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## **REACH Compliance Project:**

### **Recommendations for registrants to improve data quality in registration dossiers for chemicals ≥ 1000 tpa**

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## List of Abbreviations

<b>CAS</b>	Chemical Abstracts Service
<b>DNEL</b>	Derived No-Effect Level
<b>EC</b>	European Community
<b>ECHA</b>	European Chemicals Agency
<b>EU</b>	European Union
<b>IUCLID</b>	International Uniform Chemical Information Database
<b>IUPAC</b>	International Union of Pure and Applied Chemistry
<b>NOAEL</b>	No Observed Adverse Effect Level
<b>PBT/vPvB</b>	Persistent, bioaccumulative, toxic/very persistent, very bioaccumulative
<b>REACH</b>	Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals
<b>PNEC</b>	Predicted No-Effect Concentration
<b>(Q)SAR</b>	(Quantitative) Structure-Activity Relationship
<b>SIEF</b>	Substance Information Exchange Forum
<b>SIP</b>	Substance Identity Profile
<b>SVHC</b>	Substance of very high concern
<b>TMI</b>	Test Material Information
<b>UVCB</b>	Substances of Unknown or Variable composition, Complex reaction products or Biological materials

# 1 Introduction

## Recommendations to Registrants

The presented recommendations are intended to support registrants to improve the quality of their registration dossiers. The present general and endpoint specific recommendations are addressing registrants of phase-in substances manufactured or imported in quantities of 1000 tonnes per year or more. Based on the outcome of a project on data availability in REACH registrations it is recommended that registrants scrutinise whether an update of their registration dossiers is necessary to meet their following legal obligations

- ▶ fulfilling the information requirements either with respect to the standard testing regime or a justification based on data waiving and/or surrogate data;
- ▶ to update their registration dossiers whenever new information became available, e.g. updated guidance documents or new information on substances;
- ▶ to verify that all information was properly migrated from IUCLID 5 into IUCLID 6.

Registrants should be aware that registration dossiers are selected for Compliance Checks by the European Chemicals Agency (ECHA) either randomly or concern-driven through IT- or manual screening. Therefore, proactive updates of registration dossiers are recommended.

In the European Union (EU), chemicals manufactured or imported in quantities of one tonne per year (tpa) or more have to be registered with the European Chemicals Agency (ECHA). The respective manufacturers and importers must provide sufficient information to demonstrate the safe use of their chemicals. The standard information requirements depend on the manufactured or imported quantity of the substance. These are specified together with the rules for their waiving or adaptation in Annexes VII to XI of the Regulation (EC) No. 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (in short REACH) (EC, 2006). Furthermore, a Chemical Safety Assessment should be included in the Chemical Safety Report required for substances in quantities of 10 tpa or more. If the substance has particular hazardous and/or PBT (persistent, bioaccumulative, toxic) and/or vPvB (very persistent, very bioaccumulative) properties, an exposure assessment and a risk assessment should be carried out (REACH Article 14(4)). The responsibility of providing data in compliance with the information requirements lies with the registrants.

The data availability in REACH registrations was investigated within a project funded by the German Federal Ministry for the Environment, Nature Conservation, Building and Nuclear Safety. In the REACH Compliance Project<sup>1</sup>, decision trees were used to screen the data availability in registration dossiers for selected environmental and human health endpoints<sup>2</sup>. 1814 lead and individual registration dossiers of phase-in substances produced or imported in quantities of  $\geq 1000$  tpa and submitted to ECHA until March 2014 were evaluated. One main finding of the project was that a high percentage of the dossiers used data waiving or adaptations to fulfil standard information requirements (Springer et al., 2015). Subsequently, the fulfilment of formal requirements for data waiving and adaptations was evaluated (Oertel et al., 2017). In order to do so, the justifications for data waiving and/or surrogate data were analysed and their accordance to the respective REACH Annexes was checked.

<sup>1</sup> <https://www.umweltbundesamt.de/publikationen/reach-compliance-data-availability-of-reach>

<sup>2</sup> Within the project the following endpoints were assessed: developmental and reproductive toxicity, mutagenicity, repeated dose toxicity, biotic and abiotic degradation, bioaccumulation, ecotoxicity and environmental exposure assessment.

Further in-depth analysis was performed on those datasets of the investigated endpoints that could not be definitively concluded on the basis of formal criteria and on specific case groups which have not been taken into account previously, e.g. weight of evidence approaches.

Another task within the project was to assess substance sameness of the registered substances within joint submissions from lead and member dossiers. Furthermore, the substance identity of the registered substance and the test material used for the standard testing regime was compared in lead and individual registration dossiers to conclude on its identity.

The overall project results and additional observations from the step-wise evaluation of registration dossiers were used to deduce the general and endpoint specific recommendations in the following chapters. The presented recommendations are intended to support registrants to improve the quality of their registration dossiers.

Each recommendation consists of a brief description of the problem observed in registrations, the recommendation to registrants and the respective guidance documents (Figure 1). The relevant documents on regulation and guidance are referenced specifically for each identified problem.

The relevance and frequency of observed problems was considered as far as possible and, if reasonable, minor problems have been addressed collectively by a general recommendation.

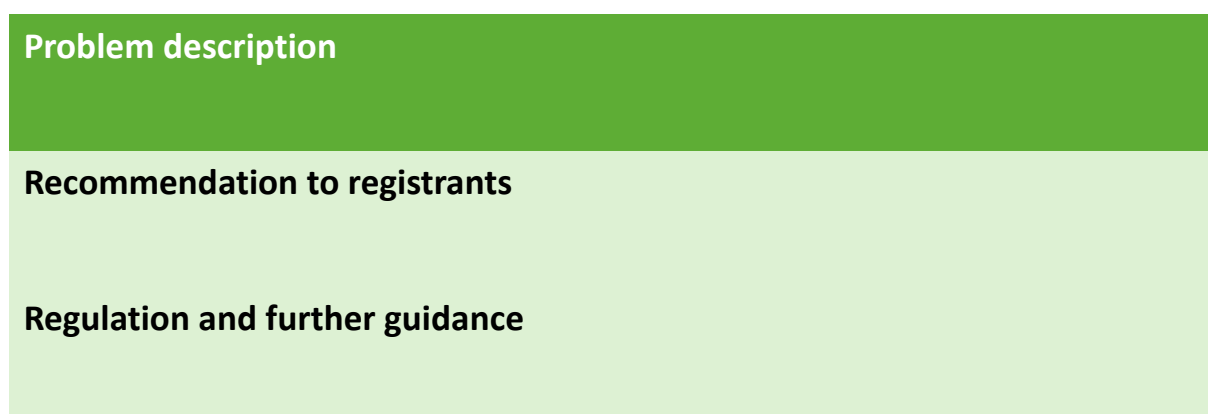
Many problems identified within the REACH Compliance Projects have been also highlighted in ECHA's Annual Evaluation progress reports over the years (ECHA, 2015; ECHA, 2016b; ECHA, 2017e). However, it should be noted that in this project all substances registered above 1000 tpa were assessed with a standard method, while ECHA's annual feedback is related to issues identified during the Compliance Checks performed under REACH.

ECHA is continuously publishing new information and tools to support registrants updating their registration dossiers. The recent implementation of the International Uniform Chemical Information Database (IUCLID) version 6 in June 2016 and other current developments were considered as far as possible in the outlined recommendations.

As this document is not continuously updated but static (as of November 2017) it is possible that since publication some of the identified problems may have already been fixed by registrants. However, it is noted that the majority (64 %) of registration dossiers submitted since 2008 have never been updated (ECHA, 2016l).

While IUCLID 6 was not yet available for the registration dossiers assessed within this project, the new version of IUCLID (version 6)/REACH-IT, released in June 2016, supports registrants in improving the quality of their registration dossiers. The recommendations may also be useful for registrants for verifying whether all information provided in IUCLID 5 was properly migrated to IUCLID 6.

Figure 1: Scheme of the presented recommendations.



## 2 General recommendations

### 2.1 Substance identity and test material identity

The parameters on substance identification are given in REACH Annex VI section 2: For the unequivocal identification of each substance the required information “shall be sufficient to enable each substance to be identified” (EC, 2006). The information should include (REACH Annex VI section 2; (EC, 2006)):

- ▶ name or other identifier of each substance,
- ▶ information related to molecular and structural formula of each substance, and
- ▶ composition of each substance.

If it is not technically feasible or if it does not seem scientifically necessary to provide information about the aspects mentioned above, the reasons should be explained in a comprehensible manner (EC, 2006).

The criteria for substance identification and naming are different depending on substance type. Information is provided in the “Guidance for identification and naming of substances under REACH and CLP –Version 2.1 – May 2017” (ECHA, 2017g). For many substances a straightforward identification may be possible, whereas for some substances other or additional information on the substance identification is required. Substances can be divided into two main groups (ECHA, 2017g):

- ▶ “Well defined substances’: Substances with a defined qualitative and quantitative composition that can be sufficiently identified based on the identification parameters of REACH Annex VI section 2.”
- ▶ “UVCB substances’: Substances of Unknown or Variable composition, Complex reaction products or Biological materials. These substances cannot be sufficiently identified by the above parameters.”

“Well defined substances” include mono- and multi-constituent substances since they are defined by their composition. A mono-constituent substance is a substance in which its “main constituent is present to at least 80 % (w/w)”, whereas within a multi-constituent substance “more than one main constituent is present in a concentration  $\geq 10$  % and  $< 80$  % (w/w)” (ECHA, 2017g). In the REACH Compliance Project registered mono-constituent substances showed a high concordance of substance sameness in lead and member dossiers of joint submissions. The analysis of substance sameness of multi-constituent substances revealed considerable inconsistencies, although this substance type should also be clearly defined (Recommendation 2.1-1 and 2.1-2).

For UVCB substances a comparison of the substance identity between lead and member dossiers was often difficult. The information was frequently not available in IUCLID sections 1.1 and 1.2 or not comparable between lead and member dossiers. Therefore, for the majority of UVCB joint submissions a conclusion on sameness could not be drawn.

The substance identity profile (SIP) in the new version of IUCLID (version 6)/REACH-IT should be used to define the agreed substance identity of a joint submission. It addresses boundary compositions for defining substance sameness (ECHA, 2016m). A justification is required if a mono-constituent substance deviates from the 80 %-rule and a multi-constituent from the 80/10 %-rule (ECHA, 2017g).

#### Recommendation 2.1-1

**The substance sameness in lead and member dossiers is given for the majority of joint submissions for mono-constituent substances, but only for a lower proportion of multi-constituent substances. For the majority of UVCB joint submissions the sameness could not be assessed.**

- ▶ Each substance should be clearly identifiable by information required in IUCLID section 1.1 and 1.2. Each registrant should verify that the substance is part of the correct joint submission and that all information needed for substance identification is given in the registration dossier.
- ▶ Concerning well-defined substances the 80 %- and 80/10 %-rule should be followed. Deviations from these rules should be justified in a scientifically substantiated manner. The justification should be provided in IUCLID 6 section 1.2 under 'Justifications for deviations' for each composition. The composition of the substance including its impurities should be clearly declared.
- ▶ The source(s) used and the manufacturing process, including definite process elements, of UVCB substances should be described in IUCLID 6 section 1.2, in the field 'Description of composition'. The typical concentrations and concentration ranges of the known constituents should be given. Unknown constituents should be described as far as possible.

##### **ECHA documents**

Guidance for identification and naming of substances under REACH and CLP – Version 2.1 – May 2017 (ECHA, 2017g)

Information on manual verification at completeness check – 2017 (ECHA, 2017h)

Manual: How to prepare registration and PPORD dossiers – Version 4.0 – May 2017 (ECHA, 2017i)

Q&As ID: 0712 (ECHA, 2016c), Q&As ID: 1196 (ECHA, 2016h), Q&As ID: 1197 (ECHA, 2016g),

Q&As ID: 1199 (ECHA, 2017a), Q&As ID: 1200 (ECHA, 2016f), Q&As ID: 1319 (ECHA, 2017f)

#### Recommendation 2.1-2

**For UVCB substances a comparison of substance identity between the lead and member dossiers is difficult because information is frequently not available or not comparable within joint submissions.**

- ▶ Information regarding the boundary composition for constituents needs to be provided to assure justified data sharing within a Substance Information Exchange Forum (SIEF).
- ▶ Uniform descriptions of other substance-specific identifiers, such as the process or the source, should be made available for a SIEF as well as statements in the member dossiers that address the comparability with the lead dossier (UVCB substances).

##### **ECHA documents**

Guidance for identification and naming of substances under REACH and CLP – Version 2.1 – May 2017 (ECHA, 2017g)

Q&As ID: 1196 (ECHA, 2016h), Q&As ID: 1199 (ECHA, 2017a), Q&As ID: 1200 (ECHA, 2016f),

Q&As ID: 1447 (ECHA, 2017n), Q&As ID: 1450 (ECHA, 2017j)

Transition to the new IT tools – how to prepare – March 2016 (ECHA, 2016m)

For each endpoint all studies marked as key studies, excluding grouping/read-across approaches, were assessed in the REACH Compliance Project (Recommendation 2.1-3 and 2.1-4). The sameness of the registered substance with the test material used in the key studies was checked by using specific indicators, i.e. substance name and European Community (EC) number or Chemical Abstracts Service (CAS) number.

The new version of IUCLID (version 6)/REACH-IT includes improved reporting for the test material. The test material information (TMI) is now summarised in one main document (TMI record) and linked to the respective endpoint study record. The qualitative picklist to link the test material with section 1 from previous IUCLID versions was removed. A TMI record includes all information on the test material, e.g. composition and concentration ranges. Since the TMI records are retained in an inventory they can be re-picked in each endpoint study record with the same test material (ECHA, 2016m).

#### Recommendation 2.1-3

##### The identity of the test material used in key studies is not sufficiently defined.

- ▶ The registrant is responsible to ensure that the test materials are consistently reported in the dossier.
- ▶ “The test material should be reported to the level of detail available and relevant” (ECHA, 2017i).
- ▶ ‘Test material identity’ should be specified with unique numerical identifiers (EC number or CAS number and/or IUPAC name). In addition, the purity and impurities should be given in case of defined substances.
- ▶ The composition of a UVCB test material should be described as far as possible.
- ▶ A justification should be provided to demonstrate that the test material used in key studies can be considered consistent with the registered substance (in particular for UVCB substances).
- ▶ The correct migration of the test material information from IUCLID 5 to 6 should be verified by the registrant.

##### ECHA documents

IUCLID 6 webinar – Switching from IUCLID 5.6 to IUCLID 6 (for advanced users) (ECHA, 2016e)  
Manual: How to prepare registration and PPORD dossiers – Version 4.0 – May 2017 (ECHA, 2017i)  
Transition to the new IT tools – how to prepare – March 2016 (ECHA, 2016m)

#### Recommendation 2.1-4

##### The identity of the test material used in key studies is different from that of the registered substance.

- ▶ The compositional information on the test material should be provided within the robust study summary.
- ▶ If the test material used in key studies is different from the registered substance, then
- ▶ a read-across approach should be considered or
- ▶ a justification should be provided that the composition of the test material is relevant to the composition of the registered substance.
- ▶ The application of a read-across approach requires providing adequate test material information.

##### ECHA documents

IUCLID 6 webinar – Switching from IUCLID 5.6 to IUCLID 6 (for advanced users) (ECHA, 2016e)  
Manual: How to prepare registration and PPORD dossiers – Version 4.0 – May 2017 (ECHA, 2017i)  
Transition to the new IT tools – how to prepare – March 2016 (ECHA, 2016m)

## 2.2 General rules of REACH Annex XI

Each lead and individual registration dossier should contain the physico-chemical, toxicological, and ecotoxicological information of the registered substance according to REACH Annexes VII to X and all relevant available information. ECHA addressed the correct presentation of information in IUCLID in its manual “How to prepare registration and PPORD dossiers” (ECHA, 2017i).

Waiving and adaptations of standard information requirements can be applied according to the rules set out in Annexes VII to XI of the REACH Regulation (EC, 2006). REACH Annex XI offers possibilities to adapt or to omit testing due to technical or exposure-based reasons and includes alternatives to animal testing such as weight of evidence, (Q)SAR and grouping of substances and read-across approaches. If the registrant uses an adaptation, e.g. (Q)SAR, an appropriate endpoint study record should be provided for the surrogate data. All available information on the substance should be provided within the endpoint study record by registrants (ECHA, 2016j).

When adapting or omitting the required standard information an unequivocal attribution to one of the rules specified in the REACH Annexes VII to X or XI should be provided (ECHA, 2016j).

### 2.2.1 Weight of evidence approach

The weight of evidence approach consists of the combination of information from different independent sources to fulfil the standard information requirements. This may be necessary if a study shows deficiencies and is as a stand-alone not sufficient to fulfil the information requirements or if several studies provide different or conflicting conclusions. In the latter case, it may be possible to combine the information from the studies to draw conclusions on the respective endpoint and to avoid further testing. The approach should be provided with an adequate documentation and justification (ECHA, 2016j). Therefore, at least two endpoint study records should be submitted for the same endpoint (ECHA, 2017i).

The “Practical guide: How to use alternatives to animal testing to fulfil your information requirements for REACH registration” offers a detailed description of possible approaches within REACH registrations (ECHA, 2016j). Also the Endpoint specific guidance documents of ECHA encourage weight evidence approaches (ECHA, 2017b; ECHA, 2017c; ECHA, 2017d).

The available evidence depends on reliability and relevance of the included data. The robustness and consistency of the different data sources should be taken into account to support the justification (ECHA, 2016j).

Within the REACH Compliance Project, weight of evidence approaches were evaluated by focussing on selected criteria (*e.g.* how the approach was implemented in the registration dossier). Although a proper weight of evidence approach should include more than one endpoint study record flagged as ‘weight of evidence’ (ECHA, 2017i), the pure intention of the registrant to combine different pieces of information was regarded as weight of evidence approach and was checked as far as possible within the scope of the REACH Compliance Project. Identified shortcomings often resulted from the inappropriate documentation of the different sources of information included in the weight of evidence approach (Recommendation 2.2-1) and the incorrect use of the term “weight of evidence” in general (Recommendation 2.2-2). Further, the different sources of information were often not sufficient to fulfil the information requirements for a specific endpoint in the overall view (Recommendation 2.2-3).

## Recommendation 2.2-1

**A weight of evidence approach combines different independent sources of information to fulfil the information requirement for a particular endpoint. In some cases additional information is reported within the weight of evidence summary but the information provided would have required an endpoint study record. In other cases supporting studies are available but not flagged as weight of evidence.**

- ▶ If the information from only one single source is assumed to be insufficient to fulfil the information requirements, a weight of evidence approach should be used.
- ▶ A weight of evidence approach consists of several independent pieces of information which in combination allow drawing conclusions on particular properties of a substance.
- ▶ A robust study summary for each study or source of information within the weight of evidence approach should be provided.
- ▶ The information should be provided as several endpoint study records; “ECHA only accepts a WoE [weight of evidence] approach if it is substantiated in IUCLID by several ESRs [endpoint study records] along with appropriate documentation on various sources of evidence” (ECHA, 2016j).
- ▶ All endpoint study records belonging to the weight of evidence approach should be flagged as such in the IUCLID field ‘Adequacy of study’.
- ▶ The endpoint summary based on the different endpoint study records should comprehensively summarise all findings, describe how each piece of information is considered (“line of evidence”) and draw an appropriate conclusion for the respective endpoint.
- ▶ Where necessary, the decision on inclusions or exclusions of studies in the weight of evidence approach should be explained and made transparent. A short description can be provided in IUCLID under ‘Justification for type of information’.

**REACH Regulation**

Annex XI 1.2 (EC, 2006)

**ECHA documents**

Guidance on Information Requirements and Chemical Safety Assessment – Chapter R.7a: Endpoint specific guidance – Version 6.0 – July 2017 (ECHA, 2017b)

Guidance on Information Requirements and Chemical Safety Assessment – Chapter R.7b: Endpoint specific guidance – Version 4.0 – June 2017 (ECHA, 2017c)

Guidance on Information Requirements and Chemical Safety Assessment – Chapter R.7c: Endpoint specific guidance – Version 3.0 – June 2017 (ECHA, 2017d)

Manual: How to prepare registration and PPORD dossiers – Version 4.0 – May 2017 (ECHA, 2017i)

Practical guide: How to use alternatives to animal testing to fulfil your information requirements for REACH registration – Version 2.0 – July 2016 (ECHA, 2016j)

## Recommendation 2.2-2

A weight of evidence approach should be provided when e.g. one source of information alone may be insufficient as a key study or different studies show conflicting results. Sometimes the term “weight of evidence” (e.g. data waiving or an endpoint conclusion was supported by the wording “weight of evidence”) is used incorrectly by the registrants.

- ▶ The weight of evidence approach represents “an evidence-based approach involving an evaluation of the relative weights of different pieces of the available information [...] in an objective way by using a formalised procedure or expert judgement” (ECHA, 2016j).
- ▶ It is an approach to weigh different sources of results (e.g. experimental, read-across and/or (Q)SAR results) concerning the respective endpoint.
- ▶ Weight of evidence should not be flagged if the intention is to waive a study based on the endpoint specific rules (REACH Annexes VII to X column 2).

**REACH Regulation**

Annex XI 1.2 (EC, 2006)

**ECHA documents**

Guidance on Information Requirements and Chemical Safety Assessment – Chapter R.7a: Endpoint specific guidance – Version 6.0 – July 2017 (ECHA, 2017b)

Guidance on Information Requirements and Chemical Safety Assessment – Chapter R.7b: Endpoint specific guidance – Version 4.0 – June 2017 (ECHA, 2017c)

Guidance on Information Requirements and Chemical Safety Assessment – Chapter R.7c: Endpoint specific guidance – Version 3.0 – June 2017 (ECHA, 2017d)

Manual: How to prepare registration and PPORD dossiers – Version 4.0 – May 2017 (ECHA, 2017i)

Practical guide: How to use alternatives to animal testing to fulfil your information requirements for REACH registration – Version 2.0 – July 2016 (ECHA, 2016j)

## Recommendation 2.2-3

**The weight of evidence approach should be documented in a reliable, robust, and transparent manner. However, in some cases it is not clearly documented whether all sufficient aspects of testing are considered (in particular concerning non-guideline studies).**

- ▶ A weight of evidence approach consists of several independent pieces of information which allows an assumption/a conclusion about the particular properties of a substance.
- ▶ The endpoint summary should include and summarise information from the different sources.
- ▶ The conclusion should “consider the quality of the available data, the consistency of the results, the severity and the type of effects of concern and the relevance of the available data for the property” (ECHA, 2016j).
- ▶ Associated uncertainties and their impacts should be addressed, e.g. if key parameters are not covered, the test duration does not seem to be adequate or reporting in the referenced sources is insufficient.
- ▶ The conclusion should be comprehensible on the basis of the available information in the registration dossier (“line of evidence”). It is advised to consult the endpoint specific guidance on weight of evidence (see references below).

**REACH Regulation**

Annex XI 1.2 (EC, 2006)

**ECHA documents**

Evaluation under REACH – Progress Report 2016 (ECHA, 2017e)

Guidance on Information Requirements and Chemical Safety Assessment – Chapter R.7a: Endpoint specific guidance – Version 6.0 – July 2017 (ECHA, 2017b)

Guidance on Information Requirements and Chemical Safety Assessment – Chapter R.7b: Endpoint specific guidance – Version 4.0 – June 2017 (ECHA, 2017c)

Guidance on Information Requirements and Chemical Safety Assessment – Chapter R.7c: Endpoint specific guidance – Version 3.0 – June 2017 (ECHA, 2017d)

Manual: How to prepare registration and PPORD dossiers – Version 4.0 – May 2017 (ECHA, 2017i)

Practical guide: How to use alternatives to animal testing to fulfil your information requirements for REACH registration – Version 2.0 – July 2016 (ECHA, 2016j)

**2.2.2 Qualitative or quantitative structure-activity relationships**

The registrant can use qualitative or quantitative structure-activity relationships ((Q)SARs) to adapt the standard information requirements. Therefore, the (Q)SAR models should meet criteria for validity as given in REACH Annex XI 1.3 (ECHA, 2016j). On this basis, the following criteria were evaluated for (Q)SARs within the REACH Compliance Project:

- ▶ Are validation criteria for the (Q)SAR model reported?
- ▶ Does the substance fall within the applicability domain of the respective (Q)SAR model?
- ▶ Is an adequate and reliable documentation of both the model and prediction available?

The evaluation of dossiers identified a considerable number of cases where a (Q)SAR study was referenced in the endpoint summary but the respective endpoint study record was not available (Recommendation 2.2-4). Other frequently observed problems were related to deficiencies in the study documentation and the usage of insufficiently validated or inappropriate models (Recommendations 2.2-5 to 2.2-8). It should be noted that within the REACH Compliance project, evaluation of (Q)SARs was limited to environmental endpoints. However, the derived recommendations can also be transferred to other endpoints, since the formal criteria apply for (Q)SARs in general.

## Recommendation 2.2-4

**A (Q)SAR study is referenced in the endpoint summary but the respective endpoint study record is not available.**

- ▶ The entire information needed for an independent evaluation of the (Q)SAR adaptation approach should be available.
- ▶ Each (Q)SAR study referenced in the endpoint summary requires an endpoint study record.
- ▶ Simply reporting the (Q)SAR model output without any further documentation is not sufficient.

**ECHA documents**

Guidance on information requirements and Chemical Safety Assessment – Chapter R.6: QSARs and grouping of chemicals – 2008 (ECHA, 2008b)

Manual: How to prepare registration and PPORD dossiers – Version 4.0 – May 2017 (ECHA, 2017i)

Practical guide: How to use and report (Q)SARs – Version 3.1 – July 2016 (ECHA, 2016k)

## Recommendation 2.2-5

**The QMRF/QPRF for reporting the (Q)SAR method and the prediction is not available or not complete.**

- ▶ The following information should be reported for (Q)SARs:
  - validation criteria of the model,
  - verification that the substance falls within the applicability domain of the (Q)SAR model,
  - adequacy of the results for the purposes of classification and labelling and/or risk assessment.
- ▶ It is recommended to compile the information according to the (Q)SAR model reporting format (QMRF) and the (Q)SAR prediction reporting format (QPRF):
  - The (Q)SAR Model Reporting Format (QMRF) is used to describe the algorithm of the model, its development and its validation.
  - The (Q)SAR Prediction Reporting Format (QPRF) explains how an estimate has been derived, including the endpoint, a precise identification of the substance modelled, the relationship between the modelled substance and the defined applicability domain, and the identities of close analogues.
  - The use of the OECD QSAR Toolbox (OECD, 2017) does not replace the need to prepare a QPRF.
  - The endpoint study record for a (Q)SAR prediction, containing the QMRF and the QPRF, should be created in IUCLID according to ECHA's practical guide (ECHA, 2016k).

**REACH Regulation**

Annex XI 1.3 (EC, 2006)

**ECHA documents**

Guidance on information requirements and Chemical Safety Assessment – Chapter R.6: QSARs and grouping of chemicals – 2008 (ECHA, 2008b)

Manual: How to prepare registration and PPORD dossiers – Version 4.0 – May 2017 (ECHA, 2017i)

Practical guide: How to use alternatives to animal testing to fulfil your information requirements for REACH registration – Version 2.0 – July 2016 (ECHA, 2016j)

Practical guide: How to use and report (Q)SARs – Version 3.1 – July 2016 (ECHA, 2016k)

## Recommendation 2.2-6

**The OECD validation criteria for (Q)SAR models are not addressed or fulfilled.**

- ▶ The validity of the (Q)SAR model is the first condition to be fulfilled when using a (Q)SAR result.
- ▶ ECHA follows the OECD principles for validating (Q)SAR models.
- ▶ All validity criteria of REACH Annex XI 1.3 should be addressed and fulfilled.
- ▶ The QMRf describing the scientific validity of the model should be provided.

**REACH Regulation**

Annex XI 1.3 (EC, 2006)

**ECHA documents**

Guidance on information requirements and Chemical Safety Assessment – Chapter R.6: QSARs and grouping of chemicals – 2008 (ECHA, 2008b)

Manual: How to prepare registration and PPORD dossiers – Version 4.0 – May 2017 (ECHA, 2017i)

Practical guide: How to use and report (Q)SARs – Version 3.1 – July 2016 (ECHA, 2016k)

**Other**

OECD (2004): OECD principles for the Validation, for Regulatory Purpose, of (Q)SAR Models (OECD, 2004)

OECD (2007): Guidance document on the validation of (quantitative) structure-activity relationships [(Q)SAR] models (OECD, 2007)

## Recommendation 2.2-7

**The applicability domain of the (Q)SAR model is not evaluated or the substance does not fall within the applicability domain.**

- ▶ The following elements should be evaluated carefully: Descriptor domain, structural domain, mechanistic, and metabolic domains, if possible.
- ▶ (Q)SAR predictions can only be used when the substance falls within the model's applicability domain.
- ▶ The reliability of the prediction can be considered high if close structural analogues are included in the training set of the (Q)SAR model.

**REACH Regulation**

Annex XI 1.3 (EC, 2006)

**ECHA documents**

Guidance on information requirements and Chemical Safety Assessment – Chapter R.6: QSARs and grouping of chemicals – 2008 (ECHA, 2008b)

Manual: How to prepare registration and PPORD dossiers – Version 4.0 – May 2017 (ECHA, 2017i)

Practical guide: How to use alternatives to animal testing to fulfil your information requirements for REACH registration – Version 2.0 – July 2016 (ECHA, 2016j)

Practical guide: How to use and report (Q)SARs – Version 3.1 – July 2016 (ECHA, 2016k)

**2.2.3 Read-across approach**

A read-across approach is based on the endpoint specific information from one or more substance(s) (source/s) used to predict the properties of another substance (target). When the properties of the substances are assumed to be similar (ECHA, 2014a; ECHA, 2017i), this information may be used to fill data gaps for a substance and avoid additional (animal) testing. When using this approach the registrant should provide a scientific justification and the results should be suitable for classification and labelling and/or risk assessment purposes (ECHA, 2016j). In IUCLID 6, a read-across approach requires reporting information on source and on target (ECHA, 2014a; ECHA, 2016d; ECHA, 2016m; ECHA, 2017i).

Based on structural similarities substances can be considered “similar or to follow a regular pattern” (“category approach”) (ECHA, 2016j). In a **category approach** the source information should be provided in the datasets of the category member substances. The target information (read-across outcome) should be presented within an endpoint study record flagged as ‘read-across based on grouping of substances (category approach)’ in IUCLID 6 under ‘Type of information’ (ECHA, 2016d). In this approach, a “category object” (includes the documentation of the category definition, the category members and the explanation for the grouping) should be presented in the dossier (ECHA, 2016m; ECHA, 2017i).

An “analogue approach” represents a read-across approach “between a small number of structurally-similar substances” (ECHA, 2016j). Within an **analogue approach** two separate endpoint study records, for the source as well as for the target substance, should be provided in the dataset of the registered substance. The source endpoint study record should fulfil the criteria of a “normal” endpoint study record for an experimental study. The target information should be indicated as ‘read-across from supporting substance (structural analogue or surrogate)’. The target record should be linked to the corresponding source record(s) using the IUCLID 6 table ‘Cross-reference’ (ECHA, 2016d; ECHA, 2016m; ECHA, 2017i).

In both the analogue and category approaches, the target record consists of limited information on the adequacy of the study, the target material of the read-across and the results, but no data related to the experimental setup. The field ‘Justification for type of information’ should provide the endpoint specific documentation of the read-across approach (ECHA, 2016d; ECHA, 2016m; ECHA, 2017i).

For ECHA an acceptable read-across justification is usually based on different lines of evidence. The structural similarity and differences of the target and source substances should be clarified. Toxicokinetic information can support the read-across hypothesis. The provided justification should scientifically explain why the read-across is justified (ECHA, 2014a; ECHA, 2016j; ECHA, 2017k). The Read-Across Assessment Framework includes different types of read-across approaches and should be considered (ECHA, 2017m).

Within the REACH Compliance Project the availability of a read-across justification addressing the similarity based on (1) functional group or (2) precursors, breakdown products or (3) constant pattern in the changing of potency (EC, 2006) (Recommendation 2.2-8) and criteria of relevance for the endpoint (e.g. guideline, reliability, exposure duration) were evaluated (Recommendation 2.2-9).

## Recommendation 2.2-8

**The justification of a read-across approach is not available.**

- ▶ For a read-across approach, a clearly stated hypothesis and justification should be given, including the analysis of any contradictions.
- ▶ The hypothesis and justification should be based on the “Read-Across Assessment Framework” (RAAF) (ECHA, 2017m).
- ▶ In IUCLID 6, an endpoint specific read-across justification should be provided for the target information in the endpoint study record under ‘Justification for type of information’ and should be supported with an attached justification.
- ▶ The read-across hypothesis describes the structural and other similarities identified and explains why the properties of the source substance are predictive of the properties of the target substance regarding the endpoint of interest.
- ▶ The similarities may be based on a common functional group or precursors, breakdown products or a constant pattern of changing potency, and common constituents or a common chemical class.
- ▶ Structurally similar substances could be identified by the OECD QSAR Toolbox (OECD, 2017) or similar tools.
- ▶ The read-across justification should demonstrate that the hypothesis is supported by scientifically substantiated data, e.g. by addressing the mode of action.
- ▶ For read-across based on grouping, a “category object” (including the documentation of the category definition and justification of the grouping (ECHA, 2016d)) should be presented in the dossier.
- ▶ The test material information (TMI) record should be included for both the source and target substances in the read-across approach and should be specified (CAS-, EC-number, IUPAC name and/or composition). Impurities and potentially different substance compositions should be considered.

**REACH Regulation**

Annex XI 1.5 (EC, 2006)

**ECHA documents**

ECHA Newsletter No 1 – February 2017 (ECHA, 2017k)

How to bring your registration dossier in compliance with REACH Tips and Hints – Part 5 Read-across (Webinar) – 12.02.2014 (ECHA, 2014a)

IUCLID 6 advanced users webinar – Part 2 (ECHA, 2016d)

Manual: How to prepare registration and PPORD dossiers – Version 4.0 – May 2017 (ECHA, 2017i)

Practical guide: How to use alternatives to animal testing to fulfil your information requirements for REACH registration – Version 2.0 – July 2016 (ECHA, 2016j)

Read-Across Assessment Framework (RAAF) – March 2017 (ECHA, 2017m)

Transition to the new IT tools - how to prepare – March 2016 (ECHA, 2016m)

**Other**

OECD (2017): QSAR Toolbox 4.1 (OECD, 2017)

## Recommendation 2.2-9

**The read-across approach did not provide a key study for the experimental data of the source substance with a reliability of 1 or 2 and/or the exposure duration is not comparable or not addressed.**

- ▶ A read-across approach requires documentation of each source study as well as the prediction for the target substance in endpoint study records (ECHA, 2016d; ECHA, 2017i).
- ▶ In any case, the source studies used should comply with the respective information requirement of REACH Annexes VII to X. These should be reported as an experimental study record. A robust study summary for each source study should be included in the dossier.
- ▶ The endpoint study record of the source study should include the adequate and reliable description and documentation of the key parameters and exposure duration of the performed test.
- ▶ The quality of the source study should be evaluated carefully. The scoring system of Klimisch et al. (1997) is recommended to specify the reliability of the data:
  - 1 = reliable without restrictions,
  - 2 = reliable with restrictions,
  - 3 = not reliable,
  - 4 = not assignable.
- ▶ The source study of a read-across approach should comply with the criteria for a key study in terms of adequacy and reliability.
- ▶ The target record should contain information on the read-across approach, e.g. justification of the approach, link to the source study, correction for the molecular weight etc., whereas the experimental study details do not need to be reported there.

**REACH Regulation**

Annex XI 1.5 (EC, 2006)

**ECHA documents**

Guidance on information requirements and Chemical Safety Assessment – Chapter R.4: Evaluation of available information – December 2011 (ECHA, 2011b)

How to bring your registration dossier in compliance with REACH Tips and Hints – Part 5 Read-across (Webinar) – 12.02.2014 (ECHA, 2014a)

IUCLID 6 advanced users webinar – Part 2 (ECHA, 2016d)

Manual: How to prepare registration and PPORD dossiers – Version 4.0 – May 2017 (ECHA, 2017i)

Practical guide: How to use alternatives to animal testing to fulfil your information requirements for REACH registration – Version 2.0 – July 2016 (ECHA, 2016j)

Read-Across Assessment Framework (RAAF) – March 2017 (ECHA, 2017m)

**Other**

Klimisch et al. (1997): A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data (Klimisch et al., 1997)

**2.2.4 Substance-tailored exposure-driven testing**

Testing may be omitted in accordance with REACH Annex XI 3.2 on the basis of the exposure scenario(s) developed in the Chemical Safety Report (substance-tailored exposure-driven testing). The registrant should provide an adequate justification based on a thorough exposure assessment. This justification should meet any one of the criteria outlined in REACH Annex XI 3.2 (a) to (c) (EC, 2006). The REACH Compliance Project formally assessed whether these criteria for substance-tailored exposure-driven testing were addressed in the waiving justification.

The results of the evaluation identified several cases with a reference to REACH Annex XI 3.2 (a) that failed to address or did not meet the respective criteria in the justification (EC, 2006):

- ▶ absence of or no significant exposure and
- ▶ DNEL/PNEC can be derived from results of available test data and
- ▶ exposures are always well below DNEL/PNEC.

In addition, testing was omitted with reference to REACH Annex XI 3.2. (a), even though exposure scenarios were not available in the Chemical Safety Report or the Chemical Safety Report was completely missing (Recommendation 2.2-10).

#### Recommendation 2.2-10

**Standard information is waived according to REACH Annex XI 3.2 (a) but none or not all criteria listed are addressed in the justification, exposure scenarios are not available in the Chemical Safety Report or the Chemical Safety Report is missing.**

- ▶ It should be clearly stated that testing is omitted on the basis of exposure scenarios developed in the Chemical Safety Report and a justification according to the criteria of REACH Annex XI 3.2 should be provided.
- ▶ For exposure-based waiving under REACH Annex XI 3.2 (a) the following information should be provided:
  - exposure scenarios covering the manufacture and each use of the registered substance in the Chemical Safety Report,
  - a comprehensible justification which includes and explains all criteria of REACH Annex XI.
- ▶ Exposure scenarios are the basis for the justification and should confirm (EC, 2006):
  - the absence of or no significant exposure,
  - that DNEL/PNEC can be derived from results of available test data,
  - that exposures are always well below DNEL/PNEC.
- ▶ If a Chemical Safety Report is not attached, a justification should be provided which addresses the conditions of Article 14(2) of the REACH Regulation.

#### **REACH Regulation**

Annex XI 3.2 (EC, 2006)

Article 14(2) (EC, 2006)

#### **ECHA documents**

Guidance on Information Requirements and Chemical Safety Assessment – Chapter R.7a: Endpoint specific guidance – Version 6.0 – July 2017 (ECHA, 2017b)

Information on manual verification at completeness check – 03.02.2017 (ECHA, 2017h)

Practical guide: How to use alternatives to animal testing to fulfil your information requirements for REACH registration – Version 2.0 – July 2016 (ECHA, 2016j)

### 3 Specific recommendations

Within the REACH Compliance Project, the formal conformity of waiving and adaptations of the standard information requirements was evaluated for selected endpoints on the basis of the specific rules in column 2 of REACH Annexes VII to X and the general rules of Annex XI. Finally, the problems identified were used to deduce the following endpoint specific recommendations.

#### 3.1 Human health endpoints

##### 3.1.1 Repeated dose toxicity

Repeated dose toxicity studies should give information about adverse toxicological effects caused by the repeated exposure to a substance and may also provide data relevant for other endpoints such as reproductive toxicity. Testing for repeated dose toxicity comprises a tiered approach which includes screening studies and repeated dose toxicity studies of different duration (sub-acute, sub-chronic and chronic). Concerning the appropriate route of administration the most likely route of human exposure should be taken into account (ECHA, 2017b).

The following recommendations are derived from the observation within the scope of the REACH Compliance Project. Screening studies or short-term tests are only sufficient to fulfil the information requirements, if they show adverse effects that can be used for a relevant classification and NOAEL (no observed adverse effect level) derivation (Recommendation 3.1-1).

##### Recommendation 3.1-1

**For the endpoint repeated dose toxicity only screening (OECD 422) or short-term (28-days) studies are provided. These studies show no adverse effects or show adverse effects which cannot be used for a relevant classification and NOAEL extrapolation.**

- ▶ The standard information requirements for the high tonnage chemicals ( $\geq 1000$  tpa) include a sub-chronic repeated dose toxicity study (90 days).
- ▶ The sub-chronic toxicity study (90 days) does not need to be conducted if “a reliable short-term toxicity study (28 days) is available showing severe toxicity effects according to the criteria for classifying the substance as R48, for which the observed NOAEL-28 days, with the application of an appropriate uncertainty factor, allows the extrapolation towards the NOAEL-90 days for the same route of exposure” (EC, 2006).
- ▶ Subtle (adverse) effects or the lack of effects in the 28-days study require further testing if the studies are **not** sufficient for classification and risk assessment.

##### **REACH Regulation**

Annex IX 8.6.1 and 8.6.2 (EC, 2006)

##### **ECHA documents**

Guidance on Information Requirements and Chemical Safety Assessment – Chapter R.7a: Endpoint specific guidance – Version 6.0 – July 2017 (ECHA, 2017b)

### 3.1.2 Toxicity to reproduction

Effects of chemicals on reproductive ability and development are obviously serious hazards for human health. The endpoint toxicity to reproduction comprises adverse effects of chemicals on fertility and reproduction ability of the parental generation and on the development of the offspring during pregnancy and lactation period (pre- and postnatal) (ECHA, 2017b).

In 2014, ECHA confirmed that prenatal developmental toxicity testing in a second species is a standard information requirement for substances manufactured or imported in quantities of 1000 tpa or more (ECHA, 2014b). In several dossiers neither data on testing in a second species nor waiving/adaptation for this information requirement have been provided (Recommendation 3.1-2).

Screening studies and short-term tests are only sufficient to fulfil the information requirements, if they show adverse effects which can be used for a relevant classification and NOAEL derivation (Recommendation 3.1-3). Another observed problem refers to waiving according to specific rules given in REACH Annex X 8.7 column 2. In some cases not all criteria obligatory for this waiving were addressed in the justifications (Recommendation 3.1-4).

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#### Recommendation 3.1-2

**For chemicals  $\geq$  1000 tpa information on prenatal developmental toxicity testing in a first and second species is required. Waiving or adaptation options for omitting the testing in a second species need to be applied.**

- ▶ Registrations for substances manufactured or imported at or above 1000 tpa require information about pre-natal development toxicity test in a second species. This is a standard information requirement under the REACH Regulation.
- ▶ Dossiers lacking this information should be updated with an adaptation statement, an available study result, or a testing proposal for the required test.

**REACH Regulation**

Annex X 8.7 (EC, 2006)

**ECHA documents**

ECHA Newsletter No 5 – October 2014 (ECHA, 2014b)

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#### Recommendation 3.1-3

**For the endpoint toxicity to reproduction only information on e.g. screening (OECD 421 or 422) or short-term tests (28-day study) are provided. These studies show no adverse effects or show adverse effects which are not used for a relevant classification (toxic for reproduction category 1A or 1B) and NOAEL extrapolation.**

- ▶ The standard information requirements for the registration of high-tonnage chemicals consist of the pre-natal development toxicity test in two species and the extended one-generation reproductive toxicity study in one species.

**REACH Regulation**

Annex X 8.7 (EC, 2006)

**ECHA documents**

Guidance on Information Requirements and Chemical Safety Assessment – Chapter R.7a: Endpoint specific guidance – Version 6.0 – July 2017 (ECHA, 2017b)

## Recommendation 3.1-4

**The standard information is waived according to REACH Annex X 8.7 column 2, 3<sup>rd</sup> bullet point but at least one of the three criteria listed is not addressed in the justification.**

- ▶ Each data waiving requires an adequate justification.
- ▶ The justification should explain how **all three** criteria of column 2, 3<sup>rd</sup> bullet are fulfilled: “substance is of low toxicological activity [...], no systemic absorption occurs via relevant routes of exposure [...] and there is no or no significant human exposure.” (EC, 2006).

**REACH Regulation**

Annex X 8.7 (EC, 2006)

**ECHA documents**

Guidance on Information Requirements and Chemical Safety Assessment – Chapter R.7a: Endpoint specific guidance – Version 6.0 – July 2017 (ECHA, 2017b)

Information on manual verification at completeness check – 03.02.2017 (ECHA, 2017h)

## 3.2 Environmental endpoints

### 3.2.1 Abiotic degradation

Abiotic or non-biological degradation can occur by physico-chemical processes such as hydrolysis, oxidation and photolysis. These processes can greatly influence the fate and behaviour of substances in aquatic environments and sediments. Further consideration may need to be given to major degradation products for classification and labelling, PBT/vPvB (persistent, bioaccumulative, toxic/very persistent, very bioaccumulative) assessment and Chemical Safety Assessment. If a substance is manufactured or imported in quantities greater than 10 tpa, a hydrolysis test as a function of the pH value should be conducted according to REACH Annex VIII 9.2.2.1. However, it is possible to omit this test in accordance with column 2 of REACH Annex VIII 9.2.2.1, if:

- ▶ the substance is highly insoluble in water, or
- ▶ the substance is readily biodegradable.

In addition, the general rules for adaptations to the standard information requirements of REACH Annex XI apply. When the standard information is not provided for other reasons than those outlined by the specific or general rules of REACH, this fact and the reasons should also be clearly stated. The adequate documentation of the entire information needed for an independent evaluation of the adaptation approach is mandatory in all cases.

The evaluation within the REACH Compliance Project identified several dossiers where hydrolysis testing was omitted by stating that the molecular structure of the substance is hydrolytically stable and/or does not contain hydrolysable functional groups. However, a scientific basis for the suggested structure-property relationship was often not provided (Recommendation 3.2-1). In some cases testing was omitted by stating that the substance is readily biodegradable or highly insoluble without providing the necessary data to justify these statements (Recommendation 3.2-2 and Recommendation 3.2-3). Furthermore, testing was omitted by stating that the substance is inorganic, even though data on stability and transformation are likewise required for inorganic substances (Recommendation 3.2-4).

### Recommendation 3.2-1

**Testing is omitted by stating that the substance is hydrolytically stable or does not contain hydrolysable functional groups, but the scientific basis for the suggested structure-property relationship was often not provided.**

- ▶ The waiving justification should meet either the specific rules of REACH Annex VIII 9.2.2.1 column 2 or general rules of Annex XI.
- ▶ (Q)SARs and grouping methods (read-across and category approaches) could be used to indicate the presence or absence of hydrolysable substructures.

**REACH Regulation**

Annex VIII 9.2.2.1 column 2, Annex XI (EC, 2006)

**ECHA documents**

Guidance on information requirements and Chemical Safety Assessment – Chapter R.6: QSARs and grouping of chemicals – 2008 (ECHA, 2008b)

Waiving information requirements (Webinar) – 10.12.2009 (ECHA, 2009)

### Recommendation 3.2-2

**Testing is omitted by stating that the substance is readily biodegradable, but appropriate information on biodegradation is missing.**

- ▶ The registrant should provide the entire information needed for an independent evaluation of the adaptation based on ready biodegradability.
- ▶ If the waiving justification refers to ready biodegradability, the underlying study should be adequately documented.

**REACH Regulation**

Annex VIII 9.2.2.1 column 2 (EC, 2006)

### Recommendation 3.2-3

**Testing is omitted by stating that the substance is highly insoluble, but appropriate information on water solubility is missing.**

- ▶ The registrant should demonstrate that the aqueous environment may not be the principal environmental compartment of concern.
- ▶ If the waiving justification refers to water solubility, the respective study should be adequately documented.

**REACH Regulation**

Annex VIII 9.2.2.1 column 2 (EC, 2006)

**ECHA documents**

Guidance on Information Requirements and Chemical Safety Assessment – Chapter R.7b: Endpoint specific guidance – Version 4.0 – June 2017 (ECHA, 2017c)

## Recommendation 3.2-4

**Testing is omitted by stating that the substance is inorganic, even though data on stability and transformation are also required for inorganic substances.**

- ▶ The waiving justification should meet either the specific rules of REACH Annex VIII 9.2.2.1 column 2 or the general rules of Annex XI.
- ▶ Inorganic substances may dissociate in the environment or undergo other transformation reactions. The character of instability and the rate of transformation need to be described.

**REACH Regulation**

Annex VIII 9.2.2.1 column 2, Annex XI (EC, 2006)

**ECHA documents**

Guidance on Information Requirements and Chemical Safety Assessment – Chapter R.7b: Endpoint specific guidance – Version 4.0 – June 2017 (ECHA, 2017c)

**3.2.2 Bioaccumulation**

Information on the bioaccumulation potential of the substance is used for classification and labelling and may inform on the necessity for conducting a long-term test on ecotoxicity and assessment of the risk of secondary poisoning. The bioaccumulation potential also plays an important role in the identification of PBT/vPvB substances and thus in the identification of substances of very high concern (SVHC). The REACH Regulation Annex IX 9.3.2 stipulates a bioaccumulation test, preferably performed in fish, as a mandatory test requirement. According to column 2 of REACH Annex IX 9.3.2 the study does not need to be conducted if:

- ▶ the substance has a low potential for bioaccumulation (for instance a  $\log K_{ow} \leq 3$ ) and/or a low potential to cross biological membranes, or
- ▶ direct and indirect exposure of the aquatic compartment is unlikely.

In addition, the general rules for adaptations to the standard information requirements of REACH Annex XI apply. When the standard information is not provided for other reasons than those outlined by the specific or general rules of REACH, this fact and the reasons should also be clearly stated. Adequate documentation of the entire information needed for an independent evaluation of the adaptation approach is mandatory in all cases.

The waiving of bioaccumulation testing was often justified with an octanol-water partition coefficient equal to or smaller than three ( $\log K_{ow} \leq 3$ ). However, this approach requires a reliable measured or predicted  $\log K_{ow}$ , which is not always presented (Recommendation 3.2-5).

The registrants often concluded that the aquatic bioconcentration factor of a substance is lower than 2000 because of a calculated  $\log K_{ow}$  higher than 10 and no other information was considered to conclude on that the substance is not bioaccumulative (ECHA, 2017l) (Recommendation 3.2-6).

Moreover, testing was omitted by stating that the substance has a low potential to cross biological membranes, but only part of the relevant information was provided (Recommendation 3.2-7). Another encountered problem was that testing is omitted with an inappropriate justification, e.g. that the substance is a UVCB substance (Recommendation 3.2-8).

## Recommendation 3.2-5

**Bioaccumulation testing is omitted by stating that the substance has a  $\log K_{OW} \leq 3$ , but the applied model for the prediction of  $\log K_{OW}$  is not validated for the assessed substance.**

- ▶ (Q)SAR models may be used if they are restricted to substances for which their applicability is well characterised (see also chapter 2.2.2).
- ▶ ECHA's practical guide on using and reporting (Q)SARs describes how to assess the reliability of (Q)SAR predictions (see also chapter 2.2.2).

**REACH Regulation**

Annex IX 9.3.2 (EC, 2006)

**ECHA documents**

Guidance on Information Requirements and Chemical Safety Assessment – Chapter R.7a: Endpoint specific guidance – Version 6.0 – July 2017 (ECHA, 2017b)

Manual: How to prepare registration and PPORD dossiers – Version 4.0 – May 2017 (ECHA, 2017i)

Practical guide - How to use and report (Q)SARs – Version 3.1 – July 2016 (ECHA, 2016k)

## Recommendation 3.2-6

**It is concluded that the bioconcentration factor is lower than 2000 when the calculated  $\log K_{OW}$  is higher than 10, but the reliability of the prediction is not considered.**

- ▶ If a calculated  $K_{OW}$  is higher than 10, results should be interpreted with care, considering other information, e.g. molecular diameter/weight/length, in a weight of evidence approach (ECHA, 2017l).
- ▶ It is recommended to apply more than one model to estimate the  $\log K_{OW}$  value and the results should be carefully evaluated by expert judgement (see also chapter 2.2.2 in this document).

**ECHA documents**

Guidance on Information Requirements and Chemical Safety Assessment – Chapter R.7c: Endpoint specific guidance – Version 3.0 – June 2017 (ECHA, 2017d)

Guidance on Information Requirements and Chemical Safety Assessment – Chapter R.11: PBT/vPvB assessment – Version 3.0 – June 2017 (ECHA, 2017l)

## Recommendation 3.2-7

**Testing is omitted by stating that the substance has a low potential to cross biological membranes, but only part of the relevant information to support this statement is provided.**

- ▶ All relevant information on the bioaccumulation potential of a substance should be gathered and considered.
- ▶ Molecular size and weight based adaptations should be used in a weight of evidence approach together with other information, e.g.  $\log K_{OW}$ , octanol solubility, (Q)SARs, read-across with other substances, and in vitro data on biotransformation.

**ECHA documents**

Guidance on Information Requirements and Chemical Safety Assessment – Chapter R.11: PBT/vPvB assessment – Version 3.0 – June 2017 (ECHA, 2017l)

## Recommendation 3.2-8

**Testing is omitted by stating that the substance is a UVCB substance.**

- ▶ Dossiers on UVCB substances also need to address bioaccumulation. Being a UVCB is not an adequate waiving argument for this endpoint.
- ▶ UVCB substances require a case-by-case consideration of the approach to define the appropriate information and methods necessary for meeting the requirements of REACH.
- ▶ Deficiencies in substance identification should be tackled or justified.
- ▶ When possible the assessment must address the bioaccumulation potential of the individual structures, starting with the available experimental evidence.
- ▶ Where experimental data is insufficient for a judgement, (Q)SAR models may be used.

**ECHA documents**

Guidance on Information Requirements and Chemical Safety Assessment – Chapter R.7c: Endpoint specific guidance – Version 3.0 – June 2017 (ECHA, 2017d)

Guidance on Information Requirements and Chemical Safety Assessment – Chapter R.11: PBT/vPvB assessment – Version 3.0 – June 2017 (ECHA, 2017l)

**3.2.3 Ecotoxicity**

The determination of the aquatic toxicity of a substance plays a key role in hazard and risk assessment (e.g. classification and labelling and Chemical Safety Assessment), as well as in the identification of PBT/vPvB substances under the REACH Regulation. The evaluation of data concerning the endpoint ecotoxicity within the REACH Compliance Project was restricted to aquatic life or, more precisely, the pelagic zone, and here only to fish and invertebrates (mainly *Daphnia*). The short-term and long-term tests on invertebrates and fish are standard information requirements according to REACH Annexes VII 9.1, VIII 9.1.3 and IX 9.1. However, it is possible to omit the ecotoxicity testing in accordance with the specific criteria of column 2 in the respective REACH Annexes. In addition, the general rules for adaptations to the standard information requirements of REACH Annex XI apply. When the standard information is not provided for other reasons than those outlined by the specific or general rules of REACH, this fact and the reasons should also be clearly stated. Adequate documentation of the entire information needed for an independent evaluation of the adaptation approach is recommended in all cases.

The identified deficiencies for the ecotoxicity data were often related either to the type of study provided in general or to the type of study selected for Chemical Safety Assessment. For example, for fish long-term testing some registrants provided studies according to OECD Test Guideline 204 or ISO 10229-1, even though these guidelines are only acceptable as short-term tests (Recommendation 3.2-9). Additionally, the predicted no-effect concentration (PNEC) for Chemical Safety Assessment was in some cases based on (Q)SAR, although experimental studies were available as key study or within a weight of evidence approach (Recommendation 3.2-10). Other deficiencies were related to inappropriate justifications for waiving a test. For example, testing was omitted by stating that testing is technically not possible, but a detailed explanation of the technical limitations of the respective method was often missing (Recommendation 3.2-11). Furthermore, testing was omitted by stating that the substance is highly insoluble, but required information on water solubility was often not available (Recommendation 3.2-12).

### Recommendation 3.2-9

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**Studies according to OECD Test Guideline 204 or ISO 10229-1 are provided for long-term testing in fish, even though these guidelines are only accepted as short-term test.**

- ▶ Only studies in which sensitive life-stages (juveniles, eggs, and larvae) are exposed can be regarded as long-term fish tests (e.g. OECD Test Guideline 210).
- ▶ Studies according to OECD Test Guideline 204 and ISO 10229-1 are accepted as short-term tests but not as long-term fish tests.

**ECHA documents**

Guidance on Information Requirements and Chemical Safety Assessment – Chapter R.7b: Endpoint specific guidance – Version 4.0 – June 2017 (ECHA, 2017c)

### Recommendation 3.2-10

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**The derivation of a PNEC is based on a (Q)SAR study, although experimental studies are given as key study or within a weight of evidence approach.**

- ▶ For derivation of PNECs all available hazard information needs to be evaluated.
- ▶ If the PNEC is based on a (Q)SAR study, this study should be also identified as key study in the technical dossier. Nevertheless, experimental studies should be taken into account.
- ▶ To be transparent it should be stated in the endpoint summary which key studies are selected for the PNEC calculation.

**ECHA documents**

Guidance on Information Requirements and Chemical Safety Assessment – Chapter R.10: Characterisation of dose [concentration]-response for environment – May 2008 (ECHA, 2008a)

## Recommendation 3.2-11

**Testing is omitted by stating that testing is technically not possible, but a detailed explanation of the technical limitations of the respective method is missing.**

- ▶ Testing for a specific endpoint may be omitted, if it is technically not possible to conduct the study as a consequence of the properties of the substance (e.g. very volatile, highly reactive or unstable). The OECD guidance document on aquatic toxicity testing of difficult substances and mixtures should be consulted, e.g. for substances with very low water solubility.
- ▶ The relevant properties should be documented and a detailed written justification should be provided.
- ▶ The guidance given on the technical limitations of a specific method should always be considered.
- ▶ For gases and volatile substances guidance is available in the ECHA guidance documents (ECHA, 2017c) and OECD Test Guideline 23.

**REACH Regulation**

Annex XI 2 (EC, 2006)

**ECHA documents**

Guidance on Information Requirements and Chemical Safety Assessment – Chapter R.7b: Endpoint specific guidance – Version 4.0 – June 2017 (ECHA, 2017c)

Guidance on information requirements and Chemical Safety Assessment – Chapter R.5: Adaptation of information requirements – Version 2.1 – December 2011 (ECHA, 2011a)

Waiving information requirements (Webinar) – 10.12.2009 (ECHA, 2009)

**Other references**

OECD (2000): Guidance document on aquatic toxicity testing of difficult substances and mixtures (OECD, 2000)

## Recommendation 3.2-12

**Ecotoxicity testing is omitted by stating that the substance is highly insoluble, but appropriate information on water solubility is missing.**

- ▶ If the waiving justification is based on water solubility, the respective study should be adequately documented and conclusive.
- ▶ In the waiving statement, registrants should justify that aquatic toxicity is unlikely to occur at the water solubility limit. This may require specific information, such as that obtained from transformation/dissolution studies (inorganic substances) or from the identification of the components of the Water Accommodated Fraction (multi-constituent/UVCB substances).
- ▶ Testing cannot be waived if the registrant is unable to demonstrate that aquatic toxicity is unlikely to occur.

**ECHA documents**

Q&As ID: 0836 (ECHA, 2016n)

How to bring your registration dossier in compliance with REACH – Tips and Hints Part 1 (Webinar) – 27.09.2012 (ECHA, 2012)

### 3.2.4 Environmental exposure

The assessment of environmental exposure is required for all substances manufactured or imported in quantities of 10 tpa or greater which meet the criteria of REACH Article 14(4). These criteria include specific hazard classes or categories and the classification as PBT or vPvB substance. If none of the REACH Article 14(4) criteria are met, exposure assessment is not mandatory, unless substance-tailored exposure-driven testing is claimed. Exposure estimations are required for all human populations and environmental compartments for which exposure to the substance must be expected. Relevant human populations are, depending on the identified uses of the substance, workers, consumers, and humans liable to indirect exposure via the environment. In addition, the combined exposure from all uses and all release routes should be taken into account.

The REACH Compliance Project primarily assessed the registrants' obligation for exposure assessment with regard to REACH Article 14(4). Additionally, an in-depth analysis of presented exposure scenarios was conducted on a sample of dossiers that obviously fulfilled the minimum information requirements for a valid Chemical Safety Assessment.

In many cases, the environmental exposure assessment was already compromised by the insufficient quality of essential input parameters (e.g. Tier 1 physico-chemical/fate properties (ECHA, 2016i)). This issue may require additional attention.

Furthermore, some registrants did not provide exposure scenarios at all, although the substance met at least one criterion of REACH Article 14(4) (Recommendation 3.2-13).

Frequently, the exposure scenarios did not cover all registered uses and relevant exposure pathways (Recommendation 3.2-14) and often default environmental release factors were adapted without appropriate justification (Recommendation 3.2-15).

#### Recommendation 3.2-13

**The exposure scenarios are not provided although the substance meets at least one criterion of REACH Article 14(4).**

- ▶ The assessment of environmental exposure is required for all substances manufactured or imported in quantities of 10 tpa or greater that meet the criteria of REACH Article 14(4).
- ▶ If none of the REACH Article 14(4) criteria are met, exposure assessment is not mandatory, unless substance-tailored exposure-driven testing according to REACH Annex XI is claimed.

#### **REACH Regulation**

Article 14 (EC, 2006)

Annex I 0.6.3 (EC, 2006)

#### **ECHA documents**

Guidance on Information Requirements and Chemical Safety Assessment – Part D: Framework for exposure assessment – Version 2.0 – August 2016 (ECHA, 2016i)

Guidance on Information Requirements and Chemical Safety Assessment. Part B: Hazard assessment – Version 2.1 – December 2011 (ECHA, 2011c)

## Recommendation 3.2-14

**The assessment of environmental exposure and/or exposure of humans via environment and/or combined exposure is not available and there is no justification for the lack of information.**

- ▶ The outcome of hazard assessment determines the scope of the exposure assessment. In addition to the classified hazards the registrant should also consider effects that do not lead to classification, e.g. in case a DNEL or PNEC can be derived.
- ▶ Exposure levels should be estimated for all human populations and environmental spheres for which a hazard has been identified and exposure to the substance is known or reasonably foreseeable.
- ▶ If the substance is classified for human health hazards, each relevant route of human exposure should be addressed. This may also require exposure scenarios for the different environmental compartments to enable assessment of indirect exposure of humans via the environment.
- ▶ If the substance is classified as hazardous to aquatic life (i.e. H412, H411, H410, H400, and H413), exposure assessment is also required for the sediment and soil compartments.
- ▶ If the substance is PBT or vPvB, a qualitative exposure assessment is mandatory for water, sediment and soil.
- ▶ If environmental tests are waived based on exposure considerations environmental exposure needs to be assessed.
- ▶ The combined release to the environment from all uses and all release routes needs to be taken into account.

**REACH Regulation**

Article 14 (EC, 2006)

Annex I 5.2.4 (EC, 2006)

**ECHA documents**

Guidance on Information Requirements and Chemical Safety Assessment. Part B: Hazard assessment – Version 2.1 – December 2011 (ECHA, 2011c)

Guidance on Information Requirements and Chemical Safety Assessment – Chapter R.16: Environmental exposure assessment – Version 3.0 – February 2016 (ECHA, 2016a)

## Recommendation 3.2-15

**The adaptation of default environmental release factors defined by the Environmental Release Categories is not justified.**

- ▶ In the absence of more specific information, default environmental release factors defined by Environmental Release Categories should be used for release estimation.
- ▶ If a specific risk management measure is applied in current practice, environmental release factors can be reduced accordingly.
- ▶ Detailed explanations on the adaptation of environmental release factors should be provided in the Chemical Safety Report.

**ECHA documents**

Guidance on Information Requirements and Chemical Safety Assessment – Chapter R.16: Environmental exposure assessment – Version 3.0 – February 2016 (ECHA, 2016a)

## 4 References

EC (2006): Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC

ECHA (2008a): Characterisation of dose [concentration]-response for environment. In: Guidance on information requirements and chemical safety assessment, chapter R.10. European Chemicals Agency, Helsinki.

[http://echa.europa.eu/documents/10162/13632/information\\_requirements\\_r10\\_en.pdf](http://echa.europa.eu/documents/10162/13632/information_requirements_r10_en.pdf)

ECHA (2008b): QSARs and grouping of chemicals. In: Guidance on information requirements and chemical safety assessment, chapter R.6. European Chemicals Agency, Helsinki.

[https://echa.europa.eu/documents/10162/13632/information\\_requirements\\_r6\\_en.pdf](https://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf)

ECHA (2009): Waiving information requirements; ECHA webinar on information requirements.

[https://echa.europa.eu/documents/10162/13566/waiving\\_information\\_requirements\\_wim\\_de\\_coen\\_echa\\_en.pdf](https://echa.europa.eu/documents/10162/13566/waiving_information_requirements_wim_de_coen_echa_en.pdf)

ECHA (2011a): Adaptation of information requirements. In: Guidance on information requirements and chemical safety assessment, chapter R.5. European Chemicals Agency, Helsinki.

[https://echa.europa.eu/documents/10162/13643/information\\_requirements\\_r5\\_en.pdf](https://echa.europa.eu/documents/10162/13643/information_requirements_r5_en.pdf)

ECHA (2011b): Evaluation of available information. In: Guidance on information requirements and chemical safety assessment, chapter R.4. European Chemicals Agency, Helsinki.

[https://echa.europa.eu/documents/10162/13643/information\\_requirements\\_r4\\_en.pdf](https://echa.europa.eu/documents/10162/13643/information_requirements_r4_en.pdf)

ECHA (2011c): Part B: Hazard assessment. In: Guidance on information requirements and chemical safety assessment. European Chemicals Agency, Helsinki.

[http://echa.europa.eu/documents/10162/13643/information\\_requirements\\_part\\_b\\_en.pdf](http://echa.europa.eu/documents/10162/13643/information_requirements_part_b_en.pdf)

ECHA (2012): Aquatic Toxicity; ECHA Webinar: How to bring your registration dossier in compliance with REACH – Tips and Hints (Part 1). [https://echa.europa.eu/view-article/-/journal\\_content/cda5daf6-7d31-4a07-8d95-c1c820fa802f](https://echa.europa.eu/view-article/-/journal_content/cda5daf6-7d31-4a07-8d95-c1c820fa802f)

ECHA (2014a): Read-Across; ECHA webinar: How to bring your registration dossier in compliance with REACH Tips and Hints - Part 5.

[https://echa.europa.eu/documents/10162/13628/09\\_read\\_across\\_webinar\\_en.pdf](https://echa.europa.eu/documents/10162/13628/09_read_across_webinar_en.pdf)

ECHA (2014b): Registrants: Is your pre-natal toxicity information up-to-date? . ECHA Newsletter 5 ([https://newsletter.echa.europa.eu/home/-/newsletter/entry/5\\_14\\_registrants-is-your-prenatal-toxicity-information-uptodate](https://newsletter.echa.europa.eu/home/-/newsletter/entry/5_14_registrants-is-your-prenatal-toxicity-information-uptodate) (last accessed 2017-01-17))

ECHA (2015): Evaluation under REACH: Progress Report 2014. Report no. ECHA-15-R-03-EN, ISBN 978-92-9247-119-4, date: 2015-02-26. European Chemicals Agency, Helsinki. DOI: 978-92-9247-119-4

ECHA (2016a): Environmental Exposure Estimation. In: Guidance on information requirements and chemical safety assessment, chapter R.16. European Chemicals Agency, Helsinki. ISBN: 978-92-9247-775-2.

[https://echa.europa.eu/documents/10162/13632/information\\_requirements\\_r16\\_en.pdf](https://echa.europa.eu/documents/10162/13632/information_requirements_r16_en.pdf)

ECHA (2016b): Evaluation under REACH: progress report 2015. Report no. ECHA-15-R-20-EN, ISBN 978-92-9247-655-7. European Chemicals Agency, Helsinki. DOI: 10.2823/22390

ECHA (2016c): How do I specify unknown impurities in IUCLID? Q&As, ID: 0712.

<https://echa.europa.eu/support/qas-support/qas> (last accessed 2017-11-04)

ECHA (2016d): IUCLID 6 advanced users webinar – Part 2.

[https://echa.europa.eu/documents/10162/22840336/070916\\_iuclid\\_advanced\\_users\\_webinar\\_part\\_2\\_en.pdf](https://echa.europa.eu/documents/10162/22840336/070916_iuclid_advanced_users_webinar_part_2_en.pdf)

ECHA (2016e): IUCLID 6 webinar; ECHA webinar: Switching from IUCLID 5.6 to IUCLID 6 (for advanced users).

[https://echa.europa.eu/documents/10162/22840336/010616\\_iuclid\\_advanced\\_webinar\\_en.pdf](https://echa.europa.eu/documents/10162/22840336/010616_iuclid_advanced_webinar_en.pdf)

ECHA (2016f): My substance is a component of a mixture. Can I report the composition of the mixture as a "Legal entity composition of the substance" in IUCLID Section 1.2? Q&As, ID: 1200.

<https://echa.europa.eu/support/qas-support/qas> (last accessed 2017-11-04)

ECHA (2016g): My substance is a multi-constituent substance. I cannot derive any IUPAC name for it. What should I report in the 'IUPAC name' field of IUCLID Section 1.1? Q&As, ID: 1197.

<https://echa.europa.eu/support/qas-support/qas> (last accessed 04/11/2017)

ECHA (2016h): My substance is a UVCB substance. I cannot derive any IUPAC name for it. What should I report in the 'IUPAC name' field of IUCLID Section 1.1? Q&As, ID: 1196.

<https://echa.europa.eu/support/qas-support/qas> (last accessed 2017-11-04)

ECHA (2016i): Part D: Framework for exposure assessment. In: Guidance on information requirements and chemical safety assessment. European Chemicals Agency, Helsinki.

[https://echa.europa.eu/documents/10162/13632/information\\_requirements\\_part\\_d\\_en.pdf](https://echa.europa.eu/documents/10162/13632/information_requirements_part_d_en.pdf)

ECHA (2016j): Practical guide: How to use alternatives to animal testing to fulfil the information requirements for REACH registration. No. ECHA-16-B-25-EN, ISBN 978-92-9495-200-4, date: 2016-07-19. European Chemicals Agency, Helsinki. DOI: 10.2823/194297

ECHA (2016k): Practical guide: How to use and report (Q)SARs. No. ECHA-16-B-09-EN, ISBN 978-92-9247-809-4. European Chemicals Agency, Helsinki. DOI: 10.2823/81818

ECHA (2016l): Report on the Operation of REACH and CLP 2016. No. ECHA-16-R-08-EN, ISBN 10.2823/760148. European Chemicals Agency, Helsinki. DOI: 10.2823/760148

ECHA (2016m): Transition to the new IT tools - how to prepare. Technical information for existing registrants. No. ECHA-16-B-10-EN European Chemicals Agency, Helsinki.

[https://echa.europa.eu/documents/10162/13566/it\\_tools\\_transition\\_en.pdf](https://echa.europa.eu/documents/10162/13566/it_tools_transition_en.pdf)

ECHA (2016n): What are the criteria for deciding if a substance is highly insoluble in water or poorly water soluble? Q&As, ID: 0836. <https://echa.europa.eu/support/qas-support/qas> (last accessed 2017-11-04)

ECHA (2017a): Do I need to give a description of the manufacturing process for the identification of my UVCB substance, and, if yes, to what level of detail? Q&As, ID: 1199.

<https://echa.europa.eu/support/qas-support/qas> (last accessed 2017-11-04)

ECHA (2017b): Endpoint specific guidance (A). In: Guidance on Information Requirements and Chemical Safety Assessment, chapter R.7a. European Chemicals Agency, Helsinki. ISBN: 978-92-9495-970-6. DOI: 10.2823/337352

ECHA (2017c): Endpoint specific guidance (B). In: Guidance on information requirements and chemical safety assessment, chapter R.7b. European Chemicals Agency, Helsinki. ISBN: 978-92-9495-837-2. DOI: 10.2823/84188

ECHA (2017d): Endpoint specific guidance (C). In: Guidance on information requirements and chemical safety assessment, chapter R.7c. European Chemicals Agency, Helsinki, Helsinki. ISBN: 978-92-9495-838-9. DOI: 10.2823/43472

ECHA (2017e): Evaluation under REACH: progress report 2016. Report no. ECHA-17-R-03-EN, ISBN 978-92-9495-784-9. European Chemicals Agency, Helsinki. DOI: 10.2823/588707

ECHA (2017f): For the identification of a UVCB substance, I am supposed to provide information on the manufacturing process. Can I instead report in IUCLID what I know about the composition

of the UVCB substance? Q&As, ID: 1319. <https://echa.europa.eu/support/qas-support/qas> (last accessed 2017-11-04)

ECHA (2017g): Guidance for identification and naming of substances under REACH and CLP. No. ECHA-16-B-37.1-EN, ISBN European Chemicals Agency,, Helsinki. DOI: 978-92-9495-711-5

ECHA (2017h): Information on manual verification at completeness check. European Chemicals Agency. [https://echa.europa.eu/documents/10162/13652/manual\\_completeness\\_check\\_en.pdf](https://echa.europa.eu/documents/10162/13652/manual_completeness_check_en.pdf) (last accessed 19/06/2017)

ECHA (2017i): Manual: How to prepare registration and PPORD dossiers. No. ECHA-16-B-13-EN, ISBN 978-92-9247-865-0. European Chemicals Agency. DOI: 10.2823/511034

ECHA (2017j): My composition falls outside the boundary composition reported in the lead registration dossier. What should I do? Q&As, ID: 1450. <https://echa.europa.eu/support/qas-support/qas> (last accessed 2017-11-04)

ECHA (2017k): Newsletter February 2017, Issue 1. ECHA Newsletter 1 ([https://newsletter.echa.europa.eu/documents/6362380/22975056/newsletter\\_2017\\_issue\\_1\\_february\\_en.pdf](https://newsletter.echa.europa.eu/documents/6362380/22975056/newsletter_2017_issue_1_february_en.pdf)) (last accessed 2017-06-22)

ECHA (2017l): PBT/vPvB assessment. In: Guidance on information requirements and chemical safety assessment, chapter R.11. European Chemicals Agency, Helsinki, Helsinki. ISBN: 978-92-9495-839-6. DOI: 10.2823/128621

ECHA (2017m): Read-Across Assessment Framework (RAAF). No. ECHA-17-R-01-EN, ISBN 978-92-9495-758-0. European Chemicals Agency, Helsinki. DOI: 10.2823/619212

ECHA (2017n): What is the difference between the substance identity profile (SIP) and the boundary composition? Q&As, ID: 1447. <https://echa.europa.eu/support/qas-support/qas> (last accessed 2017-11-04)

Klimisch H.J., Andreae M., and Tillmann U. (1997): A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology* 25 (1), 1-5. DOI: 10.1006/rtph.1996.1076

OECD (2000): Guidance document on aquatic toxicity testing of difficult substances and mixtures. Report no. ENV/JM/MONO(2000)6, date: 2000-12-15. Organisation for Economic Cooperation and Development, Paris.

<http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?doclanguage=en&cote=env/jm/mono%282000%296>

OECD (2004): OECD principles for the validation, for regulatory purposes, of (quantitative) structure-activity relationship models. Organisation for Economic Cooperation and Development, Paris. <http://www.oecd.org/env/ehs/risk-assessment/37849783.pdf>

OECD (2007): Guidance document on the validation of (quantitative) structure-activity relationships [(Q)SAR] models. No. ENV/JM/MONO(2007)2, date: 2017-03-30, Paris.

<http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?doclanguage=en&cote=env/jm/mono%282007%292>

OECD (2017): QSAR Toolbox 4.1. <https://www.qsartoolbox.org/>

Oertel A., Maul K., Menz J., Kronsbein A.L., Sittner D., Springer A., Müller A.-K., Herbst U., Schlegel K., and Schulte A. (2017): REACH Compliance: Data availability in REACH registrations. Part 2: Evaluation of data waiving and adaptations for chemicals  $\geq 1000$  tpa. Report in preparation. German Federal Institute for Risk Assessment, Berlin. German Environment Agency, Dessau. <http://www.umweltbundesamt.de/>; <http://www.bfr.bund.de/de/start.html>

Springer A., Herrmann H., Sittner D., Herbst U., and Schulte A. (2015): REACH Compliance: Data Availability of REACH Registrations, Part 1: Screening of chemicals  $> 1000$  tpa. UBA TEXTE 43/2015. German Federal Institute for Risk Assessment, Berlin. German Federal Environment Agency, Dessau. <https://www.umweltbundesamt.de/publikationen/reach-compliance-data-availability-of-reach>