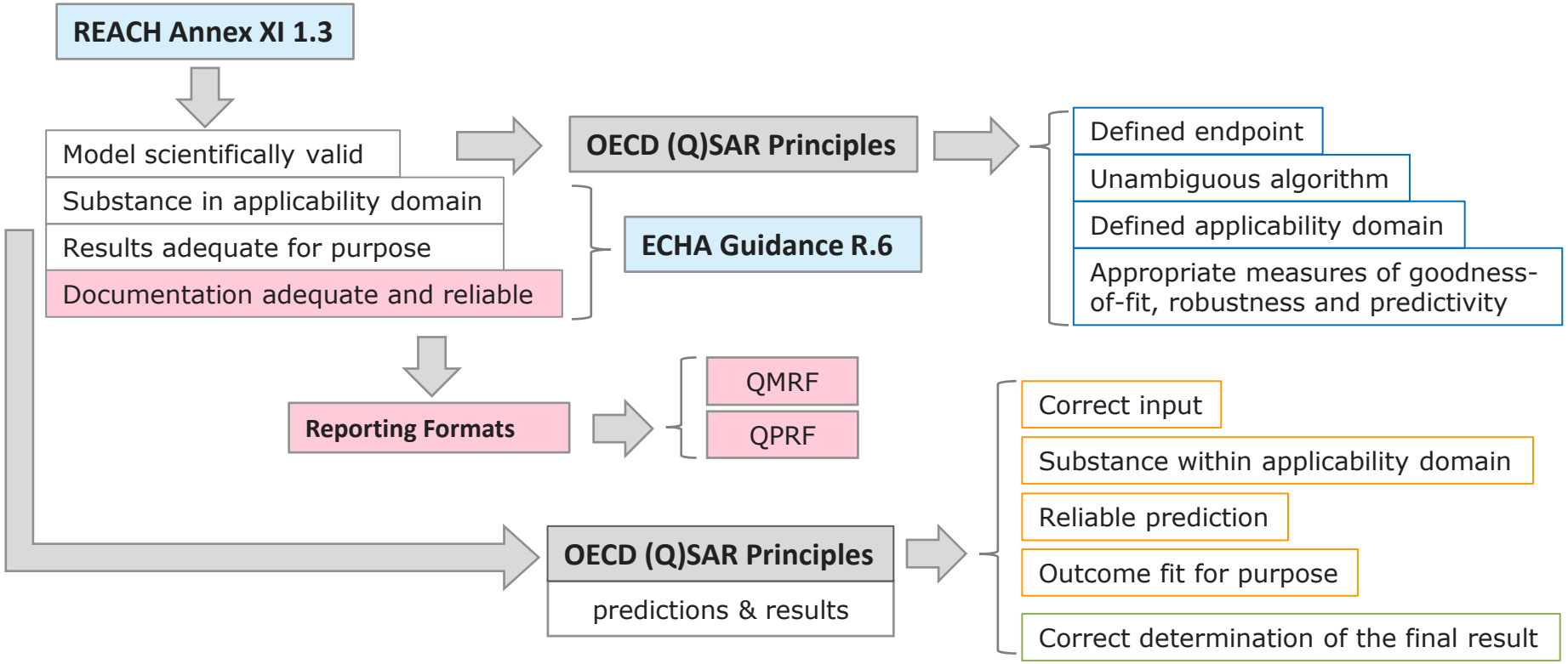
Surface tension measurements require a test material that is stable against hydrolysis during the test period and soluble in water at concentrations of > 1 mg/l. Measurements should be performed on a solution at either 90 % of the solubility limit or 1 g/l (where viscosity permits), whichever is smaller.

(Q)SAR

At the time of writing, no reliable (Q)SAR methods exist for sufficiently accurate predictions of surface tension.

Surface tension models based on pure substance data do not correspond to 'surface tension of aqueous solution' under REACH (AE 4.2)

Documentation



Take home messages

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

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

ECHA webinar on QAF in REACH dossier evaluation (March 2024)

OECD webinar on QSAR Assessment Framework (Nov 2023)

Thank you

The above represents the opinion of the authors and is not an official position of the European

doris.hirmann@echa.europa.eu

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