ECHA
EUROPEAN CHEMICALS AGENCY

GUIDANCE

Guidance on Information Requirements and Chemical Safety Assessment

Part E: Risk Characterisation

Version 3.0
May 2016

LEGAL NOTE

Guidance on information requirements and chemical safety assessment
Part E: Risk characterisation

Reference: ECHA-2016-G-04-EN
ISBN: 978-92-9495-055-0
Publ.date: May 2016
Language: EN

If you have questions or comments in relation to this document please send them (indicating the document reference, issue date, chapter and/or page of the document to which your comment refers) using the Guidance feedback form. The feedback form can be accessed via the ECHA Guidance website or directly via the following link:
https://comments.echa.europa.eu/comments_cms/FeedbackGuidance.aspx

European Chemicals Agency

Mailing address: P.O. Box 400, FI-00121 Helsinki, Finland
Visiting address: Annankatu 18, Helsinki, Finland

Preface

This document describes the information requirements under the REACH Regulation 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 the REACH Regulation.

The original versions of 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/documents/10162/13559/mb_63_2013_consultation_procedure_for_guidance_revision_2_en.pdf

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

http://echa.europa.eu/web/guest/guidance-documents/guidance-on-reach

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] 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, p.1; corrected by OJ L 136, 29.5.2007, p.3).

Document History

Version	Changes	Date
Version 1.0	First edition.	May 2008
Version 2.0	Revision of sections E.3.4.2 and E.3.4.4 Corrigendum: (i) replacing references to DSD/DPD by references to CLP (ii) implementing minor recommendations from nanomaterials from the RIP-oN3 report (iii) additional minor editorial changes/corrections (Note that references to DSD/DPD Risk phrases in Table 2 in the Appendix have not yet been updated in this version)	November 2012
Version 3.0	Revision of Section E.2 Withdrawal of Appendix E.1	May 2016

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 part E within the Guidance Document

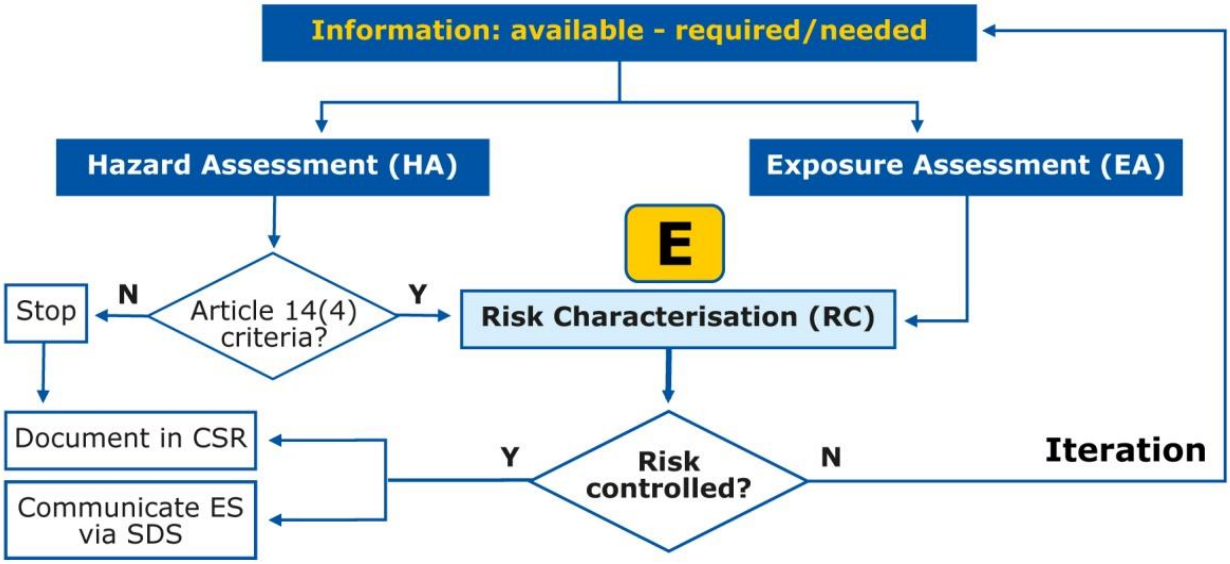

Table of Contents

Tables

E.1 Introduction

E.1.1 Aim

In risk characterisation, exposure levels are compared to quantitative or qualitative hazard information (REACH Annex I, 6). When suitable predicted no-effect concentrations or derived no-effect levels are available, risk characterisation ratios (RCRs) can be derived in order to decide if risks are adequately controlled for each environmental sphere and for each human population known to be or likely to be exposed (REACH Annex I, 6.4). When these no-effect levels cannot be established for certain effects, a qualitative assessment of the likelihood that these effects are avoided when exposure scenarios are implemented shall be carried out (REACH Annex I, 6.5).

E.1.2 Background

Risk characterisation ratios (RCRs) need, where available, to cover all end-points, populations, exposure routes and time scales, environmental and human. RCRs are derived by comparing exposure levels to suitable predicted no-effect concentrations (PNECs) or derived no-effect levels (DNELs)[2] (See Equation E- 1).

For the environmental end-points, this is the ratio of predicted environmental concentration (PEC) to PNEC (Equation E- 1).

Equation E- 1

$$RCR = \frac{PEC}{PNEC} \text{ or } \frac{Exposure}{DNEL}$$

For the human health end-points a distinction needs to be made between effects exerted by a threshold and non-threshold mode of action. For threshold effects for which a DNEL can be set, the RCR is the ratio of the estimated exposure and the DNEL (Equation E-1). For non-threshold effects (e.g. non-threshold mutagens and non-threshold carcinogens) a no-effect level, and thus a DNEL, cannot be established. However, it may be possible, if data allow, to set a DMEL (derived minimal effect level), a reference risk level considered to be of very low concern. Risk characterisation then entails a comparison between the estimated exposure and the DMEL. In this situation, the principle of Equation E- 1 may be used by replacing DNEL with DMEL, but it should be recalled that the resulting "RCR" is not related to a no-effect level. This will be referred to as a semi-quantitative Risk Characterisation.

It is to be noted that for some human health endpoints considered to have threshold effects, it may not always be possible to set a DNEL, necessitating a qualitative assessment. For a substance having quantitative data for some endpoints and qualitative data for other endpoints, the risk characterisation needs to be both (semi-)quantitative as well as qualitative.

Control of risk for a substance is demonstrated when the outcome of both the hazard assessment and exposure assessment are robust and where RCRs for all exposures (for all compartments, routes, populations and durations) related to all exposure scenarios and all end-points are below one; and where relevant qualitative risk characterisations demonstrate

[2] In calculating the RCR, both the exposure estimate and the PNEC or DNEL should be expressed using the same relevant metric(s).

that the likelihood of effects are avoided when implementing the exposure scenarios (See also Chapter A.1).

The above does not include the assessment of the physicochemical risk to human health (see Section E.2). Such an assessment must be carried out for substances which have been classified on the basis of certain physicochemical properties (explosivity, flammability or oxidising potential), or if there are other reasonable grounds for concern.

Assessment steps

The risk characterisation in the CSA is described as a series of steps that are discussed in more detail in subsequent sections:

Step 0 If the substance is classified for physiochemical danger (see Chapter R.9[3]), carry out a risk characterisation for physicochemical properties (See Section E.2).

Step 1 Collect the predicted or derived no-effect levels or minimal effect levels (PNECs, DNELs or DMELs if appropriate) for the relevant time scales, environmental ecosystems, human populations, health effects, and routes of exposure. For endpoints where no DNEL can be derived, collect other information on potency of the substance. For the derivation of this information see Chapters R.8 and R.10.

Step 2 For each exposure scenario collect the exposure values, measured or estimated, for the relevant time scales and spatial scales, environmental compartments, human populations and human routes of exposure. For a definition of short term (acute exposure) and long term (chronic exposure), please refer to the relevant hazard chapters (Chapter R.8) and the exposure estimation chapters (Chapters R.14-16).

Step 3 Compare matching exposure and predicted or derived no-effect levels or minimal effect levels for all relevant matching combinations. This is described in Section E.3.3 (humans) and Section E.4.3 (environment).

Step 4 If no predicted or derived no-effect level or minimal effect level could be derived for a substance for a certain environmental compartment or human effect, carry out a qualitative risk characterisation for that compartment/effect (see Sections E.3.4 and E.4.4). This is done in addition to Step 3 if also a PNEC or DNEL/DMEL is available for other compartments/effects.

Step 5 Calculate the sum of risk characterisation ratios of combined exposure, e.g. for each human population and for the general population (combined worker and consumer exposure) see Section E.3.5 and Section E.4.5.

Step 6 Decide on possible iterations of the CSA, taking uncertainties in the assessment into account (see Chapter R.19). The risk characterisation should demonstrate control of risks (see Chapter A.1), based on a sufficiently robust hazard and exposure assessment.

Step 7 Finalise the risk characterisation.

[3] Please note that it is proposed that Chapter R9 will be withdrawn and the content will be merged into the forthcoming update of Chapter R.7a

E.1.3 Iteration needs

If the Risk Characterisation shows that, based on the initial ES, risks are not controlled, further work would be needed. In a second iteration of the CSA, information at any point of the assessment cycle can be modified. The CSA process can be refined in a number of iterations. Such iterations must be realistic to the extent that the introduction of operational conditions (OC) and/or risk management measures (RMMs) can be implemented in practice.

In order to produce a meaningful risk characterisation it is important that the assessor both understands, and takes into account the uncertainties associated with the information/data that is provided. Uncertainties related to both the hazard assessment and the exposure assessment should be addressed in the CSA (see Step 6). Methods for uncertainty analysis can be found in Chapter R.19.

E.2 Risk characterisation for physicochemical properties

E.2.1 General aspects

Substances which are hazardous because of their physicochemical properties trigger additional requirements for the chemical safety report (CSR) and safety data sheet (SDS) under REACH, in the same way as substances which are hazardous because of their (eco)toxicological properties.

Some physicochemical properties are intimately linked to physical hazards - notably flammability, explosive properties and oxidising properties. Substances that possess these properties have the capacity to release energy, either slowly in the form of a fire, or quickly in the form of an explosion, with the potential to cause physical damage to humans and the surroundings. Human populations exposed to such an "event" are at an immediate risk of serious harm, even death, unless the risks are properly managed.

Under REACH, there is a requirement to report the physicochemical properties of a substance and assess the potential effects to human health, in order to determine the classification of the substance in accordance with Regulation (EC) No 1272/2008 (CLP Regulation). In addition, for substances registered in quantities of 10 tonnes or more per year, the registrant must carry out a chemical safety assessment according to REACH Article 14, which includes a physicochemical hazard assessment (Article 14(3)(b)). If the criteria for the hazard classes listed in Article 14(4) of the REACH regulation are fulfilled, the chemical safety assessment must include an exposure assessment, and a risk characterisation.

E.2.2 Physicochemical properties

ECHA Guidance on information requirements and chemical safety assessment Chapter R.7a: *Endpoint specific guidance* provides support on meeting the information requirements set out in Annexes VI to XI to the REACH Regulation. The information requirements relate both to those physicochemical properties that are relevant for exposure and fate considerations as well as to physical hazards, human health hazards and environmental hazards. The relevant sections in terms of a Physicochemical Hazard Assessment (as required under REACH Annex I section 2) include:

- Explosivity = Explosive properties (Section R.7.1.11 of Chapter R.7a)
- Flammability (Section R.7.1.10 of Chapter R.7a)
- Oxidising potential = oxidising properties (Section R.7.1.13 of Chapter R.7a).

Definitions, information requirements etc. are described in Chapter R.7a and will not be repeated in this Guidance. However it should be noted that while considering the above properties, the requirements described in this Section (E2) apply to substances that fulfil the criteria for any of the following hazard classes or categories:

2.1 Explosives;

2.2 Flammable gases;

2.3 Aerosols;

2.4 Oxidising gases;

2.6 Flammable liquids;

2.7 Flammable solids;

2.8 Self-reactive substance, types A and B;

2.9 Pyrophoric liquids;

2.10 Pyrophoric solids;

2.12 Substances and mixtures which in contact with water emit flammable gases;

2.13 Oxidising liquids, categories 1 and 2;

2.14 Oxidising solids, categories 1 and 2; and

2.15 Organic peroxides, types A to F.

E.2.3 Human health hazard assessment of physicochemical properties

The scope of the chemical safety assessment under REACH covers only what could be described as "normal operations" for the manufacture and/or use under foreseeable operational conditions. Neither fault nor accident conditions should be considered in the assessment. In addition, storage and on-site transfer are "uses" under REACH and therefore should be considered in the chemical safety assessment. However the carriage of dangerous substances, and dangerous substances in dangerous mixtures, by rail, road, inland waterway, sea or air is outside the scope of REACH (Article 2.1(d)).

The prevention of major accidents involving hazardous substances, is covered by the Seveso directive[4] (Directive 2012/18/EU), which covers establishments where these substances are present (e.g. during processing or storage) in quantities above certain thresholds. Depending on the amount of dangerous substances present, establishments are categorised as lower or upper tier establishments, the latter being subject to more stringent requirements. Substance and use information, generated through REACH and CLP processes, supports the substance users in fulfilling their obligations under Seveso.

Minimum requirements for improving the safety and health of workers potentially at risk from explosive atmospheres are covered by the ATEX 99/92/EC directive[5]. Employers must classify areas where hazardous explosive atmospheres may occur into zones. The classification given to a particular zone, and its size and location, depends on the likelihood of an explosive atmosphere occurring and its persistence if it does. The explosion protection document is intended to provide an overview of the results of the risk assessment and the consequent technical and organisational protective measures for a plant and its working environment. Equipment and protective systems in the places where hazardous explosive atmospheres may be present must be chosen in accordance with the categories in Directive 2014/34/EU[6], unless otherwise provided in the explosion protection document on the basis of the risk assessment. Further criteria such as temperature class, type of protection and explosion group must be considered to ensure safe operation of equipment in hazardous places. These criteria depend on the combustion and explosion properties of the substances used.

According to REACH the potential effects to human health shall be assessed as a minimum (REACH Annex I section 2.2) for flammability, explosivity and oxidising potential. It should be noted, however, that a substance may be capable of producing a fire or explosion without being classified into one of the hazard classes or categories listed in E.2.2. For example, a substance may present an adverse effect to human health due to it providing a potential dust explosion hazard if present in the form of small particles (combustible dust). Therefore an explanation of the hazard could be provided, with an indication and justification of any action or decision taken in order to ultimately communicate relevant risk management measures to

[4] http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32012L0018
[5] http://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:31999L0092
[6] http://eur-lex.europa.eu/legal-content/DE/TXT/?uri=CELEX:32014L0034

the user.

According to REACH Annex I the steps of the physicochemical hazard assessment undertaken by the registrant, include:

2.3 The assessment of each effect shall be presented under the relevant heading of the Chemical Safety Report (Section 7)[7] *and where required and in accordance with Article 31, summarised in the Safety Data Sheet under headings 2 and 9.*

In the case of a flammable liquid, this would include an entry in the chemical safety report under the heading 6.2 Flammability, with an overview of the information available, including the flash point.

2.4 For every physicochemical property, the assessment shall entail an evaluation of the inherent capacity of the substance to cause the effect resulting from the manufacture and identified uses.

This evaluation of the inherent capacity of the flammable liquid to cause a fire could look something like:

The potential effects in this case are determined by the flash point of the liquid, the concentration of the air-substance vapour mixture, and the availability of ignition sources.

- The flash point of the flammable liquid is 13°C, which means that at ambient temperatures it will give off a sufficient concentration of vapours to form an ignitable mixture with air, resulting in a potential fire hazard.

- The lower and upper explosion/flammability limits are between 3.3 and 19.0% by volume of air. While it is a relatively narrow range, since the lower limit is only a few percent it only takes a small amount of vapours in the air to form an ignitable mixture.

- The substance vapour is heavier than air (relative vapour density: 1.6) and therefore it will not easily disperse, which means the vapour can travel considerable distances to find an ignition source.

Spray mists of this flammable liquid in air will burn at any temperature if an ignition source is present.

- This flammable liquid flows easily. Burning liquids can flow under doors, and into neighbouring buildings, spreading fire widely.

- Materials such as wood, cardboard and cloth can absorb this flammable liquid and give off hazardous (flammable) vapours.

- The substance is not self-reactive and its auto-ignition temperature is significantly higher than the normal ambient temperature (for this substance it is 365°C). Auto-ignition in this case cannot be achieved without a heat source.

2.5 The appropriate classification developed in accordance with the criteria in Regulation (EC) No 1272/2008 shall be presented and justified.

In this example this could be: Flammable liquid, Category 2, H225: Highly flammable liquid and vapour. This should also be reported in the Classification and Labelling section of IUCLID,

[7] This legal quote refers to REACH Annex I Section 7 which describes the CSR format, and not the CSR heading 7.

and Section 3 of the Chemical Safety Report (if one is required).

E.2.4 How to present the risk characterisation

This risk characterisation, documented in the chemical safety report, consists of an assessment of the likelihood and severity of an event occurring due to the physicochemical properties of the substance (REACH Annex I, section 6.3). For any exposure scenario, the risks [to humans] can be considered adequately controlled, throughout the lifecycle of the substance that results from manufacture and identified uses, if the likelihood and severity of an event occurring due to the physicochemical properties of the substance [as determined in the physicochemical hazard assessment] is negligible.

The level of risk could be described either quantitatively or qualitatively, dependent on the availability of relevant information. The German Technical Rule for Hazardous Substance (TRGS 800[8]) Fire Protection Measures (and associated EMKG module for fire and explosion risk[9]), is one method that could be used for assessing flammable liquids, to establish the conditions of use for which the risk is adequately controlled. Whichever method is employed good practices must be followed in data collection, documentation and analysis to ensure that the risk assessment is robust and transparent.

When considering "likelihood and severity", it may be reasoned, in the context of the REACH physicochemical properties, that "severity can always be high" where a fire or explosion is concerned. Therefore the focus should be to reduce the "likelihood of an event" on the basis of the operational conditions and risk management measures in place.

E.2.5 Risk management measures

The specification of the risk management measures is a key element of the assessment, leading to control or reduction of the risk for the identified uses. The risk management measures that are appropriate depend on the physicochemical properties (a Category 1 flammable liquid may require a greater degree of protection than a Category 3 flammable liquid) and the conditions of use. Some examples are listed below, in a hierarchical structure based on their potential effectiveness in preventing, or protecting against, an (adverse) event. It should be noted that only some of the measures such as the engineering controls clearly reduce the likelihood of an event affecting humans. While certain administrative controls, personal protective equipment (PPE) and labelling could also be argued as reducing this likelihood, those such as emergency response measures generally reduce the severity of an event. It should also be noted that one or more measures may be required to adequately control the risk from the physicochemical properties of a substance in a specific identified use.

E.2.5.1 The hierarchy of control

Effective control in the workplace is achieved through the application of a "hierarchy of control", an established concept[10], with elements described in Article 6 of the Chemical Agents Directive (Directive 98/24/EC). The first potential solutions that should generally be considered are elimination and substitution. However, elimination or substitution of the substance is not included here as it is not an option for the registrant at the point of carrying out a CSR. The

[8] http://www.baua.de/en/Topics-from-A-to-Z/Hazardous-Substances/TRGS/TRGS-800_content.html
[9] http://www.baua.de/en/Topics-from-A-to-Z/Hazardous-Substances/pdf/Fire-explosion-risk.pdf
[10] https://oshwiki.eu/wiki/Hierarchy_of_prevention_and_control_measures

other elements of the hierarchy can be presented as:

Engineering controls: refers to the design of the process plant and equipment to maximise containment, to control the working environment to which the substance is subjected, to limit contact between the substance and workers etc. Some examples are:

- Isolation: physical separation of the substance from humans and other entities (substances, ignition sources[11] etc.) - probably the most decisive measure reducing the likelihood of an adverse event
- Storing the substance under a controlled temperature environment
- Providing controlled explosion channels (overpressure protection)
- Using equipment that is appropriately ATEX certified, earthed etc.
- Providing ventilation (general (mechanical) or local exhaust ventilation).

Administrative controls: management tools that include the modification of operational conditions (to change the way people work). They seek to reduce the exposure opportunity, to control the way the work is carried out, to limit exposure time, and ensure that the work activity is carried out in a pre-determined way. Some examples are:

- Adherence to standard operating procedures
- Use of "permit to work" systems for specific activities (e.g. cleaning and maintenance)
- Systematic hazard identification and periodic update of the analysis
- Operators receiving targeted training in the storage, handling and use of the substance
- Safety data sheets made available in each relevant workplace position for consultation
- Labelling indicating the potential hazards of the contents of containers
- Periodic inspection and maintenance of PPE, tools and safety devices
- Emergency preparedness: predefined escape routes, emergency exits, escape and rescue plans etc.
- Restricted access (authorised/trained personnel only)
- Hazardous area classification (zones), where hazardous explosive atmospheres may occur cf. ATEX 99/92/EC.

PPE: personal protective equipment should provide individual protection against any hazards that remain after engineering and administrative controls have been applied. Although it appears low down in the hierarchy of control, PPE may still be required and may in certain circumstances, be the best available option (e.g. for infrequent tasks of short duration). Apart from the standard PPE such as gloves, safety goggles etc. some examples specific to physicochemical properties are:

- Wear fire/flame resistant/retardant antistatic clothing
- Remove/Take off immediately all contaminated clothing. Rinse skin with water/shower.

Others:
Spill management (e.g. bunding) and emergency response, (e.g. firefighting) could also be a consideration in terms of good practices to follow (and are normally indicated in the SDS), however they do not reduce the likelihood of an event and therefore do not contribute to demonstrating that the risk is negligible in the context of REACH.

E.2.6 Communication of risk management measures downstream

Fulfilling one of the hazard classes of REACH Article 14(4) obliges the registrant to carry out an exposure assessment. The exposure assessment shall cover all hazards identified in the hazard assessments and the PBT/vPvB assessment (REACH Annex I section 5.0). For the hazards

[11] For example according to (EN 1127-1)

identified in the physicochemical hazard assessment, an exposure estimation is not relevant, as the objective here is to demonstrate a risk characterisation that is negligible, rather than to compare it with a threshold level. Thus the exposure scenario generated for the chemical safety report, and the exposure scenario communicated to the substance (downstream) user, should contain the relevant information on the risk management measures to achieve this negligible risk characterisation.

Where several exposure scenarios would contain the same text relating to risk management measures designed to address risks from physicochemical properties, it may be more useful to explain them once in the main body of the SDS, e.g., in Section 7. In this case, every exposure scenario to which these risk management measures are relevant must refer to the relevant section of the main body of the SDS, so that the (downstream) user has fast and easy access to all relevant information for his specific use. Given that the exposure scenarios are provided to the (downstream) user together with the SDS, as an extended SDS, the user will find all the relevant information to address the hazards of the substance, including these physicochemical hazards, within the same document.

Normally uses consist of different tasks, and within an exposure scenario these different tasks can be introduced and described in so-called contributing scenarios. Also in this case, the contributing scenarios, their introduction and description and the SDS are part of one and the same document, the extended SDS. In this situation, the supplier of the extended SDS may prefer to provide the relevant information on the risk management measures addressing physicochemical hazards once in the exposure scenario, rather than repeating in every contributing scenario.

E.3 Risk characterisation for human health (Steps 1-5)

E.3.1 General aspects

Having conducted the hazard assessment for all relevant human health endpoints and populations (Chapters R.1-R.8) and the exposure estimation (Chapters R.14-R.18); a quantitative, and in some cases also a qualitative, risk characterisation is carried out. For certain endpoints further considerations are outlined in Appendices R.8-8 to R.8-12.

It should be acknowledged that the whole risk characterisation process, whether quantitative or qualitative, depends heavily upon expert judgement. Therefore, the approach taken in reaching a conclusion needs to be as transparent as possible and needs careful explanation/justification as to assumptions, decisions, uncertainties and adequacy of the available data set.

E.3.2 Step 1 and 2: collect hazard and exposure information

Human health risk characterisation is basically an integration of the findings from the exposure and effects assessment in order to reach a conclusion on whether risks are controlled. A logical start for the risk characterisation is therefore to recap the main findings from the previous phases of the safety assessment.

Under REACH, this risk characterisation needs not be conducted for all relevant health effects, but only for the leading health effect(s). For effects with DNELs or DMELs this means the toxicological effect that results in the most critical DNEL (or DMEL) for a given exposure pattern (duration, frequency, route and exposed human population) associated with an exposure scenario. However, if a substance exerts also effects for which no DNEL or DMEL can be derived, it may not be straightforward to identify the leading health effect.

In any case, it is suggested to first establish an overview of the critical DN(M)ELs derived for all relevant combinations of population/route/exposure pattern (see Section R.8.7) and the matching exposure estimates. As indicated in Chapter R.8, in principle DNELs (or DMELs, for e.g. genotoxic carcinogens) should be derived for all the required and available data on a substance, in order to identify the critical DNEL (or DMEL) for the leading health effect to be used in a (semi-) quantitative risk characterisation. The critical DNEL (or DMEL, e.g. when the critical effect is non-threshold carcinogenicity) being then the lowest of these DNELs or DMELs for a given exposure pattern.

However, as indicated above and in Chapter R.8, it might not always be possible to derive a DNEL or DMEL for a certain endpoint. For such a substance, having DNELs or DMELs for some endpoints and only data of a qualitative nature for some other endpoints, it is not evident a priori what is/will be the leading health effect. It cannot be excluded that the 'quantitative' endpoints will be more critical than the 'qualitative' endpoints, except maybe for non-threshold mutagenicity (cat. 1A & 1B), non-threshold carcinogenicity (cat. 1A & 1B) and possibly respiratory sensitisation. Therefore, in most cases for such a substance, for a given exposure pattern, both (semi-)quantitative risk characterisation (Step 3), based on the critical DN(M)EL, as well as a purely qualitative risk characterisation (Step 4), for the endpoints for which no DNEL or DMEL could be derived needs to be performed. Both assessments should demonstrate control of risks.

For endpoints, with effects for which no DNEL/DMEL can be derived, other measures of potency (see Section R.8.6) can be used for the qualitative risk characterisation. How to conduct the Risk Characterisation is further detail in Step 4 (see Section E.3.4).

E.3.3 Step 3: Quantitative and semi-quantitative risk characterisation

The (semi-)quantitative risk characterisation is carried out by comparing the estimated exposure for relevant exposure scenarios with the critical DN(M)EL for the leading health effect. This is done separately for each relevant combination of exposure pattern with

1. population exposed:
   - workers
   - general population
   - consumers
   - humans exposed via the environment

   and
2. exposure route:
   - inhalation
   - dermal
   - oral.

In Section E.3.3.1 and E.3.3.2 below, a list of the different exposure/DN(M)EL ratios that should be considered for each population is reproduced below from Section R.8.7.3. Please note that for simplicity only DNELs are mentioned, but it is equally valid for DMELs.

E.3.3.1 Workers

For **systemic, long-term effects**, DNELs are generally needed for worker dermal and inhalation exposure. In a first tier these two worker DNELs usually need to be derived and used to assess the occupational exposure.

DNEL	Duration and routes of exposure to humans corresponding to the DNEL
Worker-DNEL long-term dermal	Repeated worker dermal exposure for a day or more (this exposure is generally modelled as a dermal daily deposition expressed in mg substance/cm^2 skin)
Worker-DNEL long-term inhalation	Repeated worker inhalation exposure for a day or more (exposure is modelled or measured as a daily air concentration in mg substance/m^3)[12]

For **systemic, acute** effects, one DNEL is normally relevant to compare with peak occupational exposures.

[12] Please note that other metrics could be relevant, such as cm^2/m^3 (relevant for nanomaterials) and nanoparticle number/m^3 (especially relevant for fibres).

DNEL	Duration and routes of exposure to humans, corresponding to the DNEL
Worker-DNEL acute inhalation	Worker inhalation peak exposure

Rarely, and on a case-by-case basis, a systemic DNEL acute dermal for workers may need to be derived. However, in a first tier, single dermal occupational exposure should be compared against the corresponding long-term DNEL.

For both **acute and long-term local effects**, four (external) DNELs may have to be derived for substances causing irritation, corrosion and/or sensitisation (assuming that the data allow setting a DNEL), for a comparison with external occupational dermal and inhalation exposure levels.

DNEL	Duration and routes of exposure to humans corresponding to the DNEL
worker-DNEL acute dermal local	Worker dermal single exposure
worker-DNEL acute inhalation local	Worker inhalation peak exposure
worker-DNEL long-term dermal local	Repeated worker dermal exposure
worker-DNEL long-term inhalation local	Repeated worker inhalation exposure

E.3.3.2 General population (consumers / humans exposed via the **environment)**

For **systemic, long-term effects**, DNELs for the general population may need to be derived if the substance is present in consumer–available products or is released to the environment and present as an environmental contaminant. In a first tier potentially three DNELs need to be derived and used to assess the exposure of consumers and humans via the environment.

DNEL	Duration and routes of` exposure to humans, corresponding to the DNEL
General Population-DNEL long-term oral	Repeated exposure oral of the general population (consumers, humans via the environment, expressed as mg/kg/day)
General Population-DNEL long-term dermal	Repeated dermal exposure of the general population (consumers)(generally modelled as a dermal daily exposure expressed in mg substance/cm^2 skin)

General Population-DNEL long-term inhalation	Repeated inhalation exposure of the general population (consumers or humans via the environment)(modelled or measured as a daily air concentration in mg substance/m^3)

Occasionally, in case of peak exposures, one DNEL is normally relevant for **systemic, acute** effects.

DNEL	Duration and routes of exposure to humans, corresponding to the DNEL
General Population - DNEL acute inhalation	Occasional inhalation exposure (minutes-hours) of the general population (consumers, humans via the environment)

Rarely, and on a case-by-case basis, a systemic DNEL acute may need to be assessed for the general population for the other routes (dermal, oral). However, in a first tier, single dermal and oral exposure of the general population should be compared against the corresponding long-term DNELs.

For both **acute and long-term local effects**, four external DNELs may have to be derived for substances causing irritation, corrosion and/or sensitisation (assuming that the data allow setting a DNEL), for a comparison with external dermal and inhalation exposure levels (oral is not relevant) of the general population.

DNEL	Duration and routes of exposure to humans corresponding to the DNEL
General Population - DNEL acute dermal local	Dermal single exposure of the general population (consumers)
General Population - DNEL acute inhalation local	Inhalation peak exposure of the general population (consumers or humans via the environment)
General Population - DNEL long-term dermal local	Repeated dermal exposure of the general population (consumers)
General Population - DNEL long-term inhalation local	Repeated inhalation exposure of the general population (consumers or humans via the environment)

E.3.3.3 Interpretation of the quantitative and semi-quantitative risk characterisation

REACH Annex I, 6.4 states that for any exposure scenario the risk to humans can be considered to be controlled if exposure levels do not exceed the appropriate DNEL, i.e. if the RCR <1. A DNEL is therefore a level of exposure which should not be exceeded and indicates adequate control of risks.

For non-threshold effects with a DMEL, the interpretation is different. As explained in Section R.8.1.1, a DMEL is not equivalent to a DNEL: where a DNEL expresses a derived value below which exposures should be controlled – with the underlying assumption that such an exposure level would be below a no-effect-level, the underlying assumption for non-threshold effects is that a no-effect-level cannot be established and a DMEL therefore expresses an exposure level corresponding to a low, possibly theoretical, risk. A DMEL is therefore a risk-related reference value, which can be established via two approaches: the 'Large Assessment Factor' (EFSA) approach and the 'Linearised' approach (see Section R.8.5)[13].

Using the EFSA approach, one DMEL value is obtained, that expresses an exposure level corresponding to a low, possibly theoretical, risk, which could be seen as a tolerable risk.

Using the 'Linearised' approach, different DMEL values can be calculated, representing different lifetime cancer risks, e.g., a risk for cancer in 1 per 100.000 exposed (10^{-5}) or 1.000.000 exposed individuals (10^{-6}). Although there is no EU legislation setting the 'tolerable' risk level for carcinogens in the society, cancer risk levels have been set and used in different contexts (See Appendix R.8-14 for various values previously applied within and outside the EU). Based on these experiences, 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.

This approach for non-threshold substances offers additional guidance to risk managers in differentiating exposure scenarios for which existing control measures already result in very low human health risks from those for which existing control measures are less effective. For workers, the requirements of the Carcinogens and Mutagens Directive (2004/37/EC) shall be complied with. This requires compliance with objectives to prevent exposure, substitution of dangerous chemicals by less dangerous chemicals and, where this is not technically possible, by minimisation of exposure. However, the DMEL approach is useful when preparing chemical safety assessment to judge the remaining/residual likelihood of risks.

In summary, when the leading health effect is a threshold effect with a DNEL, the quantitative risk characterisation is as follows:

$$RCR = \frac{\text{Exposure}}{\text{DNEL}}$$

If Exposure < DNEL → Risk is adequately controlled

If Exposure > DNEL → Risk is NOT controlled

When the leading health effect is a non-threshold effect for which a DMEL has been derived (e.g. for non-threshold carcinogenicity), a semi-quantitative risk characterisation can be conducted:

If Exposure < DMEL → Exposure is controlled to a risk level of low concern

If Exposure > DMEL → Risk is NOT controlled.

In both cases the interpretation of the risk characterisation should be accompanied with a

[13] Please note that application of DMELs cannot lead to *adequate control of risks as defined in section 6.4 of REACH Annex I*, since it is considered a semi-quantitative aid to risk characterisation according to Annex I, Section 6.5.

qualitative discussion, for instance addressing aspects that could not be dealt with in a (semi-)quantitative way. This should include uncertainties related to the exposure assessment as well as the hazard assessment (Chapter R.19).

If the risk characterisation shows that risk is not controlled (see Chapter A.1), an iteration of the CSA is needed. This can be done by generating more refined exposure and/or hazard information or by introducing new RMMs (see Section E.3.5). Iterations of the CSA process should continue until the RC shows that risks are controlled/risks are of very low concern or if it is concluded that it is not possible to demonstrate control of risk (see Chapter E.4.7).

Furthermore, if endpoints for which no DNEL/DMEL could be derived were flagged under Step 1, also Step 4 (see Section E.3.4 below) needs to be conducted.

E.3.4 Step 4: Conduct qualitative risk characterisation

E.3.4.1 Introduction and approach

The purpose of the qualitative risk characterisation is to assess: ".the likelihood that effects are avoided when implementing the exposure scenario…" (REACH Annex 1, Section 6.5). The qualitative risk characterisation approach described in the following has to be completed when there is no basis for setting a DNEL or DMEL for a certain human health endpoint, i.e. when the available data for this effect do not provide quantitative dose-response information, but there exist toxicity data of a qualitative nature. The endpoints for which the available data may trigger a qualitative risk characterisation are: irritation/corrosion, sensitisation, acute toxicity, carcinogenicity and mutagenicity. The types of qualitative information that may be available for these different endpoints are indicated below. A more detailed description of the assessment of these endpoints can be found in Chapter R.8 (Section R.8.5.1 and Appendices R.8-8 to R.8-11).

It is to be stressed that when data are available that allow the derivation of a DNEL or DMEL[14] for an endpoint (including irritation/corrosion, sensitisation[15], acute toxicity, carcinogenicity and mutagenicity), the quantitative or semi-quantitative approach (see Section E.3.3) should be followed. Having DNELs or DMELs for all the required and available data on a substance makes it fairly easy to identify the leading health effect for that substance for the relevant exposure patterns. By contrast, for a substance having DNELs or DMELs for some endpoints and data of a qualitative nature for other endpoints, it is difficult to identify the leading health effect for the relevant exposure patterns. A priori, it cannot be excluded that the 'quantitative' endpoints will be more critical than the 'qualitative' endpoints mentioned above, except maybe for non-threshold mutagenicity (cat. 1A & 1B), non-threshold carcinogenicity (cat. 1A & 1B) and possibly respiratory sensitisation. Therefore, the risk characterisation for such a substance in most cases needs to be both (semi-)quantitative (based on the lowest DN(M)EL for the endpoints for which a DNEL or DMEL could be derived) as well as qualitative, for the endpoints for which no DNEL or DMEL could be derived. Both assessments should demonstrate control of risks.

The general approach when no DNEL for an endpoint is available aims at reducing/avoiding contact with the substance. However, implementation of risk management measures (RMMs) and operational conditions (OCs) needs to be proportional to the degree of concern for the health hazard presented by the substance. For example, it is not appropriate to apply the

[14] Note that a DMEL from a legal point of view is related to Risk Characterisation according to REACH Annex I, Section 6.5; i.e. a semi-quantitative aid to assessing the likelihood that effects are avoided.
[15] Note that for skin sensitisers the qualitative approach (risk characterisation) to define the RMMs and OCs should be the first step and the derivation of a DNEL (if possible) should be performed to judge the remaining/residual likelihood of risks after these RMMs and OCs are implemented.

same control strategy to irritating substances as to substances that are strong sensitizers or mutagenic.

Consequently, the approach suggested in this section is based on the principle that the higher the hazard, the stricter the controls need to be. At the same time, this implies that the lower the hazard, the less strict the controls. The RMMs/OCs for these lower hazards (e.g. irritation) will often not be sufficient to control exposures when there are other relevant effects for which DNELs can be derived (e.g. reproduction toxicity or repeated dose toxicity). Therefore, as indicated above, the (semi-)quantitative and qualitative risk characterisation needs to be run in parallel to cover for all effects and to decide on the leading health effect.

To provide practical guidance for the qualitative approach, a hierarchy/categories of hazards (high, moderate and low) is proposed, associated with a hierarchy of RMMs/OCs (below). This means that the conditions of use (operational conditions (OCs) and risk management measures) as set out in the exposure scenario (that determine the exposure level) need to reflect the severity of the hazard.

For each hazard for which no DNEL or DMEL can be derived, it is proposed to allocate them to one of three categories (see Table E.3-1 below), which are based on three key factors:

(i) Whether or not the toxicological endpoint will have a theoretically identifiable dose threshold and thus a potentially 'safe' level of exposure, but where the data typically available for such effect do not allow setting a DNEL. For example, a substance which causes irritation or acute toxicity is considered as having a threshold of effect, whereas a substance which is genotoxic in vivo will be unlikely to have one.

(ii) The seriousness of the resultant health effect in terms of irreversibility, life-threat and long-term consequences. For example, cancer and heritable damage are considered to be more serious than irritation because of their life-threatening and long-term consequences; or sensitisation is considered to be more serious than mild acute toxicity because of its irreversibility and long-term consequences.

(iii) The potency of the substance in relation to a particular toxicological endpoint. For example, more stringent control would be advocated for a strong skin sensitizer than for a moderate one. The same is also true for a strong corrosive substance in relation to an irritant. It should be noted that potency information for the hazards for which no DNEL or DMEL can be derived is not always available. For mutagenicity, carcinogenicity and respiratory sensitisation, information on the relative exposure levels at which effects occur will often not be available (which may improve in future due to development of more relevant methods to detect the potency of these effects), whilst for corrosivity, irritation, skin sensitisation and acute toxicity, some limited potency information should be accessible.

To ensure consistency in the allocation of substances to the three hazard bands of high, moderate and low, a simple and transparent approach to hazard identification is required. It is proposed that the EU hazard classification system R-phrases / hazard statements are used as descriptors of the hazards since the classification R-phrases / hazard statements for these hazards tend to reflect the qualitative and semi-quantitative nature of the information that is usually available for these endpoints.

The classification R-phrases / hazard statements are assigned on the basis of the known (or sometimes predicted) hazardous properties of a substance, and are used to indicate the nature of the health hazard, for example, irritancy, systemic toxicity or cancer. The R-phrases / hazard statements indicate if the health hazard relates to an effect which could occur from a single exposure to the substance, or an effect which is associated with repeated exposure to the substance. The R-phrases are also used to indicate the route of exposure which is of

concern, whether oral, dermal or inhalation or a combination of these. For some but not all toxicological endpoints, the relative potency of the substance can also be indicated by the R-phrase/ hazard statement.

The following sections provide a description of the endpoints in question and outline a stepwise approach for arriving at proportional risk management measures (for inclusion in the exposure scenarios).

E.3.4.2 Health endpoints for which a qualitative assessment may be necessary[16]

Irritation/corrosion

For **irritation and corrosion**, usually the available in vitro and in vivo studies tend to provide only qualitative (yes or no) or semi-quantitative/potency information (for example, corrosive after 3 minutes or 4 hours exposure; higher or lower scores for erythema, oedema and other irritative effects), as explained in Appendix R.8-9. It should be noted, however, that if there are data suitable for deriving a DNEL for these effects, especially for respiratory tract irritation, the qualitative approach should not be applied.

Substances classified as Skin corrosive Category 1A according to CLP (or as Corrosive with the R-phrase R35 according to DSD), which relates to strong corrosive effects, are allocated to the high hazard band on the basis that exposure to such extreme corrosive substances should be strictly contained.

Substances classified for

3. Skin corrosion Category 1B/1C in CLP (Corrosive with R34 in DSD)
4. Serious eye damage Category 1 in CLP (Serious eye damage with R41 in DSD) or
5. Skin, eye and respiratory irritation simultaneously (i.e. with H315, H319 and H335) in CLP (Irritating to eyes, respiratory tract and skin with R36/37/38 in DSD),

which relate to corrosive or severe irritant effects to the eye or irritant effects to the eyes, respiratory tract and skin simultaneously, are allocated to the moderate hazard band on the basis that exposure to such corrosives, eye damaging or irritant substances should be well-controlled.

Substances classified in one or two of the categories for skin, eye or respiratory irritation (i.e. with H315, H319 or H335) in CLP (with R-phrases R36, R37 or R38 in DSD), which relate to irritant effects, are allocated to the low hazard band on the basis that effects due to such moderately irritant substances are anticipated at higher concentrations when compared to the high and moderate hazard band irritants.

For these effects, it should be noted that the potency normally decreases with lowering concentration of the substance. This may therefore be a good first approach to manage the risks. The generic C&L concentration limits of 10% for skin or eye irritants (Category 2), 5 % for skin corrosives (Category 1/1A/1B/1C) and 3% for substances causing serious eye damage (Category 1) according to CLP (20 % for irritants, 10% for corrosives and 5% for strong corrosives according to DPD) should however not be used as defaults for control of risks as

[16] Both hazard classes, categories and statements according to CLP and corresponding "type of effect" and risk phrases according to DSD are used in this section, as well as in the table E. 3-1. The DSD will be repealedat 1 June 2015.

these levels do not automatically ensure that effects will not occur. Such an approach should therefore only be applied when substance-specific information allows the identification of a specific concentration limit with no effects. However, as noted above, dilution to these levels would be a good first approach for controlling risks before considering further risk management.

It should be verified whether or not the RMMs/OCs proposed are sufficient to also cover for other relevant effects for which DNELs can be derived (e.g. reproduction toxicity or repeated dose toxicity). Exposures should be controlled at least to these levels. This is especially important when dilution results in a situation that RMMs/OCs to control irritation/corrosion no longer apply.

Example: when a substance is a skin irritant, the RMMs/OCs may not be sufficient to cover for systemic dermal effects. This is also likely to be true for effects occurring after inhalation or oral exposure. So, what is needed for this substance are (to the extent the relevant DNELs are available): a quantitative risk characterisation to address systemic dermal effects, a quantitative risk characterisation for the inhalation and oral routes of exposure, where relevant, as well as a qualitative risk characterisation for the local dermal irritation.

Skin sensitisation

For substances classified as **skin sensitisers** (Category 1/1A/1B) according to CLP (or with R43 in DSD), several studies (see criteria in 3.4.2.2.3, Annex I, CLP, section 3.4.2.3 in ECHA Guidance on the Application of the CLP Criteria, and Appendix R.8-10) provide potency information, by which substances can be divided into extreme, strong and moderate[17]sensitisers Extreme and strong skin sensitizers (classified in Sub-category 1A in CLP) are allocated to the high hazard band on the basis that exposure to such potent skin sensitising substances should be strictly contained and dermal contact avoided. Moderate skin sensitisers (classified in Sub-category 1B in CLP) are allocated to the moderate hazard category band on the basis that exposure to these moderate skin sensitising substances should be well-controlled. In cases where the available data does not allow potency categorisation of a sensitising substance, the substance should be classified as Category 1, thus, the RMMs and OCs applicable to high hazard band should be considered.

Since sensitisation is essentially systemic in nature, it is important for the purposes of risk management to acknowledge that skin sensitisation may be acquired by other routes of exposure than dermal. There is therefore a need for cautious use of known contact allergens in products to which consumers or workers may be exposed by inhalation.

It should be verified whether or not the RMMs/OCs proposed are sufficient to also cover for other relevant effects for which DNELs can be derived (e.g. reproduction toxicity or repeated dose toxicity). Exposures should be controlled at least to these levels, not only for the dermal route of exposure, but also for the inhalation and oral routes of exposure (when relevant).

Respiratory sensitisation

Substances classified as **respiratory sensitisers** according to CLP (with R42 in DSD), may be allocated into sub-category 1A (strong sensitisers) or 1B (other sensitisers) on the basis of

[17] For skin sensitisation, potency division based on human data as well as on LLNA, Guinea pig maximisation test and the Buehler test, include division into strong and other sensitisers (in Category 1A or 1B, respectively). Strong sensitisers may be further divided into extreme and strong sensitisers for the purpose of setting specific concentration limits as outlined in section 3.4.2.3 in Guidance on the Application of the CLP Criteria (see also Appendix R.8-10)

weight of evidence considerations mainly based on human data if available (see criteria in 3.4.2.1.2, Annex I, CLP, section 3.4.2.3.1 in ECHA Guidance on the Application of the CLP Criteria). However, currently there are no available methods to determine thresholds and DNELs for respiratory sensitisers (see also Appendix R.8-11). Therefore, substances classified as a respiratory sensitizer (Category 1/1A/1B/1C) in CLP (assigned R42 in DSD) should normally result in a qualitative assessment for the hazard level of concern . Respiratory sensitisers according to CLP (with R42 in DSD) are allocated to the high hazard band on the basis that exposure to such substances should be strictly contained because they may cause serious health effects for which a dose threshold is not usually identifiable.

There is evidence from both human and animal studies, which indicate that effective sensitisation of the respiratory tract can result from dermal contact with a chemical respiratory allergen (see Section R.7.3). Thus, it is thought, that the effective prevention of respiratory sensitisation requires appropriate protection of both respiratory tract and skin. The generic advice is that appropriate strategies to control the risk of sensitisation to chemical allergens will require consideration of providing protection for all routes of exposure.

With the strict control needed for a respiratory sensitizer, the RMMs/OCs may be sufficient to also cover for other relevant effects for which DNELs can be derived. In that case, a qualitative risk characterisation for the respiratory sensitising effect may suffice, and there is no need to conduct a quantitative risk characterisation, unless control of all risks cannot be demonstrated.

Acute toxicity

The data required under REACH for **acute toxicity** should in principle enable the establishment of a (semi-)quantitative level for use in quantitative risk characterisation. However, usually quantitative risk characterisation is not possible for acute toxicity. In parallel, a qualitative risk characterisation for this endpoint could be performed for substances of very high or high acute toxicity classified in Category 1, 2 and 3 according to CLP (as T+ and T with R26, R27, R28, R23, R24 or R25 in DSD) when the data are not sufficiently robust to allow the derivation of a DNEL (see also Appendix R.8-8). This may e.g. apply when the lethality data have been obtained for a different route of exposure than the relevant route of human exposure.

Substances classified for acute toxicity in Categories 1 and 2 according to CLP (or with R26, R27 or R28 in DSD) are allocated to the high hazard band on the basis that exposure to such very (acutely) toxic substances should be strictly contained. Substances classified for acute toxicity in Category 3 according to CLP (with the R-phrases R23[18] , R24 or R25 in DSD) are allocated to the moderate hazard band on the basis that exposure to such acutely toxic substances should be well-controlled.

It should be verified whether or not the RMMs/OCs proposed are sufficient to also cover for other relevant effects for which DNELs can be derived (e.g. reproduction toxicity or repeated dose toxicity). Exposure should be controlled at least to these levels.

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

STOT-SE is defined as "specific, non-lethal target organ toxicity arising from a single exposure to a substance or mixture" (Guidance on the Application of the CLP Criteria, ECHA 2009). The standard animal studies that provide information for this classification are normally acute

[18] Please note that R23 corresponds to Acute toxicity Category 2 for vapours according to CLP criteria.

toxicity studies or effects may be observed after single exposure in repeated dose toxicity studies. However, acute DNELs are usually not derived, since there is no established accepted methodology and since acute DNELs are not necessary, as the long-term DNEL is normally sufficient to ensure that acute effects do not occur. According to R.8, "DNEL for acute toxicity should be derived if an acute toxicity hazard (leading to C&L) has been identified and there is a potential for peak exposure". Therefore, for STOT-SE effects DNEL would not be expected as acute toxicity C&L is generally characterised in terms of lethality.

Carcinogenicity / Mutagenicity

There may be cases when neither a DMEL nor a DNEL can be set for a **carcinogen**, because no suitable (semi-)quantitative animal or human data are available to establish relevant dose descriptors. In such circumstances, a qualitative assessment should be performed[19]. Carcinogens classified in Category 1A and 1B in CLP (Category 1 or 2 in DSD), are allocated to the high hazard band on the basis that exposure to such substances should be strictly contained because they may cause serious health effects based on sufficient evidence of carcinogenicity derived from human or animal data and for which a dose threshold is not usually identifiable for many of these carcinogens. Non-genotoxic carcinogens which are classified in Category 2 in CLP (or in Category 3 in DSD) are in principle allocated to the moderate hazard band, because they are regarded to represent a lower concern than Category 1A and 1B carcinogens according to CLP (Category 1 or 2 in DSD) as there may be only limited evidence of carcinogenicity based on human or animal data. On the other hand, if the mode of action or carcinogenic potency remains unclear then these Category 2 carcinogens according to CLP (Category 3 in DSD) could be assigned to the high hazard band, on a case by case basis.

It is to be noted that for many carcinogens (whether Category 1A, 1B or 2 according to CLP or Category 1, 2 or 3 according to DSD), the qualitative approach as outlined above would not be applied, because in order to classify, information allowing the derivation of a DN(M)EL would be available.

For in vivo **mutagens** with no relevant dose-response information and no cancer data, neither a DMEL nor a DNEL can be derived. In such circumstances, a qualitative assessment should be performed. Mutagens classified in Category 1A, 1B or 2 in CLP (Category 1, 2 or 3 in DSD) are allocated to the high hazard band on the basis that exposure to such substances should be strictly contained because they may cause serious health effects for which a dose threshold is not usually identifiable. It should be noted that even the Category 2 mutagens in CLP (Category 3 in DSD) should be assigned to the high hazard band, with respect to the RMM/OCs needed, on the basis that they are usually considered as suspected germ cell mutagens i.e. suspected category 1B mutagens (suspected category 2 mutagens in DSD) and treated as suspected genotoxic carcinogens i.e. suspected category 1B carcinogens (suspected category 2 carcinogens in DSD). However, when it is shown in the assessment of the toxicokinetic behaviour that the substance does not reach the germ cells and shown in a carcinogenicity study that the substance does not cause cancer (locally or systemically), the Category 2 mutagen according to CLP (Category 3 mutagen in DSD) can be assigned to the moderate hazard band

With the strict control needed for mutagens (Cat 1A, 1B or 2 in CLP/ Cat. 1, 2 and 3 in DSD) and carcinogens classified in Category 1A, 1B or in Category 2 if potent, according to CLP (Cat 1, 2 or 3, if potent in DSD), the RMMs/OCs aimed at avoidance of exposure will likely be sufficient to also cover for other relevant effects for which DNELs can be derived, for all routes of exposure. In that case, a qualitative risk characterisation will suffice, and there is no need to

[19] As already noted, also the Carcinogens and Mutagens Directive (2004/37/EC) shall be complied with in the workplace. See Section E.3.3.3

conduct a quantitative risk characterisation.

The information that is used for assignment of the substance to the appropriate hazard category needs to be in line with the REACH information requirements, which in some situations may require further information (see Annex VII through X of REACH and Section R.7.7).

E.3.4.3 Step-wise approach for the qualitative assessment, including development of exposure scenarios (ES)

The steps set out in this approach are similar to those set out in the standard approach for conducting chemical safety assessments, including development of exposure scenarios, exposure estimation and risk characterisation. It should be read in conjunction with the more detailed guidance on how to develop an ES and estimate exposure. The main difference is that the lack of a (semi-)quantitative DNEL or DMEL for one or more endpoints triggers the need for more qualitative judgements of whether or not the exposure will be controlled to a sufficiently low level when the operational conditions and risk management measures set out in the exposure scenarios are implemented. What is considered to be sufficient will depend on the nature of the effect and the type and efficiency of operational conditions and Risk Management Measures. Moreover, as REACH requires coverage of the lead health effect for the relevant exposure patterns, it should be verified whether the qualitative endpoint is indeed the leading health effect, or whether the risk characterisation will be driven by DNELs or DMELs from other endpoints. The proportionality stressed by the Regulation implies that for well controlled industrial uses and absence of downstream users, the evidence to prove control of risks will be easier to obtain.

The approach below mainly addresses occupational exposure, but some recommendations on consumer exposure and indirect exposure via the environment are also given.

1. **Identify the R-phrases / hazard statements and allocate substances to the appropriate hazard category (see previous section and Table E.3-1)**

   While R-phrases / hazard statements correctly describe the hazard of most substances, there are cases where the most recent information on the effects might be inconsistent with the current classification. Thus, whenever scientific evidence would suggest that there is a more appropriate R-phrase/hazard category to be used for a substance, this should be considered and justified in the CSR.

2. **Consider the most likely exposure routes (e.g., dermal, inhalation and oral) separately**

   Depending on the physical-chemical properties or the use pattern of the substance, some routes of exposure may be irrelevant. If so, this should be justified. Information on likely exposure routes may also be available from specific R-phrases. The purpose of this step is to find out what are the likely exposure routes which may lead to the expression of the hazard with the ultimate goal of selecting the most appropriate RMM-package and corresponding operational conditions (OCs). (A more detailed and thorough analysis of the potential for exposure is made in step 4.)

3. **Develop initial Exposure Scenarios**

   An initial exposure scenario should include a sufficiently detailed description of the operational conditions and risk management measures that are currently applied for the manufacture and identified uses of the substance through the supply chain. As a minimum, it should already incorporate those measures based on the applicable R-phrases / hazard statements. If, based on the initial ES, it cannot be demonstrated in the CSA process that risks are controlled, further work is needed. In such iteration(s) of the CSA, information at any point of the assessment cycle can be re-assessed and modified if needed. The CSA process can be refined in any number of

iterations, until risks are shown to be controlled. Such iterations must be realistic to the extent that the recommended operational conditions and RMMs can be implemented in practice.

For substances where it is not possible to derive a DNEL or DMEL there are additional issues that can be considered with respect to RMMs/OCs. The concentration in which a corrosive or irritant substance is used is one such issue. As already noted above, use of dilutions of corrosive or irritant substances in mixtures may lower the risk for these endpoints. In such cases, it should be verified whether the risk characterisation might be driven by other endpoints. Although there are generic classification concentration limits for irritation and corrosion, these do not automatically represent safe levels for these effects nor for other effects caused by the substance.

4. **Conduct an exposure estimation/assessment according to Part D of the Guidance Document**

   For these substances special emphasis should be placed on the likelihood of contact of the substance with the skin, eyes and respiratory tract, including frequency and intensity. This may involve detailed assessment/description of exposure events and types of emission/releases from a process. The possibility of peak exposures should be covered, especially when the risks caused by sensitizers and corrosives are assessed.

   It is recommended that the higher the hazard of a substance, the more detailed the assessment of exposure should be. This is because a more detailed assessment will be needed for the identification and justification of RMMs and OCs that are needed to control actual exposure or contact with e.g. strong sensitizers or strong corrosives.

   In some cases the physical properties of a substance would determine that the exposure is minimal or that certain routes of exposure are very unlikely. For example, if the vapour pressure of a liquid is very low, and aerosol generation and extra heat can be excluded, the inhalation exposure will be minimal and for that substance there is unlikely to be need of local ventilation or respirator use.

5. **Qualitatively characterise risks and iterate assessment if needed**

   The outcome of the previous step should give a feel for the degree of exposure and likelihood of contact. This information should be used to qualitatively judge whether the initial exposure scenario is likely to reduce exposure in a way that effects are avoided.

   If yes, these considerations should be documented in the chemical safety report and the initial ES becomes the final ES.

   If not, the assessment and exposure scenario should be iterated, consideration should be given to whether or not the operational conditions or RMMs can be adjusted. Once the ES has been adjusted a new exposure assessment is conducted (Step 4). Iterations are continued until it is concluded that implementation of the derived exposure scenario is likely to reduce exposure in a way that effects are avoided.

E.3.4.4 Use the principles in Table E.3-1 to adjust the RMMs/OCs on iteration

As noted above, the level of control (and therefore implemented and recommended RMMs and OCs) should be higher the more hazardous the substance. As the RMMs/OCs recommended in this section are fairly generic, it should be realised that the concrete measures at the workplace generally have to be adapted to the local conditions and the ES under REACH is only a starting point for risk assessment under Directive 98/24/EC.

The table reflects the following general observations:

6. It needs to be emphasised that technical measures, such as closed systems, control of releases, and local ventilation are the primary RMMs to be used in controlling exposure. The use of PPE in the working environment should be seen as last resort when deciding on control measures and should only be used when all other options have been exhausted;
7. All of the recommended RMMs/OCs associated with a specific hazard band should be considered in developing the exposure scenarios for the manufacture and the identified uses of the substance through the supply chain. As the RMMs/OCs recommended in this section are fairly generic, these may have to be adapted to the specific exposure scenarios.
8. For substances categorised as having a **high** hazard profile (i.e. in CLP: category 1A and 1B carcinogens potent category 2 carcinogens, category 1A, 1B and 2 mutagens, very (acutely) toxic substances classified in Category 1 or 2, strong corrosives (Category 1A), extreme/strong skin sensitizers and respiratory sensitizers), a very high level of containment, automatic dosing/feeding to the process, and appropriate PPE are recommended in **occupational** settings (see Table E.3-1) in order to avoid exposure;
9. For substances in the **moderate** hazard band (i.e., category 2 carcinogens[20], acutely toxic substances (Category 3), corrosives, strong irritants and moderate sensitizers), the suggested general risk management measures are less strict. This implies that for example, very high levels of containment or automatic loading/feeding would not be the default RMMs, but good standard of general ventilation, minimisation of manual phases, segregation of the emitting process, minimising number of staff exposed and containment as appropriate should be considered/applied. It is emphasised that before the risk management measures are selected, risk characterisation should take place, to relate exposure and the hazard properties. For example, a frequent and high exposure to a moderate sensitizer would require efficient risk management measures, whereas infrequent use of very low volumes of a rather hazardous but non-volatile substance may trigger less stringent risk management;
10. For substances in the **low** hazard band (i.e. moderate irritants), the suggested general risk management measures are less stringent; they include minimisation of manual work, use of work procedures that minimise splashes and spills and avoidance of contact.
11. For all hazard bands, the appropriateness of the RMMs/OCs should be demonstrated (see Part D), not only to control the risk for the 'qualitative' endpoint in question, but also that of the 'quantitative' endpoints, should they be more critical.
12. Risk management measures for corrosive or sensitising substances in **consumer mixtures** are limited. Since the actual implementation of technical controls and PPE is usually difficult to achieve in practice, product-integrated measures (such as the maximum volume of the bottle, high viscosity of the product, child resistant fastening) are often the only appropriate RMMs. Placing on the market of such mixtures should in general be discouraged. There may, however, be cases where the mixture can be safely diluted before use and potential contact with the skin or the eyes avoided (e.g. strong alkaline as toilet cleaners). Diluted mixtures, child-resistant fastenings and product formulation, which prevent splashes (e.g. viscous or paste-like formulation of the oxidative hair bleaching products) as well as labelling and use instructions are commonly recognised RMMs for consumer products (See Section R.13.2.3).

[20] Category 2 carcinogens according to CLP.

13. Concerning the exposure of **"humans via the environment"** no risk management measures are normally needed for irritant, corrosive and moderate skin sensitising substances, because when the substances are released to the environment they are diluted and the risk is thereby efficiently reduced;
14. The persistency and liability to bioaccumulation has to be taken into account when assessing the exposure via the environment and defining the necessary risk management measures and operational conditions for handling of carcinogens.

The prevention of the "human via the environment" exposure to acutely toxic substances and strong sensitizers should be based on a case by case assessment.

All RMMs and OCs identified above should be documented in the final ES in the CSR and communicated as Annex to the SDS.

Table E.3-1 Hazard bands of systemic and local effects, suggestions for general risk management measures and operational conditions (RMMs/OCs) and PPE to be considered when developing exposure scenarios #

Note that these hazard bands only apply when no DNEL or DMEL can be set.

Category of danger/Type of effect/ Risk phrase (DSD)	R phrase code	Type of effect/ hazard statement (CLP)	Hazard statement code	Exposure route	Risk Management Measures and Operational Conditions	
					General	PPE
HIGH HAZARD						
Carcinogens Category 1 and 2		**Carcinogenicity Category 1A and Category 1B**			- Any measure to eliminate exposure should be considered; - Very high level of containment required, except for short term exposures e.g. taking samples; - Design closed system to allow for easy maintenance; - If possible keep equipment under negative pressure; - Control staff entry to work area; - Ensure all equipment well maintained; - Permit to work for maintenance work; - Regular cleaning of equipment and work area; - Management/supervision in place to check that the	- Substance/task appropriate respirator; - Substance/task appropriate gloves; - Full skin coverage with appropriate barrier material; - Chemical goggles.
May cause cancer	R45	May cause cancer	H350	Inhalation, oral, dermal		
May cause cancer by inhalation	R49	May cause cancer by inhalation	H350i	Inhalation		
Mutagens Category 1 and 2		**Germ cell mutagenicity Category 1A and 1B**				
May cause heritable genetic damage	R46	May cause genetic defects	H340	Inhalation, oral, dermal		
Mutagens Category. 3*		**Germ cell mutagenicity Category 2***				
Possible risk of irreversible effects	R68	Suspected of causing genetic defects	H341	Inhalation, dermal, oral		
Strong corrosive		**Skin corrosion Category 1A**				- Face shield; - Substance/task appropriate gloves; - Full skin coverage with appropriate barrier material; - Chemical goggles.
Causes severe burns	R35	Causes severe skin burns and eye damage	H314	Inhalation, dermal, oral		
Acute toxicity		**Acute toxicity Category1 and**				- Substance/task appropriate respirator;

		Category 2			RMMs in place are being used correctly and OCs followed; - Training for staff on good practice; - Procedures and training for emergency decontamination and disposal; - Good standard of personal hygiene - Recording of any 'near miss' situations - Sensitizers - Without prejudice to relevant national legislation, pre-employment screening and appropriate health surveillance	- Substance/task appropriate gloves; - Full skin coverage with appropriate barrier material; - Chemical goggles.
Very toxic	R26	Fatal if inhaled	H330	Inhalation		
Very toxic	R27	Fatal in contact with skin	H310	Dermal		
Very toxic	R28	Fatal if swallowed	H300	Oral		
Extreme/strong skin sensitizer* **		**Skin sensitization Category 1 or 1A*** **				- All skin and mucous membranes with potential exposure protected with appropriate PPE
May cause sensitisation by skin contact	R43	May cause an allergic skin reaction	H317	Dermal		
Respiratory sensitizer		**Respiratory sensitization Category 1, 1A or 1B**				- Appropriate respirator mandatory unless complete containment is verified for all phases of the operation;
May cause sensitization by inhalation	R42	May cause allergy or asthma symptoms or breathing difficulties if inhaled	H334	Inhalation		
Very serious irreversible effects-single exposure		**Specific Target Organ Toxicity-Single Exposure Category 1**				- Substance/task appropriate respirator; - Substance/task appropriate gloves; - Full skin coverage with appropriate barrier material; - Chemical goggles
Very toxic: danger of very serious irreversible effects through inhalation	R39/26	Causes damage to organs	H370	Inhalation		
Very toxic: danger of very serious irreversible effects in contact with skin	R39/27	Causes damage to organs	H370	Dermal		
Very toxic: danger of very serious irreversible effects if swallowed	R39/28	Causes damage to organs	H370	Oral		
Toxic: danger of	R39/23	Causes damage to	H370	Inhalation		

very serious irreversible effects through inhalation		organs				
Toxic: danger of very serious irreversible effects in contact with skin	R39/24	Causes damage to organs	H370	Dermal		
Toxic danger of very serious irreversible effects if swallowed	R39/25	Causes damage to organs	H370	Oral		
MODERATE HAZARD						
Carcinogens Category3**		**Carcinogenicity Category 2****			- Containment as appropriate; - Minimise number of staff exposed; - Segregation of the emitting process; - Effective contaminant extraction; - Good standard of general ventilation; - Minimisation of manual phases; - Avoidance of contact with contaminated tools and objects; - Regular cleaning of equipment and work area; - Management/supervision in place to check that the RMMs in place are being used correctly and OCs followed; - Training for staff on good practice; - Good standard of personal	- Substance/task appropriate gloves; - Skin coverage with appropriate barrier material based on potential for contact with the chemicals; - Substance/task appropriate respirator; - Optional face shield; - Eye protection.
Limited evidence of carcinogenicity	R40	Suspected of causing cancer	H351	Inhalation, dermal, oral		
Corrosive		**Corrosivity Category 1B and Category 1C**				
Causes burns	R34	Causes severe skin burns and eye damage	H314	Inhalation, dermal, oral		
Acute toxicity		**Acute toxicity Category 3**				
Toxic	R23	Toxic if inhaled	H331	Inhalation		
Toxic	R24	Toxic in contact with skin	H311	dermal		
Toxic	R25	Toxic if swallowed	H301	oral		
Possible risk of irreversible effects-single exposure		**Specific Target Organ Toxicity-Single Exposure Category 2**				
Harmful: possible risk of irreversible effects through inhalation	R68/20	May cause damage to organs	H371	Inhalation		

Harmful: possible risk of irreversible effects in contact with skin	R68/21	May cause damage to organs	H371	dermal	hygiene.	
Harmful: possible risk of irreversible effects if swallowed	R68/22	May cause damage to organs	H371	Oral		
Irritants		**Eye and skin irritation Category 2 and Specific Target Organ Toxicity-Single Exposure Category 3 (respiratory irritation)******				
to the eyes, skin and respiratory system simultaneously	R36/37/38	Causes serious eye irritation May cause respiratory irritation Causes skin irritation	H319 H335 and H315	Eyes, inhalation, dermal		
Moderate skin sensitizer***		**Skin sensitization category 1B*****				
May cause sensitisation by skin contact	R43	May cause an allergic skin reaction	H317	Dermal		
Eye damage		**Eye damage Category 1**				- Chemical goggles
Risk of serious damage to eyes	R41	Causes serious eye damage	H318	Eyes		
LOW HAZARD						
Eye Irritant		**Eye irritation Category 2**			- Minimisation of manual phases/work tasks,	- Chemical goggles
Irritating to the eyes	R36	Causes serious eye irritation	H319	Eyes	- Work procedures minimising of splashes and spills;	

Skin Irritant		**Skin irritation Category 2**			- Avoidance of contact with contaminated tools and objects; - Regular cleaning of equipment and work area; - Management/supervision in place to check that the RMMs in place are being used correctly and OCs followed; - Training for staff on good practice. - Good standard of personal hygiene.	- Face shield; - Substance/task appropriate gloves; - Full skin coverage with appropriate light-weight barrier material.
Irritating to skin	R38	Causes skin irritation	H315	Dermal		
Irritant to the respiratory system		**STOT SE 3**				- Substance/task appropriate respirator
Irritating to the respiratory system	R37	May cause respiratory irritation	H335	Inhalation		

DISCLAIMER: the general RMMs/OCs and PPE mentioned are suggestions only. The appropriateness of the RMMs/OCs used should always be demonstrated. Also, the exposure estimate resulting from the incorporation of these RMMs/OCs into the exposure scenario should be compared with the critical DNEL or DMEL for the quantitative endpoints, in order to demonstrate control of risks for these effects as well, in case they are more critical than the qualitative endpoint under discussion. ECHA's practical guide 15 on "How to undertake a qualitative human health assessment and document it in a chemical safety report" complements this guidance giving refined methodologies to perform a qualitative risk assessment and practical examples.

***** Category 2 mutagens according to CLP (Category 3 mutagens according to DSD) are in principle allocated to the high hazard band on the basis that they are usually considered as suspected germ cell mutagens (suspected Muta. 1B according to CLP/Muta. Cat. 2 in DSD) and treated as suspected genotoxic carcinogens (suspected Carc. 1B according to CLP/ Carc. 2 according to DSD). However, when it is shown in the assessment of the toxicokinetic behaviour that the substance does not reach the germ cells and shown in a carcinogenicity study that the substance does not cause cancer (locally or systemically), the category 2 mutagen (Muta. 3 according to DSD) can be assigned to the moderate hazard band.

****** Non-genotoxic carcinogens which are classified in Category 2, CLP (Carc.3 according to DSD) are in principle allocated to the moderate hazard band, because they are regarded to represent a lower concern than Category 1A and 1B carcinogens (Carc. 1 and Carc. 2 in DSD) as there may be only limited evidence of carcinogenicity based on human or animal data. On the other hand, if the mode of action or carcinogenic potency remains unclear, then these Category 2 carcinogens (Cat.3 according to DSD) could be assigned to the high hazard band, on a case by case basis.

******* For skin sensitisation, potency categorisation based on human data as well as on LLNA, Guinea pig maximisation test and the Buehler test, include categorisation into strong and other sensitisers (in Category 1A or 1B, respectively) in CLP. Strong sensitisers may be further divided into extreme and strong sensitisers - for the purpose of setting specific concentration limits - as outlined in section 3.4.2.3 in Guidance on the Application of the CLP Criteria (see also Appendix R.8-10)

******** Only if the 3 hazard statements are attributed to the substance simultaneously, "moderate hazard" is assigned, otherwise "low hazard" is assumed.

E.3.5 Step 5: combined exposures

In situations where the same person is potentially exposed to the same substance in the same setting via different routes of entry into the body or from different products containing the same substance, exposure scenarios reflecting these concomitant exposures should be assessed in the exposure estimation. These scenarios – typically related to workplaces and aggregated exposure for consumers – need specific attention in the risk characterisation step (see Section E.3.5.1).

In addition, humans are exposed at work, from consumer products and via environmental exposures. It should be considered in which cases it is relevant to make risk characterisation for such scenarios, representing exposure from all sources. Typically it is most relevant to combine consumer exposures with indirect exposure of humans via the environment.

In special cases, where exposure occurs to a substance as well as to several very closely related and similar acting chemical substances (e.g. different salts of a metal or closely related derivatives of organic substances), the exposure evaluation and risk characterisation should reflect this aspect. If data are available the exposure assessment should also include a scenario concerning this combined exposure. One way to conduct risk characterisation for combined exposure to closely related analogues could be to add exposures and to use a toxicological descriptor from a representative substance among the analogues. If data do not allow for a quantitative assessment, an attempt should be made to address the issue in a qualitative way.

E.3.5.1 Risk characterisation in case of exposure via various routes

All human populations (workers, consumers, humans indirectly exposed via the environment) may be concurrently exposed to a specific substance via different routes of exposure. Route-specific exposure specifically contributes to the total internal body burden. Thus, concurrent exposure via various routes of exposure needs to be accounted for when characterising overall systemic health risks.

It is recommended to perform human health risk characterisation in case of exposure via various routes in a two-step procedure. For this two-step procedure it is favourable to express exposure levels and route-specific DNELs (if needed, established via route-to-route extrapolation) as external values (e.g. in mg/m³ for inhalation). In the first step route-specific risks should be dealt with separately; risk managers should concentrate on those route-specific risk management measures relevant for the route of exposure with the highest risk characterisation ratio (RCR).

By the time all route-specific health risks are controlled (all route-specific exposures are lower than the corresponding route-specific DNELs) the remaining health consequences due to concurrent exposure via the various routes have to be considered. This is especially needed in cases where the RCR for each separate route is slightly below one (i.e., control of risks), but is likely to exceed one if adding exposure via the different routes. Assuming an identical toxicological profile for the various routes of exposure (e.g. liver toxicity is the key event for the various routes of exposure) the overall risk is calculated according to the following formula:

RCR (for simultaneous exposure via three routes) = RCR (oral) + RCR (dermal) + RCR (inhalation)

The calculation has to be performed for chronic effects, and if relevant, separately for acute effects. Separate calculations are performed for the different populations (workers and the general population). The overall health risk to humans in case of exposure via various routes

can only be considered controlled if the overall risk characterisation ratio (the total RCR for the specified routes in parallel) is less than the reference value of 1.

For most substances, there will only be toxicity data from one exposure route, and DNELs for the other routes have to be generated by means of route-to-route extrapolation (see Section R.8.4.2). Since there will not be toxicity data for all routes, a conservative but relevant assumption (considering the lack of data for some routes) is that there will be similar target organs for all routes of exposure. The formula above should thus be used.

In some cases, substances may have toxicity data showing similar target organs for all routes of exposure, and the formula above should, of course, be used. If the data shows different main target organs or target effects (for which the DNELs are based on; e.g., liver for one route and kidney for the second), but that the overall toxicity profile contains the same organs (liver and kidney being affected by both routes), the recommended formula might not fully represent the true situation. However, it is recommended to use the unmodified formula as a default, conservative approach even in case of differing main route-specific organ toxicity, but to additionally express the corresponding uncertainty in a qualitative manner (e.g., by comparing NOAEL for second route liver and kidney toxicity). As an example, if the liver toxicity is the most critical adverse effect by the oral route and has a NOAEL of 10 mg/kg/day, and for dermal exposure there is a NOAEL for kidney toxicity of 20 mg/kg/day and there is a NOAEL for liver toxicity only slightly higher, e.g., 40 mg/kg/day, the formula (by using the oral NOAEL of 10 and the dermal NOAEL of 20 mg/kg/day) will be reasonably accurate. However, the bigger the difference is in the ratio of NOAEL for second route kidney and liver toxicity, the more conservative the formula will be.

In very rare cases, studies may demonstrate completely different target organs after exposure through different routes, and in those cases the addition of route-specific RCRs seems not relevant and the formula above should not be used.

The quality of the proposed procedure for risk characterisation in case of exposure via various routes critically depends both on the reliability of the route-specific exposure assessments and the route-specific derivation of DNELs. For some specific substances available toxicological knowledge for humans does allow for an integrated risk assessment based on biomonitoring data (see Appendix R.8-5 for examples). The use of biomonitoring is, however, not always straight forward. Potential issues concerning biomonitoring includes, e.g.;

15. that there are no matching effect data to compare the biomonitoring data with,
16. ethical (and in some cases legal) considerations when sampling from humans, and it especially relates to blood sampling (urine and breath sampling is generally easier and is preferred over blood sampling),
17. that it may be resource-intensive. This applies both to validating the science behind the biomonitoring and for the technical conduct of the biomonitoring.

Still, if biomarkers of exposure can be reliably measured and if reliable information on the biomarker-response relationship is available, the assessment of the integrated risk for various routes of exposure is considered more valid and more predictive based on biomonitoring data than on the approach via the route-specific risk characterisation ratios. But even in this data-rich situation knowledge on the relative route-specific contribution of exposure to the overall risk is considered helpful in order to inform risk managers to concentrate on the most effective route-specific risk management measures.

Additionally, in each case the applicant has to assess the need for an assessment of combined exposure, i.e., exposure from different uses of a substance. Normally, occupational exposure will greatly exceed all other exposure, and the contribution from consumer use or from exposure via the environment may not need to be added. However, for substances with

consumer use, and which may be present in potential food items (as indicated by the EUSES-modelling), the combined exposure may need to be assessed for the general public exposed both via the food and via consumer products. Also for this case, the formula above can be used.

E.4 Risk characterisation for the environment (steps 1-5)

E.4.1 General aspects

Having conducted the hazard assessment for all environmental compartments (Part B, Chapter R.10) and the exposure assessment (Chapter R.16) either a quantitative or a qualitative risk characterisation is carried out.

The quantitative risk characterisation is carried out by comparing the PEC with the PNEC. This is done separately for each of the following environmental protection targets:

Inland environmental protection targets:

18. aquatic ecosystem;
19. terrestrial ecosystem;
20. atmosphere;
21. predators (fish- and worm-eating);

- micro-organisms in sewage treatment plants (STPs)

Marine environmental protection targets:

22. aquatic ecosystem;
23. predators and top predators.

Risk characterisation of particular effects not covered by the other protection targets, e.g. ozone depletion, photochemical ozone creation potential (c.f. Annex 1 (0.10)), shall be done on a case-by-case basis and this should be documented and justified in the CSR.

The risk characterisation for the environment is based on the tonnage relevant for the registration or the evaluation of a substance. The risk is characterised on two spatial scales:

- The regional scale, accounting for overall emissions into a region.
- The local scale, accounting for local emission and the regional background concentration which is added to this.

Depending on the tonnage that is relevant for a specific CSA, the contribution of a substance to the regional background can range between insignificant and significant. Because this contribution depends on other factors as well, e.g. identified uses and substance properties), it always needs to be calculated and assessed, both individually and as part of the local risk characterisation. See Chapter R.16 for elaboration on the spatial scales in the environmental exposure estimation.

E.4.2 Step 1 and 2: collect hazard and exposure information

The effect values are expressed as the predicted no effect concentrations, the PNECs, which are derived for all relevant environmental compartments. The derivation of the PNECs is described in Part B and Chapter R.10. The environmental exposure is expressed as environmental concentrations, i.e. the PECs. The derivation of the PECs for the relevant environmental compartments is described in Chapter R.16.

E.4.3 Step 3: Calculate the risk characterisation ratios

A list of the different PEC/PNEC ratios that should be considered for the inland and marine environments is given in Table E.4-1 and Table E.4-2, respectively.

Table E.4-1 Overview of PEC/PNEC ratios considered for inland risk assessment *

Local	Regional
Water: $PEClocal_{water}/PNEC_{water}$	Water: $PECregional_{water}/PNEC_{water}$
Sediment: $PEClocal_{sediment}/PNEC_{sediment}$	Sediment: $PECregional_{sediment}/PNECs_{ediment}$
Soil: $PEClocal_{soil}/PNEC_{soil}$	Soil: $PECregional_{agr.soil}/PNEC_{soil}$
RMicroorganisms: $PEC_{stp}/PNEC_{microorganisms}$	
Predators, fish eating $(0.5 \cdot PEClocal,oral_{fish} + 0.5 \cdot PECregional,oral_{fish})/PNECoral$	
Predators, worm-eating $(0.5 \cdot PEClocal,oral_{worm} + 0.5 \cdot PECregional,oral_{worm})/PNECoral$	

*These ratios are derived for all stages of the life-cycle of a compound. The regional risk characterisation for each compartment is based on the sum of regional PNECs for all life-cycle stages. The PEC-local for each life-cycle stage and compartment is based on the sum of the local concentration and the PEC-regional (sum).

Table E.4-2 Overview of PEC/PNEC ratios considered for marine risk assessment *

Local	Regional
Water: $PEClocal_{seawater}/PNEC_{saltwater}$	Water: $PECregional_{seawater}/PNEC_{saltwater}$
Sediment: $PEClocal_{sediment}/PNEC_{marine\ sediment}$	Sediment: $PECregional_{sediment}/PNEC_{marine\ sediment}$
Predators $[(PEClocal_{seawater,ann} + PECregional_{seawater}) \cdot 0.5 \cdot BCF_{fish} \cdot BMF_1]/PNECoral_{predator}$	
Top predators $[(0.1 \cdot PEClocal_{seawater,ann} + 0.9 \cdot PECregional_{seawater}) \cdot BCF_{fish} \cdot BMF_1 \cdot BMF_2]/PNECoral_{top\ predator}$	

* These ratios are derived for all stages of the life-cycle of a compound. The regional risk characterisation for each compartment is based on the sum of regional RCRs for all life-cycle stages. The PEC-local is based on the sum of the local concentration and the PEC-regional

(sum).

For the air compartment usually only a qualitative assessment of abiotic effects is carried out. If there are indications that one or more of these abiotic effects occur for a given substance, expert knowledge should be consulted or the substance be handed over to the relevant international group, e.g. to the responsible body in the United Nations Environment Programme (UNEP) for ozone depleting substances. In some cases also an assessment of the biotic effects to plants can be carried out.

If a refinement of the risk characterisation is possible but the necessary data are not available, further information and/or testing may be required. A decision must be taken as to whether both the PEC and PNEC will be iterated or only one of them. If additional information needs to be generated, it should be based on the principles of lowest cost and effort, highest gain of information and the avoidance of unnecessary testing on animals.

E.4.3.1 Aquatic environment

The concentration of the chemical in surface water is compared to the no-effect concentration for aquatic organisms. This is done for the local as well as the regional freshwater and marine environment. On the local scale, the concentration during an emission episode is taken. It should be noted that the local ratios have to be defined for all relevant stages of the life cycle and for each application of the substance.

Equation E- 2

$$RCRlocal_{water} = \frac{PEClocal_{water}}{PNEC_{water}}$$

Equation E- 3

$$RCRlocal_{water,marine} = \frac{PEClocal_{water}}{PNEC_{water,marine}}$$

Equation E- 4

$$RCRreg_{water} = \frac{PECreg_{water}}{PNEC_{water}}$$

Equation E- 5

$$RCRreg_{water} = \frac{PECreg_{water}}{PNEC_{water}}$$

Input

$PEClocal_{water}$	local PEC in surface water during emission episode	[$kg_c.m^{-3}$]
$PECreg_{water}$	regional steady-state PEC in surface water	[$kg_c.m^{-3}$]
$PEClocal_{water,marine}$	local PEC in marine water during emission episode	[$kg_c.m^{-3}$]
$PECreg_{water,marine}$	regional steady-state PEC in marine surface water	[$kg_c.m^{-3}$]
$PNEC_{water}$	PNEC for aquatic compartment	[$kg_c.m^{-3}$]
$PNEC_{water,marine}$	PNEC for marine aquatic compartment	[$kg_c.m^{-3}$]

Output

$RCRlocal_{water}$	RCR for local water compartment	[-]
$RCRreg_{water}$	RCR for regional water compartment	[-]
$RCRlocal_{water,marine}$	RCR for local marine water compartment	[-]
$RCRreg_{water,marine}$	RCR for regional marine water compartment	[-]

E.4.3.2 Terrestrial compartment

The concentration of the chemical in agricultural soil is compared to the no-effect concentration for terrestrial organisms. This is done for the local as well as the regional environment. On the local scale, the concentration averaged over 30 days is used. It should be noted that the local ratios have to be defined for all relevant stages of the life cycle and for each application of the substance. For substances with a log *Kow* greater than 5, the equilibrium-partitioning method is used in a modified way. For these substances, the PEC/PNEC in soil is increased by a factor of 10 to account for uptake via ingestion of soil.

Equation E-6

$$RCRlocal_{soil} = \frac{PEClocal_{soil}}{PNEC_{soil}}$$

Equation E-7

$$RCRreg_{soil} = \frac{PECreg_{agric}}{PNEC_{soil}}$$

If EP*terr* = yes and log *Kow*> 5 then

Equation E-8

$$RCRlocal_{soil} = \frac{PEClocal_{soil}}{PNEC_{soil}} \cdot 10$$

If EP*terr* = yes and log *Kow*> 5 then

Equation E-9

$$RCRreg_{soil} = \frac{PECreg_{agric}}{PNEC_{soil}} \cdot 10$$

Input

$PEClocal_{soil}$	local PEC in agricultural soil, averaged over 30 days	[$kg_c.kg_{wwt}^{-1}$]
$PECreg_{agric}$	regional steady-state PEC in agricultural soil	[$kg_c.kg_{wwt}^{-1}$]
$PNEC_{soil}$	PNEC for soil compartment	[$kg_c.kg_{wwt}^{-1}$]
EPterr	equilibrium partitioning used for PNEC?	[yes/no]
Kow	octanol-water partition coefficient	[$m^3.m^{-3}$]

Output

$RCRlocal_{soil}$	RCR for local soil compartment	[-]
$RCRreg_{soil}$	RCR for regional soil compartment	[-]

E.4.3.3 Sediment compartment

The concentration of the chemical in sediment is compared to the no-effect concentration for sediment-dwelling organisms. This is done for the local as well as the regional freshwater and marine environment. It should be noted that the local ratios have to be defined for all relevant stages of the life cycle and for each application of the substance. For substances with a log *Kow* greater than 5, the equilibrium-partitioning method is used in a modified way. For these substances, the PEC/PNEC in sediment is increased by a factor of 10 to account for uptake via ingestion of sediment. It should be noted that a risk characterisation for sediment is only feasible if measured data are used to overwrite the estimates for PEC and/or PNEC in sediment (otherwise, equilibrium partitioning is applied to derive both PEC and PNEC).

Equation E-10

$$RCRlocal_{sed} = \frac{PEClocal_{sed}}{PNEC_{sed}}$$

Equation E-11

$$RCRlocal_{sed,marine} = \frac{PEClocal_{sed,marine}}{PNEC_{sed,marine}}$$

Equation E-12

$$RCRreg_{sed} = \frac{PECreg_{sed}}{PNEC_{sed}}$$

Equation E-13

$$RCRreg_{sed,marine} = \frac{PECreg_{sed,marine}}{PNEC_{sed,marine}}$$

If EP*sed* = yes and log *Kow*> 5 then:

Equation E-14

$$RCRlocal_{sed} = \frac{PEClocal_{sed}}{PNEC_{sed}} \cdot 10$$

Equation E-15

$$RCRreg_{sed} = \frac{PECreg_{sed}}{PNEC_{sed}} \cdot 10$$

If EPsed_{marine} = yes and log *Kow*> 5 then:

Equation E-16

$$RCRlocal_{sed,marine} = \frac{PEClocal_{sed,marine}}{PNEC_{sed,marine}} \cdot 10$$

Equation E-17

$$RCRreg_{sed,marine} = \frac{PECreg_{sed,marine}}{PNEC_{sed,marine}} \cdot 10$$

Input		
$PEClocal_{sed}$	local PEC in sediment	[$kg_c.kg_{wwt}^{-1}$]
$PEClocal_{sed,marine}$	local PEC in marine sediment	[$kg_c.kg_{wwt}^{-1}$]
$PECreg_{sed}$	regional steady-state PEC in sediment	[$kg_c.kg_{wwt}^{-1}$]
$PECreg_{sed,marine}$	regional steady-state PEC in marien sediment	[$kg_c.kg_{wwt}^{-1}$]
$PNEC_{sed}$	PNEC for the sediment compartment	[$kg_c.kg_{wwt}^{-1}$]
$PNEC_{sed,marine}$	PNEC for the marine sediment compartment	[$kg_c.kg_{wwt}^{-1}$]
EPsed	equilibrium partitioning used for PNEC for sediment?	[yes/no]
$EPsed_{marine}$	equilibrium partitioning used for PNEC for marine sediment?	[yes/no]
Kow	octanol-water partition coefficient	[$m^3.m^{-3}$]
Output		
$RCRlocal_{sed}$	RCR for local sediment compartment	[-]
$RCRlocal_{sed,marine}$	RCR for local marine sediment compartment	[-]
$RCRreg_{sed}$	RCR for regional sediment compartment	[-]
$RCRreg_{sed,marine}$	RCR for regional marine sediment compartment	[-]

E.4.3.4 Micro-organisms in STP

The concentration of the chemical in the sewage treatment plant is compared to the no-effect concentration for micro-organisms. This is done for the local environment only. The concentration during an emission episode is used. It should be noted that the ratios have to be defined for all relevant stages of the life cycle and for each application of the substance.

Equation E-18

$$RCR_{stp} = \frac{PEC_{stp}}{PNEC_{micro-organisms}}$$

Input		
PEC_{stp}	local PEC in STP during emission episode	[$kg_c.m^{-3}$]
$PNEC_{micro-organisms}$	PNEC for STP micro-organisms	[$kg_c.m^{-3}$]
Output		
RCR_{stp}	RCR for sewage treatment plant	[-]

E.4.3.5 Predators in freshwater and marine environment

The concentration of the chemical in fish and in fish-eating predators is compared to the no-effect concentration for birds and mammals. Local and regional concentrations are combined for calculating the concentration in fish and fish-eating predators. It should be noted that the ratios have to be defined for all relevant stages of the life cycle and for each application of the

substance.

Equation E-19

$$RCR_{oral,\ fish} = \frac{PEC_{oral,\ fish}}{PNEC_{oral}}$$

Equation E-20

$$RCR_{oral,\ fish,marine} = \frac{PEC_{oral,\ fish,marine}}{PNEC_{oral}}$$

Equation E-21

$$RCR_{oral,\ fish\ predator,marine} = \frac{PEC_{oral,\ fish\ predator,marine}}{PNEC_{oral}}$$

Input		
$PEC_{oral,fish}$	PEC in fish (local and regional combined)	[$kg_c.kg_{wwt}^{-1}$]
$PEC_{oral,fish,marine}$	PEC in marine fish (local and regional combined)	[$kg_c.kg_{wwt}^{-1}$]
$PEC_{oral,fishpredator,marine}$	PEC in marine fish-eating predator (local and regional combined)	[$kg_c.kg_{wwt}^{-1}$]
$PNEC_{oral}$	PNEC for birds and mammals	[$kg_c.kg_{wwt}^{-1}$]
Output		
$RCR_{oral,fish}$	RCR for fish-eating birds/mammals (freshwater environment)	[-]
$RCR_{oral,fish,marine}$	RCR for fish-eating birds/mammals (marine environment)	[-]
$RCR_{oral,fishpredator,marine}$	RCR for top-predators (marine environment)	[-]

E.4.3.6 Worm-eating predators

The concentration of the chemical in earthworms is compared to the no-effect concentration for birds and mammals. There is only one concentration in earthworms as local and regional are combined in this concentration. It should be noted that the ratios have to be defined for all relevant stages of the life cycle and for each application of the substance.

Equation E-22

$$RCR_{oral,worm} = \frac{PEC_{oral,worm}}{PNEC_{oral}}$$

Input		
$PEC_{oral,worm}$	PEC in worm (local and regional combined)	[$kg_c.kg_{wwt}^{-1}$]
$PNEC_{oral}$	PNEC for birds and mammals	[$kg_c.kg_{wwt}^{-1}$]
Output		
$RCR_{oral,worm}$	RCR for worm-eating birds and mammals	[-]

E.4.4 Step 4: conduct qualitative risk characterisation

When no quantitative risk characterisation can be carried out, for example for remote marine areas or when either PEC or PNEC cannot be properly derived, a qualitative risk characterisation should be conducted.

A human health hazard assessment or environmental hazard assessment in accordance with REACH, Annex I, and the estimation of the long-term exposure of humans and the environment (Annex I, Section 5) cannot be carried out with sufficient reliability for substances satisfying the PBT and vPvB criteria. This necessitates a separate PBT and vPvB assessment (Chapter R.11). For a qualitative assessment of risks for PBT and vPvB substances, the approach should be used as described in Section R.11.2.2.

For some substances it may not be possible to undertake a full quantitative risk assessment, using a $PEC_{water}/PNEC_{water}$ ratio because of the inability to calculate a $PNEC_{water}$. This can occur when no effects are observed in short-term tests. However, an absence of short-term toxicity does not necessarily mean that a substance has no long-term toxicity, particularly when it has low water solubility and/or high hydrophobicity. For such substances, the concentration in water (at the solubility limit) may not be sufficient to cause short-term effects because the time to reach a steady-state between the organism and the water is longer than the test duration.

For these substances, therefore, it is recommended to conduct a qualitative risk assessment in order to decide if further long-term testing is required. Such an assessment should take full account of the level of exposure (PEC_{local} or $PEC_{regional}$, as appropriate) as well as of the probability that long-term effects may occur despite the absence of short-term effects. Thus, especially for non-polar organic substances with a potential to bioaccumulate (log Kow> 3), the need for long-term testing is more compelling. For ionised substances or surfactants the determination of a trigger value on the basis of other physicochemical properties, e.g. K_d should be an indicator to consider long-term tests. Taking all this into account, long-term toxicity tests should be considered for substances with log Kow> 3 (or BCF > 100) and a PEC_{local} or $PEC_{regional}$> $1/100^{th}$ of the water solubility. When the $logK_{OW}$ is not a good indicator of bioconcentration, or where there are other indications of a potential to bioconcentrate (see Section R.7.10), a case-by-case assessment of the presumable long-term effects will be necessary.

E.4.5 Step 5: combined exposures

In special cases, where exposure occurs to a substance as well as to several very closely related and similar acting chemical substances (e.g. different salts of a metal or closely related derivatives of organic substances), the exposure evaluation and risk characterisation should reflect this aspect. If data are available the exposure assessment should also include a scenario concerning this combined exposure. If data do not allow for a quantitative assessment, the issue can be addressed in a qualitative way.

E.4.6 Step 6: Decide on possible iterations of the CSA

In this step, a decision should be made on possible iterations of the CSA, taking uncertainties in the assessment into account (see Chapter R.19). For populations and environmental spheres where control of risk cannot be demonstrated, iterations of the CSA for these parts may be needed. One or more of the following options are available:

24. Improve hazard information
25. Improve exposure information and/or consider to introduce sufficient RMMs
26. Conclude that it is not possible to demonstrate control of risk, and provide the necessary documentation that uses are advised against.

E.4.6.1 Uncertainty analysis

This phase of the (iterative) CSA, is the most logical place to consider the overall uncertainties that are noticed and recorded in the preceding phases of the CSA:

27. Both hazard and exposure assessment carry a degree of uncertainty that is integrated in the RCR
28. The uncertainty in the outcome of a CSA iteration is relevant information that can be used to decide if risks are controlled or that too much uncertainty is still associated with it which needs to be addressed in further iterations of the CSA

Quantifying uncertainty in the RCR may help in making more rational decisions on control of risks. It is therefore proposed to use uncertainty analysis (see Chapter R.19) to determine if the RCR is a robust estimate of (relative) risk. The advantage of an uncertainty analysis is that in principle, all available data contribute to the analysis and transparency and credibility are improved. Chapter R.19 provides a tiered assessment to focus on the main uncertainties.

E.4.7 Step 7: Finalise the CSA

The CSA can be finalised if the risk characterisation demonstrates that risks are controlled/risks are controlled to a level of very low concern for all relevant combinations of population/route/exposure pattern or if it is concluded that it is not possible to demonstrate control of risk for some identified use or uses.

EUROPEAN CHEMICALS AGENCY
ANNANKATU 18, P.O. BOX 400,
FI-00121 HELSINKI, FINLAND
ECHA.EUROPA.EU