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# Guidance on information requirements and chemical safety assessment

## Part B: Hazard assessment

Version 2.1

December 2011

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***Guidance on information requirements and chemical safety assessment***
***Part B: Hazard Assessment***

**Reference:** ECHA-11-G-16-EN
**Publ.date:** December 2011
**Language:** EN

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# PREFACE

This document describes the information requirements under REACH with regard to substance properties, exposure, use and risk management measures, and the chemical safety assessment. It is part of a series of guidance documents that aim to help all stakeholders with their preparation for fulfilling their obligations under the REACH Regulation. These documents cover detailed guidance for a range of essential REACH processes as well as for some specific scientific and/or technical methods that industry or authorities need to make use of under REACH.

The guidance documents were drafted and discussed within the REACH Implementation Projects (RIPs) led by the European Commission services, involving stakeholders from Member States, industry and non-governmental organisations. After acceptance by the Member States Competent Authorities the guidance documents had been handed over to ECHA for publication and further maintenance. Any updates of the guidance are drafted by ECHA and are then subject to a consultation procedure, involving stakeholders from Member States, industry and non-governmental organisations. For details of the consultation procedure, please see:

http://echa.europa.eu/doc/about/organisation/mb/mb_14_2011_consultation_procedure_guidance.pdf

The guidance documents can be obtained via the website of the European Chemicals Agency

http://echa.europa.eu/reach_en.asp

Further guidance documents will be published on this website when they are finalised or updated.

This document relates to the REACH Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006[1].

1 Corrigendum to 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 (OJ L 396, 30.12.2006); amended by amended by: Council Regulation (EC) No 1354/2007 of 15 November 2007 adapting Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), by reason of the accession of Bulgaria and Romania, Commission Regulation (EC) No 987/2008 of 8 October 2008 as regards Annexes IV and V; Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures; Commission regulation No 453/2010 of 20 May 2010 as regards Annex II; Commission Regulation No 252/2011 of 15 March 2011 as regards Annex I; Commission Regulation No 366/2011 of 14 April as regards Annex XVII (Acrylamide), Commission Regulation No 494/2011 of 20 May 2011, as regards Annex XVII (Cadmium).

**Document History**

| Version | Comment | Date |
|---|---|---|
| Version 1 | First edition | May 2008 |
| Version 1.1 | Correct reference to section R.7.12 has been included in the last paragraph of B.6.2.1 | October 2008 |
| Version 2 | Chapter B.8 added | August 2011 |
| Version 2.1 | Corrigendum replacing references to DSD/DPD by CLP references (including the substitution of R-phrases by hazard statements)<br>Editorial changes | December 2011 |

**Convention for citing the REACH regulation**

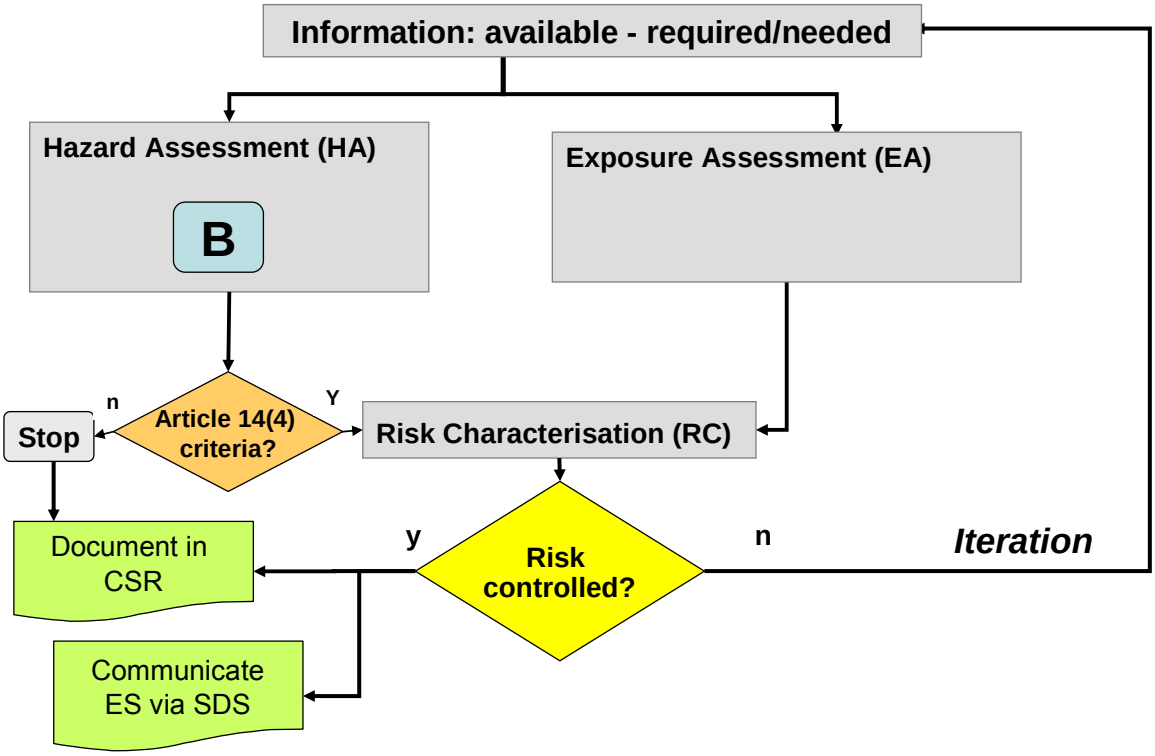
Where the REACH regulation is cited literally, this is indicated by text in italics between quotes.

**Table of Terms and Abbreviations**

See Chapter R.20

**Pathfinder**

The figure below indicates the location of Chapter B.8 within the Guidance Document



# TABLE OF CONTENTS


**B.1 INTRODUCTION ..... 1**

**B.1.1 Aim of this module ..... 1**

**B.1.2 Steps in the hazard assessment ..... 1**

**B.2 INFORMATION GATHERING AND EVALUATION PROCESS ..... 2**

**B.2.1 Information requirements under REACH ..... 2**

**B.2.2 Information Gathering and Evaluation ..... 2**

**B.3 INFORMATION GATHERING – PRACTICAL ASPECTS ..... 5**

**B.3.1 Information sources ..... 5**

**B.3.2 Recording the search strategy (Section R.3.2) ..... 5**

**B.3.3 Data sharing ..... 6**

**B.4 EVALUATION OF AVAILABLE INFORMATION ..... 7**

**B.4.1 Relevance ..... 7**

**B.4.2 Reliability ..... 7**

**B.4.3 Adequacy ..... 7**

B.4.3.1 Test data ..... 7

B.4.3.2 Non-testing data ..... 8

B.4.3.3 Human data ..... 9

**B.4.4 Evaluation and integration of all available information including Weight of Evidence ..... 10**

**B.5 SPECIAL FACTORS AFFECTING INFORMATION REQUIREMENTS AND TESTING STRATEGIES ..... 11**

**B.5.1 Adaptations under Annex XI ..... 11**

**B.5.2 Other factors influencing further information needs ..... 11**

**B.6 ENDPOINT SPECIFIC GUIDANCE ..... 13**

**B.6.1 Physico-chemical properties ..... 13**

B.6.1.1 Flammability ..... 14

B.6.1.2 Explosivity ..... 15

B.6.1.3 Oxidising properties ..... 15

B.6.1.4 Other physico-chemical properties ..... 16

**B.6.2 Human health endpoints ..... 17**

B.6.2.1 Guidance on toxicokinetics ..... 17

B.6.2.2 Irritation and corrosion ..... 18

B.6.2.3 Skin and respiratory sensitisation ..... 19

B.6.2.4 Acute toxicity ..... 19

B.6.2.5 Repeated dose toxicity ..... 20

B.6.2.6 Reproductive and developmental toxicity ..... 21
B.6.2.7 Mutagenicity ..... 21
B.6.2.8 Carcinogenicity ..... 22
**B.6.3 Environmental endpoints ..... 23**
B.6.3.1 Aquatic toxicity ..... 23
B.6.3.2 Sediment toxicity ..... 24
B.6.3.3 Toxicity to sewage treatment plant micro-organisms ..... 24
B.6.3.4 Degradation/biodegradation ..... 25
B.6.3.5 Aquatic bioconcentration and bioaccumulation ..... 25
B.6.3.6 Terrestrial bioaccumulation ..... 26
B.6.3.7 Long-term toxicity to birds ..... 27
B.6.3.8 Terrestrial toxicity ..... 27

**B.7 DERIVING THRESHOLD AND NON-THRESHOLD EFFECT LEVELS ..... 28**
**B.7.1 Characterisation of dose/concentration-response for human health ..... 28**
B.7.1.1 Objective and key issues ..... 28
B.7.1.2 Legislative requirements for setting DNELs ..... 30
B.7.1.2.1 Derivation of DNEL ..... 30
B.7.1.2.2 If no DNEL can be derived ..... 30
B.7.1.3 Overview of aspects to be considered in derivation of DNEL(s) / DMEL(s) ..... 31
B.7.1.4 How to derive DNEL(s) ..... 32
B.7.1.4.1 Identifying dose descriptors and deciding on mode of action ..... 32
B.7.1.4.2 Modification of the relevant dose descriptor(s) per endpoint to the correct starting point ..... 32
B.7.1.4.3 Application of assessment factors to the corrected starting point to obtain endpoint-specific DNEL(s) for the relevant exposure pattern ..... 32
B.7.1.5 Derivation of DMEL(s) for non-threshold endpoints ..... 33
B.7.1.5.1 The ‘Linearised’ approach ..... 33
B.7.1.5.2 The ‘Large Assessment Factor’ approach (“EFSA” approach) ..... 34
B.7.1.6 The qualitative approach when no dose descriptor is available for an endpoint ..... 34
B.7.1.7 Select the leading health effect(s) for relevant exposure patterns ..... 35
**B.7.2 Predicted No Effect Concentration (PNEC) for the environment ..... 36**
B.7.2.1 General principles of derivation of PNEC values ..... 36
B.7.2.2 Derivation of PNEC for freshwater ..... 38
B.7.2.3 Derivation of PNEC for marine water ..... 39
B.7.2.4 Derivation of PNEC for sediment and soil ..... 39
B.7.2.5 Derivation of PNEC for sewage treatment plant (STP) ..... 40
B.7.2.6 Derivation of PNECs for the air compartment ..... 40
B.7.2.7 Derivation of PNECs for predators and top predators ..... 40

**B.8 SCOPE OF EXPOSURE ASSESSMENT ..... 43**
**B.8.1 Background and aim of the chapter ..... 43**
**B.8.2 General principles ..... 44**
**B.8.3 Establishing whether exposure assessment is required ..... 45**

**B.8.4 Scope of exposure assessment ..... 47**

B.8.4.1 Scope of exposure assessment related to toxicological hazards for human health ..... 48

B.8.4.1.1 Classified acute hazards ..... 50

B. 8.4.1.2 Classified long-term hazards ..... 50

B.8.4.1.3 Non classified hazards ..... 50

B.8.4.2 Scope of exposure assessment related to environmental hazards ..... 51

8.4.2.1 Classified hazards ..... 53

8.4.2.2 Non-classified hazards ..... 53

**B.8.5 Types of exposure assessment and risk characterisation ..... 54**

B.8.5.1 Human health ..... 54

B.8.5.2 Environment ..... 55

**Appendix 1 Hazard classes in Annex I to Regulation (EC) No 1272/2008 ..... 56**

**Appendix 2 Classification related to human health effects after short-term exposure ..... 57**

**Appendix 3 Classification related to human health effects after long-term exposure ..... 58**

**Appendix 4 Classification related to environmental effects ..... 59**

## TABLES

Table B-7-1: High to low dose risk extrapolation factors used to derive a DMEL ..... 34

Table B-7-2: Summarising the derivation of an endpoint-specific DNEL/DMEL ..... 36

Table B-8-1: Exposure assessment – overview ..... 47

Table B-8-2: Types of human health exposure assessment and risk characterisation ..... 54

## FIGURES

Figure B-7-1: Illustration of the different steps of the quantitative human health risk assessment for threshold endpoints ..... 29

Figure B-8-1: Overview of the decision making process leading to the need to perform an exposure assessment for human health and the environment ..... 46

Figure B-8-2: Overview of the decision making process to identify the required scope of exposure assessment with regard to human health ..... 49

Figure B-8-3: Overview of the decision making process to identify the required scope of exposure assessment with regard to the environment ..... 52

# B.1 INTRODUCTION

## B.1.1 Aim of this module

The Part R, which is primarily aimed at experienced toxicologists, ecotoxicologists and risk assessors, provides detailed information and extensive guidance on collection and assessment of all the relevant and available information on the intrinsic properties of the substances to be registered under REACH, on the information requirements specified by the Regulation, on the identification of data gaps and on the generation of the additional information required to meet the needs of the Regulation. The Part R contains guidance on many of the more complex issues under REACH including the testing requirements in Annexes VII-X, the integrated testing strategies (ITSs) for each endpoint and the adaptations of the standard testing regime in accordance with Column 2 of the Annexes VII to X and Annex XI.

This module provides a more concise overview of the information requirements under REACH, the integrated testing strategies for each endpoint and the possibilities of adapting these. It is aimed at non-experts who may need to understand the testing approach in order to engage with experts in compiling registration dossiers and directs the user to the relevant sections of the more detailed Part R providing introductory guidance with regard to:

1. The information requirements specified by REACH
2. The process of gathering and evaluating all available data for their adequacy, reliability and completeness
3. The use of all data including those from alternative testing approaches and methods
4. Guidance on the strategies for generation of additional data needed for hazard assessment, and classification and labelling

## B.1.2 Steps in the hazard assessment

In this module, as with its Part R counterpart, the guidance begins with a description of how the standard information requirements in REACH vary according to the tonnage of a substance and the overall process to be followed for meeting the needs of the regulation (Chapter B.2). The steps of the process are further defined, beginning with the gathering of all relevant and available information (Chapter B.3) followed by the hazard assessment of the available information, a process that comprises three elements, which result in sections in the chemical safety report:

Step 1. Evaluation and integration of available information (Chapters B.4 to B.6)

Step 2. Classification and Labelling

Step 3. Derivation of the hazard threshold levels for human health and the environment (Chapter B.7)

Classification and labelling (step 2) is not further covered in Part B, but Chapter R.7 includes guidance on which information can be considered appropriate for the classification and labelling of substances. The classification and labelling criteria for substances and mixtures are provided in Annex I to Regulation (EC) No 1272/2008 (CLP Regulation).

# B.2 INFORMATION GATHERING AND EVALUATION PROCESS

## B.2.1 Information requirements under REACH

Standard information requirements

Article 10 of REACH outlines the minimum information that must be submitted as part of a registration. Generally, the information requirements increase with increasing tonnage manufactured or imported, as outlined in Article 12 of REACH; Annexes VI-XI of the regulation outline the detailed information requirements for each tonnage band (see also Section R.2.1).

Article 12(1) and Annex VI expressly require that all physicochemical, toxicological and ecotoxicological information that is relevant and available to the registrant shall be included in the registration dossier. As a minimum this shall include the information specified in the Annexes VII-X taking into account the general rules for adaptation of these standard testing regimes as defined in Annex XI.

The standard information requirements for registration and evaluation of a substance are listed in column 1 of Annex VII for substances registered in quantities ≥ 1 t/y Annex VIII for ≥ 10 t/y, Annex IX for ≥ 100 t/y and Annex X for ≥ 1000 t/y. Every time a new tonnage band is reached, the requirements of the corresponding Annex have to be fulfilled. This means that information on a substance that is registered at, for example, the 100 t/y band will have to fulfil the requirements for Annex VII and VIII as well as Annex IX. The precise information required for each substance will differ according to tonnage, use and exposure. The Annexes shall thus be considered as a whole and in conjunction with the overall requirements of registration, evaluation and the duty of care.

Adaptations of the standard information requirements

Column 2 of Annexes VII-X list specific rules according to which the standard information requirements may be omitted, replaced by other information, provided at a different time or tonnage level or adapted in another way. In addition to these specific rules the required standard set of information may be adapted according to the provisions of Annex XI. All adaptations of the standard information requirements must be justified in the registration and CSR (where required) and the reasons for each adaptation should be clearly stated.

More detailed guidance on the information requirements and the appropriate adaptations is given in the Part R, Chapters R.1 to R.6 dealing with the generic aspects and Chapter R.7 providing the guidance specific to the individual physicochemical parameters and the human health and environmental effects endpoints.

## B.2.2 Information Gathering and Evaluation

Annex VI describes four steps that need to be followed by the registrant to fulfil the information requirements for a substance: (see also Section R.2.2)

Step 1: Gather and share existing information

Step 2: Consider information needs

Step 3: Identify information gaps

Step 4: Generate new information or propose a testing strategy

Step 1

In step 1, the registrant must collect all physicochemical, toxicological and ecotoxicological information that is relevant and available to him regardless of whether information on a given endpoint is required or not at the specific tonnage level. This includes available existing test data

as required in accordance with Annexes VII-X, data from other in vivo or in vitro testing, data generated by non-testing methods (e.g. from (Q)SARs, grouping, read-across, weight of evidence), epidemiological data, and any other data that may assist in identifying the presence or absence of hazardous properties of the substance.

Such information may be obtained from a variety of sources such as in-house data of companies, from other manufacturers and importers of the substance by cooperation in a SIEF (REACH Article 29), from the Agency upon request (REACH Article 26) or from databases or other sources in the open literature or accessible on the internet. This information gathering step may also include the establishment of membership of the substance in a proper chemical category (cf. Annex XI, 1.5) and the information this provides (incl. read-across from other substances), as well as the information that is retrievable from computational tools, i.e. (Q)SAR models. (Sections R.4.3.2 and R.6)

At this stage the registrant should assess all relevant and available information on physicochemical and environmental fate properties, toxicity and ecotoxicity of the substance for its reliability, relevance, adequacy and completeness. Although the reliability criteria are of a general nature, the decision on whether a single piece of information is reliable (i.e. how to assign it a specific level of reliability, e.g. using the Klimisch score) is endpoint specific. (Section R.4.2)

In addition, the registrant should collect information on exposure, use and risk management measures. This may require more details on, e.g., manufacture (if within EU), use, handling and disposal of the substance or of articles containing the substance (i.e. covering its whole life cycle) as well as the nature of the exposures, i.e. routes, frequency and duration. Considering all this information together, the registrant will be able to determine the need to generate further information.

All data gathering activities should be well documented, to allow a proper assessment of the completeness of the registration dossier and to avoid repetition at a later stage as each manufacturer or importer (and downstream user and distributor) is required to assemble and keep available all information he requires to carry out his duties under REACH for 10 years after the last manufacture or import of the substance.

Step 2

At step 2, the registrant needs to identify from Annexes VII to X the standard information requirements according to the tonnage he manufactures or imports. These standard requirements may have to be adapted in accordance with specific criteria for the endpoint in question as provided in column 2 of the annexes, or in accordance with the general criteria for adaptation of information requirements given in Annex XI (Sections R.2.1 and R.5.1).

For specific endpoints, column 2 specifies rules according to which the standard information can be omitted or is required. In many cases, these rules refer to information on other properties or endpoints of the substance in question and such information should also be reliable, i.e. have undergone the assessment under step 1 (Chapter R.7).

When the registrant makes use of the Annex XI criteria (i.e. regarding the scientific necessity of the information, the technical possibility for testing, and exposure-based waiving) to adapt the standard information requirements, he should base this on reliable and adequate information as it is specified in Annex XI and should document this in accordance with the guidance provided (Section R.5.1).

Specific rules apply to phase-in substances manufactured or imported in a tonnage of more than or equal to 1 t/y, but below 10 t/y, if they do not fulfil the criteria in Annex III. In that case, the standard information requirements are restricted to all physicochemical, toxicological and ecotoxicological information that is relevant and available to the registrant and as a minimum the physicochemical endpoints in Annex VII. The registrant needs to document thoroughly that the criteria of Annex III are not fulfilled, i.e. by submitting available and reliable information on properties relevant for the classification criteria and/or on the uses as appropriate. More detailed guidance on adaptation of

the information requirements on Annex VII substances is given in the Part R. (Sections R.2.1 and R.2.3)

Step 3

In step 3, the registrant compares the information needs for the substance identified in step 2 with the reliable and relevant information already available as identified in step 1. For endpoints where the REACH regulatory requirements cannot be fulfilled with relevant and available information, data should be obtained in accordance with the procedures of step 4.

Step 4

When a data gap has been identified in step 3 for information requirements included in Annexes VII or VIII, the registrant needs to conduct a test in accordance with Article 13.

When a data gap has been identified in step 3 for information requirements included in Annexes IX or X, the registrant needs to develop a testing proposal and include it in the registration dossier in accordance with Article 10(a)(ix). Whilst waiting for the results of this testing, the registrant should implement and/or recommend interim risk management measures and include them in his exposure scenarios and chemical safety report as documentation for control of risks (cf. REACH, Annex I, 0.5).

For each endpoint listed in column 1 of Annexes VII-X, an integrated testing strategy (ITS) has been generated to provide an endpoint-specific guidance on how to gather and assess available information, and consider new data needs and testing strategies. An overview of these testing strategies is presented in Chapter B.6 and details can be found in Sections R.7.1 to R.7.11.

# B.3 INFORMATION GATHERING – PRACTICAL ASPECTS

In Chapter R.3, detailed guidance is given on information searching strategies and sources of information that may be consulted in the critical first step of assembling all of the available information on a substance, or information that may be useful to inform on the properties of that substance. The following sections of this document provide only a brief summary of the direction and advice given in the indicated chapters of the Part R.

## B.3.1 Information sources

Under REACH, registrants are obliged to collect and submit all relevant and available information on the intrinsic properties of a substance, regardless of the quantity manufactured or imported, including: (see also Section R.3.1)

- substance identity
- physico-chemical properties
- exposure/uses/occurrence and applications
- mammalian toxicity
- toxicokinetics (Section R.7.12)
- chemical categories (Section R.6.2)
- ecotoxicity
- environmental fate, including chemical and biotic degradation

A critical first step is to assemble all of the available information on a substance and any relevant information that may clarify the properties of the substance. This necessary information can be obtained from a large number of sources that include but are not limited to:

- in-house company and trade association files (including test data)
- databanks and databases of compiled data
- agreed data sets such as the OECD HPV Chemicals Program
- published literature
- internet search engines and relevant websites
- (Q)SAR models (Section R.6.1)
- data sharing in the substance information exchange forum (SIEF)

Further information and guidance on the type of data that may be useful accompanied by a list of helpful articles on searching for health and hazard information and an indicative list of some major available databases and databanks can be found in Sections R.3.1 to R.3.4. Furthermore, a list of (Q)SAR models is available at the ECB website (http://ecb.jrc.it/QSAR)

## B.3.2 Recording the search strategy (Section R.3.2)

The exact search strategy for a particular substance will depend largely on that substance. Whatever strategy is employed, it is important to record what assumptions are made, what is done and when it is done as well as its outcome.

## B.3.3 Data sharing

Under Article 29 of REACH, a Substance Information Exchange Forum (SIEF) will be established for all phase-in substances where there is more than one potential registrant. The aim of the SIEF will be to facilitate sharing of information for the purposes of registration and to avoid duplication of studies. To achieve this, agreement is needed on access rights to animal testing studies in line with the obligatory conditions of sharing data in the SIEF. Generally, the SIEF should agree on and jointly submit information derived from application of the testing annexes VII to XI, the classification and labelling of the substance and any proposals for further testing. Further detailed guidance on this aspect is given in *Guidance on Data Sharing*.

# B.4 EVALUATION OF AVAILABLE INFORMATION

All available information that has been gathered on a substance needs to be assessed for its adequacy for classification and labelling, determination of PBT or vPvB status and the derivation of a dose descriptor to be used in the chemical safety assessment (CSA). The information should be evaluated for its completeness (does the available information meet the information required under REACH) and quality (relevance, reliability and adequacy).

## B.4.1 Relevance

Relevance is the extent to which data and tests are appropriate for a particular hazard identification or risk characterization.

## B.4.2 Reliability

Reliability is the inherent quality of a test report or a publication relating to preferably standardized methodology and the way the experimental procedure and results are described to give evidence of the clarity and plausibility of the findings. It is important to distinguish between reliable methods and reliable information.

The Klimisch code (Section R.4.2) is a scoring system for data reliability. The system consists of 4 reliability categories:

1. Reliable without restrictions
2. Reliable with restrictions
3. Not reliable
4. Not assignable

This, and other similar scoring systems, allows ranking and organization of the information for further review.

New toxicology and ecotoxicology tests should be carried out in compliance with the principles of GLP and preferably using regulatory acceptable protocol (such as EU and OECD protocols). Existing data may have been generated prior to GLP requirements and standardisation of methods and thus the reliability of existing studies must be carefully evaluated.

## B.4.3 Adequacy

Adequacy is the usefulness of the data for hazard and risk assessment purposes.

### B.4.3.1 Test data

<u>Use of test data derived from EU or international standardised methods</u>

According to REACH, Article 13(3), tests required for generating information on intrinsic properties of substances shall be conducted in accordance with the test methods included in a Commission Regulation or in accordance with other international test methods recognised by the Commission or the Agency as being appropriate. Toxicological and ecotoxicological tests and analyses shall be carried out in compliance with the principles of Good Laboratory Practice (GLP). The new Test Methods Regulation (Council Regulation (EC) No 440/2008) contains all the test methods previously included in Annex V to Directive 67/548/EEC. Data generated by any of these methods are *per se* considered adequate for regulatory use. Other internationally standardised test methods

may future be recognised by the Commission or the Agency as being adequate for generating data for regulatory use.

It is the intention of the Commission that the TM Regulation be adapted to technical progress whenever a new test method has been developed, scientifically validated and accepted for regulatory use by the National Coordinators of the Member states.

Use of test data derived from other methods

Test data derived from other types of experiments and/or without being in compliance with the GLP principles may also be considered adequate for use under REACH provided the conditions described in REACH, Annex XI (1.1) are met.

Use of *in vitro* data within REACH

Special considerations must be taken into account when evaluating adequacy of *in vitro* data. Distinction must be made between the suitability of the methodology and the adequacy of the data produced by a method. Two categories of *in vitro* methods are currently referred to within REACH as suitable:

- Validated methods. Examples include *in vitro* tests for skin corrosion and *in vitro* genotoxicity tests such as the Ames Salmonella typhimurium mutagenicity test.
- *In vitro* tests that meet internationally agreed pre-validation criteria from e.g. ECVAM.

The criteria for full validation and acceptance of a test method (including *in vitro* assays) are given in OECD GD 34 (Section R.4.3.1, Table R.4.-1).

Use of adequate information derived from *in vitro* methods

Adequate information from *in vitro* studies can be used in the following ways:

- Information from scientifically validated *in vitro* tests accepted for regulatory purposes may fully or partly replace animal testing depending on the purpose for which the test method was validated. A main criterion for acceptance for regulatory use is the adequacy of the information generated in such an *in vitro* assay for the purpose of classification and labelling and/or risk assessment.
- Information derived from suitable *in vitro* methods can be used for adapting the standard testing regime as set out in Annex XI. For details, see Section R.4.3.1.

### B.4.3.2 Non-testing data

Non-testing data consists of data generated by (Q)SAR models and experts systems and data obtained by grouping approaches (analogue and chemical category approaches).

(Q)SAR data

(Q)SAR data may support waiving of testing or serve as a trigger for further testing. According to REACH Annex XI, (Q)SAR results may be used instead of testing when all of 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/or risk assessment.
- Adequate and reliable documentation of the applied method is provided.

If any of these conditions are not met, the (Q)SAR results can not be used instead of testing but may be used as a part of Weight of Evidence approach.

A guide to (Q)SAR models can be found in the REACH guidance, Chapter R.6: (Q)SARs and grouping of chemicals

(http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_r6_en.pdf?vers=20_08_08 ), information on how to assess their validity is provided at the OECD website (www.oecd.org/env/existingchemicals/qsar).

(Q)SAR models should be documented using the (Q)SAR Model Reporting Format (QMRF) and individual model predictions should be documented using (Q)SAR Prediction Reporting Format (QPRF). The assessment of (Q)SAR validity and (Q)SAR estimate reliability needs to be supplemented with an assessment of the relevance of the prediction for the regulatory purpose which includes an assessment of completeness. Comprehensive guidance on (Q)SAR models and expert systems is provided in the Section R.6.1, focussing in particular on:

- how to establish the validity of a (Q)SAR model,
- how to establish the adequacy of a (Q)SAR model result for regulatory purposes,
- how to document and justify the regulatory use of a (Q)SAR mode, and
- where to find information on (Q)SAR models.

Data obtained by read-across and grouping approaches

Read-across and grouping approaches can be used to fulfil information requirements under REACH. A registrant making use of such methods needs to provide scientific justification and demonstrate that the approach used is adequate for the regulatory purpose (classification and labelling and/or risk assessment). The adequacy of the approach needs to be assessed for individual substances of interest. Comprehensive guidance on grouping approaches is provided in the Section R.6.2, focussing in particular on:

- the category concept, its mechanistic basis and the relationship between categories and QSARs,
- the main approaches for data gap-filling such as read-across, trend analysis and QSARs,
- the stepwise procedures for analogue read-across and chemical categories,
- specific issues to be considered for specific types of categories, and
- practical aspects of forming and documenting category approaches.

### B.4.3.3 Human data

Four major types of human data may be submitted and used for different purposes:

1. Analytical epidemiology studies on exposed populations (case-control, cohort and cross-sectional studies) are useful for identifying a relationship between human exposure and effects and may provide the best data for risk assessment.
2. Descriptive or correlation epidemiology studies are useful for identifying areas for further research but are not very useful for risk assessment since they often can only identify patterns or trends but cannot ascertain the causal agent or degree of human exposure.
3. Case reports may demonstrate effects which cannot be observed in experimental animals. Thorough assessment of the reliability and relevance of case reports is needed because they often lack critical information on e.g. substance purity, human exposure, and effects.
4. Controlled studies in human volunteers are acceptable in very rare cases. Testing with human volunteers is strongly discouraged but when good quality data are already available, they should be used as appropriate in well justified cases.

### B.4.4 Evaluation and integration of all available information including Weight of Evidence

The weight of evidence (WoE) approach is not a scientifically well-defined term or an agreed formalised concept. It involves assessing the relevance, reliability and adequacy of each piece of available information, holding the various pieces of information up against each other and reaching a conclusion on the hazard. This process always involves expert judgement. It is important to document and communicate how the evidence-based approach was used in a reliable, robust and transparent manner.

# B.5 SPECIAL FACTORS AFFECTING INFORMATION REQUIREMENTS AND TESTING STRATEGIES

## B.5.1 Adaptations under Annex XI

As noted in Section B.2.2, adaptations to the standard information requirements under REACH are possible under certain conditions; in addition to endpoint-specific considerations listed in column 2 of Annexes VII-X, Annex XI defines three areas for adaptation:

1. Testing does not appear scientifically necessary:

   Existing data, Weight of Evidence approaches, non-testing methods and *in vitro* methods may provide information that may be judged to be valid, reliable, relevant and adequate for the intended purpose (classification and labelling, PBT assessment, and/or risk assessment). More detailed guidance is given in the Section R.5.2.1.

2. Testing is technically not possible:

   REACH Annex XI section 2 states that 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:

   - Testing may be waived based on physico-chemical properties of a substance, such as low water solubility, vapour pressure, reactivity etc., that preclude the application of certain test methods.
   - Administration of precise and consistent doses of a substance may be impossible because of its physico-chemical properties e.g. testing of non-water soluble compounds for fish toxicity and in submerged cell cultures.

   More detailed guidance on these aspects is given in the Section R.5.2.2.

3. Substance-tailored exposure driven waiving or testing:

   In certain situations, the exposure pattern of the substance to be registered may justify adaptation of the testing strategy leading to omission, triggering, replacement or modification of the studies required for compliance with REACH. Further information and guidance on exposure driven waiving and triggering of information needs can be found in Annex VIII (sections 8.6 and 8.7), Annex IX, Annex X and Annex XI of REACH as well as in Chapter R.5.1 and Chapter R.7 of the current Guidance.

Any adaptation should be properly justified and documented based either on a qualitative or semi-quantitative weight of evidence approach (due to column 2 options) or on a quantitative exposure assessment in accordance with Annex I, including development of exposure scenarios (due to Annex XI options).

## B.5.2 Other factors influencing further information needs

Toxicokinetics

Information on the toxicokinetics of a substance may identify the optimal study type and design including dose settings, or even make further testing unnecessary. Further information on toxicokinetics can be found in Section R.7.12.

Substances requiring special considerations during testing

The appropriate information and methods used for substances designated as *Non-standard substance*, *Complex substance* or *Substances of Unknown or Variable composition*, *Complex*

*reaction products* or *Biological material* (UVCB substances) need to be evaluated on a case-by-case basis. Further guidance on these considerations is given in the Section R.7.13.

# B.6 ENDPOINT SPECIFIC GUIDANCE

The Chapter R.7 contains detailed specific guidance on gathering, evaluating and, where necessary, generating of information on the physicochemical properties and the different human health and environmental endpoints to help registrants provide adequate and relevant information for registration under REACH.

A crucial component of these endpoint-specific sections is the Integrated Testing Strategy (ITS) which gives guidance on how to define and generate relevant information on substances in order to meet the requirements of REACH.

This document provides the basic principles of the guidance given for each of the endpoints in the section R which should be consulted for more in-depth advice and information. The following general considerations regarding the endpoint specific guidance should be borne in mind:

- The endpoints in the hazard assessment are interrelated:

  Information collected within one endpoint may influence hazard/risk assessment of another endpoint and may be usable in more than one endpoint.

- The methods for generating additional information should be reliable:

  New tests should be conducted in accordance with test methods specified in a Commission Regulation or by methods recognized by the Commission or the Agency as being appropriate. New (eco)toxicology tests should be compliant with GLP or other comparable standards.

- Degradation products and metabolites should be considered:

  Further investigation may be required for degradation products and metabolites if considered relevant for the chemical safety assessment, PBT assessment or classification and labelling.

- The appropriate route of exposure for toxicity testing should be selected:

  The choice of route of exposure should take into consideration all available information such as physicochemical properties of the substance and the relevant route(s) of human exposure. Route-to-route extrapolation may be possible on a case-by-case basis.

For each endpoint for which information is available or required, a robust study summary should be developed in IUCLID 5. If more than one study on the same endpoint is available (e.g. more than one test or both testing and non-testing data), the key study should be identified. In general, the key study is the study giving rise to the highest concern, unless it is justified that this study is not valid or adequate. In that case, a robust study summary shall be developed also for the study demonstrating a higher concern than the key study even if not used for the hazard assessment.

## B.6.1 Physico-chemical properties

The registration dossier of the substance includes data on most of the general physico-chemical properties already at a low tonnage level (links to the relevant Sections in Chapter R.7 are provided in the list):

***Manufacture/import of 1 tonne or more/year***

- State of the substance at 20 $^{o}$C and 101,3 kPa
- Melting/freezing point (Section R.7.1.2)
- Boiling point (Section R.7.1.3)
- Relative density (Section R.7.1.4)
- Vapour pressure (Section R.7.1.5)
- Surface tension (Section R.7.1.6)

- Water solubility (Section R.7.1.7)
- Partition coefficient in-octanol/water (Section R.7.1.8)
- Flash-point (Section R.7.1.9)
- Flammability (Section R.7.1.10)
- Explosive properties (Section R.7.1.11)
- Self-ignition temperature (Section R.7.1.12)
- Oxidising properties (Section R.7.1.13)
- Granulometry (Section R.7.1.14)

***Manufacture/import of 100 tonnes or more/year***

- Stability in organic solvents and identity of relevant degradation products (only required if stability of the substance is considered to be critical) (Section R.7.1.16)
- Dissociation constant (Section R.7.1.17)
- Viscosity (Section R.7.1.18)

In the chemical safety report the potential effects to human health shall be assessed for at least three physico-chemical properties: explosivity, flammability and oxidizing potential. The assessment of the potential effects arising from the capacity of hazardous chemicals to cause accidents, in particular fires, explosions or other hazardous chemical reactions covers:

- hazards resulting from the physicochemical nature of the chemical agents,
- risk factors identified in their storage, transport and use, and
- the estimated severity in the event of occurrence.

The objective of the hazard assessment for physicochemical properties shall be to determine the classification and labelling of a substance in accordance with the CLP Regulation. If the data are inadequate to decide whether a substance should be classified for a particular end-point, the registrant shall indicate and justify the action or decision he has taken as a result.

Further information on the specific physico-chemical hazard assessment is given in Chapter R.9.

### B.6.1.1 Flammability

Flammability of a substance is an important safety consideration. Special precautions need to be taken during the handling, use and storage of flammable substances to avoid fires or explosions. Flammability is usually seen as the ease with which a substance can burn or be ignited. Rarely a substance can be spontaneously flammable (pyrophoric) or ignite on contact with water.

Based on the information collected a distinction can be made in the classification and labelling of flammable substances and its potential source of ignition (e.g. contact with water, electrostatic sparks, welding/soldering) which - in combination - can create serious effects for human health.

The respective hazard class will determine the technical means to be taken to avoid dangerous events which, in combination with other endpoints like i) explosive limits, ii) flash points (applicable only for liquids) or iii) self-ignition temperature, can lead to clear restrictions in the conditions of use.

*Gases*: A flammable gas is a gas having a flammable range with air at 20°C and standard pressure (101.3 kPa). The Lower Explosive Limit (LEL) and Upper Explosive Limit (UEL) should be determined and documented in the CSR or a statement that the gas is non-flammable should be given. The LEL and UEL are usually expressed as % of gas in air by volume.

*Liquids:* The flash point is a key measure of the flammability of a liquid. It measures the lowest temperature at which the vapour/air mixture above the liquid can be ignited. This gives some indication of how easy it is to initiate the burning of this substance.

*Solids*: A flammable solid is one that is readily combustible. It is especially difficult to extinguish a fire in metal powders. It is useful to know of any explosive properties before testing is carried out. The fastest burning rate should be recorded, together with the purity, physical state and moisture content of the test substance.

### B.6.1.2 Explosivity

Explosivity is defined as the tendency of a substance to undergo violent and rapid decomposition, under appropriate conditions, to produce heat and/or gas. Whether or not a substance with explosive properties can cause an explosion depends on a number of factors. To overcome these variables standard tests with fixed parameters have been devised.

For the majority of substances, explosivity is not a concern and testing can be waived based on a consideration of the structure. Gases do not need to be tested and liquids do not need to be tested for sensitivity towards friction.

The screening procedures described in Section R.7.1.11 represent a testing strategy for explosive properties.

The European Commission has issued a guidance of good practice for the assessment and prevention of formation of explosive atmospheres at the workplace, avoiding ignition of explosive atmospheres and controlling the effects of explosion[2]. Other obligations for assessment and safe use of explosive substances are addressed under Directive 96/82/EC on the control of major accident hazards involving dangerous substances (see Section R.9.1).

### B.6.1.3 Oxidising properties

Substances with oxidizing properties can give rise to a highly exothermic reaction in contact with other substances, in particular with flammable substances (see above and Section R.7.1.10). They can have irritating effects to skin, eyes and to the respiratory tract as they can react with the human tissue under formation of high temperatures thus destructing biological material.

For the majority of substances, oxidising properties are not a concern and testing can be waived based on a consideration of the structure. For solids, testing should not be performed on explosive or highly flammable substances. Organic peroxides form a separate class of substances that are always oxidising.

Guidance on the collection and evaluation of available information is available in Section R.7.1.13. The screening procedures described represent an integrated testing strategy for oxidising properties. If applied correctly, only substances which are suspected to give a positive result in one of the oxidising properties tests will need to be tested.

Not all substances that have oxidizing properties are indeed hazardous; some are mildly oxidizing only and present very little hazard. To distinguish those that are hazardous, a substance's oxidizing properties are compared to those of standard reference substances.

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[2] **Communication from the Commission concerning the non-binding guide of good practice for implementing Directive 1999/92/EC of the European Parliament and of the Council on minimum requirements for improving the safety and health protection of workers potentially at risk from explosive atmospheres, available at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2003:0515:FIN:EN:PDF**[2] Further information can be found in http://ec.europa.eu/employment_social/emplweb/publications/publication_en.cfm?id=56

### B.6.1.4 Other physico-chemical properties

A number of other physico-chemical properties are also important when making chemical safety assessment.

**The boiling point** is one of the most useful properties for the characterisation of organic compounds. Besides indicating the physical state (liquid or gas) of a substance at ambient or room temperature, boiling point serves as an indicator of volatility even for laymen, with higher boiling points indicating lower volatility. The boiling point is a key input in equations that provide estimates of a chemical's vapour pressure as a function of temperature.

The boiling point value is also useful for the identification of pure substances and with melting point and refractive index, as criteria of purity. The results obtained for mixtures or impure samples are to be interpreted with care. The boiling point is one of the criteria used in assigning a substance to an appropriate flammability category (see above).

**Vapour pressure** is a key parameter in determining the fate and behaviour of a substance and subsequent exposure of workers, consumers and the environment. The vapour pressure of a chemical provides considerable insight into the transport and partitioning of a chemical in the environment and in commercial settings. The volatility of a pure chemical is dependent upon the vapour pressure, and volatilisation from water is dependent upon the vapour pressure and water solubility. The form in which a chemical will be found in the atmosphere is dependent upon the vapour pressure. Water surface condition and wind speed will have a significant effect on any evaporation of chemicals.

Vapour pressure data is required as a pre-requisite for animal and environmental studies. It informs whether a substance may be available for inhalation as a vapour and whether occlusive conditions are necessary for dermal studies (to limit evaporation from skin).

**Water solubility** is a significant parameter, especially for environmental assessments, as the mobility of a test substance is largely determined by its solubility in water. Also, water solubility can affect adsorption and desorption on soils and volatility from aquatic systems. The knowledge of the water solubility is a prerequisite for setting up test conditions for e.g. aquatic toxicity, bioaccumulation.

Determination of water solubility is not required if the substance is hydrolytically unstable at pH 4, 7 or 9 with a half-life less than 12 hours, readily oxidisable in water, or flammable in contact with water. Water solubility, hydrolytic stability and acid dissociation constant are inter-related, and it is not possible to measure any of these without some knowledge of the other two.

**The n-octanol/water partition coefficient ($K_{ow}$)** is one of the key physico-chemical parameters, and it is used in numerous estimation models and algorithms for environmental partitioning, sorption, bioavailability, bioconcentration, bioaccumulation and also human toxicity and eco-toxicity. As such $K_{ow}$ is a critical parameter for chemical safety assessment (CSA), classification and labelling (C&L), and PBT assessment and needs to be determined with the greatest possible accuracy. $K_{ow}$ does not need to be determined if the substance is purely inorganic.

The n-octanol/water partition coefficient ($K_{ow}$) is defined as the ratio of the equilibrium concentrations of a dissolved substance in a 2-phase system consisting of the largely immiscible solvents n-octanol and water (Section R.7.1.8). $K_{ow}$ is moderately temperature-dependent and typically measured at 25°C. It can be determined either by an appropriate estimation method based on the molecule's structure or by a laboratory test. In the literature and in on-line chemical databases predicted and measured $K_{ow}$ values can be found for a wide range of organic substances. High-quality experimentally derived or peer-reviewed $K_{ow}$ values assigned as 'recommended values', are preferred over other determinations of $K_{ow}$.

## B.6.2 Human health endpoints

There are certain generic principles, relevant for information requirements and hazard assessment, which should be considered for most effect endpoints:

- When the end-point specific Information Strategies are followed, the information should be sufficient to make a classification decision with respect to the hazard and to provide the necessary data for the hazard assessment and DNEL derivation.
- According to REACH Annex VI, the registrant should gather all available test data on the substance to be registered as well as all other available and relevant information on the substance regardless whether testing for a given endpoint is required or not at the specific tonnage band.
- Where there is an information gap that needs to be filled, new data shall be generated (REACH Annexes VII and VIII), or a testing strategy shall be proposed (REACH Annexes IX and X), depending on the tonnage level. New tests on vertebrates shall only be conducted or proposed as a last resort when all other data sources have been exhausted.
- Toxicological information can be obtained from data bases and publications such as books, scientific journals, criteria documents, monographs and other publications. Also published data on structural analogues and physico-chemical properties can be relevant.
- In principle, three types of *adaptations* from testing are possible due to exposure considerations: exposure-based waiving of a study, exposure-based triggering of further studies, or selection of appropriate exposure route. These adaptations are not relevant for all endpoints (see Chapter R.5).
- In the category approach, not every substance needs to be tested for every endpoint. However, the information finally compiled for the category must prove adequate to support a hazard assessment, a risk assessment and a classification for the category and its members. The final data set must allow one to assess the untested endpoints, ideally by interpolation between and among the category members.
- Adherence to the relevant test guidelines and the GLP ensures the reliability of the data (ref. to data assessment in Chapter R.4).
- Dose related increase in the effect is one of the criteria for assessing the positive test results. In some cases, effects such as saturation of bio-activation may lead to a constant response at higher exposure levels.
- The derivation of DNELs is required for the chemical safety assessment (CSA) of substances manufactured/imported/used in quantities from 10 t/y upwards, but not for substances at 1-10 t/y.
- If data is available for several species, then the most sensitive species should be chosen for the purposes of the chemical safety assessment, provided it is the most relevant to humans.

In the chapters below, the endpoint-specific information requirements and guidance for the hazard assessment are summarized.

### B.6.2.1 Guidance on toxicokinetics

Although REACH does not specifically require generation of toxicokinetic information, it does require that all relevant available information is used to assess the toxicokinetic behaviour of a substance, and that human health hazard assessment considers the toxicokinetic profile of the substance. The toxicokinetic profile of a substance describes its absorption, distribution, metabolism and excretion.

Knowledge of the toxicokinetic behaviour of a substance derived from available data might make further testing unnecessary in terms of predictability of other properties. Toxicokinetic studies can provide useful and important information, for example on the bioavailability of a substance, the (non)-linearity and saturation of absorption, metabolic or excretion pathways, the accumulation of parent compounds or metabolites in tissues, the potential bioactivation of a substance and its toxicological mode of action. It is important to keep these and other similar factors in mind during data interpretation, when designing categories, for interspecies and inter-route extrapolations and while optimising testing design, for example when choosing the appropriate doses for *in vivo* studies. Toxicokinetic modelling (empirical or physiologically-based) may be able to estimate the toxicokinetics of a substance quicker and cheaper than classical *in vitro* and *in vivo* studies and in addition reduce the use of experimental animals. More extensive guidance on toxicokinetic data and their application is given in the Section R.7.12.

Appendices to the Section R.7.12 list examples and information relevant to toxicokinetics, including numerous useful physiological parameters for common laboratory species and humans (Appendix R.7.12-1), the future use of *in silico* (computational) and/or *in vitro* methods (Appendix R.7.12-2), an example of the development of an assessment factor using PBK modelling (Appendix R.7.12-3) and calculations of dermal absorption percentage based on *in vivo* rat studies in combination with *in vitro* data and a proposal for a tiered approach to risk assessment (Appendix R.7.12-4).

### B.6.2.2 Irritation and corrosion

Irritation and corrosion refers local effects on the skin, in the eyes or in respiratory system. Corrosivity causes irreversible damage of the tissues whereas dermal, eye or respiratory irritation are considered to be reversible and usually less severe.

Information requirements on irritation/corrosion are set already at the lowest tonnage band (1-10 t/y). At first, all available data on humans and animals, the current classification, pH of the substance and existing acute toxicity studies by dermal route need to be assessed. Strongly acidic or alkaline substances as well as strong oxidants are known to be irritant or corrosives, depending on the concentration. When conclusion on irritation and corrosion can not be drawn from available data for substances at 1-10 t/y band, in vitro tests need to be performed. At the next tonnage band (10-100 t/y), in vivo skin and eye irritation studies are the standard information requirement. However, specific rules of adaptation in column 2 of the relevant annex (VIII) and general rules of adaptation (annex XI) need to be considered before in vivo testing is proposed. Currently there is no validated test for respiratory irritation. Substances which are corrosive on the skin in vivo should not be tested in the eye. For detailed information strategy and requirements, see Section R.7.2.6.

In some cases, relevant data comes from occupational case studies and reports. The general guidance on evaluation of the data quality should be applied, when assessing the human data (see Chapter R.4). For skin and eye, the results of in vivo test results are relevant, because the mechanisms of these local effects are considered to be the same in animals and in human. Some inter-species differences have been found in the mechanism of respiratory irritation. A chemical known or predicted to be corrosive to the skin is automatically considered to be severely irritating to the eye. QSAR or read-across/category data may be used according to principles set in Annex XI.

Human data on dermal and respiratory irritation can be available, and has been the basis of setting the Occupational Exposure Limits (OELs) in a number of cases. In case a substance meets the relevant classification criteria, further testing is usually not necessary. Detailed guidance on the assessment and integrated testing strategy (ITS) is given in Section R.7.2

The information on the exact concentration that causes the irritation or corrosion is not always available. When that information is missing, a qualitative approach has to be taken, where yes/no answer is obtained from the tests, and RMMs would be driven by the severity of the effect (see Part E). For corrosive substances, strict measures have to be taken to prevent any contact. Occasionally, when the clinical signs of irritation or corrosion were recorded in the

dermal/inhalation repeated dose study, a DNEL can be obtained and used for risk characterization (see appendix 9 in R.8).

### B.6.2.3 Skin and respiratory sensitisation

Skin sensitisation is caused by agents that can activate the immune system, which leads to allergic response. Following subsequent exposures of the skin, allergic contact dermatitis or atopic dermatitis may be provoked. After inhalation exposure, adverse health effects include asthma or extrinsic allergic alveolitis. Respiratory hypersensitivity can be caused by immunological or non-immunological mechanisms.

Information requirement on skin sensitisation, (usually a LLNA test), is set at the tonnage band of 1-10 t/y. In vivo testing with corrosive substances at concentration or dose, which causes corrosivity, shall be avoided. Available data, when it is sufficient for classification and pH of the substance need to be considered before in vivo testing. For respiratory sensitisation, there are no standard information requirements. In some cases the available human data may be sufficient for the hazard assessment.

Evidence for local toxicity, skin inflammation and available information of skin irritation should be considered when LLNA results are assessed. The LLNA has been shown to correlate relatively well with the human data on skin sensitisation and may therefore be used for hazard assessment.

Human data, e.g. diagnostic clinical studies, workers medical surveillance and case reports (in the medical literature) may be used when assessing the sensitization potential of substances. When reliable and relevant, human data will normally be preferable over animal data. However, lack of positive findings in humans does not necessarily overrule positive and good quality animal data.

Analysis with (Q)SAR models may be useful, since it can be based on the fact that skin sensitisation potential of a chemical is related to its ability to react with skin proteins to form covalently linked conjugates and recognition of these by the immune system. In most cases this due to electrophilic reactivity of the substance. QSAR models for respiratory sensitisation are not yet available.

There are no officially adopted *in vitro* tests for skin or respiratory sensitisation. Detailed guidance on assessment and ITS is given in Section R.7.3.

For skin sensitizers the first approach should be the qualitative risk characterization based on potency categorization (strong/extreme and moderate sensitizers) and by defining the risk management measures (RMMs) as described in Part E. The DNEL should be set (if possible) to judge the remaining/residual likelihood of risks after the RMMs are implemented. The establishment of a DNEL can be based on the data from the LLNA study and/or by the Weight of evidence using LLNA data and historical human data.

### B.6.2.4 Acute toxicity

Acute toxicity refers to adverse effects, which result from a single or short term exposure. The relevant mechanisms and symptoms vary. Pathological changes in organs and tissues, which may result in death, are often observed. Several systemic effects may cause acute toxicity, basal and selective cytotoxicity being examples of the underlying mechanisms. Corrosive substances cause acute toxicity; since the corrosivity local it is dealt with in the chapter of irritation/corrosion.

Information requirements on acute toxicity via oral route are set at the tonnage band of 1-10 t/y. Corrosive substances and those already tested via inhalation, need not to be tested. At the next tonnage band (10-100 t/y), the standard information requirement covers also dermal and inhalation tests. The requirement is adapted depending on physical properties of the substance and the likely route of human exposure.

Human data on acute toxicity can be available e.g. in poison information centres and in clinical case reports. Human cases are a reflection of exceptional exposures, and should be carefully considered when the RMMs are selected. Compared with some other endpoints, there are relatively few (Q)SAR models capable of predicting acute toxicity. Relevant existing data on acute toxicity on animals may be obtained from scientific literature and from data bases.

While there are currently no *in vitro* tests that have been officially adopted, there are tests on cytotoxicity under validation, which can be possible replacement of the acute oral systemic toxicity tests.

By the end of the assessment of acute toxicity, the nature and reversibility of the toxic effects should be considered. If no signs of acute toxicity were seen at the limit test (typically 2000 mg/kg) classification of the substance with respect to acute toxicity is usually not required. For detailed guidance see Section R.7.4.

The LD50 and LC50 data may give sufficient basis for obtaining a DNEL. In some cases, however, the qualitative approach is more appropriate because the tests do not provide information on all aspects of acute toxicity in humans. Above 10 t/y, the establishment of acute toxicity DNEL is unnecessary in most cases, as the DNEL based on repeated dose toxicity is normally sufficient to ensure that adverse effects do not occur.

When a limit test has been conducted, and no adverse effects on health have been observed, then the limit dose can be regarded as the dose descriptor in setting the DNEL.

In rare cases, when the acutely toxic dose can not be defined, due to the limitations of the test protocols, a qualitative risk characterization of acute toxicity shall be performed for substances showing a very high acute toxicity / toxicity after single exposure (i.e. classified as Acute Tox 1 and 2 or STOT SE 1 according to the CLP Regulation). Very strict RMM will apply for these substances (e.g., closed systems, etc) in order to ensure control (see Part E). Basically, the RMM should ensure that peak concentrations exceeding the long-term DNEL will not occur. Note that usually the standard acute toxicity test results enable quantitative risk characterisation.

When there is a potential for high peak exposures (for instance when sampling or connecting/disconnecting vessels) and if an acute toxicity hazard (leading to C&L) has been identified, DNEL for peak exposures (shorter than 15 minutes) should be set (See Section R.8, appendix 8).

### B.6.2.5 Repeated dose toxicity

Repeated dose toxicity refers to general toxic effects that occur after daily dosing with a substance for 28 or 90 days, or major part of the lifespan, in case of chronic exposure. Effects examined in these studies may include changes in morphology, physiology, growth or life span, clinical chemistry or behaviour.

At the tonnage band of 10-100 t/y standard information requirements for on 28-day study is set and 90-day study is due at the next tonnage level. The most appropriate route of exposure in testing is the likely route of human exposure.

Before in vivo testing, e.g. physicochemical properties of the substance, existing animal test data, toxicokinetics data, specific toxicity (e.g. immunotoxicity, neurotoxicity), corrosivity, human exposure and SAR need to be considered. For the detailed ITS, see Section R.7.5.6 and Annex VIII.

According to test guidelines, the highest of three dose levels should be chosen with the aim to induce toxicity but not death. A descending sequence of dose levels should be selected with a view to demonstrating any dosage related response and a no-observed-adverse-effect level (NOAEL) at the lowest dose level.

It is noteworthy that also reproduction and developmental toxicity studies may provide information on the general toxicological effects arising from repeated exposures.

Data on repeated dose studies should be such that they enable the dose-response relationship and effect-threshold to be set and furthermore, can serve as the basis for CSA and classification of substances. When reliable and relevant, the available positive epidemiological data would be preferable over animal data. Currently, no available in vitro alternatives to animal testing are approved for detection of toxicity after repeated exposure. QSAR approaches are currently not well validated for repeated dose toxicity and no firm recommendations can be made concerning their use in a testing strategy in this area. For more details see Section R.7.5.

Typically, a NOAEL or LOAEL can be obtained from repeated dose toxicity studies. At least, intra and inter-species assessment factors are normally applied (see Section B.7.1). In case adverse effects are not observed in a limit test (up to 1000 mg/kg of body weight) the substance does not usually need to be assessed for repeated dose toxicity.

### B.6.2.6 Reproductive and developmental toxicity

Reproductive toxicity refers to effects such as reduced fertility, effects on gonads and disturbance of spermatogenesis and also covers developmental toxicity. Developmental effects refer to e.g. growth and developmental retardation, malformations and functional deficits in the offspring.

Information requirements are first set at the tonnage band 10-100 t/y, where a screening test for reproductive/developmental toxicity is required. At the 100-1000 t/y band, pre-natal developmental toxicity study shall be performed. Two-generation reproductive toxicity study is required, if the 28- or 90-day study indicates adverse effects on reproductive organs or tissues.

A two-generation reproduction toxicity study is the standard information requirement at above 1000 t/y. At any tonnage band, carcinogens and germ cell mutagens, for which risks are controlled, testing is not required. Factors that can influence the testing requirements are QSARs, mutagenic and carcinogenic properties, available data from humans exposed to the substance and concerns for endocrine disruption.

Epidemiological studies, conducted in the general population or in occupational cohorts, may provide information on reproductive toxicity. Although not aimed directly at investigating reproductive toxicity, repeated-dose toxicity studies may reveal effects on reproductive organs in test animals. The purpose of the assessment is to distinguish between a *specific effect* on reproduction and adverse reproductive effect which is a non-specific consequence to *general toxicity,* although, in many cases the data will not allow a definite distinction to be made.

SAR offers approaches for assessing the reproductive toxicity for example in case the toxicity potential may be extrapolated or interpolated across a homologous series or a category. Currently there are no officially adopted guidelines for in vitro tests of relevance to reproductive toxicity. Three tests have recently been declared to be scientifically validated by the European Centre for the Validation of Alternative Methods and positive results of these tests may be useful. For more guidance see Section R.7.6.

When the available data allows, DNEL value for effects on fertility ($DNEL_{fertility}$) as well as for developmental toxicity ($DNEL_{development}$) should be derived. Usually, the reproductive toxicity is considered to have an underlying dose threshold mechanisms and a NOAEL or LOAEL value should normally be provided by the test data.

### B.6.2.7 Mutagenicity

Risks caused by mutagenic substances have to be controlled order to prevent genetic damage/alterations. These alterations may lead to cancer in case they take place in somatic cells or they may cause heritable genetic damage if they take place in germ cells.

Standard information requirements on mutagenicity start already at the lowest tonnage level (in vitro gene mutation study in bacteria). At the next tonnage band, 10-100 t/y, information on induction of both gene mutations and chromosome aberrations in vitro is required. In case a

mutagenic effect is seen in the in vitro studies, information from an appropriate in vivo somatic cell genotoxicity study is required. Data based on (Q)SARs or grouping data may be available. The information requirements of REACH annexes do not require these types of data to be obtained, but they would be useful in the weight of evidence analysis. In many cases the accuracy of QSAR data will be sufficient to help, or allow either a testing or a specific regulatory decision to be made, while, in other cases, the uncertainty may be unacceptable due to the severe consequences of a possible error. Human data would be available only occasionally.

When assessing the test data, metabolic activation and physical-chemical properties of the test substance need to be considered. Toxicokinetics data is important when analyzing whether the test compound actually reached the target organ. Usually in vivo experiment and data obtained using mammalian cell lines is considered to be of higher significance. Relevance of indicator type of tests, such as DNA binding and SCE assays is considered to be lower. Substances which are mutagenic in somatic cells in vivo and can reach germ cells are assessed as if they can cause heritable genetic damage and, consequently, classified as category 2 mutagens. For detailed guidance see Section R.7.7.1.

DNEL can not usually be obtained from the data available. Therefore, qualitative approach has to be taken where strict measures have to be taken to prevent any human exposure to a mutagenic substance. The qualitative assessment and the respective risk management categories are explained in Part E.

### B.6.2.8 Carcinogenicity

Carcinogenic substances can increase the incidence of tumours in the exposed population. Carcinogenesis may involve both mutations and non-genetic events. While the underlying mechanism in many cases is the occurrence of a genetic damage, there are other, non-genotoxic mechanisms, such as sustained cell proliferation and altered intercellular communication. Genotoxic carcinogenicity differs from many other types of toxicity in that the effect is delayed. In case genotoxic mechanisms are involved, the effect is considered to have no effect-threshold.

Standard information requirements on carcinogenicity are set only at the highest tonnage level (above 1000 t/y). However, even at that level, the need d for carcinogenicity testing will depend on e.g. whether the use is widespread dispersive or exposure is frequent/long-term and whether the substance is classified as mutagen category 3 or is able to induce hyperplasia and/or pre-neoplastic lesions in repeated dose studies.

Since cat 1A and 1B mutagens are likely carcinogens and the risk is assumed to be managed accordingly, normally they do not need to be tested.

An ITS for mutagenicity aims to provide an “early warning” on carcinogenic risk. There is considerable evidence of a positive correlation between the mutagenicity of substances in vivo and their carcinogenicity in long-term studies with animals. Furthermore, hyperplasia and pre-neoplastic lesions seen in repeated dose toxicity studies may contribute to the weight of evidence for carcinogenic potential.

QSAR or read-across/category data may be available or could be obtained. These types of data would be useful, because structural alerts of carcinogenicity are well characterized and open sources of information (e.g. ready made QSARs, see Section R.7.7.8) are available on certain groups of substances.

A weight of evidence approach is important when carcinogenic potential is assessed.

When carcinogenicity bioassay(s) or reliable human epidemiological data are available that would be most relevant information in the assessment. Mostly however, that information is not available. It is important that the underlying mode of action (threshold or not) is addressed in the assessment, since it affects setting of DMEL and RMMs.

For regulatory purposes, it is usually agreed that a substance with sufficient evidence on genotoxicity, should be dealt with as if it is a carcinogen. Substances with some, but insufficient evidence on carcinogenicity have to be assessed case by case. Short and medium term bioassays and studies in transgenic rodents should be considered when available and they might even be proposed instead of conventional rodent bioassay. Assessment of carcinogenicity at lower that 1000 t/y band is based e.g. on mutagenicity data, repeated dose toxicity studies and QSAR/categories (see Section R.7.7.8).

For a non-threshold carcinogen, with adequate animal cancer data, Derived Minimal Effect Level (DMEL) approach is taken. This implies the use of endpoint-specific large assessment factor, i.e. 10 000 to ensure that the exposure causes a minimal risk. (The specific dose descriptor BMDL10 is divided by that AF. This and other "linearized" approaches are described in Section R.8.5.2. When it is not possible to set a DMEL, a qualitative approach in the assessment has to be taken; the strictest level of RMMs would be necessary to address the risks caused by carcinogens (see Part E).

## B.6.3 Environmental endpoints

### B.6.3.1 Aquatic toxicity

Aquatic toxicity refers to intrinsic property of a substance to be detrimental to an aquatic organism in short-term and/or long-term exposure to that substance.

Waterborne exposure to substances is generally considered the predominant route, but aquatic organisms may also be exposed via food (e.g. to lipophilic substances). A distinction is made between short-term (so-called acute) effects and long-term effects (chronic):

**Acute toxicity:** Toxicity to aquatic organisms exposed to substances within a duration in the range of hours to a few days (relatively short in comparison to the duration of the life-cycle of the organisms). Effects are normally expressed as median lethal or effect concentrations ($L/EC_{50}$), which is the test concentration at which 50% of the organisms is affected or at which 50% effect is measured for a specifically defined endpoint (e.g. growth rate effects on algae).

**Chronic toxicity:** Toxicity to aquatic organisms exposed to substances for a prolonged period. Exposure (test) duration may vary widely depending on the species used, but is in general relatively long in relation to the length of the life-cycle of the organism. Such chronic effects usually include a range of endpoints such as survival, growth and reproduction. The highest tested concentration where an effect has not been observed (No Observed Effect Concentration or NOEC[3]) is the most frequently used parameter, which may often be replaced by an $EC_{10}$ that can be estimated based on the concentration-effect relationship.

Additional information regarding the details and derivation of such values can be found in Section R.7.8.4.1.

The minimum information that should be available includes short-term toxicity data on invertebrates and growth inhibition data on aquatic plants at the lowest tonnage band (1-10 t/y) and short-term toxicity data on fish at the next tonnage band (10-100 t/y). At higher tonnage bands, data on the long-term effects on invertebrates and fish should be considered depending on the outcome of the CSA.

Although classification is based on available information, a complete comparison with the criteria would require information on acute aquatic toxicity to fish, *Daphnia* and algae. A lack of long-term

[3] The formal scientific definition of NOEC (No Observed Effect Concentration) is "the concentration immediately below the LOEC which when compared with the control has no statistically significant effect compared to the control" (OECD 211, 1998b).

effects at 1 mg/L may be used for de-classifying a substance. More information will be made available in the Guidance on Classification and Labelling.

Further guidance on how to make a PBT assessment can be found in Part C.

All available aquatic toxicity data needs to be evaluated in the hazard assessment and, if suitable, used to derive an overall Predicted No-Effect-Concentration (PNEC) for the aquatic compartment. The minimum data set required is short-term or long-term data for all three trophic levels. Depending on the outcome of an eventual risk characterisation, further information may be useful.

Section R.7.8.4.1 provides detailed information on interpretation of existing data including guidance on use of non-testing data and testing data, recommended species, relevant endpoints and reliability of data. Information on dealing with difficult substances can also be found in Section R.7.8.4. Appendix R.7.8-1 provides additional information on properties of substances, test systems and other factors influencing the evaluation of aquatic tests.

Section R.7.8.5 provides guidance on the assessment of the toxicity of the substance in cases where the total amount of available information is suitable for regulatory decisions and in cases, where there are data gaps which have to be filled.

In Section R.7.8.5.4 specific considerations are given on how to draw overall conclusions for the different regulatory endpoints with respect to aquatic toxicity, i.e. classification and labelling, PBT assessment and CSA. Section R.7.8.5.3 includes an ITS for aquatic toxicity.

### B.6.3.2 Sediment toxicity

Sediments may act as both a sink for chemicals through sorption (binding) of contaminants to particulate matter, and as a source of chemicals to particle feeders through resuspension or back to the water phase by desorption. Due to this process sediments mitigate the effects of surface water contamination but may prolong exposure over time and may thus present a hazard to aquatic communities (both pelagic and benthic) which is not directly predictable from concentrations in the water column. Therefore, substances that are potentially capable of depositing on or sorbing to sediments to a significant extent have to be assessed for toxicity to sediment-dwelling (benthic) organisms.

Due to the generally long-term exposure of benthic organisms to sediment-bound substances, long-term tests with sub-lethal endpoints like reproduction, growth or emergence are most relevant.

For the endpoint toxicity to sediment organisms there are no standard data requirements at production or import levels up to 1000 t/y (Annex VII, VIII and IX). However, the need for (test) data may be triggered at tonnages below 1000 t/y for substances with log $K_{ow}$ >3 or with other properties suggesting adsorption to sediment is likely.

At tonnages ≥ 1000 t/y, long-term toxicity testing shall be proposed by the registrant if the results of the CSA indicate the need to investigate further the effects of the substance and/or relevant degradation products on sediment organisms. The choice of the appropriate test(s) depends on the result of the CSA.

Section R.7.8.10.1 provides detailed information on interpretation of existing data including guidance on use of non-testing data and testing data. Information concerning preferred organisms, relevant endpoints, exposure pathways, sediment composition, spiking methods, feeding, exposure duration, water quality, test system and design is available as well.

### B.6.3.3 Toxicity to sewage treatment plant micro-organisms

Toxicity to sewage treatment plant (STP) micro-organisms should be assessed with the aim to protect the biodegradation and nutrient removal functions, and process performance in general, of municipal and industrial STPs.

Information on activated sludge respiration inhibition is required as of volumes of 10 t/y and above. Respiration inhibition is only one of many possible effects on microbes, but it is the most widely accepted indicator of the combined activity of sludge micro-organisms. Information on nitrification inhibition should be obtained if there are indications that the substance may be toxic to nitrifying bacteria.

Toxicity to sewage treatment plant micro-organisms is not used for environmental hazard classification and for PBT/vPvB assessment. The data will only find application in CSA where a $PNEC_{micro\text{-}organisms}$ (here called PNECstp) should be derived and used as toxicity measure for the calculation of the risk to STPs.

Mainly experimentally-derived microbial inhibition data will be used to derive a PNECstp, in the absence of well-established QSARs for STP toxicity. The available microbial toxicity data need to be evaluated and, if suitable, used to derive a predicted no effect concentration (PNECstp).

The main objective of the ITS for STP toxicity is to ensure that all available relevant exposure and effects information can be used in an integrated way before any new testing is initiated. The ITS allows the refinement of unfavourable screening-level data by means of higher tier testing. The proposed scheme can be followed for both industrial and/or domestic (i.e. municipal) sewage treatment plants, as applicable from the chemical's release pattern.

### B.6.3.4 Degradation/biodegradation

Degradation is the loss or transformation of a chemical substance in the environment, due to abiotic or biotic processes. Abiotic or non-biological degradation can occur by physico-chemical processes such as hydrolysis, oxidation and photolysis. Biodegradation can proceed in the presence of oxygen (aerobic biodegradation) or in the absence of oxygen (anaerobic biodegradation). Consideration should be given to whether the substance being assessed can be degraded to give stable and/or toxic degradation products. Where such degradation can occur, the assessment should give due consideration to the properties (including toxic effects and bioaccumulation potential) of the products that might arise.

The minimum information which should be available already at the 1-10 t/y band, is information on the ready biodegradability (of organic substances). At the next tonnage band (10-100 t/y) also information on hydrolysis should be available. At higher tonnages, further information on degradation in various environmental compartments should be considered depending on the outcome of the CSA.

Information on the degradability of chemicals may be used for hazard assessment (e.g. for classification and labelling), risk assessment (for chemical safety assessment) and persistency assessments (for PBT/vPvB assessment).

Assessment of degradation and persistency is normally based on data obtained in standardised tests for ready biodegradability and hydrolysis. Predictions from biodegradation QSAR models may also be considered. Results of tests simulating the biodegradation in water, aquatic sediment and soil are considered higher tier data that can also be used for these purposes. Other types of test data that may be considered in an assessment of the potential environmental hazard or risk include sewage treatment plant (STP) simulation data, inherent biodegradability, anaerobic biodegradability, biodegradability in seawater and abiotic transformation. In determining which higher tier or simulation degradation data are required, consideration should be given to the partitioning behaviour of the chemical and its release or emission pattern. (See Section R.7.9)

### B.6.3.5 Aquatic bioconcentration and bioaccumulation

*Bioconcentration* is the accumulation of a substance dissolved in water by an aquatic organism. The *bioconcentration factor* (BCF [L/kg]) is the ratio of the concentration of a substance in an organism to the concentration in water once a steady state has been achieved. It can be derived in

two ways, static or dynamic (Section R.7.10.1.1). Static and dynamic (kinetic) BCFs of equal validity are interchangeable for regulatory purposes.

*Accumulation* is a general term for the net result of absorption (uptake), distribution, metabolism and excretion (ADME) of a substance in an organism. These processes are discussed in detail in the mammalian toxicokinetics guidance document (Section R.7.12).*Bioaccumulation* refers to uptake from all environmental sources including water, food and sediment. The *bioaccumulation factor* (BAF) can be expressed as the steady-state ratio of the substance concentration in an organism to the concentration in water or sediment. These factors can be used to estimate the concentration of a chemical in an organism living in contaminated water or sediment.

*Biomagnification* refers to accumulation via the food chain. It may be defined as an increase in the (fat normalized) internal concentration of a substance in organisms at succeeding trophic levels in a food chain. The biomagnification potential can be expressed as either a biomagnification factor (BMF) or a trophic magnification factor (TMF).

At a tonnage of ≥ 100 t/y, the conduction of a bioaccumulation study in an aquatic organism (preferably fish) should be considered.

The bioaccumulation potential needs to be considered in relation to long-term effects and environmental hazard classification. For the majority of non-ionised organic substances, classification may be based initially on the log $K_{ow}$ if no reliable measured fish BCF is available.

The bioaccumulation potential ('B') is part of the PBT/vPvB assessment. Reliable measured BCF data for fish or an invertebrate are generally necessary for final conclusions on B in PBT or vPvB. A screening assessment can be made against screening criteria based on the log Kow for those organic substances that are expected to accumulate via passive diffusion.

In the CSA, fish BCF and BMF values are used for the secondary poisoning assessment for wildlife, as well as for human dietary exposure. A BMF for birds and mammals may also be relevant for marine scenarios. An invertebrate BCF can be used to model a food chain based on consumption of sediment worms or shellfish.

If the log $K_{ow}$ (only relevant for non-ionised organic substances) is not a good indicator of accumulation potential (see Section R.7.10.6), the ITS should be followed and an *in vivo* test may be required. If no fish BCF is available, reliable BCFs determined for non-fish species may be used.

A predicted BCF may be used for first tier risk assessment. If the PEC/PNEC ratio based on worst case BCF or default BMF values indicates potential risks at any trophic level, the BCF/ BMF can be refined if needed. A *weight of evidence* procedure can be used for expert judgement on the available data and to decide on the need for additional testing (Section R.7.10.5).

### B.6.3.6 Terrestrial bioaccumulation

Bioaccumulation from soil to terrestrial species is expressed by the biota-to-soil accumulation factor (BSAF), similar to the biota-to-sediment accumulation factor for benthic organisms. Alternatively, the concentration in the organism may be related to the concentration in soil pore water by calculating a BCF [L/kg]. These factors can be used to estimate the concentration of a chemical in an organism living in contaminated soil.

REACH does not require information on terrestrial bioaccumulation, but depending on the outcome of the CSA, the conduction of such a study may be useful.

If a substance is non-ionisable organic compound, $K_{ow}$-based estimation methods can be used to generate the necessary terrestrial BCF information. If the predicted BCF value suggests a risk, information on bioaccumulation needs to be refined. In general, test data will only be needed at the 1,000 t/y band, if the CSA identifies the need for further terrestrial bioaccumulation information. Field monitoring might provide additional data on the risk of bioaccumulation. (See Section R.7.10.12)

### B.6.3.7 Long-term toxicity to birds

Avian toxicity studies can measure sublethal and lethal effects of short-term oral exposure, sublethal or lethal effects of medium-term (up to several days) or lethal and reproductive effects of long term (up to 20 weeks) dietary exposure. However, due to poor correlation between short and long term effects, only long term studies are considered suitable for CSA purposes.

The aim of an avian toxicity test is to provide data that can be used to assess secondary poisoning, if the CSA demonstrates the need for such a study (notably relevant for substances with a potential to bioaccumulate and high mammalian toxicity).

Data obtained from species used in standard test methods are assumed to be representative of all species. Dietary studies are preferred, since these are most relevant to the exposure route under investigation. (See Section R.7.10.18)

### B.6.3.8 Terrestrial toxicity

Due to the complexity and diversity of the terrestrial environment, a comprehensive effect assessment for the whole compartment can only be achieved by a set of assessment endpoints covering (i) the different routes by which terrestrial organisms may be exposed to substances (i.e. air, food, pore water, bulk-soil) and (ii) the most relevant taxonomic and functional groups of terrestrial organisms (micro-organism, plants, invertebrates, vertebrates) being potentially affected.

The scope of the terrestrial effect assessment under the adopted REACH regulation is restricted to soil organisms in a narrow sense, i.e. on non-vertebrate organisms living the majority of their lifetime within the soil and being exposed to substances via the soil pathway and in line with the previous practice in the environmental risk assessment of new and existing substances in the EU.

Information on short-term toxicity to soil organisms should be considered for substances ≥ 100 t/y, unless direct and indirect exposure is unlikely. For substances ≥ 1000 t/y, information on long-term toxicity should be considered depending on the outcome of the CSA.

Information on toxicity to terrestrial organisms is not used for classification and labelling and neither for the PBT assessment. When relevant exposure of the terrestrial environment is likely, this compartment shall be considered in the CSA.

Different types of information are relevant when assessing terrestrial exposure and subsequent toxicity to soil organisms. Useful information includes chemical and physical properties of substances and test systems as well as available testing data (*in vitro* and *in vivo*) and results from non-testing methods, such as the Equilibrium Partitioning Method. (See Section R.7.11)

# B.7 DERIVING THRESHOLD AND NON-THRESHOLD EFFECT LEVELS

## B.7.1 Characterisation of dose/concentration-response for human health

### B.7.1.1 Objective and key issues

Under REACH, manufacturers, importers and downstream users have to ensure that they manufacture, place on the market or use substances in such a way that they do not adversely affect human health. In order to assess this, a comparison between the expected exposure and the potential for adverse effects must be made. This chapter will give a brief overview of how to characterise the potential for adverse effects, i.e. 'the potency' of the substance as an input for the risk characterisation (Part E). The section aims at giving some understanding of the process and concepts to the uninformed reader. A more detailed description is presented in Chapter R.8. It is acknowledged that it will require a great deal of toxicological expertise and experience to appreciate the detailed guidance and to conduct a safety assessment.

For a comprehensive hazard and safety assessment, information is needed with respect to the substances' fate in the body (toxicokinetics, i.e. absorption, distribution, metabolism, and excretion) and on the following human health endpoints; acute toxicity, irritation and corrosivity, sensitisation, repeated dose toxicity, mutagenicity, carcinogenicity, and reproductive toxicity as well as any other available information on the toxicity of the substance. It should be noted that according to REACH the standard requirements for these endpoints are tonnage-dependent. However, before conducting testing to generate such data, all available information should first be collected and assessed, including properly collected and reported human data (see Chapters R.3 and R.4). The evaluation of this hazard information should aim at identifying the NOAEL (or another dose descriptor) for the leading health effects and the uncertainties surrounding the NOAEL. Subsequently, a DNEL (Derived No-Effect Level) is derived by dividing the NOAEL with assessment factors representing the uncertainties (e.g., with respect to extrapolation between species and among humans). The DNEL represents a level of exposure above which humans should not be exposed. In cases where no DNEL(s) can be derived, REACH requires a qualitative assessment to be performed. However, for the non-threshold endpoints (e.g. non-threshold carcinogenicity), if data allow, the development of a (semi)quantitative reference value (DMEL=derived minimal effect level) may be useful (see below). Figure B.7-1 illustrates the different steps of the quantitative DNEL procedure.

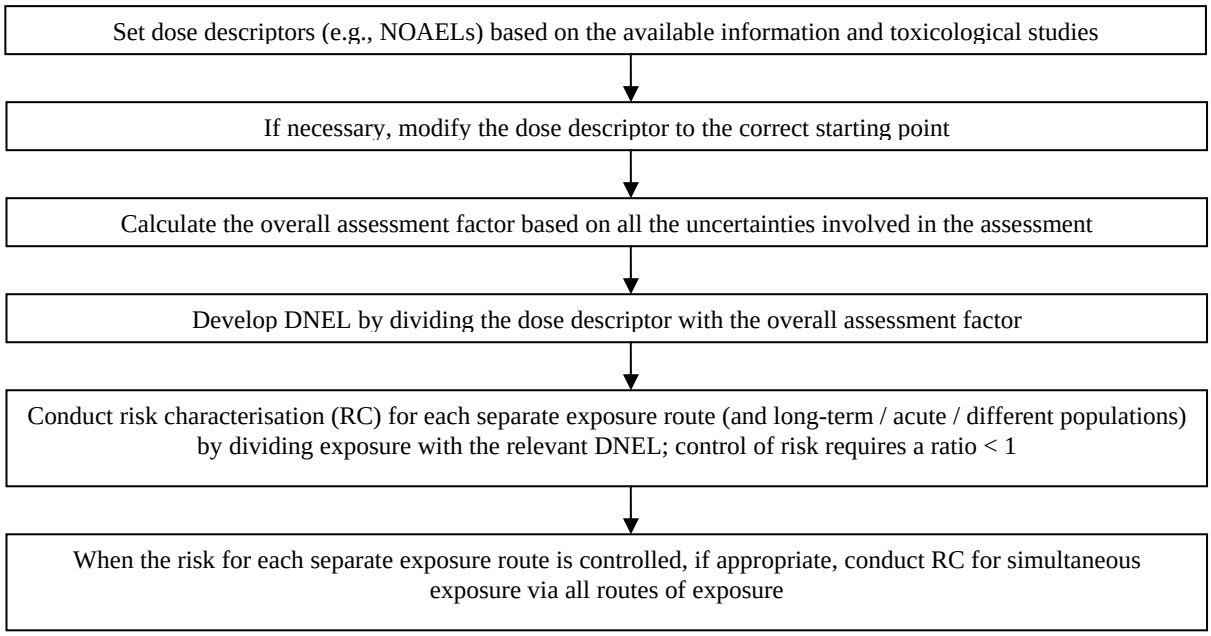


**Figure B-7-1:** Illustration of the different steps of the quantitative human health risk assessment for threshold endpoints

NB: This figure only relates to quantitative risk characterisation. It is further outlined below and in Part E when and how this shall be supplemented by a qualitative risk characterisation.

**Conclusions on classification and labelling of the substance in relation to need for exposure assessment and risk characterisation (RC)**

One objective of the human health hazard assessment is the classification and labelling of the substance in accordance with the CLP Regulation. From the above described hazard assessments per human health endpoint, it can be concluded whether the substance fulfils the criteria for any of the hazard classes or categories listed in Article 14(4) of the REACH Regulation, as amended from 1 December 2010 by Article 58(1) of the CLP Regulation, namely:

- hazard classes 2.1 to 2.4, 2.6 and 2.7, 2.8 types A and B, 2.9, 2.10, 2.12, 2.13 categories 1 and 2, 2.14 categories 1 and 2, 2.15 types A to F.
- hazard classes 3.1 to 3.6, 3.7 adverse effects on sexual function and fertility or on development, 3.8 effects other than narcotic effects, 3.9 and 3.10.
- hazard class 4.1:
- hazard class 5.1,

These classes and categories (only) will henceforth be described as “Article 14(4) hazard classes or categories” (i.e. specifically excluding PBT or vPvB properties)

In case the substance is classified, an exposure assessment and risk characterisation are required, in order to ensure that the risks associated with the estimated exposure values (for all actual exposure scenarios of the substance for manufacture, identified uses and life–cycle stages resulting from those) are controlled. Where possible, DNELs should be derived, also for non-classified substances.

## B.7.1.2 Legislative requirements for setting DNELs

### B.7.1.2.1 Derivation of DNEL

Where possible, DNEL(s) shall be derived for all substances subject to registration that are manufactured/imported/used in quantities of 10 tonnes or more per year, as part of the chemical safety assessment (CSA). DNEL(s) should be documented in the chemical safety report (CSR). In case an exposure assessment and risk characterisation is required, the DNEL is subsequently to be:

- used in the risk characterisation part of the CSA, and
- communicated as part of the safety data sheet (SDS).

With respect to the derivation of DNEL(s), REACH inter alia specifies that it may be necessary to identify different DNELs for each relevant human population (e.g. workers, consumers and humans exposed indirectly via the environment) and possibly for certain vulnerable sub-populations (e.g. children, pregnant women) and for different routes of exposure (oral, dermal, inhalation) and for different exposure durations. When establishing the DNEL, the uncertainties in the assessment shall be taken into account (e.g., involving species differences, differences in sensitivity among humans, and quality of the database). The DNEL can be considered as an 'overall' No-Effect-Level for a given exposure (route, duration, frequency), accounting for uncertainties/variability in these data and the human population exposed.

For workplace exposure, there may already exist occupational exposure limits (OELs). Under certain circumstances OELs and/or the underlying information used for setting the OELs can be used to derive DNELs. Further information is in Appendix R.8-13.

The exposure/DNEL comparison for each exposure scenario in principle represents a simple tool for RC, especially for downstream users who do not have the hazard data at their disposal. For any exposure scenario, the risk to humans can be considered to be adequately controlled if exposure levels do not exceed the appropriate DNEL.

### B.7.1.2.2 If no DNEL can be derived

It may not always be possible to derive DNEL(s) for an end-point. The most obvious cases are when test data are absent, either because no testing is needed based on exposure arguments (see Chapter R.5 for details), or because testing was technically not possible as a consequence of the properties of a substance.

More importantly, this may also apply when

- a substance exerts its effect by a non-threshold mode of action (e.g., mutagens and genotoxic carcinogens). In that case it is generally assumed, as a default assumption that even at very low levels of exposure residual risks cannot be excluded. Consequently, a dose without potential effects cannot be established,
- a substance exerts its effect by a threshold mode of action, but the available data do not allow to reliably identify the threshold (e.g., sensitisation and irritation).

If it is not possible to derive a DNEL, then REACH requires, that "a qualitative assessment of the likelihood that effects are avoided when implementing the exposure scenario shall be carried out", in the risk characterisation part of the CSA.

In the **qualitative approach** emphasis is placed on assessing the adequacy of control of exposure in the human population of interest by using other information than a DNEL to qualitatively describe the potency of the health effect, which is then used for development of Exposure Scenarios with risk management measures and operational conditions for controlling exposures and thereby risks.

It can be useful for non-threshold effect (e.g. non-threshold carcinogens) to include in this qualitative assessment a **semi-quantitative** element in order to assess the likelihood that effects are avoided. In such cases, and assuming that data are available to allow this, the registrant should develop a **DMEL** (derived minimal effect level), i.e. a reference risk level which is considered to be of very low concern for a certain exposure scenario. DMELs derived in accordance with the guidance should be seen as a tolerable level of effects and it should be noted that it is not a level where no potential effects can be foreseen, but rather expresses an exposure level corresponding to a low, possibly theoretical, risk. A DMEL is a risk-related reference value that should be used to better target risk management measures.

It should be stressed that for carcinogens and mutagens, the Carcinogens Directive (2004/37/EC) requires that workplace exposures are avoided/minimised as far as technically feasible. As REACH does not overrule the Carcinogens Directive, the approach to controlling workplace exposure should therefore comply with this minimisation requirement. The DMEL approach is useful when preparing chemical safety assessment to judge the remaining/residual likelihood of risks. Based on such judgement the registrant may need to refine the way he uses or recommends to use the substance by revising the relevant tentative exposure scenario(s) for use of the substance.

### B.7.1.3 Overview of aspects to be considered in derivation of DNEL(s) / DMEL(s)

Based on the specification given in REACH, several aspects need to be considered in deriving DNEL(s). It is to be noted that there is a need for expertise in doing this.

**Data requirements** The derivation of DNELs is required for the chemicals assessment (CSA) of substances manufactured/imported/used in quantities from 10 t/y upwards. For derivation of DNELs, all available hazard information needs to be evaluated and, where possible, dose descriptors (N(L)OAEL, benchmark dose, etc.) need to be established. The data may originate from observations in studies with humans, studies with experimental animals (e.g., 28/90 days repeated dose toxicity studies), in vitro studies, and non-testing sources ((Q)SAR), read across or chemical categories). As further toxicological information is requested at each higher tonnage level, allowing more robust assessments, DNEL(s) should be reconsidered at each higher tonnage levels. The same applies if significant new toxicological information becomes available.

**Uncertainty/variability** REACH requires differences between toxicity data (often obtained from animal studies) and the real human exposure situation to be addressed, taking into account variability and uncertainty within and between species. In order to address these differences, assessment factors (AF) should be applied. The applied AFs only correct for uncertainties/variability in the effect data, not for exposure uncertainties.

**Populations and routes** DNELs may have to be derived for workers (dermal and inhalation exposure) and the general population (consumers and humans via the environment; dermal, inhalation, and/or oral exposure). If relevant, also combined exposures via different routes may need to be assessed. Under certain circumstances it might also be necessary to derive DNELs for certain subpopulations, i.e. covering a particular higher sensitivity of children.

**Duration of exposure** Depending on the exposure scenario, the exposure duration can vary from a single event to an exposure for several days/weeks/months per year, or it might even be continuous (as is, e.g., the case of humans exposed via the environment). Since the duration of exposure will often have an impact on the effect(s) that may arise, DNELs may have to be derived for various exposure durations ($DNEL_{long\text{-}term}$ and $DNEL_{acute}$), thereby matching as closely as possible the exposure duration in the toxicity study with the exposure duration in the exposure scenario.

**Systemic and local effects** Depending on the substance, DNELs may have to be established for systemic effects, for local (dermal or inhalation) effects, or for both.

**Units** Exposure estimates are normally expressed as external values (i.e. amount of substance on the skin or concentration in the inhaled air). DNEL should therefore, as a default, be expressed in

the corresponding external exposure values. Relevant, external dose units for the DNEL are mg/person/day, (or mg/cm$^2$ body area/day), mg/kg bw/day, and mg/m$^3$ for dermal, oral, and inhalation exposure, respectively.

### B.7.1.4 How to derive DNEL(s)

#### B.7.1.4.1 Identifying dose descriptors and deciding on mode of action

As part of the evaluation of the toxicity studies, dose descriptors (e.g., NOAEL, NOAEC, BMD, LD50, LC50, T25) should be identified for the endpoint concerned For a particular endpoint, it may be possible that data from more than one relevant and valid study are available (e.g. in different species, with different durations) and more than one dose descriptor for the endpoint is identified. Since it is not possible to know beforehand which of these dose descriptors will turn out to be the most relevant for the endpoint-specific DNEL, it might therefore sometimes be relevant to derive DNELs for more than one dose descriptor per endpoint, prior to selecting the lowest DNEL for that endpoint. This will depend on expert judgement, including the use of a weight of evidence approach. An integral part of this step is consideration of the mode of action.

- If the substance exerts its effect by a threshold mode of action, a DNEL will have to be derived for that endpoint based on the most relevant dose descriptor. If the available data do not allow to reliably identifying the threshold, and thus no quantitative dose descriptor and DNEL can be derived, a qualitative/semi-quantitative approach has to be adopted (see Section B.7.1.6).
- If the substance exerts its effect by a non-threshold mode of action (e.g. genotoxic carcinogens), in principle any level of exposure carries a risk, and thus no dose without effect can be established. For these effects, as already mentioned in Section B.7.1.2.2, a DMEL(s) should be derived as part of the qualitative approach, if there are data allowing this.
- If the data do not allow setting a DNEL or DMEL, the strictly qualitative assessment outlined in Section B.7.1.6 should be applied).

If a substance has both threshold and non-threshold effects, DNELs should still be developed in parallel to the qualitative approach.

#### B.7.1.4.2 Modification of the relevant dose descriptor(s) per endpoint to the correct starting point

In a few situations, the dose descriptor will not be directly comparable to the exposure assessment in terms of exposure route, units and/or dimensions. In these situations, it is necessary to convert the dose descriptor for the threshold effect (e.g. NOAEL) into a correct starting point (e.g. corrected NOAEL) (Section R.8.4.2).

This applies:

1) when there is a difference in bioavailability between experimental animals and humans;

2) the animal dose descriptor is for another exposure route than the human exposure (requiring route-to-route extrapolation);

3) there are differences in human and experimental exposure conditions;

4) for differences in respiratory volumes between experimental animals and humans

#### B.7.1.4.3 Application of assessment factors to the corrected starting point to obtain endpoint-specific DNEL(s) for the relevant exposure pattern

The next step in the calculation of a DNEL is to address uncertainties in the extrapolation of experimental data to the real human exposure situation (Section R.8.4). All these

uncertainties/differences are individually addressed by assessment factors (AFs). In the ideal situation, the value for each individual assessment factor should be based on substance-specific information. However, default assessment factors most often need to be used.

The default AF for **interspecies differences** addresses differences in sensitivity between experimental animals and humans, with the default assumption that humans are more sensitive than experimental animals. This AF is not needed when human data are used as the starting point for the risk characterisation.

Humans differ in sensitivity to toxic insult due to a multitude of biological factors such as genetic polymorphism, age, gender, health status and nutritional status. These **intraspecies differences** are greater in humans than in the more inbred experimental animals. Therefore AFs to account for these differences within a **general population** and **workers population**, as appropriate, need to be applied.

An AF allowing for differences in the experimental **exposure duration** and the duration of exposure for the population and scenario under consideration needs to be considered taking into account that a) in general the experimental NOAEL will decrease with increasing exposure times and b) other and more serious adverse effects may appear with increasing exposure times. The AF for the **dose-response relationship** should take into account the dose spacing in the experiment, the shape and slope of the dose-response curve (very shallow and very steep curves may warrant an AF), and the extent and severity of the effect seen at the LOAEL.

An AF on the **quality of the whole database** should, if justified, be applied to compensate for the potential remaining uncertainties in the derived DNEL. Special consideration should be given to NOAELs (or other dose descriptors) derived from alternative data, e.g. in vitro data, (Q)SAR, read across or chemical categories.

The **overall assessment factor** is obtained by simple multiplication of individual AFs. In order to derive endpoint-specific DNEL(s) for the relevant exposure pattern (duration, frequency, route and exposed human population), the overall AF is to be applied directly to the corrected dose descriptor(s) in the following manner (exemplified with NOAEL as the dose descriptor):

$$Endpoint-specific \quad DNEL = \frac{NOAEL_{corr}}{AF_1 * AF_2 * _ * AF_n} = \frac{NOAEL_{corr}}{Overall \quad AF}$$

### B.7.1.5 Derivation of DMEL(s) for non-threshold endpoints

This guidance document sets out two (default) methodologies which can be applied for deriving a DMEL (Section R.8.5). The ‘Linearised’ approach, essentially results in DMEL values representing a lifetime cancer risk considered to be of very low concern. The ‘Large Assessment Factor’ approach similarly results in DMEL values representing a low concern from a public health point of view. If data allow, more sophisticated methodologies for deriving a DMEL may be applied. The choice of such alternative methodologies should be justified.

#### B.7.1.5.1 The ‘Linearised’ approach

This approach of deriving a DMEL basically is driven by the assumption of a linear dose response relationship between tumour formation and exposure. This element of the linearised approach is incorporated in the *high to low dose extrapolation* assessment factor. The T25 (dose giving 25 % of the animals tumours) should be used as the default dose-descriptor as the starting point for linear extrapolation. When necessary, the relevant dose descriptor(s) are modified to the correct starting point as described above for the DNEL derivation, but with additional consideration of differences between occupational and lifetime conditions of exposure. Assessment factors should in principle be considered as above, although in practice generally only the assessment factor for differences in metabolic rate (allometric scaling) is to be applied (with exceptions of local tumours

and when an inhalation study is used as starting point for deriving an inhalation DMEL expressed as concentration in air).

The preceding steps (correction of the starting point, and application of assessment factors) should result in the relevant (i.e. with regard to route and absorption) human equivalent lifetime daily dose, HT25 ('Human T25'). The *high to low dose* extrapolation step is the next step to arrive at the DMEL, i.e. an exposure level that is considered to represent a risk level considered to be of very low concern (acknowledging the fact that for non-threshold carcinogens a dose level without any residual cancer risk cannot be identified). If a bench-mark dose (BMD10 – derived dose assumed to give 10% of the animals' tumours) is used as the dose descriptor, a slightly higher extrapolation factor needs to be used.

**Table B.7-1-7-1:** High to low dose risk extrapolation factors used to derive a DMEL

| High to low dose risk extrapolation factor (HtLF) | | Default value systemic tumours<br>For T25 ; for BMD10 |
|---|---|---|
| High-to-low-dose extrapolation | In case of e.g.: - $10^{-5}$ risk<br>- $10^{-6}$ risk | 25.000 ; 10.000<br>250.000 ; 100.000 |

The DMEL (based on a T25 as a starting point) for e.g. a risk for cancer of one per 100.000 exposed ($10^{-5}$) is derived in the following way:

$$DMEL \quad representing \quad 10^{-5} \quad risk = \frac{T25_{corr}}{AF_1 * _ * HtLF} = \frac{T25_{corr}}{AS * 25000}$$

'AF' is abbreviation for assessment factor and 'AS' for algometric scaling. Details are explained in Chapter R.8. Cancer risk levels of **$10^{-5}$** and **$10^{-6}$** could be seen as indicative tolerable risks levels when setting DMELs for workers and the general population, respectively.

#### B.7.1.5.2 The 'Large Assessment Factor' approach ("EFSA" approach)

This approach to characterise and evaluate carcinogenic risks involves the application of several assessment factors to the starting point rather than linear extrapolation of the dose descriptor, and uses the BMDL10 (lower confidence limit of the BMD10) as preferential dose descriptor. The dose descriptor is modified, where necessary, and the corrected dose descriptor is then divided by a total assessment factor of 10.000 (for the general population) or 5.000 (for workers), respectively.

See Chapter R.8 for further details of how these overall large assessment factors are derived The DMEL for the general population via this procedure is arrived at from a $BMDL10_{corr}$ in the following way:

$$DMEL = \frac{BMDL10_{corr}}{AF_1 * AF_2 * _ * AF_n} = \frac{BMDL10_{corr}}{10000}$$

### B.7.1.6 The qualitative approach when no dose descriptor is available for an endpoint

When no reliable dose descriptor can be set for an endpoint, a more qualitative approach has to be chosen. This may apply for acute toxicity, irritation/corrosion, sensitisation, and mutagenicity/carcinogenicity. In this situation qualitative indications of the potency of the substance are used for developing exposure scenarios with risk management measures (RMM) and operational conditions (OCs) for controlling risk. Part E outlines an approach linking the exposure scenario development in a way proportional to the nature and severity of the hazard. This builds on the principles that management of risks for which no DNEL values can be derived are addressed in

a way that the higher the hazard, the stricter the risk management that should be put in place (See Section R.8.6 and Part E on risk characterisation for further details).

#### B.7.1.7 Select the leading health effect(s) for relevant exposure patterns

Following the derivation of endpoint-specific DNEL(s) or DMEL(s) and qualitative description of the endpoints for which no DNEL/DMEL can be set, the leading health effect(s) and the corresponding critical DN(M)EL(s) will be selected and/or qualitative description of potency established (Section R.8.7 and Part E).

The following briefly addresses selection of critical DNEL/DMELs. Further details on how to address endpoints for which no DNEL/DMEL can be derived are given in Chapter R.8 and Part E.

The critical DN(M)EL, used for the (semi-)quantitative risk characterisation, should be the lowest DN(M)EL obtained for the relevant combination of population/route/exposure pattern.

The selected DNELs or DMELs are then used in relation to the exposures associated with the exposure scenarios. For **systemic, long-term effects**, five DN(M)ELs may be relevant (depending on exposure routes and exposed populations). In most cases, long-term DNELs are needed for worker dermal and inhalation exposure routes. Additionally, three long-term DNELs may need to be set for the general population (dermal, oral and/or inhalation) if the substance is present in consumer–available products or is released to the environment and present there as an environmental contaminant.

For some substances, for which there is a potential for peak exposures, the long-term DNELs (to be complied with *on average* over e.g. a working day) may not ensure a sufficient level of protection against acute systemic effects as shorter term high exposures could be significantly above the long-term DNEL. As a rule of thumb, this may be the case when actual peak exposure levels significantly exceed the average daily exposures. In these cases, a $DNEL_{acute}$ needs to be set and assessed in relation to the peak exposure levels that humans may experience. Normally this will involve a worker-$DNEL_{acute}$ for inhalation, but could also apply to consumers, and theoretically also to other routes of exposure.

For both **acute and long-term local effects**, DNELs may need to be set for workers and the general population exposed via the dermal and inhalation routes (i.e., four local DNELs).

**Table B-7-2:** Summarising the derivation of an endpoint-specific DNEL/DMEL

| Endpoint | Quantitative dose descriptor[1] (appropriate unit) or qualitative assessment | | Corrected dose descriptor (appropriate unit) | | Overall AF applied | Endpoint-specific DNEL/DMEL (appropriate unit) | |
|---|---|---|---|---|---|---|---|
| | Local effect[2] | Systemic effect[3] | Local[2] | Systemic[3] | | Local[2] | Systemic[3] |
| Endpoint (……toxicity)<br>- oral<br>- dermal<br>- inhalation | | | | | | | |

[1] Select the relevant population

[2] Units are mg/m$^3$ for inhalation; and mg/cm$^2$ skin, mg/person/day (e.g. calculated based on the deposited amount per cm$^2$ times the actually exposed body area) or a measure of concentration for dermal exposure

[3] Units are mg/m$^3$ for inhalation, and mg/kg bw/day for oral and dermal exposure

Overall, therefore, the (semi)-quantitative procedure involves identifying a dose descriptor based on the available studies (column 2), correcting it to appropriate unit (column 3), calculating the overall assessment factor (column 4), and finally dividing the dose descriptor with the AF to obtain the final DNEL/DMEL (column 5). This should be done for local and systemic effects, and for the relevant exposure routes.

Part E outlines in detail how to conduct quantitative Risk Characterisation based on qualitative and/or (semi-)quantitative dose-response information.

## B.7.2 Predicted No Effect Concentration (PNEC) for the environment

This section comprises an introductory part outlining general principles of PNEC derivation (section B.7.2.1) followed by one part for each type of PNEC value, which can be derived (Sections B.7.2.2 to B.7.2.7).

### B.7.2.1 General principles of derivation of PNEC values

Aim

To derive a Predicted No-Effect-Concentration for long and/or short term exposure of a given environmental compartment ($PNEC_{comp}$).

Background

The PNEC is the concentration of a chemical in any compartment below which unacceptable effects on the aquatic ecosystem and its organisms will most likely not occur during long term or short term exposure. The PNEC is ideally derived from toxicity data for organisms living in the compartment in question that have been obtained through laboratory testing or by non-testing methods. However, if no experimental data are available for organisms of a given compartment (e.g. soil), a PNEC value can be estimated based on results of tests with aquatic organisms.

Basically, the available information on aquatic toxicity depends on the quantity manufactured or imported of the substance. Typically, data on short-term toxicity will be available for organisms representing 3 different trophic levels/groups of organisms (algae, invertebrates, fish) when a substance is manufactured or imported in a quantity of more than 10 and less than 100 t/y, but data from other groups of organisms or on long-term toxicity may occasionally be available as well. For higher tonnages, more data will often be available (cf. REACH, Annexes VII-X).

Because the diversity in ecosystems is high and only a few species are used in the laboratory, it is considered most likely that ecosystems will be more sensitive to the chemicals than individual organisms in the laboratory. Therefore, results of tests are not used directly for the risk assessment but used as a basis for extrapolation of the PNEC.

Extrapolation methods have been developed for estimating PNEC values for chemicals in aquatic and terrestrial environments. Two different types of extrapolation methods exist: assessment factor methods and sensitivity distribution methods.

*Assessment factor methods*

The general principle of these methods is that the result from a laboratory test is divided by an appropriate assessment factor (AF). The sparser the available data, the higher is the assessment factor. PNECs are estimated by division of the lowest value for the toxicity with the relevant assessment factor. Results of long-term tests (expressed as EC10/NOEC for a sublethal parameter) are preferred to those of short-term tests ($EC/LC_{50}$), because such results give a more realistic picture of effects on the organisms during their entire lifecycle.

In establishing the size of these assessment factors, a number of aspects have been addressed to extrapolate from single-species laboratory data to a multi-species ecosystem. These areas comprise:

- intra- and inter-laboratory variation of toxicity data;
- intra- and inter-species variations (biological variance);
- short-term to long-term toxicity extrapolation;
- laboratory data to field impact extrapolation.

*The sensitivity distribution methods*

When sufficient information is available for a mathematical description of the distribution of the sensitivities among different species, this can be used for estimating a low exposure concentration that is protective for the high majority of species in an ecosystem.

The sensitivity distribution methods are based on statistical calculations and require experimentally determined NOEC values for a number of tests (minimum of 10) with species from different taxonomic groups (minimum of 8). These methods aim at calculating a concentration, which is assumed to protect a certain percentage (e.g. 95%) of the species of the ecosystem against toxic effects.

The assumptions and requirements for the sensitivity distribution methods are described in detail (Section R.10.3.1.3.) When the available data do not fulfil these requirements (which is most often the case), the assessment factor methods are used. Therefore, the assessment factor methods are most frequently used and only these methods are described in this document. Detailed information on the sensitivity distribution methods can be found in Section R.10.3.1.3.

<u>Assessment steps</u>

The typical approach will be to use the AF method. Thus, the following assessment steps apply:

- For the environmental compartment, select key studies for each trophic level/group of organisms
- Identify the most sensitive trophic level/group of organisms and within this group the species with the lowest effect concentration
- Identify the appropriate assessment factor (AF) as a function of the available information
- Divide the lowest effect concentration with the assessment factor for deriving the $PNEC_{comp}$

Calculation

For the determination of the PNEC the following general equation can be used:

$$PNEC_{comp} = \frac{Min\{EC_{comp}\}}{AF}$$

Input

| Parameter | Description | Source |
|---|---|---|
| Min{$EC_{comp}$} | The lowest valid effect concentration for organisms from the compartment, i.e. EC50 or LC50 for short-term toxicity or EC10/NOEC for long-term toxicity, typically given in [mg/L] or [mg/kg] | Technical Dossier [cf. Art. 10 (a) (vi) and (vii)] |
| AF | Assessment factor, the size of which depends on the type and amount of toxicity information available | Chapter R.10.3.1 |

Output

| Parameter | Description | Use |
|---|---|---|
| $PNEC_{comp}$ | Predicted No-Effect-Concentration for the compartment in question, typically given in [mg/L] or [mg/kg] | Risk assessment |

### B.7.2.2 Derivation of PNEC for freshwater

Depending on the available toxicity data for aquatic organisms, assessment factors are selected for extrapolating single-species toxicity tests to a PNEC for protecting organisms living in the aquatic compartment. The following trophic levels are distinguished for the freshwater and marine environment:

- algae (primary producers);
- invertebrates / *Daphnia* (primary consumers);
- fish (secondary consumers);
- other species (e.g. decomposers).

The specific assessment factors to be used depending on the ecotoxicity data available are provided in Chapter R.10.3.1.

**Example:**

A dossier for a substance manufactured in quantities between 10 and 100 tonnes (Annex VIII requirements) has the following ecotoxicity data

Algae: *Scenedesmus subspicatus* EC50 (72 hours) = 10 mg/L

Invertebrates: *Daphnia magna* EC50 (48 hours) = 1 mg/L

Fish: *Pimephales promelas* EC50 (96 hours) = 0.8 mg/L

In this situation only short-term ecotoxicity data are available. The most sensitive trophic level is the fish with an EC50(96 hours) = 0.8 mg/L (=min{$EC_{hwater}$}).

According to Section R.10.3.1.2 the assessment factor (AF) to use when only short term toxicity data are available on the three trophic levels is 1000.

The PNEC*water* = 0.8 / 1000 = 0.0008 mg/L = 0.8µg/L

If intermittent release is identified for a stage of the life cycle, only short-term effects need to be considered for risk characterisation of that stage (only for the aquatic compartment). Intermittent release is defined as “intermittent but only recurring infrequently i.e. less than once per month and for no more than 24 hours” (Section R.16.2.1.5). Specific assessment factors have to be applied on the available short term toxicity data as specified in Section R.10.3.3.

### B.7.2.3 Derivation of PNEC for marine water

Different assessment factors are used for the derivation of PNEC for marine water. The greater diversity of taxa in the marine environment, compared to freshwaters, may result in a broader distribution of species sensitivity. In those cases where only data for freshwater or saltwater algae, crustaceans and fish are available a higher assessment factor should be applied than that for the derivation of $PNEC_{water}$ for freshwaters. This higher assessment factor reflects the greater uncertainty in the extrapolation. Where data is available for additional marine taxonomic groups, for example rotifers, echinoderms or molluscs the uncertainties in the extrapolation are reduced and the magnitude of the assessment factor applied to a data set can be lowered.

The specific assessment factors to apply are provided in Section R.10.3.2.3.

### B.7.2.4 Derivation of PNEC for sediment and soil

The $PNEC_{sediment/soil}$ can be derived in two ways depending on the data available.

- Results of tests with sediment/soil living organisms
- Using the equilibrium partitioning method (EPM) when only toxicity data (results of tests or non-test methods) for aquatic (pelagic) organisms are available

The $PNEC_{sediment/soil}$ is most of the time first derived by using the EPM and toxicity data for aquatic organisms as results of tests with sediment/soil living organisms are rarely available.. If data are available on aquatic organisms only, the $PNEC_{sediment/soil}$ is estimated based on the assumptions that the sensitivity of pelagic and sediment living organisms is comparable but that in sediment/soil, the availability of the substance is reduced due to sorption to the (organic matter of the) sediment/soil. This implies the use of partitioning calculations, assuming that equilibrium is obtained. The availability of data with sediment living organisms is decisive of whether one or both of the approaches must be used.

<u>Equilibrium partitioning</u>

If only data from aquatic organisms are available, the $PNEC_{sediment/soil}$ is calculated from equilibrium partitioning.

- Find $PNEC_{water}$ or in the case of marine sediment $PNEC_{saltwater}$
- Find Koc (key study) identified under
- Use standard characteristics of sediment and conditions
- Perform calculation according to equation below

To determine the $PNEC_{sediment}$ for the freshwater and marine compartment the following equation should be used:

$$PNEC_{sediment} = (0.783 + 0.0217 \cdot K_{oc}) \cdot PNEC_{water}$$

The $PNEC_{sediment}$ is applicable for standard sediment based on freshly settled suspended solids with 10% solids and 10% organic carbon.

To determine the $PNEC_{soil}$ the following equation should be used:

$$PNEC_{soil} = (0.174 + 0.0104 \cdot Koc) \cdot PNEC_{water}$$

The $PNEC_{soil}$ is applicable for standard soil with 60% solids, 20% water and 20% air, and with 2% organic carbon in the soil solids.

Assessment factor method

If data with sediment or soil living organisms are available, the typical approach will be the assessment factor method as described in Section B.7.2.1 using the assessment factors provided in Sections R.10.5.2.2 for sediment and R.10.6.2 for soil.

### B.7.2.5 Derivation of PNEC for sewage treatment plant (STP)

The $PNEC_{micro\text{-}organisms}$ is the concentration of a chemical in water below which unacceptable effects on the micro-organisms in sewage treatment plants (STP) will most likely not occur even during continuous (long-term) exposure.

The $PNEC_{micro\text{-}organisms}$ is normally derived from toxicity data for micro-organisms in activated sludge that have been obtained through laboratory testing or by non-testing methods. Results from an activated sludge respiration inhibition test are assumed to be available. Other data may be available as described in Section R.10.4.

The assessment factors used to determine the $PNEC_{micro\text{-}organisms}$ are provided in Section R.10.4.2.

### B.7.2.6 Derivation of PNECs for the air compartment

Although not standardised procedure exists, several options are available to consider effect data for the air compartment (e.g. for exposure of organisms by gaseous substances) as both biotic and abiotic effects are considered (see Section R.10.7).

### B.7.2.7 Derivation of PNECs for predators and top predators

Substances that are bioaccumulative and have a low degradability may accumulate in food chains and, eventually, cause toxic effects in predatory fish, birds and mammals (so called (top) predators) at higher levels of the food chains, including man. This effect is called secondary poisoning.

Especially the uptake through the food chains eventually leading to secondary poisoning should be considered and a strategy for the assessment of secondary poisoning has been developed. This strategy takes account of the $PEC_{comp}$, the direct uptake and resulting concentration in food of living organisms and the mammalian and avian toxicity of the chemical. On this basis, possible effects are estimated on birds and mammals in the environment via uptake through the food-chain water/soil → living organisms → predator → top predator mammal or bird. The length of the food chain is dependent of the compartment in question.

Thus, if a substance has a bioaccumulation potential and a low degradability, it is necessary to consider whether the substance also has a potential to cause toxic effects if accumulated in higher organisms. This assessment is based on classifications on the basis of mammalian toxicity data, i.e. the classification STOT (repeated exposure) category 1 or 2 (H372 “Causes damage to organs through prolonged or repeated exposure, H373 “May cause damages to organs through prolonged or repeated exposure”) toxic for reproduction category 1A, 1B or 2 (H360F “May damage fertility”, H360D “May damage the unborn child”, H360f “Suspected of damaging fertility”, H361d “Suspected of damaging the unborn child”, H362 “May cause harm to breast-fed children”). If this is the case, a detailed assessment of secondary poisoning should be conducted.

The assessment of secondary poisoning takes place as a tiered process

1. Evaluate the bioaccumulative potential of the substance

Collate information regarding BCF or Log $K_{ow}$ and degradability

Compare to the following criteria

- log $K_{ow} \geq 3$; ***or***;
- BCF $\geq$ 100
- ***and*** there is no mitigating property such as ready biodegradability or hydrolysis (half-life less than 12 hours)

If these are fulfilled, proceed to the subsequent step.

2. Calculate the no-effect concentration in food ($PNEC_{oral,predator}$)

The typical approach will be to use the AF method. Thus, the usual assessment steps pertain:

- For the environmental compartment, select key studies among available oral toxicity data for birds or mammals (i.e. collate data from toxicity studies reporting on dietary and oral exposure, preferably long term studies reporting NOECs on for e.g. mortality, reproduction or growth)
- In case toxicity data are given as NOAEL only, these NOAELs must be converted to NOECs by use of conversion factors, which are dependent on the mammal or bird species studied. The conversion factors are given in Table R.10-12 of Section R.10.8.
- Identify the key study among groups of organisms with the lowest effect concentration
- Identify the study giving the lowest $LC50_{bird}$, $NOEC_{bird}$ or $NOEC_{mammal}$. This is $TOX_{oral}$
- Identify the appropriate assessment factor (AF) as a function of the available information. The assessment factors are provided in Section R.10.8.
- Divide the lowest effect concentration with the assessment factor for deriving the $PNEC_{oral,predator}$

The following equations can be used to derive the $PNEC_{oral,predator}$

$$NOEC_{oral,predator} = NOAEL_{oral,predator} \cdot CONV_{predator}$$

$$PNEC_{oral,predator} = \frac{TOX_{oral,predator}}{AF_{oral,predator}}$$

## Part B: Hazard Assessment

### Input

| Parameter | Description | Source |
|---|---|---|
| $PEC_{comp}$ | Predicted concentration in aqueous phase | [Result of exposure estimates] |
| log $K_{ow}$ | Partition coefficient octanol/water | Dossier |
| $NOAEL_{oral,predator}$ | The lowest valid effect concentration from dietary or oral toxicity studies on birds or mammals, typically given in [mg/kg bw/day] | Dossier |
| $NOEC_{oral,predator}$ | The lowest valid effect concentration from dietary or oral toxicity studies on birds or mammals, given in [mg/kg food] | Dossier [or calculated from $NOAEL_{predator}$] |
| $TOX_{oral,predator}$ | The lowest $LC50_{bird}$, $NOEC_{bird}$ or $NOEC_{mammal}$ | Dossier [or $NOEC_{oral,predator}$ from above] |
| $AF_{oral,predator}$ | Assessment factor, the size of which depends on the type and amount of toxicity information available | Table R.10-13 in section R.10.8.2 |

### Output

| Parameter | Description | Use |
|---|---|---|
| $PEC_{oral}$ | Predicted concentration in prey/food typically given in [mg/kg] | Risk assessment for secondary poisoning |
| $PEC_{oral,predator}$ | Predicted No-Effect-Concentration of prey/food, typically given in [mg/kg] | Risk assessment for the soil compartment |

# B.8 SCOPE OF EXPOSURE ASSESSMENT

## B.8.1 Background and aim of the chapter

Article 14(1) and (4) of REACH require that exposure assessment and subsequent risk characterisation be carried out for substances subject to registration, which are manufactured or imported in a quantity equal to or greater than 10 tonnes/year, and where the registrant concludes in the hazard assessment that the substance fulfils the criteria for classification in any of the hazard classes or categories listed in Article 58(1) of Regulation (EC) No 1272/2008 (CLP Regulation), amending Article 14(4) of the REACH Regulation from 1 December 2010, namely:

- hazard classes 2.1 to 2.4, 2.6 and 2.7, 2.8 types A and B, 2.9, 2.10, 2.12, 2.13 categories 1 and 2, 2.14 categories 1 and 2, 2.15 types A to F.
- hazard classes 3.1 to 3.6, 3.7 adverse effects on sexual function and fertility or on development, 3.8 effects other than narcotic effects, 3.9 and 3.10.
- hazard class 4.1:
- hazard class 5.1;
- or PBT, vPvB properties.

These classes, categories and properties will henceforth be described as “Article 14(4) hazard classes, categories or properties”.

On this basis, if it is decided that exposure and risk characterisation is required for a substance, the next step is to decide the scope of the exposure assessment. According to Annex I of REACH exposure assessment has to cover **all** hazards that have been identified according to sections 1 to 4 of Annex I of REACH. For the sake of clarity it should be noted that such identified hazards necessitating exposure assessment are of three types:

- hazards for which there are classification criteria and there is information to establish that the substance meets the criteria and is therefore classified;
- hazards for which there are classification criteria and there is information on these properties of the substance showing that it does have these properties, but the severity of the effects is lower than the criteria for classification and so the substance is not classified;
- iii) hazards for which currently no classification criteria exist, but there is information to show that the substance has such hazardous properties.

To illustrate hazard identification, in particular for the unclassified cases, it is useful to consider the OECD definition of hazard identification: hazard identification should address the different “types and nature of adverse effects that an agent has as inherent capacity to cause in an organism, system or (sub) population”[4]. Adverse effect means “a change in the morphology, physiology, growth, development, reproduction, or life span of an organism, system, or (sub) population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences”.[5]

Furthermore, REACH specifies in Annex I that exposure assessment shall consider all stages of the life-cycle of the substance resulting from the substance’s manufacture and the identified uses.

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4 http://www.who.int/ipcs/publications/methods/harmonization/en/terminol_part-II.pdf - OECD definition of hazard identification.

5 http://www.inchem.org/documents/harmproj/harmproj/harmproj1.pdf - OECD definition of adverse effects (IPCS RISK ASSESSMENT TERMINOLOGY, 2004).

For each life-cycle stage, exposure assessment must cover any exposures that relate to the **identified hazards** from the hazard assessment performed as the first part of the chemical safety assessment as described above.

The aim of exposure assessment is to achieve safe use of the substance. Thus the exposure scenario(s) developed from the assessment need to ensure "control of risks" resulting from all identified hazards.

This guidance is to support registrants in determining the required scope of exposure assessment based on the outcome of hazard assessment for human health and environmental effects. It is based on the principles and guidance already contained in other chapters of the Guidance on Information Requirements and Chemicals Safety Assessment (IR/CSA Guidance).

This guidance does not cover matters addressed in other guidance, such as:

- exposure arguments to decide on triggering or waiving of registration data as set out in Annexes VIII to X;
- exposure assessment requirements for substance-tailored exposure-driven testing for waiving of standard information requirements according to Annex XI section 3 (see Guidance Chapter R.5);
- the additional scope of exposure assessment for substances that have PBT or vPvB properties (see Guidance Chapter R.11);
- the presentation in the Chemical Safety Report (CSR) of risk management measures and the risk characterisation for physicochemical hazards, since the assessment for these hazards follows other principles than the exposure assessment for toxicological and eco-toxicological hazards. (Note that a review of Guidance Chapter R.9 is in progress to address this issue).

## B.8.2 General principles

The hazard assessments for **human health** and the **environment** according to Annex I of REACH include the following steps:

1. Evaluation of information
   - hazard identification based on all relevant available information [6] and
   - establishment of quantitative dose (concentration) – response (effect) relationship or semi-quantitative or qualitative analysis, where this is not possible;
2. Classification and labelling;
3. Identification of PNECs and DNELs.

Companies preparing a registration dossier and carrying out a Chemical Safety Assessment (CSA) will need to decide i) whether exposure assessment and risk characterisation are needed, and if yes, ii) what is the required scope of the exposure assessment. Thus, the result of the hazard assessment may trigger one of the following scenarios:

[6] "Available information" means information available to the registrant when meeting the information requirements laid down in Annex VI to XI and when having carried out the evaluation of this information. Please note: Considerations on use and exposure may already be relevant for fulfilling the information requirements e.g. in order to determine the likely/unlikely routes of exposure for humans or whether or not soil/sediments are likely to be exposed. Such considerations on use and exposure may include identification of uses to be avoided, operational conditions to be ensured to exclude exposure or risk management to be communicated to customers. Also release and exposure quantification may be needed to justify that exposure is absent.

- the substance does **not meet** the criteria for **any** of the Article 14(4) hazard classes, categories or properties[7]: in this case, an exposure assessment is **not mandatory**;
- the substance meets the criteria for **at least one** of the hazard classes or categories (physical, health or environmental), or is assessed as having any of the properties set out in Article 14(4) of REACH,: in this case, exposure assessment is **mandatory** and should be considered for **all** standard exposure estimations as listed in Table B-8-1.

Additionally, note that if a registrant adapts the standard information requirements based on exposure considerations in accordance with Annex XI section 3 ("substance-tailored exposure driven testing"), an exposure assessment is **mandatory** to fulfil the conditions therein.

As discussed in Section B.8.1, exposure assessment is not only limited to the classifiable hazards or adverse effects observed at doses/concentrations where classification is triggered, but should cover all hazards identified in step 1 of the hazard assessment (evaluation of information). The following are examples of such circumstances where exposure assessment would also cover non-classified hazardous properties:

- classification criteria are not yet defined for a certain type of hazard (e.g. environmental hazard related to soil and sediment or air) [8]. Even in the absence of classification criteria, hazards may have been identified (for example by observation of adverse effects in sediment-dwelling or soil-dwelling organisms);
- hazards are predicted by models, e.g. the equilibrium partitioning method to screen for potential risk in the sediment or soil compartments based on the aquatic PNEC;
- classification criteria are defined (e.g. for aquatic toxicity or chronic toxicity for human health), but based on relevant available information, it is concluded that the criteria are not fulfilled and hence the substance is not classified as hazardous for a certain endpoint (e.g. no *Specific Target Organ Toxicity* resulting from repeated exposure [STOT-RE] up to 100 mg/kg/d in a 90 days oral study). Nevertheless there may be adverse effects observed in the eco-toxicity or toxicity studies at higher concentration or dose than those which trigger classification, and these must be considered in the hazard assessment and may lead to the derivation of a DNEL or PNEC.

Based on the identification of hazards, the classification assigned and DN(M)EL and PNEC derived, the registrant can conclude for which toxicological effects, routes of exposure and environmental protection targets exposure assessment is required.

## B.8.3 Establishing whether exposure assessment is required

Figure B-8-1 provides an overview of the decision making process to decide on the need for exposure assessment based on the different outcomes from the hazard assessment. If none of the classification criteria are met and the registrant demonstrates that the substance does not fulfill the criteria for being regarded as PBT or vPvB, no exposure assessment is required at all (i.e. it is not mandatory). If the criteria for any of the Article 14(4) hazard classes, categories or properties[9] are met , the registrant will need to determine the appropriate scope of the exposure assessment for human health and for the environment.

[7] In this context "properties" refers to PBT and vPvB (see Section B.8.1)

[8] See endpoint-specific guidance on soil and sediment organisms, plants exposed via air, STP organisms and predators via the food chain as well as assessment of ozone formation, eutrophication and acidification potential and any other relevant environmental hazard (IR/CSR Guidance Chapter R.7).

[9] In this context "properties" refers to PBT and vPvB (see Section B.8.1)

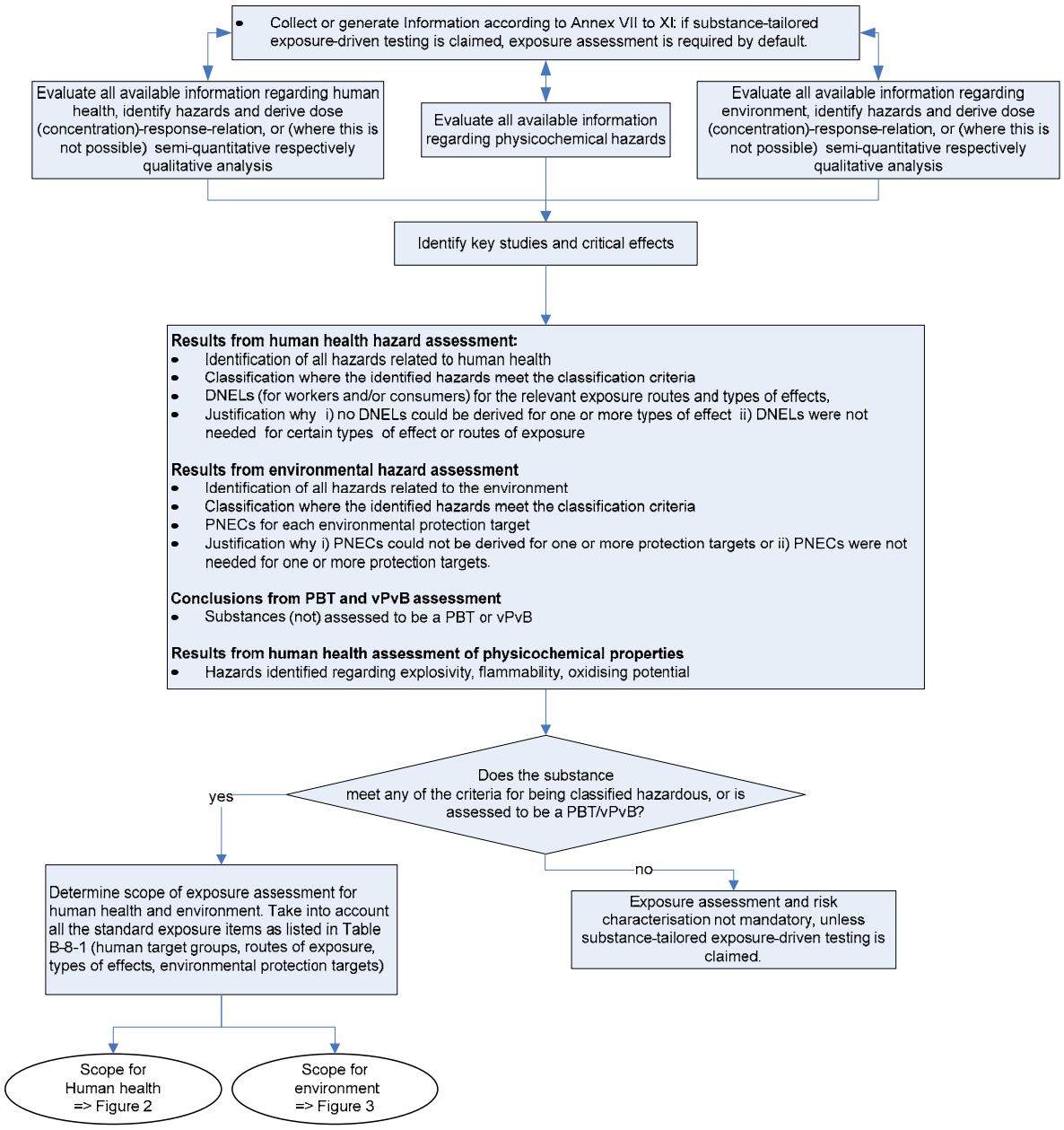



**Figure B-8-1**: Overview of the decision making process leading to the need to perform an exposure assessment for human health and the environment

## B.8.4 Scope of exposure assessment

Table B-8-1 provides an overview of the scope of an exposure assessment as suggested in chapters R.8, R.10 and R.16 of the IR/CSA Guidance. Up to 35 exposure estimations can be considered in a standard exposure assessment: these are presented in Table B-8-1[10]. However, the registrant may have assessed some types of hazard or routes of exposure as not being relevant for the substance (e.g. absence of acute adverse effects on all routes), and thus the corresponding exposure assessment can be omitted depending on the outcome of the hazard assessment. Other exposure assessments may be further sub-differentiated (e.g. sensitive worker or consumer (sub) populations).

**Table B-8-1:** Exposure assessment – overview

| Hazard assessment section | Target group | Route of exposure or environmental compartment | Type of effect | Potential no of exposure estimates |
|---|---|---|---|---|
| Human Health | Worker | Inhalation | Acute and chronic,, local and systemic | 4 |
| | | Dermal | | 4 |
| | | Eyes | | 1 |
| | Consumer | Inhalation | Acute and chronic, local and systemic | 4 |
| | | Dermal | | 4 |
| | | Eyes | | 1 |
| | | Oral | Acute and chronic, local and systemic | 4 |
| | Man via environment | Inhalation | Chronic systemic | 1 |
| | | Oral (food and drinking water) | | 1 |
| Environment | | Water pelagic (freshwater, marine) | | 2 |
| | | Water sediments (freshwater, marine) | | 2 |
| | | Aquatic food chain (freshwater predator, marine predator, marine top predator) | | 3 |
| | | Sewage treatment | | 1 |
| | | Air[11] | | 1 |
| | | Soil (agricultural) | | 1 |
| | | Soil food chain | | 1 |
| Number of standard exposure estimations for exposure assessment | | | | 35 |

Based on evaluation of the available hazard information for a substance it can be decided whether an exposure assessment for a specific target group, type of effect and duration of exposure and a subsequent risk characterisation according to Annex I to REACH is required.

Figures B-8-2 and B-8-3 provide the workflows for systematically considering the exposure assessment requirements based on the outcome of the hazard assessment on human health and the environment. These workflows start from the classified hazards for the substance and the related exposure assessment. In addition the registrant should consider:

[10] For the environment, the list of protection targets is aligned with the CSR format as generated with ECHA's *Chemical Safety Assessment and Reporting Tool* (Chesar). Exposure estimates for grassland and groundwater (terrestrial ecosystem) are not specifically mentioned here since they are not protection targets on their own but only needed to estimate exposure of man via the environment.

[11] This concerns for example effects on higher plants or impact on the ozone layer.

- whether adverse effects have been observed in studies conducted at the highest practicable & biologically-relevant concentration on toxicological endpoints e.g. according to OECD and EU Guidelines (e.g. 1000 mg/kg/d in OECD Guideline as a limit test for 90-day oral toxicity study);
- whether adverse effects have been observed in studies conducted at the highest practicable & biologically-relevant concentration on environmental toxicity e.g. according to OECD and EU Guidelines (e.g. 100 mg/l in OECD guideline as a limit test for acute aquatic toxicity), taking into account the properties of the substance determining the environmental fate.

If no adverse effects have been observed in studies at the highest recommended concentrations/doses tested, this would **normally** indicate that no hazard has been identified and no DNEL or PNEC can be derived[12] and hence exposure assessment for that route of exposure, type of effect or protection target would not be needed. If the study was not conducted according to the standard EU or OECD guideline and adverse effects are seen, (particularly where the dose levels at which effects are seen are only slightly greater than the limit dose in an OECD guideline for that endpoint), the registrant should either provide justification for disregarding the effects (e.g. because they are not biologically relevant), or carry out an exposure assessment as for any other identified hazard.

### B.8.4.1 Scope of exposure assessment related to toxicological hazards for human health

Figure B-8-2 presents a schematic diagram for systematically considering the exposure assessment needs of the different human populations, routes of exposure, types of effects and duration of exposure. This is based on the principles described in Part E (Risk Characterisation) and Chapter R.8 (Dose [Concentration]-Response regarding Human Health) of the IR/CSA Guidance. **Please note**: to enable risk characterisation for **man via the environment** exposure estimates for the different environmental compartments are systematically required when a DNEL is derived for long term systemic exposure via the inhalation and oral routes for the general population.

For both workers and consumers no short-term or long-term exposure assessment needs to be performed if no adverse effects have been observed for any of the relevant human health endpoints. Also, the assessment for exposure of man via the environment (food, drinking water and ambient air) can be omitted in this case.

[12] **Please note**: Not always applicable to environmental hazards from substances with low water solubility. Please also note that severe (eco)toxicological effects (e.g. mortality) observed only slightly above the limit dose would still require an exposure assessment.

## Part B: Hazard Assessment

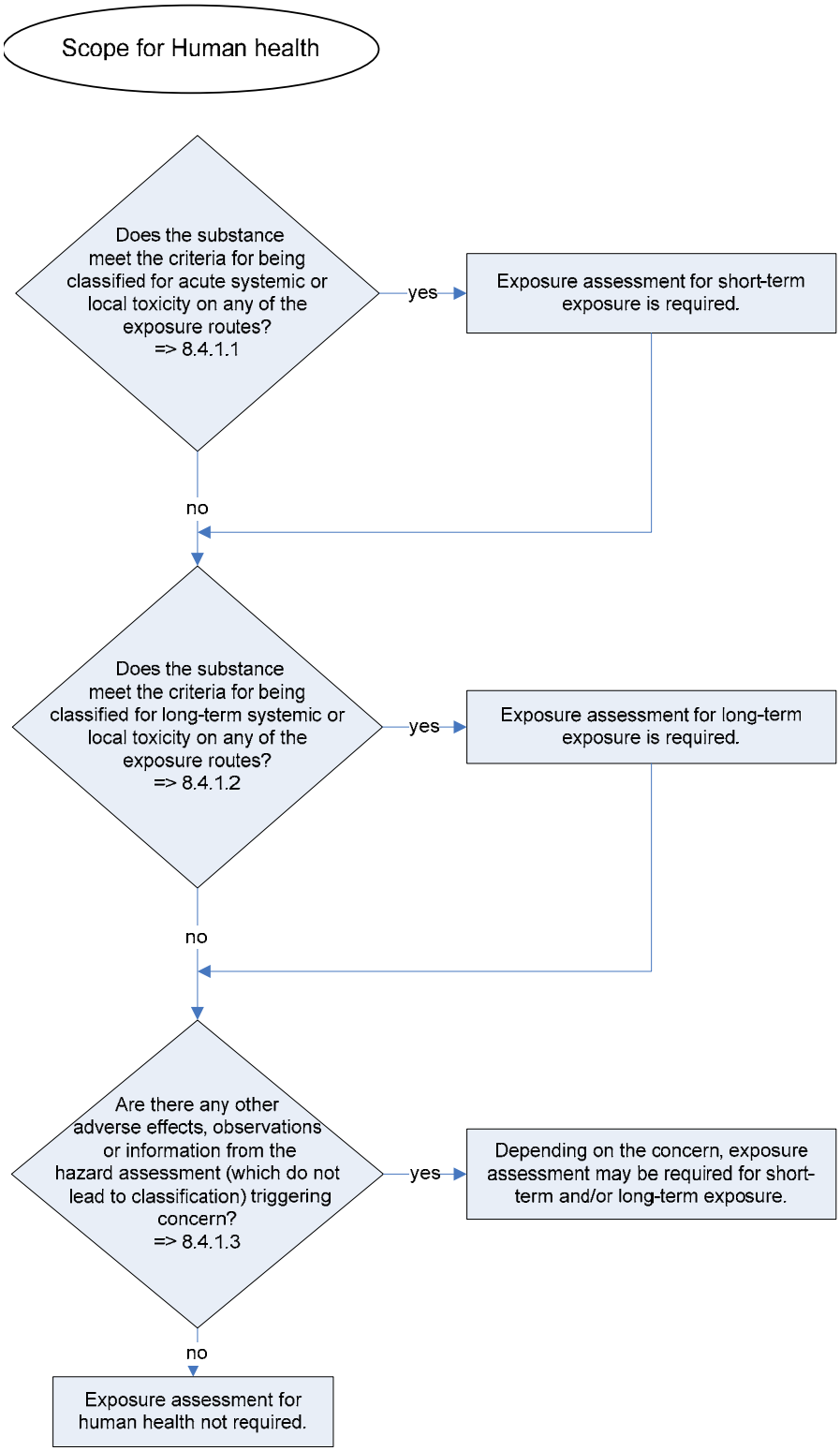



**Figure B-8-2:** Overview of the decision making process to identify the required scope of exposure assessment with regard to human health

#### B.8.4.1.1 Classified acute hazards

Appendix 2 provides a table with the classifications that may trigger the need for assessment related to short-term exposure. Where a short-term DNEL is available[13], corresponding short-term exposure assessment needs to be made using the same reference period as the DNEL (e.g. 15 min for workers) to quantitatively demonstrate that this DNEL will not be exceeded. Where no DNEL is available, a qualitative risk characterisation is required justifying that the risk management measures described in the exposure scenario sufficiently minimise/prevent short-term exposure.

Special consideration should be given to possible irreversible/severe adverse effects due to a short-term exposure. In reproductive toxicity, even a single short-term exposure may cause irreversible reproductive failure. A specific concern may arise from classified or non-classified developmental toxicity effects that are associated with or caused by a short-term exposure. A single short-term exposure during a sensitive time point of embryonic and/or foetal development may lead to malformation or other developmental hazards. To control the risk of these adverse effects it must be ensured that the estimated or measured short-term exposure does not exceed the daily DNEL for reproductive toxicity. Therefore, it is recommended that, in cases where a reproductive DNEL has been set, the exposure assessment should cover both short-term and long-term exposure with regard to both level and frequency of exposure.

#### B. 8.4.1.2 Classified long-term hazards

Appendix 3 provides a table with classifications that trigger the need to assess long-term exposure. Where a DNEL is available the exposure assessment needs to quantitatively demonstrate that the long-term DNEL will not be exceeded by the average exposure over a working day (for workers) or a consumer day (for consumers). Where no DNEL is available, a qualitative risk characterisation is required justifying that the risk management measures described in the exposure scenario sufficiently minimise/prevent exposure.

#### B.8.4.1.3 Non classified hazards

In addition to the classified hazards the registrant should consider adverse effects not leading to classification. If the criteria for classification of the identified hazard are not met, it may still be possible to derive a DNEL and thus an exposure assessment will be required (see cases c) and d) below). If a substance does not meet the criteria for classification and a DNEL cannot be derived, there may still be a hazard, so the registrant will then need to consider the level and type of hazard identified and to justify the conditions of use described in the exposure scenario in a qualitative risk characterisation (see cases a) and b) below). The following are examples of such cases but others may occur in practice as well:

- case a): evidence from human data, structural alerts and/or classification for skin sensitisation may suggest that the substance could have respiratory sensitising properties but the information is not definitive enough to meet the classification criteria. **Please note**: there may be limited data on these kinds of effects for which there is no standard information requirement in REACH. Therefore, in these cases, the existing evidence may lead to the conclusion that there is a hazard and hence an exposure assessment is needed;
- case b): evidence that the substance may have adverse effects in the respiratory tract, e.g. from acute studies on local irritation, in the absence of suitable repeated dose inhalation toxicity data to assess this endpoint;
- case c): effects observed that do not lead to classification for repeated dose toxicity but nevertheless are regarded as adverse, such as severe effects occurring only at exposure levels above the classification cut off for repeated dose toxicity;

[13] Available occupational exposure limits (OELs) to be taken into account, if applicable.

- case d): any other adverse effects seen for which a DNEL can be derived but which do not lead to classification.

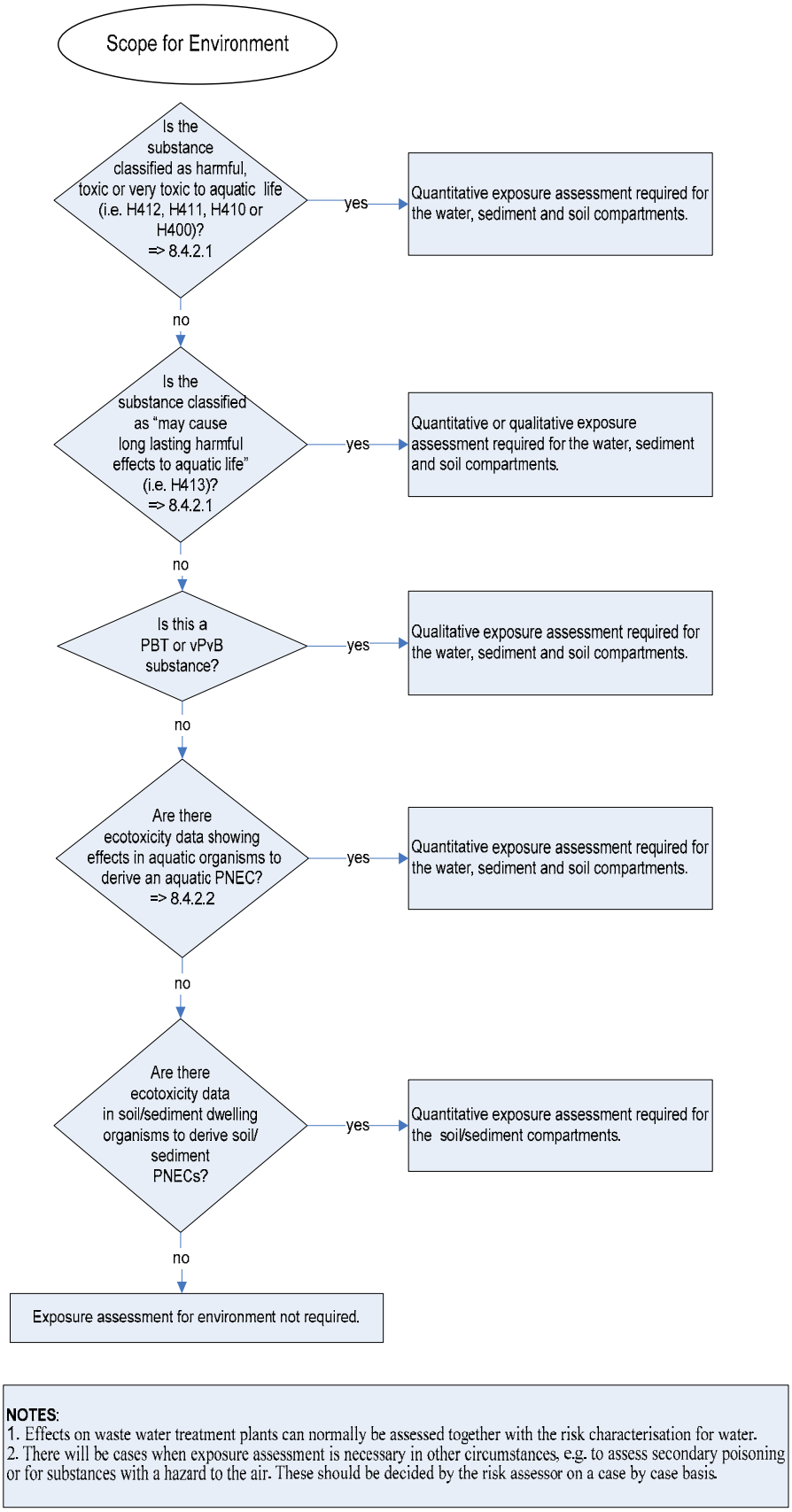
### B.8.4.2 Scope of exposure assessment related to environmental hazards[14]

Figure B-8-3 illustrates the decision making process for considering exposure assessment needs for environmental protection targets.

For ecotoxicological properties, the decision making process on which environmental protection targets are to be addressed in the exposure assessment, are based on the principles already defined in chapter R.10 and R.16 of the IR/CSA Guidance. For considering the need for an exposure assessment with regard to secondary poisoning, the criteria provided in section B.7.2.7 of the IR/CSA Guidance can be applied.

The following section puts a specific emphasis on the exposure assessment and risk characterisation for poorly water soluble substances. Reference is made to the principles and workflows defined in the integrated testing strategies for water, soil and sediments, as described in Chapter 7b and 7c of the IR&CSA Guidance.

[14] Please note: This guidance does not apply to metals.




**NOTES**:
1. Effects on waste water treatment plants can normally be assessed together with the risk characterisation for water.
2. There will be cases when exposure assessment is necessary in other circumstances, e.g. to assess secondary poisoning or for substances with a hazard to the air. These should be decided by the risk assessor on a case by case basis.

**Figure B-8-3:** Overview of the decision making process to identify the required scope of exposure assessment with regard to the environment.

#### 8.4.2.1 Classified hazards

Appendix 4 provides a table with the classifications that trigger the need to assess environmental exposure.

For substances which are classified as harmful, toxic or very toxic to aquatic life (i.e. H412, H411, H410 and H400), an aquatic PNEC can be derived. In these circumstances there are unclassified hazards to the sediment and soil compartments because toxicity to aquatic organisms is used as an indicator of concern for sediment and soil organisms, and a screening risk characterisation is undertaken using the equilibration partitioning method (EPM) [15] to derive PNECs for sediment and soil. Hence quantitative exposure assessment, i.e. derivation of PECs, is mandatory for the water, sediment and soil environmental compartments.

Substances with the only environmental classification as 'May cause long lasting harmful effects to aquatic life' (i.e. H413) have been established as persistent in the aquatic environment and potentially bioaccumulative on the basis of test or other data. There are also potential hazards for these substances for the sediment and soil compartments, because these substances are potentially bioaccumulative in all organisms and are also potentially persistent in sediment and soil. Hence exposure assessment is mandatory for the water, sediment and soil environmental compartments, which may be quantitative or qualitative as appropriate.

PBT and vPvB substances have been established as persistent and bioaccumulative (and the former also as toxic) in the environment as a whole. Hence qualitative exposure assessment is mandatory for the water, sediment and soil environmental compartments.

#### 8.4.2.2 Non-classified hazards

If there are ecotoxicity data showing effects in aquatic organisms, but the substance is not classified as dangerous for the aquatic environment, an aquatic PNEC can nevertheless be derived thus indicating a hazard to the aquatic environment. In these circumstances there are also unclassified hazards to the sediment and soil compartments because toxicity to aquatic organisms is used as an indicator of concern for sediment and soil organisms and a screening risk characterisation is undertaken using the equilibration partitioning method (EPM) [16] to derive PNECs for sediment and soil. Hence quantitative exposure assessment, i.e. derivation of PECs, is mandatory for the water, sediment and soil environmental compartments.

If there are ecotoxicity data in sediment organisms showing effects, a sediment PNEC can be derived and there is a hazard to this compartment. Hence an exposure assessment for sediment is mandatory.

If there are ecotoxicity data in soil organisms showing effects, a soil PNEC can be derived and there is a hazard to this compartment. Hence an exposure assessment for soil is mandatory.

Effects on waste water treatment plants can normally be assessed together with the risk characterisation for water.

There will be cases when exposure assessment is necessary in other circumstances, for example to assess secondary poisoning or for substances with a hazard to the air. These should be decided by the risk assessor on a case by case basis.

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[15] In the absence of information from soil and sediment studies, PNECs for these protection targets may be derived from information for aquatic toxicity, based on the equilibrium partitioning method (see Chapter R.10.5.2.1 and R.10.6.1 of the IR&CSA Guidance). The equilibrium-partitioning method is applicable under the following conditions: There is no specific mode of action driving the adsorption to sediments; the substance in not highly adsorptive; the adsorption is not driven by factors other than the log Kow; no experimental soil and sediment studies are available showing that no effects are to be expected; for applying the EPM to substances with a log Pow >5 refer to IR&CSA Guidance Part E.4.3.3.

[16] See footnote 12.

## B.8.5 Types of exposure assessment and risk characterisation

The outcome of the hazard assessment determines the type of exposure assessment and risk characterisation.

### B.8.5.1 Human health

Table B-8-2 summarises the types of exposure assessment that may be required for human health and is included to illustrate the association of the scope of exposure assessment with risk characterisation and risk management (see the IR/CSA Guidance for further information). The Table combines the scope of the exposure assessment (i.e. routes of exposure and type of effects) with the type of risk characterisation required (i.e. quantitative or qualitative) and the corresponding risk management objective (i.e. limiting exposure to a RCR<1 or minimisation of exposure).

The left column in Table B-8-2 indicates whether a hazard has been identified based on observed effects. The next two columns then differentiate between the different types of classifiable effects and whether DNELs can be derived or not. A "No" in the DNEL column indicates that for the effect observed, the available data or the nature of the effect do not allow a dose-descriptor to be determined and hence it is not possible to derive a "no effect level".

This outcome then determines the type of risk characterisation (i.e. quantitative or qualitative), the risk management objective (i.e. to limit exposure to a no-effect-level or to minimise exposure) and the type of exposure estimation required (i.e. an average exposure over a day and/or short-term exposure during a single event). Where no DNEL can be derived, (semi)quantitative assessment elements may still be required. For instance, a Derived Minimal Effect Level (DMEL) may be available that can be compared with exposure estimates characterizing "minimised exposure". In the absence of a DMEL, the registrant should still provide exposure estimates as supporting evidence for the effectiveness of the risk management measures described in the exposure scenario.

**Table B-8-2:** Types of human health exposure assessment and risk characterisation

| Hazards identified | Classification criteria met[17] | DNEL can be derived | Risk management aims to: | Exposure estimate | Type of risk characterisation |
|---|---|---|---|---|---|
| Yes | Acute local | Yes | Limit exposure on specific route to RCR < 1 | Required for short-term exposure | Quantitative |
| Yes | Acute local | No | Minimise exposure on specific route | Supportive evidence potentially needed | Qualitative or semi-quantitative |
| Yes | Acute systemic | Yes | Limit combined exposure to RCR < 1 | Required for short-term exposure | Quantitative |
| Yes | Acute systemic | No | Minimise exposure on all routes | Supportive evidence potentially needed | Qualitative or semi-quantitative |
| Yes | Chronic local | Yes | Limit exposure on specific route to RCR < 1 | Required for average exposure per day | Quantitative |
| Yes | Chronic local | No | Minimise exposure on specific route | Supportive evidence potentially needed | Qualitative or semi-quantitative |
| Yes | Chronic Systemic | Yes | Limit combined exposure to RCR < 1 | Required for average exposure per day | Quantitative |
| Yes | Chronic Systemic | No | Minimise exposure on all routes | Supportive evidence potentially needed | Qualitative or semi-quantitative |
| Yes | No | Yes | If the identified hazards do not lead to a classification, the same differentiation as | | |

[17] See Hazard Statements indicating acute local and systemic effects (Appendix 2) and chronic effects (Appendix 3).

| Hazards identified | Classification criteria met[17] | DNEL can be derived | Risk management aims to: | Exposure estimate | Type of risk characterisation |
|---|---|---|---|---|---|
| Yes | No | No | in the rows above is to be made among types of effects and routes of exposure. | | |
| No | No | No | No exposure assessment required for corresponding route and type of effect. Please note: if a registrant adapts information requirements based on exposure considerations in Annex XI section 3 ("substance-tailored exposure driven testing"), this needs to be justified with an exposure assessment. Such exposure assessment should always include exposure estimates. | | |

It is important to note that, for human health:

- local and systemic effects need to be differentiated with a view to targeting risk management measures and deriving corresponding risk characterisation for single routes of exposure to a given substance (local effects), or combined routes of exposure for a given substance (systemic effects). Once the need for risk management measures has been established per route of exposure, the actual measures to limit or minimise exposure should be taken preferably at the source of exposure (i.e. containment and engineering controls in preference to personal protective equipment);
- short-term and long-term effects need to be differentiated with a view to targeting risk management and the potentially required exposure estimates for peak or event exposure;
- when differentiating among types of local effects observed and the corresponding routes of exposure, the following need to be taken into account. If dermal effects are observed, this should usually trigger considerations regarding potential effects on the respiratory route, (unless there is sufficient information available with regard to respiratory effects). It is also recommended that observation of certain acute local effects should trigger considerations whether there are mechanistically similar long-term effects. An example for this is skin or eye irritation, which may trigger a concern not only for acute but also for long-term respiratory irritation. Obviously, the effect on the respiratory tract is only relevant if the substance has a high enough vapour pressure or forms an aerosol or dust under the foreseeable conditions of use;
- the availability of a dose descriptor (and hence a possible DNEL derivation) needs to be differentiated from the situation were no DNEL can be derived for the observed effects. If no DNEL is available, the risk management measures will aim at minimising the exposure and the risks will be characterised in a qualitative way. In such a situation, the exposure estimates will support the demonstration of the effectiveness of the risk management measures rather than a quantitative risk characterisation.

### B.8.5.2 Environment

The type of exposure assessment that may be required for the environment may be quantitative or qualitative. It may be for different environmental compartments, i.e. water, sediment or soil. The protection goal to protect the environment may vary between compartments. In addition, other types of exposure assessment for risk characterisation may be needed on a case by case basis, e.g. to assess secondary poisoning or effects in air. Effects on waste water treatment plants can normally be assessed together with the risk characterisation for water.

# Appendix 1 Hazard classes in Annex I to Regulation (EC) No 1272/2008

| Hazard classes | |
|---|---|
| 2 | Physical Hazards |
| 3.1 | Acute toxicity |
| 3.2 | Skin corrosion/irritation |
| 3.3 | Serious eye damage/eye irritation |
| 3.4 | Respiratory or skin sensitisation |
| 3.5 | Germ cell mutagenicity |
| 3.6 | Carcinogenicity |
| 3.7 | Reproductive toxicity: adverse effects on sexual function and fertility or on development |
| 3.8 | Specific target organ toxicity – single exposure (other than narcotic effects) |
| 3.9 | Specific target organ toxicity – repeated exposure |
| 3.10 | Aspiration Hazards |
| 4.1 | Hazardous to the aquatic environment |
| 5.1 | Hazardous to the ozone layer |

## Appendix 2 Classification related to human health effects after short-term exposure

In the hazard assessment, it will be concluded whether any of the following phrases needs to be assigned according to the criteria described in the CLP Regulation. If such phrases are to be assigned, assessment related to short-term exposure (systemic and/or local) on one or more routes of exposure may be required.

Acute toxicity 1 and 2 H300, H310, H330

Acute toxicity 3 H301, H311, H331

Acute toxicity 4 H302, H312, H332

Specific target organ toxicity after single exposure (STOT SE):

- Damage to organs H370, H371
- Respiratory irritation H335
- Drowsiness and dizziness H336

Aspiration hazard H304

Corrosive to the respiratory tract EUH071

Toxic by eye contact EUH070

Skin Corrosion/irritation H314, H315,

Serious eye damage/irritation H318, H319

Respiratory/skin sensitisation H334, H317

Reproductive toxicity H360, H361

Germ cell mutagenicity H340, H341

**Note**: For reproductive toxicants and germ cell mutagens, assessment of short-term exposure may be relevant as well, since a single short-term exposure event may lead to adverse effects.

## Appendix 3 Classification related to human health effects after long-term exposure

In the hazard assessment, it will be concluded whether any of the following phrases needs to be assigned according to the criteria described in the CLP Regulation. If such phrases are to be assigned, assessment related to long-term exposure on one or more routes of exposure may be required.

| |
|---|
| Specific target organ toxicity after repeated exposure (STOT RE): Damage to organs H372, H373 |
| Specific target organ toxicity after single exposure (STOT SE): Respiratory irritation H335 |
| Skin cracking EUH066 |
| Corrosive to the respiratory tract EUH071 |
| Respiratory/skin sensitisation H334, H317 |
| Germ cell mutagenicity H340, H341 |
| Carcinogenicity H350, H351 |
| Reproductive toxicity H360, H361, H362 |

# Appendix 4 Classification related to environmental effects

**Water, sediments, soil and micro-organisms**

In the hazard assessment it will be concluded whether any of the following phrases needs to be assigned according to the criteria described in the CLP Regulation. In such a case, environmental exposure assessment is required.

| |
|---|
| H400 Very toxic to aquatic life |
| H410 Very toxic to aquatic life with long lasting effects |
| H411 Toxic to aquatic life with long lasting effects |
| H412 Harmful to aquatic life with long lasting effects |
| H413 May cause long lasting harmful effects to aquatic life |

**Secondary poisoning**

In the hazard assessment it will be concluded whether any of the following phrases needs to be assigned according to the criteria described in the CLP Regulation. If such phrases for human health are to be assigned, exposure assessment regarding secondary poisoning may be required if the substance has a log Kow ≥ 3 or BCF ≥ 100 and is not readily biodegradable.

| |
|---|
| H373: Causes damage to organs through prolonged or repeated exposure (cat 2) |
| H372: Causes damage to organs through prolonged or repeated exposure (cat 1) |
| H360: May damage fertility or the unborn child (cat 1A or 1B) |
| H361: Suspected of damaging fertility or the unborn child (cat 2) |
| H362: May cause harm to breast-fed child |

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