ECHA
EUROPEAN CHEMICALS AGENCY

How to apply ECHA's practical guide 'How to use and report (Q)SARs' for the assessment of substances under BPR

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How to apply ECHA's practical guide 'How to use and report (Q)SARs' for the assessment of substances under BPR

This document aims at explaining to applicants and to authorities the applicability of the QSAR Practical Guide to substances that are evaluated under the BPR. The document is complementary to the QSAR Practical Guide and the reader is expected to consult both documents.

Background

The BPR foresees in Annex IV that the standard testing regime can be adapted by the use of non-testing methods, such as (quantitative) structure-activity relationships [(Q)SARs], if certain conditions are fulfilled. Currently, ECHA's practical guide '*How to use and report (Q)SARs'* [1] [QSAR Practical Guide] only refers to REACH. On request of a Member State, ECHA investigated the applicability of the QSAR Practical Guide and ECHA's *Guidance On Information Requirements And Chemical Safety Assessment*[2] [R.6; see also references in BPR guidance Vol IV Part A and Part B+C[3]]. ECHA's (Q)SAR experts confirmed that the QSAR Practical Guide is in principle applicable to hazard assessment of biocidal active substances.

The BPC ENV working group agreed:

a) to apply the QSAR Practical Guide, developed under REACH, for the use and reporting of (Q)SAR predictions in biocide assessment, and
b) to report the data in Doc IIIA format for Review Programme cases, and
c) to report the data in IUCLID format otherwise.

The validation of the reliability for prediction on the qualitative or quantitative structure-activity relationships [(Q)SARs] is independent on the prospective use. Consequently, procedures for using (Q)SAR as an alternative method to testing are very close under REACH and BPR. Therefore, the Practical Guide and ECHA's *Guidance On Information Requirements And Chemical Safety Assessment* [R.6] is in principle applicable to hazard assessment of biocidal active substances. BPR guidance Vol IV Part A and Part B+C refers to R.6.

BPR Annex IV on the general rules for the adaptation of the data requirements states that […]
Results obtained from valid qualitative or quantitative structure-activity relationship models ((Q)SARs) may indicate the presence, but not the absence of a given dangerous property. Results of (Q)SARs may be used instead of testing when the following conditions are met:
— the results are derived from a (Q)SAR model whose scientific validity has been established,
— the substance falls within the applicability domain of the (Q)SAR model,
— the results are adequate for the purpose of classification and labelling and risk assessment, and
— adequate and reliable documentation of the applied method is provided.

The Agency shall, in collaboration with the Commission, Member States and interested parties, develop and provide guidance on the use of (Q)SARs.[…]

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[1] Practical Guide – How to use and report (Q)SARs, European Chemicals Agency, 2016, http://echa.europa.eu/documents/10162/13655/pg_report_qsars_en.pdf
[2] REACH Guidance On Information Requirements And Chemical Safety Assessment, https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[3] BPR guidance https://echa.europa.eu/guidance-documents/guidance-on-biocides-legislation

Comparison of BPR and REACH data requirements and guidance

Generally, if you intend to use the QSAR Practical Guide for BPR purposes, note that references made to REACH have comparable counterparts under BPR. This is applicable to the respective annexes, REACH-specific terminology and, partly, guidance documents. Below is a generic description of relevant parallels between REACH and BPR, followed by a full correspondence of texts provided in Annex 1.

Procedures and methods to fulfil the information requirements are similar for REACH Registrants, who submit a registration dossier, and for applicants under the BPR, who may submit dossiers for the active substances approval, the assessment of technical equivalence, and for biocidal product authorisation.

While REACH has always required data submission in the IUCLID format, the BPR only prescribes IUCLID as format for submissions from 1 September 2013 onwards, the date of BPR entry into operation. Document IIIA is the corresponding format for reporting QSARs for the dossiers submitted before 1 September 2013.

REACH Annex XI, which sets out the general rules for adaptation of the standard testing regime (waiving), is comparable to BPR Annex VI on the common principles for adaptation of data requirements.

Under REACH, data requirements for physicochemical properties, environmental fate, ecotoxicological and toxicological information are listed in REACH Annexes VII-X, and the corresponding guidance is called R.2 – R.7[2]. In comparison, information requirements for biocidal active substances and products are listed in BPR Annexes II and III and ECHA's corresponding guidance can be found in guidance documents BPR guidance Volume I-IV Part A Information Requirements[3]. The following BPR endpoints are not standard requirements under REACH:

Human Health
Toxicokinetics and metabolism studies in mammals
Physico-chemical properties

- thermal stability, identity of breakdown products
- Henry's law constant for solids and liquids if it can be calculated
- solubility in organic solvents

How to report (Q)SARs

For dossiers submitted before 01.09.2013, the applicant can report the (Q)SAR estimations either in IUCLID format or in Doc III format. For dossiers submitted since 01.09.2013, IUCLID is the prescribed data format for applicants. More information can be found in the QSAR Practical Guide[1], chapter *3.4 How to report a (Q)SAR prediction in IUCLID.* In case the evaluating MSCA wishes to report QSAR predictions, the Doc IIIA template is applicable. Annex 2 contains the Doc IIIA template.

Annex 1: REACH - BPR correspondence

The following tables list references to REACH that can be found in the QSAR Practical Guide, complemented by the respective amendment towards applicability to BPR. Please apply the modified text instead of the original wording when consulting the QSAR Practical Guide for BPR purposes.

CHAPTER 1. INTRODUCTION

CHAPTER 1. INTRODUCTION	
Original Text (QSAR Practical Guide)	**Text modified for BPR purpose**
REACH foresees in Annex XI *that the standard testing regime can be adapted by the use of non-test methods, such as (quantitative) structure-activity relationships [(Q)SARs], if certain conditions are fulfilled.*	***The BPR foresees in Annex IV*** *that the standard testing regime can be adapted by the use of non-test methods, such as (quantitative) structure-activity relationships [(Q)SARs], if certain conditions are fulfilled.*
It provides an overview of important aspects to consider when predicting properties of substances using (Q)SAR models as defined in the ***REACH*** *Regulation – aspects which ECHA also takes into account to evaluate (Q)SAR results.*	*It provides an overview of important aspects to consider when predicting properties of substances using (Q)SAR models as defined in the* ***BPR*** *– aspects which ECHA also takes into account to evaluate (Q)SAR results.*
Section 3 explains the conditions that need to be fulfilled to use (Q)SAR predictions under ***REACH****.* ***Registrants*** *are advised to explicitly include these considerations in their* ***registration*** *dossiers.*	*Section 3 explains the conditions that need to be fulfilled to use (Q)SAR predictions under* ***BPR****.* ***Applicants*** *are advised to explicitly include these considerations in their* ***dossiers for active substances or biocidal products****.*
Appendix 1 gives examples (a non-exhaustive list) of (Q)SAR programs available for ***each*** *of the* ***REACH*** *required endpoints.*	*Appendix 1 gives examples (a non-exhaustive list) of (Q)SAR programs available for* ***a number*** *of* ***BPR*** *required endpoints.*

CHAPTER 2. HOW TO GET STARTED WITH (Q)SARS

CHAPTER 2.2 SUBSTANCE CHARACTERISATION	
Original Text (QSAR Practical Guide)	**Text modified for BPR purpose**
*The chemical structure needs to be well defined, following the Guidance on identification and naming of substances under **REACH**.*	*The chemical structure needs to be well defined, following the Guidance on identification and naming of substances under **REACH & CLP**.*
CHAPTER 2.3 EXPERIMENTAL RESULTS	
Original Text (QSAR Practical Guide)	**Text modified for BPR purpose**
*[…] before using (Q)SAR models to predict a specific property of a substance, a critical first step is to assemble all of the available information on the substance. There are many information sources available for this purpose and which are further explained in the **Guidance on information requirements and chemical safety assessment - Chapter R.3: Information gathering***	*[…] before using (Q)SAR models to predict a specific property of a substance, a critical first step is to assemble all of the available information on the substance. **Please consult the Guidance on the BPR: Volume I-V (Part A).***
CHAPTER 2.4 CONDITIONS FOR USING (Q)SAR RESULTS	
Original Text (QSAR Practical Guide)	**Text modified for BPR purpose**
*Results of (Q)SARs may be used instead of testing when the conditions set in **REACH Annex XI (1.3) are met:*** ***(i) a (Q)SAR model where the scientific validity has been established should be used;*** ***(ii) the substance should fall within the applicability domain of the (Q)SAR model;*** ***(iii) the prediction should be fit for the regulatory purpose; and*** ***(iv) the information should be well documented.***	*Results of (Q)SARs may be used instead of testing when the conditions set in **BPR Annex IV (1.3) are met:*** ***— the results are derived from a (Q)SAR model whose scientific validity has been established,*** ***— the substance falls within the applicability domain of the (Q)SAR model,*** ***— the results are adequate for the purpose of classification and labelling and risk assessment, and*** ***— adequate and reliable documentation of the applied method is provided.***
CHAPTER 2.5 STRATEGY FOR USING (Q)SAR RESULTS	
Original Text (QSAR Practical Guide)	**Text modified for BPR purpose**
When using (Q)SARs, it is recommended to run all (Q)SAR models available to the **registrant** for the endpoint to be fulfilled […].	When using (Q)SARs, it is recommended to run all (Q)SAR models available to the **applicant** for the endpoint to be fulfilled […].
*Predictions that fulfil only some conditions specified in **REACH Annex XI (1.3**) should be disregarded or the reason for providing these*	*Predictions that fulfil only some conditions specified in **BPR Annex IV (1.3)** should be disregarded or*

predictions should be explained if it is considered that there are some benefits to providing these predictions. If the remaining (valid and adequate) predictions show small quantitative differences, the most conservative result should be chosen for further consideration. If those remaining predictions show significant quantitative differences, the ***registrant*** *must decide if these differences could affect the risk assessment (for demonstrating safe use) and/or classification and labelling.*	*the reason for providing these predictions should be explained if it is considered that there are some benefits to providing these predictions. If the remaining (valid and adequate) predictions show small quantitative differences, the most conservative result should be chosen for further consideration. If those remaining predictions show significant quantitative differences, the* ***applicant*** *must decide if these differences could affect the risk assessment (for demonstrating safe use) and/or classification and labelling.*

CHAPTER 3. HOW TO CHECK A QSAR PREDICTION

CHAPTER 3.1 IS THE (Q)SAR MODEL VALID?	
Original Text (QSAR Practical Guide)	**Text Modified for BPR Purpose**
As indicated in **REACH Annex XI (1.3**), the validity of the (Q)SAR model is the first condition to be fulfilled to use a (Q)SAR result.	*As indicated in **BPR Annex IV (1.3)**, the validity of the (Q)SAR model is the first condition to be fulfilled to use a (Q)SAR result.*
*A defined endpoint: the model must predict the same endpoint that would be measured to fulfil the requirements listed in **REACH Annexes VII to X**.*	*A defined endpoint: the model must predict the same endpoint that would be measured to fulfil the requirements listed in **BPR Annexes II and III**.*[4]
CHAPTER 3.3 IS THE PREDICTION ADEQUATE FOR THE PURPOSE OF C&L AND/OR RISK ASSESSMENT?	
Original Text (QSAR Practical Guide)	**Text Modified for BPR Purpose**
*(Q)SAR models predicting the biodegradation half-life of a compound cannot be used as a standalone replacement of a simulation test as they do not cover the need to identify the degradation products (**REACH Annex IX, 9.2.3 requirements**).*	*(Q)SAR models predicting the biodegradation half-life of a compound cannot be used as a standalone replacement of a simulation test as they do not cover the need to identify the degradation products (**BPR Annex II**).*
CHAPTER 3.4 HOW TO REPORT A (Q)SAR PREDICTION IN IUCLID	
Original Text (QSAR Practical Guide)	**Text Modified for BPR Purpose**
*The QMRF is normally provided by the model developer while the QPRF is prediction-specific and should be prepared by the **registrant** using the information in the software report and manual.*	*The QMRF is normally provided by the model developer while the QPRF is prediction-specific and should be prepared by the **applicant** using the information in the software report and manual.*

[4] In cases where the product is identical to the active substance.

CHAPTER 4. PRACTICAL EXAMPLES

CHAPTER 4. PRACTICAL EXAMPLES	
Original Text (QSAR Practical Guide)	**Text Modified for BPR Purpose**
*[…], only one endpoint per program (corresponding to one **REACH requirement**) has been used for each example.*	*[…], only one endpoint per program (corresponding to one **BPR requirement**) has been used for each example.*
*Those endpoints have been selected as representatives of **REACH Annexes VII or VIII** requirements for physicochemical properties, environmental fate, ecotoxicological and toxicological information.*	*Those endpoints have been selected as representatives of **BPR Annex II** requirements for physicochemical properties, environmental fate, ecotoxicological and toxicological information.*
CHAPTER 4.1 LOG KOW (EPI SUITE)	
Original Text (QSAR Practical Guide)	**Text Modified for BPR Purpose**
*[…] Partition coefficient n-octanol/water is a **REACH requirement for all substances produced or imported above one tonne/year (REACH Annex VII).***	*[…] Partition coefficient n-octanol/water is a **BPR requirement for actives substances (BPR Annex II, 3.1.10).***
CHAPTER 4.2 READY BIODEGRADABILITY (VEGA)	
Original Text (QSAR Practical Guide)	**Text Modified for BPR Purpose**
*[…] Ready biodegradability is a **REACH requirement for all substances produced or imported above one tonne/year (REACH Annex VII).***	*[…] Ready biodegradability is a **BPR requirement for actives substances (BPR Annex II, 10.1.1.2).***
CHAPTER 4.3 SHORT-TERM TOXICITY TO FISH (ECOSAR)	
Original Text (QSAR Practical Guide)	**Text Modified for BPR Purpose**
*[…] Short-term toxicity testing on fish is a **REACH requirement for all substances produced or imported above 10 tonnes/year (REACH Annex VIII).***	*[…] Short-term toxicity testing on fish is a **BPR requirement for actives substances (BPR Annex II, 9.1.1).***
CHAPTER 4.4 ACUTE TOXICITY TO RATS (T.E.S.T.)	
Original Text (QSAR Practical Guide)	**Text Modified for BPR Purpose**
*[…] Acute toxicity by oral route is a **REACH requirement for all substances produced or imported above one tonne/year (REACH Annex VII).***	*[…] Acute toxicity by oral route is a **BPR requirement for actives substances (BPR Annex II, 8.7.1).***

APPENDIX 1. QSAR MODELS RELATED TO REACH ENDPOINTS

APPENDIX 1. QSAR MODELS RELATED TO REACH ENDPOINTS	
Original Text (QSAR Practical Guide)	**Text Modified for BPR Purpose**
*The QSAR computer programs listed in this appendix are widely known and are given to inform **REACH registrants** on the QSAR models availability for **each** of the **REACH** endpoints. […] So far, most of the toxicological and ecotoxicological information required under **REACH** can rarely be fulfilled with QSAR predictions alone.*	*The QSAR computer programs listed in this appendix are widely known and are given to inform **BPR applicants** on the QSAR models availability for **a number** of the **BPR** endpoints. […] So far, most of the toxicological and ecotoxicological information required under **BPR** can rarely be fulfilled with QSAR predictions alone.*
APPENDIX 1 E. INFORMATION ON THE DANISH (Q)SAR DATABASE	
Original Text (QSAR Practical Guide)	**Text Modified for BPR Purpose**
*A **REACH registrant** who would like to report in its IUCLID registration dossier a prediction coming from the Danish (Q)SAR database should also check that the (Q)SAR model is valid […]*	*A **BPR applicant** who would like to report in its IUCLID registration dossier a prediction coming from the Danish (Q)SAR database should also check that the (Q)SAR model is valid […]*

Annex 2: (Q)SAR reporting template CAR Document IIIA

In case you don't use IUCLID for reporting the (Q)SAR estimation, complete the template below, which is based on the harmonised IUCLID template. Applicants should provide the filled template (attached below) as a Doc IIIA document to the CAR. Please refer for further instructions and examples to QSAR Practical Guide sections 3.4 *How to report a (Q)SAR prediction in IUCLID* & 4. *Practical examples*.

Administrative data

Endpoint

Adequacy of study

	key study
	supporting study
	weight of evidence
	disregarded due to major methodological deficiencies
	other information

Reliability

	1 (reliable without restriction)
	2 (reliable with restrictions)
	3 (not reliable)
	4 (not assignable)
	other

Rationale for reliability incl. deficiencies

	results derived from a valid (Q)SAR model and falling into its applicability domain, with adequate and reliable documentation / justification (Reliability 1 or 2)
	results derived from a valid (Q)SAR model and falling into its applicability domain, With limited documentation / justification (Reliability 2, 3 or 4)
	results derived from a valid (Q)SAR model, but not (completely) falling into its applicability domain, With adequate and reliable documentation / justification (Reliability 2 or 3)
	results derived from a (Q)SAR model, with limited documentation / justification, but validity of model and reliability of prediction considered adequate based on a generally acknowledged source (reliability 2 or 3)
	results derived from a valid (Q)SAR model, but not (completely) falling into its applicably domain, and documentation / justification is limited (Reliability 3 or 4)
	results derived from a (Q)SAR model, with limited documentation / justification (Reliability 4)
	other:

Justification for type of information

Either populate the fields below or attach files for QMRF (validity of the model) and QRPF (applicability of the model to a specific substance).

1 Software

2 Model (incl. version number)

3 Smiles or other identifiers as input for the model

4 Scientific validity of the (Q)SAR model
(Explain how the model fulfils the OECD principles for (Q)SAR model validation. Consider attaching the QMRF or providing a link)
- Defined endpoint:
- Unambiguous algorithm
- Defined domain of applicability
- Appropriate measures of goodness-of-fit and robustness and predictivity
- Mechanistic interpretation

5 Applicability domain
(Explain how the substance falls within the applicability domain of the model)
- Descriptor domain
- Structural and mechanistic domains:
- Similarity With analogues in the training set
- Other considerations (as appropriate)

6 Adequacy of the result
(Explain how the prediction fits the purpose of classification and labelling and/or risk assessment)

Data source

Reference

Title

Author

Reference type

Year

Bibliographic source

Data access

	data submitter is data owner
	data submitter has Letter of Access
	data no longer protected
	data published
	not applicable
	data submitter has permission to refer
	other

Data protection claimed

	yes
	yes, but willing to share
	yes, but not willing to share

Materials and methods

Principles of method

Test materials

Test material information

Specific details on test material used for the study

Results and discussion

(Q)SAR predicted results

Any other information on results including tables

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