

Regulatory use of (Q)SARs under REACH

Webinar on Information requirements
10 December 2009

Using (Q)SAR models

Application under REACH

- to fulfill information requirements
 - Use of predictions instead of test data
- as part of the Weight of Evidence (WoE) approach
- to support category justification
 - Use to justify structural and metabolic similarities
- for Integrated Testing Strategy (ITS)
 - To decide on appropriate testing strategies

The (Q)SAR concept

Definition

- **SAR** (Structure Activity Relationship) is a qualitative relationship that relates a (sub)structure to the presence or absence of a property or activity of interest.

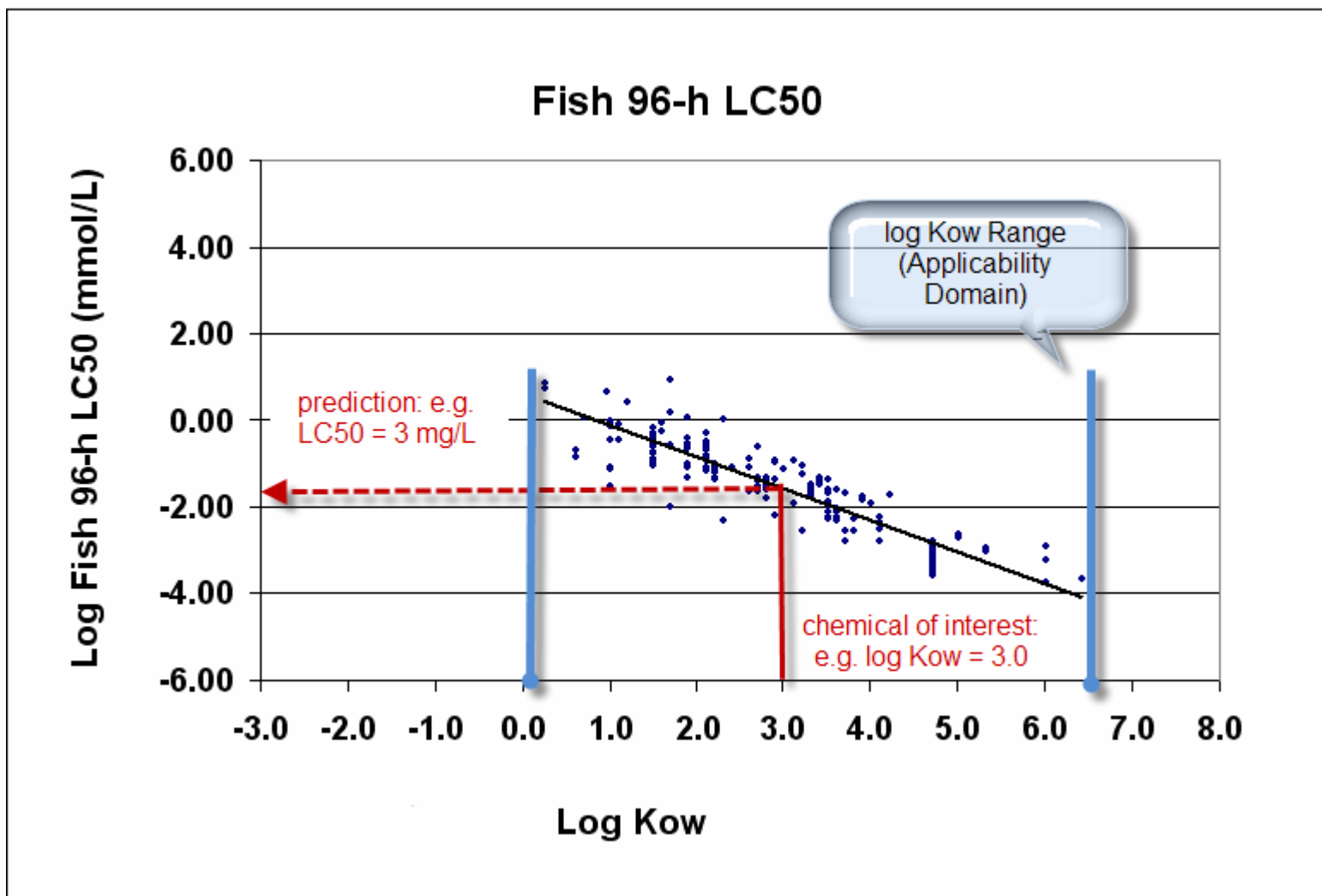


- **QSAR** (Quantitative Structure Activity Relationship) is a mathematical model relating quantitative parameters derived from chemical structures to a quantitative measure of a property or activity.

general mathematical form:

Activity = f (physico-chemical and/or structural property)

QSAR example



Regulatory use of QSARs



Prediction of properties

- The approach can be used to predict
 - physicochemical,
 - (eco)toxicological and
 - environmental fate properties

in a qualitative or quantitative manner based on the knowledge of the chemical structure.

- The results may be used instead of experimental data, provided that a number of conditions are met
- In other situations, the models would be used to provide supplementary information to experimental data

REACH Annex XI provisions for use of (Q)SARs

Results obtained from valid (Q)SAR models may indicate the **presence or absence of a certain dangerous property**.

Results of (Q)SARs may be used instead of testing when the following conditions are met:

1. results are derived from a (Q)SAR model whose **scientific validity** has been established,
2. the substance falls within the **applicability domain** of the (Q)SAR model,
3. results are **adequate** for the purpose of classification and labelling and/or risk assessment, and
4. adequate and reliable **documentation** of the applied method is provided.

Regulatory use of QSARs

1. Results are derived from a (Q)SAR model whose **scientific validity** has been established

According to the **OECD Principles**, a scientifically valid model fulfils the following requirements:

1. It has a defined endpoint.
2. It is described with an unambiguous algorithm.
3. It has a defined domain of applicability.
4. It is described with sufficient statistical characteristics.
5. It has a mechanistic interpretation, if possible.

Note: There will be no formal adoption process for (Q)SARs but the acceptance will be decided on a case-by-case basis.

Regulatory use of QSARs

2. The substance falls within the **applicability domain** of the (Q)SAR model

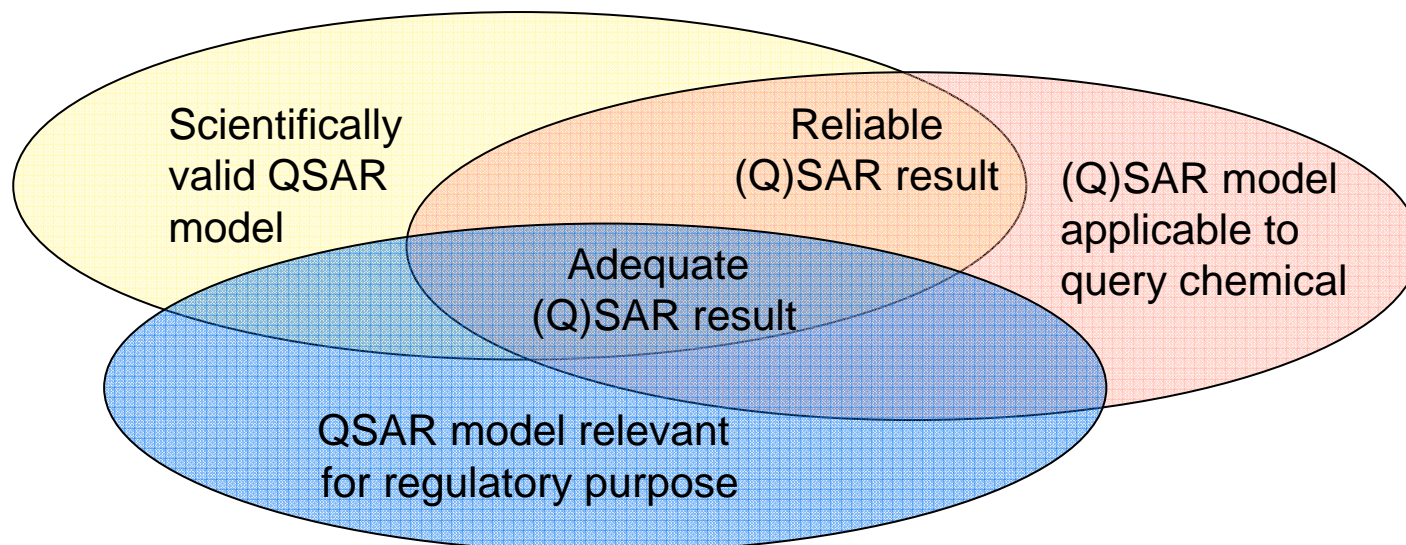
Consider:

- Chemical domain
 - structural (functional groups and their arrangement)
 - physicochemical (range and coverage)
- Biological/toxicological domain (mechanistic domain)
 - same mode of action
 - same range of activity
- Metabolic domain
 - transformation or metabolism

Regulatory use of QSARs

3. Results are **adequate** for the purpose of classification and labelling and/or risk assessment.

The **adequacy** of a (Q)SAR prediction for regulatory purposes is related to the model **validity and applicability** to a given chemical, as well as to the model relevance for a regulatory purpose. The validity and applicability together determine the (Q)SAR **reliability**.



Regulatory use of QSARs - Assessment of **adequacy**

In addition to the criteria in Annex XI, the following principles need to be considered:

- Principle of proportionality
 - The relationship between the amount of data needed and the severity of the decision
- Principle of caution
 - The relationship between the amount of information needed and the consequence of the decision based on that information being wrong

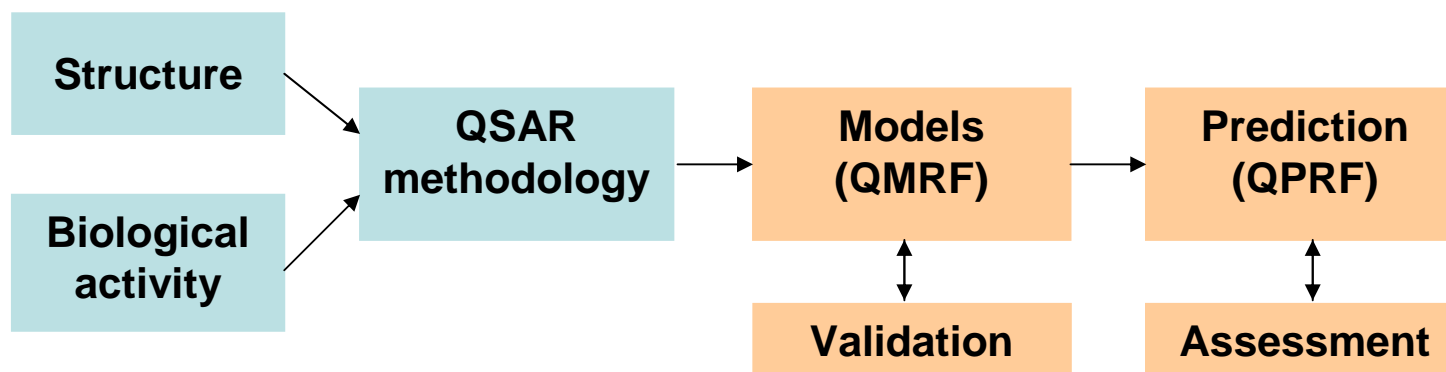
Regulatory use of QSARs

4. Adequate and reliable **documentation** of the applied method is provided

Standardised (Q)SAR Reporting Format

A (Q)SAR Model Reporting Format (QMRF) is a robust summary of a (Q)SAR model, which reports key information on the model according to the OECD validation principles

•A (Q)SAR Prediction Reporting Format (QPRF) is a description and assessment of the prediction made by given model for a given chemical

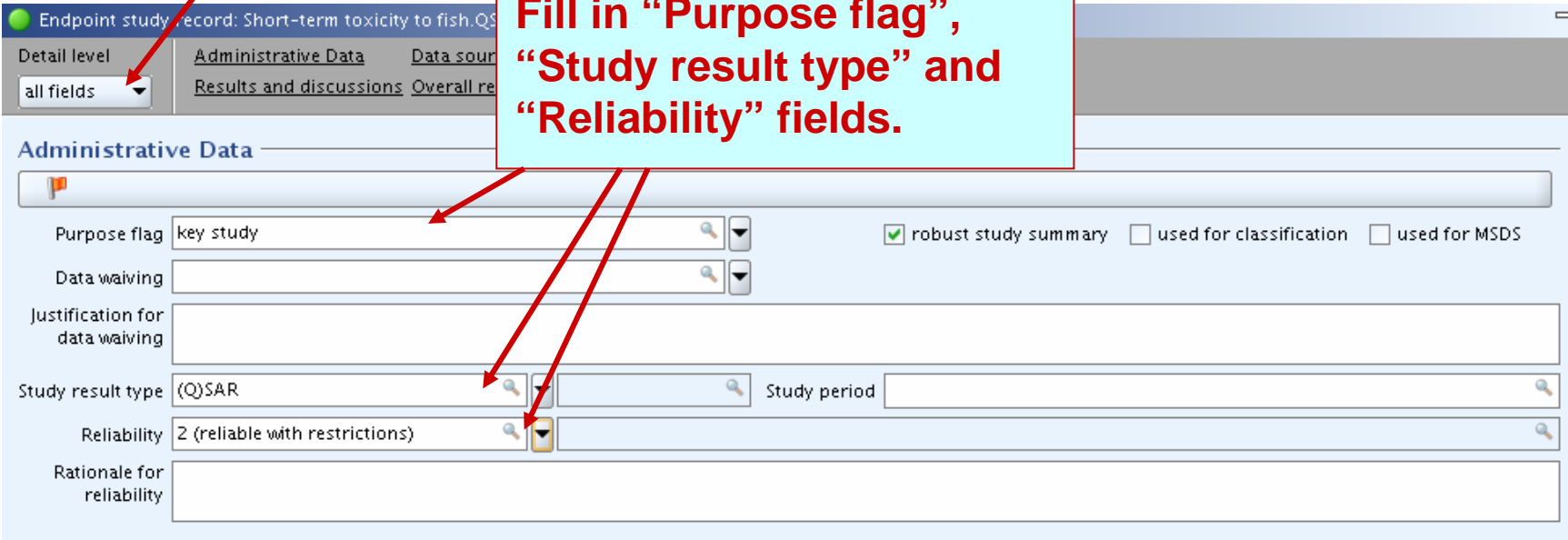


Example how to fill IUCLID 5

Administrative Data

Select "all fields" in the "Detail level" drop down menu.

Fill in "Purpose flag",
"Study result type" and
"Reliability" fields.



The screenshot shows the 'Administrative Data' section of the IUCLID 5 interface. The 'Detail level' dropdown menu is set to 'all fields'. The form contains the following fields:

- Purpose flag:** A text input field containing 'key study'.
- Data waiving:** An empty text input field.
- Justification for data waiving:** An empty text input field.
- Study result type:** A dropdown menu set to '(Q)SAR'.
- Reliability:** A dropdown menu set to '2 (reliable with restrictions)'.
- Rationale for reliability:** An empty text input field.

Additional fields and options include:

- robust study summary:** A checked checkbox.
- used for classification:** An unchecked checkbox.
- used for MSDS:** An unchecked checkbox.
- Study period:** An empty text input field.

Red arrows point from the callout boxes to the 'all fields' dropdown, the 'Purpose flag' field, the 'Study result type' dropdown, and the 'Reliability' dropdown.

Example how to fill IUCLID 5

Data Source

State whether the reference is a publication, from a software, company in-house model etc.

Information who is responsible for the model and the year when it was developed/published. It can also be the company using a software application for the prediction.

Data source

Reference

Reference type	Author	Year	Title	Bibliographic so...	Testing laborat...	Report no.	Owner company	Company study	Report date
publication	Pavan M, Worth AP, Netzeva TI	2005	Preliminary analysis of an aquatic toxicity dataset and assessment of QSAR models for narcosis	JRC Report No. 21749 EN.					

Add... Edit... Delete Move up Move down Select Insert

Data access

data submitter is data owner

“Title” – publication and / or identification of software used including the version.

“Bibliographic source” – where can model be retrieved.

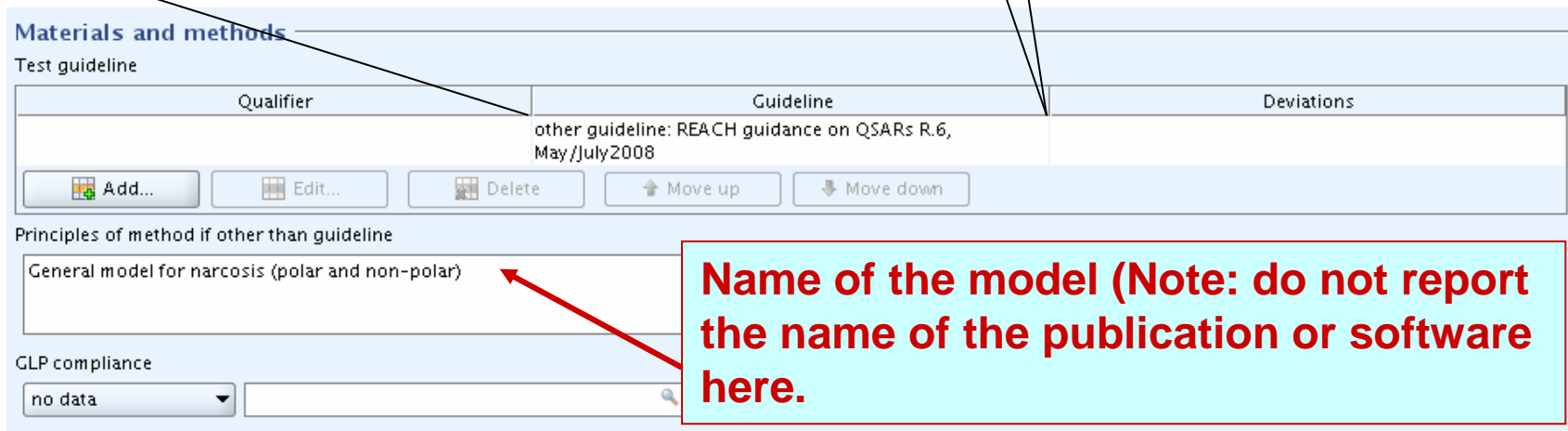
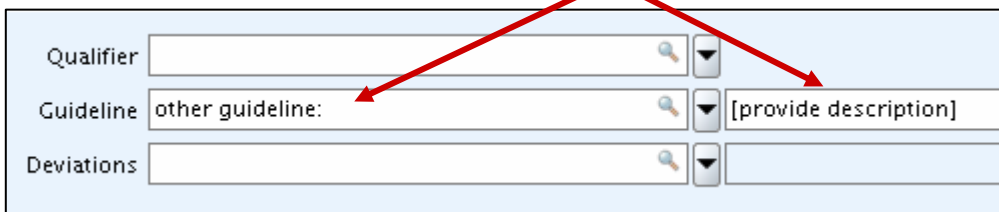
State the status of the data (e.g. data submitter is data owner if the prediction was done in house or contracted out).

Example how to fill IUCLID

Materials and methods

Select “other guideline” and provide a description OR provide the information directly in “Principles of methods if other than guideline”.

Note: The guideline used in obtaining the experimental data for the model training set could also be reported here, and also in the QMRF.



Qualifier	Guideline	Deviations
	other guideline: REACH guidance on QSARs R.6, May/July2008	

Principles of method if other than guideline

General model for narcosis (polar and non-polar)

GLP compliance: no data

Name of the model (Note: do not report the name of the publication or software here).

Example how to fill IUCLID 5

Test materials

Select “yes” if the registered substance is the same as the structure which was used for the (Q)SAR.

Select “no” if the (Q)SAR model is applied to individual constituents of multi-constituent substances or UVCBs, or if the identity is different for another reason.

Note: Confidential information can be placed in “Confidential details on test material”.

Include data on the chemical for which the prediction is made. If the chemical is different from the registered substance, the information has to be provided.

Test materials

Test material equivalent to submission substance identity
yes

Test material identity

Identifier	Identity
CAS number	128-37-0
EC name	Phenol, 2,6-bis(1,1-dimethylethyl)-4-methyl-

Add... Edit... Delete Move up Move down

Details on test material

SMILES: Oc(c(cc(c1)C)C(C)(C)C)c1C(C)(C)C
logKowvalue of 5.03 was used for narcosis model.

Include the structural representation (e.g. SMILES notation) and possible descriptor values if used and as used in the prediction.

Example how to fill IUCLID 5

Results and discussions

Please consult the Data Submission Manual 5 for instructions on how to fill the results to pass the Technical Completeness Check.

Results and discussions

Effect concentrations

Duration	Endpoint	Effect conc.	Nominal/Measured	Conc. based on	Basis for effect	Remarks (e.g. 95% CL)
96 h	LC50 log(LC50)	1.5 mg/L				

Add... Edit... Delete Move up

Details on results

Validity of model: 1. Defined Endpoint: Acute toxicity to fish (lethality);
2. Unambiguous algorithm: Linear regression QSAR; $\text{Log LC50} = -0.810 \text{ LogKow} - 1.74$;
3. Applicability domain: applicable to chemicals with logKow values in range from -1.31 to 2.00. The model is based on the rcosis mode of action, and it is recommended only when the precise mechanism (i.e. nonpolar narcosis) is known. The applicability domain includes aliphatic and aromatic hydrocarbons, halogenated aliphatic and aromatic hydrocarbons, anilines and phenoles (only when a presence of an additional substituent on the benzene ring is known).
4. Statistical characteristics: $N = 203 + 13$; and the Coefficient of Determination (R^2) = 0.83.
5. Mechanistic interpretation: related to the partitioning of the substance from water into the organism.
Adequacy of prediction: The substance testA falls within the applicability domain described above. The prediction is considered reliable taking into account that the standard deviation error of prediction of the external test set $\text{SDEP}(\text{ext})$ is 0.607. Considering the SDEP, the predicted value is not below or close to the classification limit of toxicity to aquatic environment.

REMEMBER to report on:

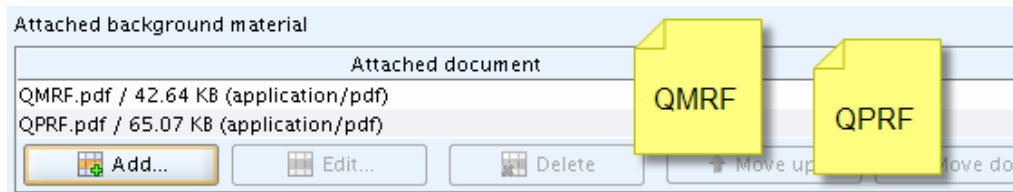
- 1. model scientifically valid**
- 2. within applicability domain**
- 3. Adequacy of results**

Include information on the validity of the model according to OECD principles, the assessment of the reliability and adequacy of the prediction

→for example here or “Any other information on results incl. tables”

Example how to fill IUCLID 5

Overall remarks, attachments



QMRF ([Q]SAR Model Reporting Format) and QPRF ([Q]SAR Predication Reporting Format) can be attached to the endpoint study record to provide further information.

Applicant's summary and conclusion

You can provide here conclusions on the adequacy assessment for a regulatory purpose (risk assessment, classification & labelling, PBT analysis) and other conclusions based on the prediction.

Applicant's summary and conclusion

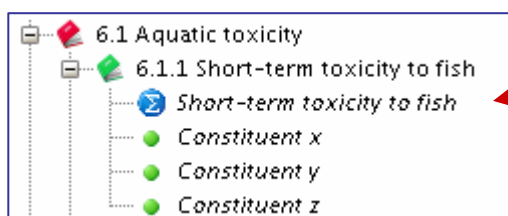
Validity criteria fulfilled

Conclusions

The substance Phenol, 2,6-bis(1,1-dimethyl)-4-methyl- was predicted to have log(LC50) of 1.5mg/L in fathead minnow after 96h exposure. The resu
The prediction should be used for classification and risk assessment.

Example how to fill IUCLID

Endpoint summary



If necessary, use the Endpoint summary to conclude on the prediction for the substance which you want to register (the substance as reported in Section 1.1 of IUCLUD 5).

Observations from registration dossiers

- Insufficient documentation why adaptation of standard testing regime can be justified
- Reporting does often not address applicability domain and whether the result is adequate for risk assessment and/or classification and labelling
- Model reporting is lacking or used model is different to the one reported
- Substance is outside applicability domain
- QSAR is used only for one constituent of a substance
- Reliability score 1 used; common practice would be max. score 2
- Using QSAR as a supporting study without a key study

Key messages

- Results of (Q)SARs may be used instead of testing when
 - (Q)SAR model is **valid**,
 - the chemical of interest falls within the **applicability domain**,
 - **results are adequate** for the purpose of C&L and/or risk assessment, and
 - adequate and reliable **documentation** of the applied method is provided.
- Results of (Q)SARs may also be used in the ITS approach and to support similarity justification of a chemical category
- In cases where there is uncertainty related to one or more information elements, (Q)SAR results may still be used in the context of a **Weight of Evidence** approach

Useful links

- ECHA: Guidance on information requirements and chemical safety assessment: [R6: QSARs and grouping of chemicals](#)
- OECD: Quantitative Structure-Activity Relationships [(Q)SARs] Project
<http://www.oecd.org/env/existingchemicals/qsar>
- DG JRC - Computational Toxicology: Reporting QMRFs
<http://ecb.jrc.ec.europa.eu/qsar/>