Guidance on information requirements and chemical safety assessment

Chapter R.5: Adaptation of information requirements

April 2010

Draft Update V.01

Guidance for the implementation of REACH

LEGAL NOTICE

This document contains guidance on REACH explaining the REACH obligations and how to fulfil them. However, users are reminded that the text of the REACH regulation is the only authentic legal reference and that the information in this document does not constitute legal advice. The European Chemicals Agency does not accept any liability with regard to the contents of this document.

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 are aimed 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/FINAL_MB_30_2007_Consultation_procedure_on_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 finalized or updated.

Convention for citing the REACH regulation

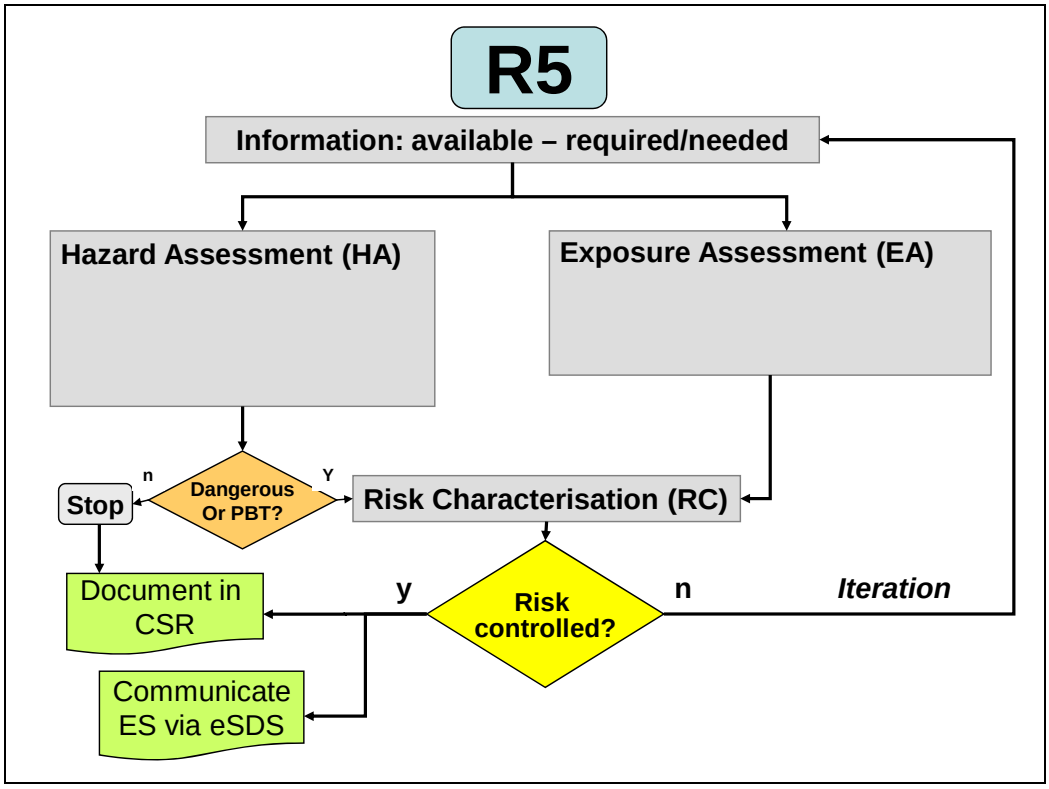
Where the REACH Regulation is cited literally, this is indicated by text in italics between quotes.

Table of Terms and Abbreviations

See Chapter R.20

Pathfinder

The figure below indicates the scope of part R.5 within the Guidance Document



Document History

Version	Section	Change made	Date
1			May 2008
2	general	Replace “exposure based waiving” (EBW) by “exposure based adaptation of information requirements” (EBA).	June 2010
	5.1.2	Adaptation to revised Annex XI (3). Annex XI (3) allows for qualitative and quantitative risk characterisation.	
	5.1.3.1	Adaptation to revised Annex XI (3) and editorial streamlining of the original text	
	5.1.3.2	Adaptation to revised Annex XI (3) and editorial streamlining of the original text	
	5.1.3.3	Editorial streamlining	
	5.1.4.2	Adaptation to revised Annex XI	
	5.1.5	Restructuring to have one section on qualitative EBA justification and one section on quantitative EBA justification: deletion of the introduction (5.1.5.1) and section 5.1.5.3 as this was duplicating information.	
	Figure 5.1	Reworked workflow to show more clearly the commonalities and differences among the three EBA options.	
	Box 1	Update with aspect related to the criteria b and c in the revised Annex XI	
	Box 2	Update with aspect related to the criteria b and c in the revised Annex XI; Inclusion of an Annex XI (3) b/c example (compressor fluid)	
	5.1.5.2.2 and 5.1.5.2.3 (previously 5.1.5.4)	Inclusion of guidance related to the understanding of “strictly controlled conditions”, and “no release” from article life cycle stage and waste life stage. It is explained how “no release” and hence exclusion of exposure can be demonstrated. The guidance text included here matches the corresponding section in the Guidance on Substances in Articles.	
	5.1.5.3 (previously 5.1.5.5	Adaptation to revised Annex XI	
	5.1.6.1	Sections 5.1.6.1 and 5.1.6.2 have been merged under the heading *documentation*, highlighting that column 2 and Annex XI adaptation do not differ regarding the content of the justification, but regarding the documentation requirements.	

Version	Section	Change made	Date
		Updating of references to the exposure scenario format.	

CONTENTS

FIGURES

R.5 ADAPTATION OF INFORMATION REQUIREMENTS

This Chapter includes guidance on the different options under REACH to adapt information requirements. Section R.5.1 deals with exposure based adaptation and triggering of information needs. Section R.5.2 provides an overview on the adaptations under Annex XI (1) when testing is scientifically not needed, and Annex XI (2) when testing is technically not possible.

It should be noted that although this guidance will provide assistance in developing the reasoned justification for derogations/adaptation from the standard testing regime, in certain cases available data showing hazardous effects could trigger the need for additional information, including testing

R.5.1 EXPOSURE BASED ADAPTATION AND TRIGGERING OF INFORMATION REQUIREMENTS

R.5.1.1 Aim of this Section

REACH requires the generation of information on the intrinsic properties of substances through testing and by other means: read-across from structurally related compounds and the use of QSARs, and by alternatives to animal testing such as *in vitro* methods. In situations where human or environmental exposure is absent or so low that additional effects information will not lead to improvement of risk management, exposure-based adaptation may be considered. This is included in step 2 of the general framework on generation of information (see Section B.2.2 and Chapter R.2).

REACH provides for the option that information requirements may be adapted based on the justification

- that exposure is absent, unlikely, not relevant or not significant, or
- that strictly controlled conditions apply for the whole life cycle of the substance (including the waste stage) ,
- and for substances incorporated into an article that the substance is not released during the whole life cycle and that the likelihood of exposure to man or the environment is negligible.

These provisions were included to avoid unnecessary animal testing. Based on adequate information on exposure, release and fulfilment of strictly controlled conditions, a decision can be taken whether it is possible to waive information requirements, or if further testing should be proposed, or if more stringent RMMs/OCs need to be introduced. **Exposure based adaptation (EBA) in this context is defined as an omission of a standard information requirement at the actual tonnage level based on exposure arguments.**

Contrary to adaptation, additional testing can be triggered if the chemical safety assessment indicates the need to investigate further the effects on humans or the environment. This is an integrated part of the chemical safety assessment and the possible iterations to demonstrate control of risks.

This guidance addresses exposure based adaptation (EBA), its terminology and guiding principles (Section R.5.1.3), the conditions for EBA (Section R.5.1.4), and how adaptation should be justified (Section R.5.1.5). Section R.5.1.6 explains how EBA should documented in the IUCLID5 dossier and the chemical safety report, when the documentation needs updating and how to communicate EBA in the supply chain. Section R.5.1.7 provides a brief overview on exposure triggered testing.

R.5.1.2 Introduction to exposure based adaptation

Column 1 of the Annexes VII to X specifies the standard information requirements for the given endpoints. These standard requirements may be omitted, triggered, replaced or adapted based on the rules stated in column 2 of these Annexes.

In addition the revised Annex XI[1] allows registrants, under certain conditions, to adapt information requirements in accordance with sections 8.6 and 8.7 of Annex VIII and in accordance with Annex IX and Annex X, based on the exposure scenario(s) and corresponding exposure estimates documented in the chemical safety report.

Adaptation can be based on two routes and needs to be adequately justified and documented:

- 'EBA based on column 2 of Annexes VIII-X': A qualitative argumentation can be applied when it is argued that exposure is absent or not significant, e.g. due to the specific uses of a substance. In most of these cases, a weight of evidence approach is needed to justify adaptation (see Section R.4.4 and Chapter R.7).
- 'EBA based on the general rules for adaptation of the standard testing regime laid down in Annex XI(3): Here it is stated that 'testing may be omitted based on the exposure scenarios developed in the chemical safety report. The justification shall be based on a thorough and rigorous exposure assessment in accordance with section 5 of Annex I (see Section R.5.1.5).

Adaptation for a specific endpoint should be documented in the IUCLID 5 dossier. When the argumentation is built on the use of exposure scenarios and related exposure estimates, the documentation in IUCLID 5 should refer to the chemical safety report

R.5.1.3 Guiding principles for exposure based adaptation

R.5.1.3.1 Terminology on adaptation

A variety of terms in relation to exposure based adaptations is used in column 2 of Annexes VIII-XI and in the revised Annex XI (3). The precise wording is given in Section R.5.1.4.

- Column 2 adaptations are to be justified with the absence of exposure ('relevant exposure can be excluded' or 'no exposure'), or exposure being unlikely (i.e. not 'absent' or 'excluded'), or not significant ('limited exposure', 'no significant exposure').
- The revised Annex XI (3.2(a)) requires exposure to be 'absent' or 'not significant', supported by a demonstration that the predicted exposure is always well below a relevant DNEL/PNEC.
- The revised Annex XI (3.2(b) and (c) requires the uses to take place under "strictly controlled conditions" (see Article 18(4)(a) to (f)) throughout manufacture and use of the substance, including the waste treatment following from these life cycle stages.
- The revised Annex XI(3.2(c)), requires that "no release" should occur during the life cycle of substances incorporated into articles and that the "likelihood of exposure" to man and environment is "negligible" (= absence of exposure)

[1] Commission Regulation (EC) No 134/2009 of 16 February 2009 amending Regulation (EC) No 1907/2006 of the European Parliament and the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) as regards Annex XI, Official Journal L046, 17/02/2009 P. 0003-0005

From this terminology overview, the underlined words will be used in this guidance to characterise the different exposure situations (see also NOIS 2007). In summary:

Exposure based adaptations may be appropriate under the following conditions:

i) exposure is absent (= exposure excluded) or not significant (= unlikely) throughout the life cycle of the substance for manufacture and all identified uses or

ii) when strictly controlled conditions apply throughout the life cycle of the substance for manufacture and all uses and

iii) no releases from the article life cycle stage (and subsequent waste life stage) is to be expected and consequently there is a negligible likelihood of exposure. Situation iii) only applies to substances incorporated into articles.

Annex XI (3.2(a)) requires that the absence or insignificance of exposure is underpinned by the derivation of a risk characterisation ratio (quantitative assessment).

Other routes of justification are based on qualitative assessment. If the justification is based on Annex XI this qualitative assessment is expected to include three elements: the description of operational conditions and risk management measures in an exposure scenario, the quantification of the resulting release/exposure for all routes and a qualitative statement why the release is low enough or the conditions are strict enough to control risks (i.e. adverse effects are avoided).

The justification may be checked in the compliance check of registration dossiers as described in Article 41(1)(b).

EBA differs from a normal risk characterisation due to the level of knowledge on hazard and exposure. For a certain endpoint a standard information requirement is omitted. This implies that a high level of confidence is needed to demonstrate “no release” or “no or no significant exposure” in order to justify this omission.

R.5.1.3.2 Risk considerations for exposure based adaptation

The interpretation in this guidance document is that exposure-based adaptation of information requirements under REACH should take into account available knowledge on i) substance chemical-physical properties, ii) hazard information covering a certain endpoint, iii) the conditions of use and iv) the expected releases and/exposure under these conditions.

If EBA is based on Annex XI (3), a qualitative or quantitative risk characterisation is required, based on a rigorous exposure assessment according to Annex 1.

- The qualitative risk characterisation establishes control of risk by demonstrating that i) strictly controlled conditions apply or ii) that no releases are to be expected and thus the likelihood of exposure is negligible.
- A quantitative risk characterisation establishes control of risk by demonstrating that the risk characterisation ratio is well below 1, taking full account of the increased uncertainty resulting from the omission of the information requirement, and that DNEL or PNEC is relevant and appropriate both to the information requirement to be omitted and for risk assessment purposes.

Exposure assessment and risk characterisation is required independent of whether any of the criteria are met to classify the substance dangerous or a PBT/vPvB according to Article 14(4).

There is the trade-off between doing the testing and obtaining better information on exposure to provide a qualitative or quantitative justification for EBA. For adaptation of some endpoints, (espe-

cially for environmental effects from long-term exposure) existing hazard information may allow derivation of threshold levels or reference levels since data from short-term exposure or physical chemical properties might be used for extrapolation. For other endpoints (e.g. repeated dose toxicity and/or reproductive toxicity at Annex VIII levels) existing toxicity data may not allow such extrapolation.

When human or environmental **exposure** can be **excluded** it is relatively simple that due to absent or no significant exposure to a substance, the derivation of a DNEL or PNEC for a specific endpoint is superfluous since the outcome of the risk assessment will in any case be no significant risk. When **exposure** is **low**, the conclusion of 'no concern' in relation to a specific endpoint needs to be based on the characterisation of risk associated with this level of exposure.

The qualitative argumentation for EBA referring to column 2 is in principal the same as for Annex XI (3). However, the justification for Annex (3) has to be done based on the exposure scenario (s) developed in the CSR, whereas for the justification of column 2 this is not required.

R.5.1.3.3 Adaptation needs consideration of the entire life cycle of a chemical

In any EBA case, all relevant stages in the life-cycle of a chemical should be taken into account for a valid justification of adaptation (see Section R.5.1.5). A prerequisite for EBA is the collection and evaluation of available knowledge the uses of the substance and on the conditions of use (operational conditions and risk management) over the whole life cycle (including the waste stage). Extensive and detailed knowledge of exposure throughout the life cycle for human and environmental exposure is essential for exposure based adaptation. Depending on the type of test that is adapted, occupational exposure, consumer exposure and human exposure via the environment as well as exposure of all environmental compartments may need to be considered. If exposure can be excluded for a specific use (e.g. no consumer exposure) the whole life-cycle still has to be considered for exposure to workers in order to determine if adaptation for a specific endpoint is appropriate.

R.5.1.4 Exposure-based adaptation options

R.5.1.4.1 Column 2 adaptations of Annexes VIII to X

Annexes VI to X specify the information requirements for registration purposes. The following exposure-based adaptation options exist, generally without precedence or priority of column 2 of Annexes VIII to X over Annex XI (3) or vice versa. Only for point 8.6 and 8.7 of Annex VIII the exposure based adaptations according to Annex XI (3) has the preference over column 2. It is possible to waive in accordance with adaptations in column 2 of Annexes VIII to X, and Annex XI, section 3, provided the conditions laid down in that column are met.

Human hazard

- In Annexes VIII, repeated dose toxicity (28 d test, 8.6) and reproductive toxicity testing (8.7) may be omitted '*if relevant human exposure can be excluded in accordance with Annex XI section 3*'
- In Annex IX, a sub-chronic toxicity test (90 d, 8.6.2) may be omitted if 'the substance is unreactive, insoluble and not inhalable and there is no evidence of absorption and no evidence of toxicity in a 28-day "limit test", *particularly if such a pattern is coupled with limited human exposure*'.

- In Annex IX, a reproductive toxicity test (8.7) may be omitted if the following combination applies: 'the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available), it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure (e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air) *and there is no or no significant human exposure*'.
- In Annex X, the same conditions for exposure-based adaptation of reproductive toxicity (8.7) testing as in Annex IX.

Environmental hazard

- In Annex IX one of the arguments given for omitting simulation studies on terrestrial (section 9.2.1.3) or sediment-organisms (section 9.2.1.4) is '*if direct and indirect exposure of [soil][sediment] is unlikely*'.
- In Annex IX, bioaccumulation testing of fish (9.3.2) may be omitted if 'direct and indirect exposure of the aquatic compartment is *unlikely*'.
- In Annex IX, toxicity testing with soil organisms (9.4) may be omitted 'if direct and indirect exposure of the soil compartment is *unlikely*'
- In Annex X, long-term toxicity tests with soil organisms (9.4) may be omitted 'if direct and indirect exposure of the soil compartment is *unlikely*'.

R.5.1.4.2 Substance-tailored exposure-driven testing (Annex XI (3))

- Section 3 of the revised Annex XI gives a possibility to omit certain information requirements based on an exposure scenario(s) developed as a part of a CSA. It can be applied starting from Annex VIII requirements (substances imported or produced starting at 10 t/y) with the following conditions: Testing according to Annex VIII (only sections 8.6 and 8.7), Annex IX and Annex X may be omitted, based on exposure scenario(s) developed in the Chemical Safety Report. In all cases, adequate justification and documentation shall be provided. The justification shall be based on an exposure assessment in accordance with section 5 of Annex I and be consistent with the criteria a) to c) of section 3.2 of Annex XI:

  "[...] (a) the manufacturer or importer demonstrates and documents that all of the following conditions are fulfilled:

  > *(i) the results of the exposure assessment covering all relevant exposures throughout the life cycle of the substance demonstrate the absence of or no significant exposure in all scenarios of the manufacture and all identified uses as referred to in Annex VI section 3.5;*
  >
  > *(ii) a DNEL or a PNEC can be derived from results of available test data for the substance concerned taking full account of the increased uncertainty resulting from the omission of the information requirement, and that DNEL or PNEC is relevant and appropriate both to the information requirement to be omitted and for risk assessment purposes;*
  >
  > *(iii) the comparison of the derived DNEL or PNEC with the results of the exposure assessment shows that exposures are always well below the derived DNEL or PNEC;*

  (b) where the substance is not incorporated in an article the manufacturer or importer demonstrates and documents for all relevant scenarios that throughout the life cycle strictly controlled conditions as set out in Article 18(4)(a) to (f) apply;

(c) where the substance is incorporated in an article in which it is permanently embedded in a matrix or otherwise rigorously contained by technical means, it is demonstrated and documented that all of the following conditions are fulfilled:

(i) the substance is not released during its life cycle;

(ii) the likelihood that workers or the general public or the environment are exposed to the substance under normal or reasonably foreseeable conditions of use is negligible; and

(iii) the substance is handled according to the conditions set out in Article 18(4)(a) to (f) during all manufacturing and production stages including the waste management of the substance during these stages".

It is important to clearly justify and document all adaptations in a transparent way in the Chemical Safety Report.

R.5.1.4.3 Exclusion of exposure according to Article 7(3)

For substances contained in articles which shall be notified according to Article 7(2), the article producer or importer may be exempted from the notification requirement if exposure of humans and the environment can be excluded during normal or foreseeable conditions (Article 7(3)). The suitable arguments for justifying the **exclusion** of exposure under Article 7 (see section 6.3 of the Guidance on Substance in Articles) correspond to the adaptation condition iii) in section 5.1.3.1 of this guidance, which are further explained in section 5.1.5.2.3. Despite the differences in the regulatory context, the justifying arguments and supporting evidence are the same.

R.5.1.5 Justification for exposure based adaptation

R.5.1.5.1 Collection of hazard and exposure information (Workflow)

A framework to systematically consider the different options for developing adaptation argumentation and documentation is presented in .

Figure R. 5-1.

STEP 1

The assessment starts when the initial hazard information has been collected. All available hazard information should be evaluated before deciding on adaptation.

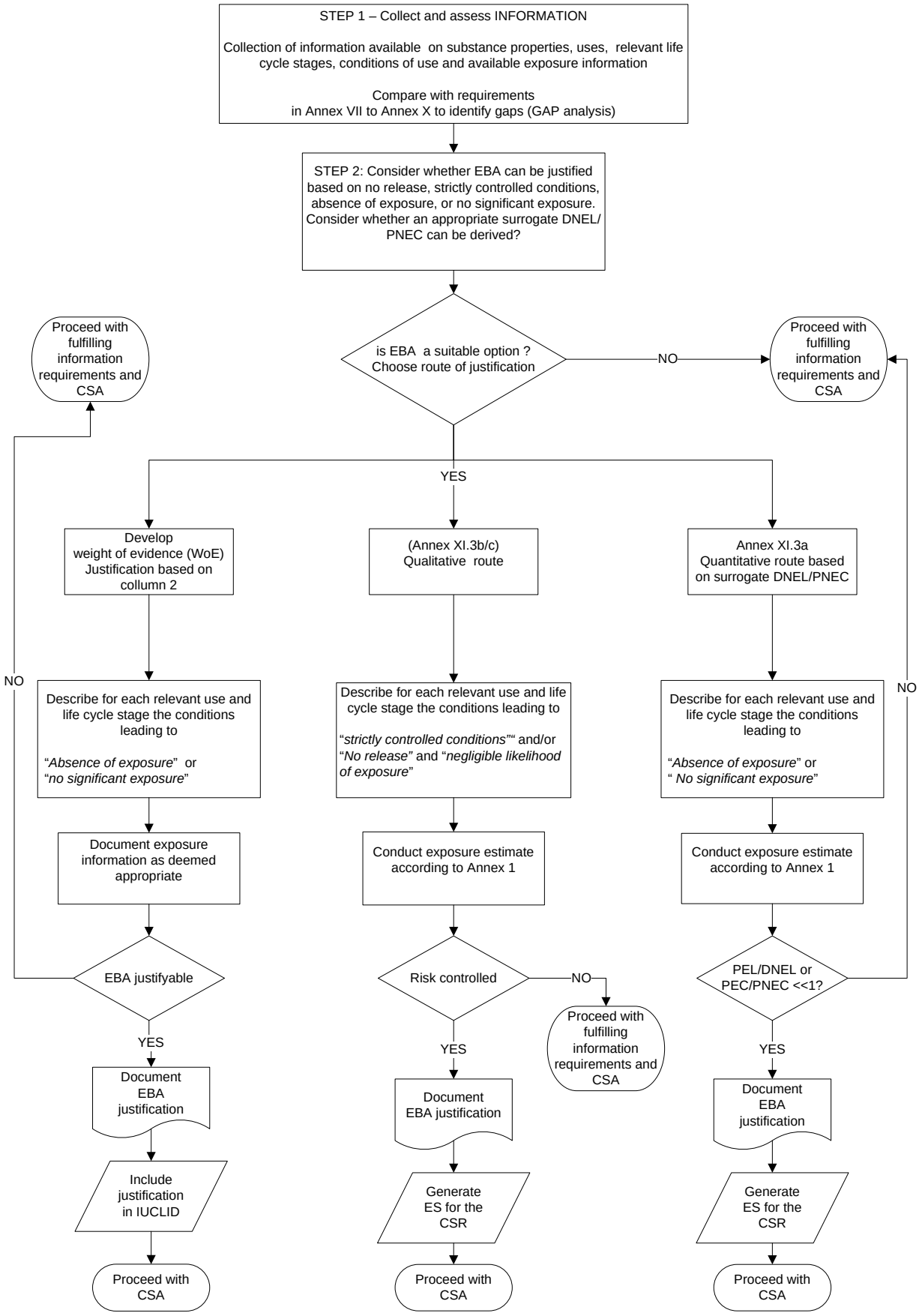
Then the life-cycle of the substance and the uses in the market of the substance should be explored, based on existing in-house information. The different uses can be described based on the use descriptor system in Chapter R.12.

The next thing to do is to systematically consider exposure routes and potential exposure of humans or the environment. Exposure of humans or environmental compartment may be absent and could be a reason for adaptation a specific test. However, exposure may still be an issue during the remainder of the life-cycle implying that the information requirement would still be required. Detailed information should be collected for lifecycle steps which may trigger exposure related to specific populations or targets (occupational, environmental, consumer exposure and exposure of humans via the environment) before an information requirement can be adapted:

- Use of a substance on its own, in preparations or in articles: manufacture of substances or production of articles, synthesis, processing aid etc., and resulting waste stages.
- Incorporation of the substance into articles and resulting service-life and waste stages

In addition, the operational conditions and risk management measures that apply to the identified uses of a substance should be considered, since these are used to document the exposure situation. As a general rule it will be difficult to justify EBA for a substance with a wide spectrum of uses since it will be difficult to demonstrate that the pre-requisites for EBA as described in section 5.1.3 are fulfilled for all these uses throughout the life-cycle. Also, sufficient justification, includind DNEL/PNEC derivation will be needed that, despite the increasing uncertainty for a quantitative risk characterisation, the registrant has chosen the option a) under Annex XI (3.2.(a) to adapt the relevant information requirements.

Figure R. 5-1 Flow diagram for deciding on exposure-based adaptation (EBA)



Please note that the footnote to Annex XI (3.2 (a)(ii) significantly limits the applicability of the quantitative justification for adapting information requirements.

STEP 2

The next step is to define if adaptation of a study is appropriate and under which conditions (see Section R.5.1.4). The registrant should decide if adaptation is based on column 2 entries to Annex VIII-X or on Annex XI entries.

If adaptation conditions do not apply, the normal procedure is followed in the hazard assessment for the relevant endpoint(s), see Chapter R.7.

R.5.1.5.2 Qualitative justification for exposure-based adaptation

For all justifications, it is key that it will be documented on what grounds the adaptation is applied (based on which REACH section), and how it was decided to waive based on exposure information, e.g. can the adaptation be documented on qualitative arguments (Column 2 adaptations and Annex XI (3.2 (b)(c)). As part of a qualitative argumentation, a reference to (semi-)quantitative information demonstrating absent or non significant exposure, no leaching etc. may need to be included, or a reference can be made to already existing studies with appropriate quantitative information. Measurements could be used in a qualitative assessment to show that exposure potential is not significant.

Several possible situations are listed in Box 1 that could lead to exposure based adaptation, due to absence of exposure or exposure not being significant. A few examples are provided in Box 2 to give an indication of the potential for EBA

Adaptation may be appropriate if the justification documents that a substance is handled under strictly controlled conditions (including rigorous containment) during its manufacture and industrial use, that there is no dispersive use and no consumers' exposure. Another example is if it can be proven (and documented with suitable evidence) that a substance is totally chemically reacted during manufacturing or if the substance is permanently bound to a matrix or otherwise rigorously contained by technical means.

Under very well documented circumstances exposure may also be considered as negligible in a specialised industrial situation with a small, well-defined and trained group of people using strict risk management measures to prevent exposure (with personal protective equipment used as a last resort when other strategies are not available or effective). Such strictly controlled conditions are for example mentioned in the requirements for handling transported isolated intermediates (Article 18(4)).

Where measured exposure data are included, then at a minimum these need to be described by European or national standards (or referred to the source where this is documented). Further guidance on measurements on exposure is given in the chapters on exposure (see Chapters D.5, R.14 to R.18). This could include the description of the number of samples, frequency of sampling, and basic sample statistics.

Box 1. Situations that are starting points to evaluate if exposure-based adaptation can be justified

Specific use or limited emissions, e.g.

- Certain uses are excluded, e.g.: no identified consumer uses
- Emissions to certain environmental compartments are excluded (e.g., air emissions are limited because the substance is a solid and no significant dusts or fumes are formed, or the substance quickly hydrolyses under the conditions of use).
- No significant or negligible likelihood exposure, due to e.g. low releases to the substance, for instance due to a combination of substance properties (low vapour pressure, solids etc.) and 'no significant emissions' due to low emission rates and/or tonnage, low frequency of use etc.

Specific operational conditions and risk management , e.g.

Use in strictly controlled conditions according to Article 18(4), leading to no or minimised release/ exposure, that should be argued in a quantitative way.

Intensity of use (duration, frequency), e.g.

Infrequent use due to the function of the substance as specialty products for highly specific occupational situations with a low frequency and duration, leading to no significant exposure,

No release and hence exclusion of exposure (= negligible likelihood of exposure) to substances incorporated in articles e.g.

- Due to chemical and physical design of the article: For instance when a substance is covalently bound to a matrix, the justification should show that there is no significant unbound residual amount, and that the covalent binding is stable (i.e., lead to no release and hence exclusion of exposure (negligible likelihood of exposure) under typical use or environmental conditions.
- Due to rigorous containment in articles (e.g. in batteries for professional use)
- Due to "no release" conditions during the waste life stage of a substance incorporated into articles:

Box 2: Examples for illustration of justified and not justified EBA

Type of study to be adapted (a)	**applied rule for adaptation**	**Substance properties or operational conditions.**	**Argumentation**
Repeated dose (28 d) (Annex VIII 8.6.1)	Annex VIII 8.6.1 column 2, with reference to Annex XI 3 b	The substance is manufactured and used under rigorous containment and "no release" conditions apply over the entire lifecycle	Rigorous containment and procedural and control technologies and "no release" conditions, as well as qualitative and quantitative risk considerations are exemplified in Appendix 1 to this document.
Repeated dose (90 d) (Annex IX 8.6.2)	Annex IX 8.6.2 column 2	The substance is unreactive, insoluble and not inhalable and there is no evidence of absorption and no evidence of toxicity in a 28-day 'limit test', particularly if such a pattern is coupled with limited human exposure.	Due to the physicochemical properties, exposure by inhalation is absent (data on volatility/granulometry). The formation of dusts/aerosols is not significant due to the specific operational conditions. Toxicological data on absorption. Robust information on negligible exposure .
Repeated dose (90 d) (Annex IX 8.6.2) and information on adsorption/desorption (Annex IX 9.3.3)	**Annex XI 3 b**	The substance is manufactured and used under rigorous containment and "no release" conditions apply over the entire lifecycle	Rigorous containment and procedural and control technologies and "no release" conditions, as well as qualitative and quantitative risk considerations are exemplified in Appendix 1 to this document.
Type of study <u>not</u> to be adapted (b)	**applied rule for adaptation**	**Substance properties or operational conditions.**	**Argumentation**
short-term repeated dose (28 d) (Annex VIII 8.6.1)	**Annex XI 3 a-c**	Substance is used in consumer mixtures	When a substance is used in consumer mixtures, then relevant human exposure is difficult to exclude.
short-term repeated dose (28 d) (Annex VIII 8.6.1)	**Annex XI 3 c**	Substance is incorporated in article during the life cycle stage relevant to consumers	While it may be possible to demonstrate that the substance is not released during the service life stage (e.g batteries or compressor fluids in refrigerators), it is difficult to exclude releases during the waste life stage. This is due to the fact that i) recollection rate of end of service life articles from consumers is usually not higher than..... % *(to be filled in)* and ii) that the matrix or the rigorous containment may be destroyed

			by milling and thermal treatment processes.
Repeated dose (90 d.) (Annex IX 8.6.2)	Annex IX 8.6.2 column 2	Repeated exposure is likely but exposure levels are uncertain.	In general when repeated human exposure to a substance can be expected, adaptation is not a possibility, unless it can be demonstrated in a quantitative justification that risk is negligible.

Qualitative justification of EBA should be based on the following understanding.

R.5.1.5.2.1 Weight of evidence approach for specific rules for adaptation under column 2

A weight of evidence approach is needed to justify and document a column 2 route for EBA. In a weight of evidence approach, relevant information on substance properties, use and use conditions, hazard and exposure should be used to develop the case (see workflow in Figure R.5.1). A general introduction on weight of evidence approaches is given in Section R.4.4.

Justifying exposure based adaptation will generally require information that satisfies the above mentioned guiding principles (see Section R.5.1.3) and is based on the main entries of the exposure scenario (see revised draft guidance on exposure scenario format[2] referring to guidance Part D, Table D.2-2).

1. Use description, based on the standard descriptor system
2. Processes and activities covered
3. Duration and frequency of use
4. Physical form of the substance and relevant concentration in product or article
5. Relevant operational conditions of use
6. Risk management measures
7. Waste management measures
8. Exposure information (measured or modelled) and reference to its source

The combination of hazard profile on the one hand and the ES entries on the other hand - focusing on substance properties, operational conditions and risk management measures, type of product, throughout the life-cycle - should lead to a weight-of evidence argumentation that exposure is absent or not significant.

R.5.1.5.2.2 Strictly controlled conditions

- Rigorous containment (Article 18(4)(a)) is the technical hardware designed to prevent releases of the substance from processes or articles. The chemical-physical properties of the substance may have an impact on the required level of rigorousness.
- There may be residual releases from rigorous containment. Procedural and control technology (hardware) shall be used to minimize these residual releases (Article 18(4)(b)). The means to

[2] http://guidance.echa.europa.eu/guidance4_en.htm, Guidance Information Requirements and Chemical Safety Assessment, Part D Exposure Scenario Building, draft update of Exposure Scenario format

achieve the required level of minimization may vary, depending on the available knowledge on the substance's hazards.
- The functioning of the hardware is to be supported by management measures ensuring that properly trained and authorised personnel handle the substance (Article 18(4)(c)). The contributions of management to the overall effectiveness of the measures can be high.

All requirements of Article 18(4) are to be fulfilled to qualify for the reduced information requirements of transported isolated intermediates or to justify exposure based adaptations according to Annex XI (3.2) respectively For further illustration of what "strictly controlled conditions" means in practice see Guidance on Registration of Intermediates.

R.5.1.5.2.3 "No release" from articles and exclusion of exposure

The potential for release of a substance from an article will depend on:

- Physicochemical properties of the substance, like vapour pressure, water solubility, stability in contact with air, water, etc.
- Structure and chemistry of the article matrix including physicochemical parameters and the way in which the substance is incorporated in it (chemically bonded or not).
- The conditions during normal or reasonably foreseeable conditions of use[3] and disposal/recovery of the article, such as:
    - Location of use (indoor or outdoor use, private homes, workplace, etc.).
    - Physical conditions at place of use (temperature, ventilation, etc.).
    - Whether or not articles are part of a comprehensive waste collection scheme.
    - The disposal/recovery technology applied to article waste.
- Concentration of the substance in the article or its parts, including substance amounts in the article matrix and non-integrated (residual) amounts

Some chemical substances are very firmly bound in the material, e.g. chromium in stainless steel, and the potential emission of chromium is therefore very low. However please note, dermal exposure to a substance in an article may even be possible if the substance is not released from the article to the environment, but is just available in the surface layer of an article getting into contact to skin.

Other substances are loosely incorporated in a matrix, e.g. softening additives in PVC. Such substances, like phthalates, are continuously emitted from the surface of the article. An alternative way in which substances may be released is through normal wear and tear of articles (abrasion). In this case, the substances are released together with the article matrix, e.g. additives in car tyres or the outside surface coatings of a car under-body.

The justification for "no release" could include for example one or more of the following elements:

- A proof that no emissions from the article, including disposal and recovery of article waste..
- A proof that the amounts of substance released from the article are contained by technical means or directly destroyed (e.g. during thermal treatment of waste).
- If the substance is contained in the article by technical means: a reasoning why the article is unlikely to be opened or to break leading to a release of the substance, in particular during the waste stage.

[3] The terms "normal conditions of use" and "reasonably foreseeable conditions of use" are explained in section 3.1.

- If the substance is embedded in the matrix of the article: a description of the stability of the article matrix and the bonds between the substance and the matrix during the different life cycle stages of the article.
- A proof that the substance remains fully immobile inside the article and does not migrate to the surface and out of it (e.g. due to the inherent physicochemical properties of the substance, or a special coating of the article).

These arguments can be based on measurements (e.g. leaching and migration tests), modelling, literature or other sources of information.

<u>No-release</u> should not mean zero in the scientific sense, but is to be interpreted as 'practically no release'. Thus, *no release* should be demonstrated case-by-case based on:

- Quantification of residual releases under the foreseeable conditions during the relevant life cycle stages (including the waste life stage) based on measurements or modelling. The method applied for quantification of residual releases is to be specified. The detection limit of a substance is not suitable as a general "*no release"* indicator. Thus, if no releases can be detected in suitable tests, the lowest release detectable with a certain method is to be used for quantifying the residual releases.
- Based on the quantification of residual release the registrant may provide (or have available) a qualitative argumentation that this release is so low that it can be considered as fulfilling the "no release" requirement. Such argumentation may for example make reference to:
    - The release is comparable to releases of a substance (e.g. a metal) from natural material under comparable test conditions.
    - Resulting exposure concentrations are in the range of the natural background concentrations.
    - The release is so low that exposure to man and the environment can be excluded (= negligible likelihood of exposure).

R.5.1.5.3 Quantitative justification for exposure-based adaptation

A quantitative justification can be submitted based on the Annex XI (3.2 (a)) requirement for exposure scenario with an accompanying exposure assessment.

The quantitative exposure estimate relevant to the test that is omitted will be compared to any derived threshold effect level (PNEC or DNEL, based on the information that *is* already available relevant for the specific test being omitted.

Please note that the footnote to Annex XI (3.2 (a)(ii) significantly limits the applicability of the quantitative justification for adapting information requirements.

- *""[...]For the purpose of subparagraph 3.2(a)(ii), without prejudice to column 2 of Section 8.7 of Annexes IX and X, a DNEL derived from a screening test for reproductive/developmental toxicity shall not be considered appropriate to omit a prenatal developmental toxicity study or a two-generation reproductive toxicity study.*

- *For the purpose of subparagraph 3.2(a)(ii), without prejudice to column 2 of section 8.6 of Annexes IX and X, a DNEL derived from a 28-day repeated dose toxicity study shall not be considered appropriate to omit a 90-day repeated dose toxicity study."*

If a no-effect level or minimal effect level cannot be derived (e.g. due to the lack of relevant hazard information for the endpoint), it may be possible to use an appropriate, accepted threshold of toxicological concern (TTC) (Kroes et al 2004). TTCs have so far only been used in Europe in a regulatory context for food contact materials and flavourings. In cases where no reliable or suitable PNEC, DNEL, DMEL or TTC is available, it will be very difficult to argue on quantitative grounds that further testing for a specific endpoint is not needed. Additional hazard data may need to be collected instead of omitting the test, or a qualitative justification for EBA (based on "strictly controlled conditions") might still be possible.

The use of occupational cut-off values (based on OELs) have been proposed for gases, fumes, dust particles and substance properties leading to no significant exposure. For substances in consumer products, cut-off values for oral, dermal and inhalation uptake have been proposed based on the classification limit for R48 (Bunke et al., 2006). For the environment, aquatic threshold levels have also been derived. If agreed cut-off values are available for a certain substance of group of substances below which the likelihood that adverse effects occur are negligible, the EBA justification should demonstrate that the exposure levels actually conform to these cut-off values. Additional scientific and regulatory discussions on these cut-off values is needed before integration into the guidance can take place (TemaNord, 2005).

If a DMEL/DNEL or PNEC or an agreed TTC or agreed cut-off level is available, the exposure assessment will continue with a risk characterization to demonstrate that risks are controlled and adaptation is appropriate (see Part E).

R.5.1.6 Document and communicate exposure based adaptation

R.5.1.6.1 Documentation

If adaptation is applied, the hazard and the use and exposure considerations, including the interaction between them should be documented, based on a qualitative or semi-quantitative justification, or a quantitative justification.

If the adaptation is based on Annex XI (3) exposure scenarios and corresponding exposure estimates are to be included into the CSR (see REACH Annex 1). Further guidance on the exposure scenario format and the corresponding exposure estimates in the CSR and the different types of risk characterisation are provided in the updated guidance Part D, Part E and Part F.

For column 2 adaptations, the weight of evidence justification (qualitative or semi-quantitative) should be given under the appropriate headings in the registration dossier referring to the appropriate specific rule(s) in column 2 or in Annex XI if reference thereto is necessary. It could be considered to use the exposure scenario format to document a qualitative assessment since (content-wise) the justifying information should be related to the regular entries into an exposure scenario. In any case, the entries into the exposure scenario reflect the principal information needs into the weight of evidence approach, that can be adapted if they are not needed to justify adaptation.

ECHA's Chemical Safety Assessment and Reporting Tool (*Chesar*) provides a workflow support as well as exposure assessment and reporting functionalities for exposure based adaptation. These functionalities can be used for both, column 2 based adaptation and Appendix XI (3) adaptation.

R.5.1.6.2 Communicate conditions of use

The last step after finishing the EBA justification is to communicate the conditions of use which apply to the identified uses for a specific EBA case. Especially if operational conditions of use or risk management measures are essential for achieving no or no significant exposure, these must be communicated downstream as prerequisites for the relevant identified use(s). The operational conditions and RMMs as specified in the weight-of evidence documentation or the ES must be communicated through the chemical supply chain via the SDS or otherwise if an SDS is not required (REACH article 32). When a CSA is required (Annex XI(3) adaptation) the exposure scenarios are to be attached to the eSDS.

R.5.1.6.3 Updating the adaptation documentation

New information after registration may trigger the obligation to update the exposure scenarios, the CSA and the CSR. Then the registration also needs to be updated. If either the hazard information or the conditions of use need to be changed in the registration update, the validity of the adaptation argumentation needs to be re-evaluated.

In case the new information relates to additional hazard information, the adaptation argumentation may need to be re-evaluated to decide if the weight of evidence argumentation is still valid.

If new information relates to new identified uses that are promoted by the substance manufacturer/importer, the adaptation argumentation should ascertain if the exposure assessment (whether qualitative or quantitative-based on exposure scenarios) is still valid.

R.5.1.7 Exposure-based triggering

Toxicological testing may be adapted by selection of appropriate exposure routes based on relevant human exposure. Likewise, eco-toxicological testing should be considered depending on the likely direct or indirect exposure of the relevant environmental compartment. Column 2 entries in Annexes VIII-X can indicate that additional testing may be triggered if the CSA indicates the need to investigate further the effects on humans or the environment. This may for example be the case where the results of the CSA indicate that exposure of humans or biota is likely to exceed toxicological thresholds. This is an integrated part of the CSA and the possible iterations to demonstrate control of risks.

In cases of exposure-based triggering, further testing may be required to reduce uncertainties on the outcome of the CSA in any direction (see the uncertainty analysis, Chapter R.19). The CSA can indicate the need to further investigate at that tonnage level if the result of a test (belonging to the standard requirements of REACH for the relevant tonnage level) possibly could lead to a change regarding one of the following:

- classification or declassification
- assignment as PBT/vPvB or not
- concern or no concern.

When the answer is yes a need for further testing is indicated. If the answer is no, further testing is not warranted unless such need is indicated in some other way in the CSA. Details on triggered testing for individual endpoints are further discussed in the endpoint-specific guidance (see Chapter R.7).

R.5.2 ADAPTATIONS UNDER ANNEX XI (1) UND (2)

The REACH Regulation outlines a number of general rules for the adaptation of the standard information requirements. In general terms, Annexes VII-X provide the standard information requirements in column 1, whereas column 2 specifies adaptation possibilities for the specific endpoints. Further guidance on their interpretation may be found in the integrated testing strategies (ITS) for specific endpoints in the relevant subsections of Chapter R.7.

In addition to these specific rules, the required standard information set may also be adapted according to the general rules contained in Annex XI of the REACH Regulation.

R.5.2.1 Testing does not appear scientifically necessary

The standard testing regime may be adapted when testing does not appear scientifically necessary according to the rules set out in REACH Annex XI section 1.

R.5.2.1.1 Use of existing data

Section 1.1.1 (physico-chemical properties) and 1.1.2 (data on human health and environmental properties) of REACH Annex XI on the use of existing data enable the use of non-GLP non-Guideline information, under certain conditions. These include the demonstration that such information covers the essential elements of the internationally accepted test method, provided documentation is sufficient and the information is adequate for the purpose of C&L and/or risk assessment.

Section 1.1.3 of REACH Annex XI considers the opportunity of evaluating historical human data, such as epidemiological studies on exposed population, accidental or occupational exposure data and clinical studies.

These approaches were used to a large extent for filling information requirements under the Existing Chemicals Regulation (EU Regulation 793/93). They were also used extensively for C&L of existing substances under the Dangerous Substance Directive (EU Directive 67/548/EEC). Whilst the criteria for classification in that Directive were based on test results generated by applying internationally accepted test methods under GLP, data for existing substances is often available for studies carried out before these internationally accepted methods were adopted, and, as a result, an element of scientific judgement is needed in evaluating these non-standard data.

R.5.2.1.2 Weight of evidence

In the evaluation process of all available information according to Annex I section 3.1.1 of the REACH Regulation, there will be cases where data from sources other than tests specifically addressing an endpoint can provide valuable information. In addition, it is reasonable to expect that there will be cases where several *inadequate* studies on a given endpoint may exist (tests not included in the test methods referred to in REACH Article 13 (3)). If a rationale can be presented to show that such tests adequately describe the endpoint of concern, a further test for that particular endpoint may not be necessary. The pooling of several such studies to satisfy a specific endpoint is a way that an evidence based analysis can be used.

Weight of evidence is closely linked to *testing/information strategies*, in that the available evidence can help to determine the possible subsequent testing steps. Results from such subsequent tests will

have an impact on the evidence based decision, which might lead to a substantiated judgement on whether there is any need for further testing.

Further guidance is provided in Section R.4.4 on the application of an evidence based approach for the evaluation of information of different types and quality. With respect to specific endpoints further guidance on how to use the weight of evidence approach is provided in Chapter R.7 (Endpoint specific guidance).

R.5.2.1.3 Non-testing methods

Non-testing methods, i.e. (Q)SARs and grouping methods (read-across and category approaches) can be used directly to fulfil information requirements in REACH, provided that they are shown to be adequate for the regulatory purpose (classification and labelling and/or risk assessment) according to the general conditions specified in Annex XI. The assessment of adequacy for non-testing data has to be judged on a case-by-case basis, taking into account the regulatory context in which the result is being proposed. Further guidance is provided in Section R.4.3.2.

In principle, all types of non-testing methods can be used to indicate the presence or absence of a particular property (or hazard), and to replace test data or to provide supplementary data on non-tested endpoints.

The determination of whether a (Q)SAR result may be used can be broken down into three main steps as specified in Section R.4.3.2.

To be used as a full replacement of an experimental test, all three conditions need to be fulfilled. In cases where some information elements are missing, (Q)SAR results may still be used in the context of a Weight of Evidence approach. Appropriate documentation must be given e.g. in the form of QMRFs and QPRFs. Detailed guidance is given in Sections R.6.1.9 and R.6.1.10.

Grouping approaches (analogue and category approaches) can be performed according to stepwise procedures described in Section R.6.2, which also describes a number of considerations useful for assessing the adequacy of the analogue or category approach. The results and regulatory conclusions obtained must be documented according to the appropriate reporting format for the analogue read-across or category (see Section R.6.2).

The grouping of substances is a scientific exercise, but its successful implementation also has a number of practical and organisational implications. For example, REACH will facilitate the grouping of similar substances as, during pre-registration of a substance, companies can also indicate other substances for which the data are relevant. In this process, a dialogue between the registrant and the authorities will be important.

Furthermore, REACH Annex XI states that *the Agency, after consulting with relevant stakeholders and other interested parties, shall issue guidance on technically and scientifically justified methodology for the grouping of substances sufficiently in advance of the first registration deadline for phase-in substances.*

The category approach, applied in its fullest extent, should enable the establishment of categories covering all possible chemicals (across company portfolios, across production volume bands, across legislative scopes and even covering substances which are no longer produced or have not (yet) been produced) and establishing through the category approach multiple relationships (the *relational features*) between the category members and their properties.

R.5.2.1.4 *In vitro* methods

REACH Annex XI makes provision for adapting the standard testing regime by suggesting consideration of adaptation (because *testing does not appear scientifically necessary*) the standard test provided the following conditions are met:

- The test has been validated according to internationally agreed validation principles
- The results are adequate for the purpose of C&L and/or risk assessment (including PBT-assessment) and
- There is adequate and reliable documentation of the method.

Furthermore, REACH Annex XI permits the use of results from *in vitro* methods that have not yet been scientifically validated provided that they are identified as being *suitable* (see Section R.4.3.1)

In addition, *in vitro* methods can play an important role in the development and use of integrated testing strategies (ITS), which provide the appropriate approach for hazard assessment. *In vitro* information as such or together with information generated by other components of the ITS may be used for meeting the information requirements of REACH through the application of an evidence based approach.

R.5.2.2 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.

The physico-chemical characteristics of a chemical may limit the possibility for performing certain (eco)toxicity assays. Depending on the endpoint, certain properties of the considered chemical might exclude testing; such properties include solubility, high volatility, colour (e.g. masking a response such as contact irritation or sensitisation), reactivity with water resulting immediately in a substance with known properties, mixing of substances that may present a danger of fire or explosion, high reactivity and impossibility of radio-labelling of substances required in certain studies.

The physico-chemical characteristics may also prevent administration of precise and consistent doses of the chemical for both *in vitro* studies and *in vivo* studies. E.g. the following needs to be scrutinised: testing of gases for oral toxicity, testing of non-water soluble compounds for fish toxicity, and testing of non-water soluble compounds in submerged cell cultures, and low volatility substances for inhalation testing.

For poorly water soluble substances (e.g. below the detection limit of the analytical method of the test substance) it may neither be possible nor relevant to try and conduct certain ecotoxicological tests, as it is difficult to maintain a high enough and constant concentration of the substance in the water. For these types of substances, different test duration and alternative test methods need to be considered. As the amount in solution will be low, instead of acute aquatic toxicity studies chronic studies may be relevant (see Section R.7.8), for bioaccumulation assessment a fish dietary bioaccumulation test may be more relevant than the normal BCF study (see Section R.7.10.1). Also special environmental compartments may be relevant to consider and hence testing with sediment-dwelling species may be both possible and more relevant, for which the details are given in (see Section R.7.10.12). Issues like this have to be considered on a case-by-case basis for the individual substance and individual endpoint. In particular the physico-chemical properties of the substance will have a decisive influence on whether testing is technically possible. In all circumstances where

proposals for adaptation of testing are based on such grounds, a detailed justification should be provided in writing.

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Appendix 1

Substance id:	Substance O
Type of case:	Exposure Based Adaptation (Annex XI.3) for repeated dose toxicity and reproductive toxicity studies (Annex VIII 8.6.1) and further information on adsorption/desorption (Annex IX 9.3.3)
Life-cycle stage(s) covered:	1. Production of Substance N 2. Formulation into compressor fluid 3. Use of compressors 4. Draining fluids and recycling or incinerating and disposal of the compressor unit
Classification:	None.
Data profile.	Limited data available.
Process description	Substance N is produced, formulated into a compressor fluid and filled into compressors for refrigeration systems. The compressors and the other parts of the refrigeration system are built and installed. For repairs, the whole system is de-installed and returned to the company that builds the systems. The refrigeration and compressor fluids are drained and either recycled or incinerated on site. Refrigeration systems are used in **industrial** situations
Rigorous containment measures	Filling lines for trucks/containers are equipped with dry break couplings to maximally prevent spillage of liquid. There is vapour return system from the storage to the tank truck. Lines are purged after filling. The filling of the compressor systems takes place in-

		doors using an automated system. The loading occurs under pressure which ensures the process has to be fully enclosed. Air from the compressors is fed through a release valve into a waste ventilation system with filters absorbing the substance. Filters are incinerated in a hazardous waste facility. No emission to the air or via waste water is foreseen.
Not fully rigorously contained processes and residual release information.		Maintenance and cleaning of mixer and pipes.
Procedural and control technologies used to minimise any emissions/exposure.		Movable Local Exhaust Ventilation and PPE/RPE worn
Qualitative/quantitative risk considerations for residual exposures/emissions.	**Residual exposure information**	Negligible, generally < 0.0001 mg/m3, dermal exposure possible but unlikely. The substance has a low vapour pressure and low water solubility and can be collected using absorbing material if spilled. No emission to the air or water environment is foreseen.
	Risk considerations	TTC of 30 microgram/kg body weight calculated and all exposures very much below this. No release to the environment is expected during the four life cycle stages. The main waste stream is as hazardous waste which is treated by incineration.