Guidance on information requirements and chemical safety assessment

Part B: Hazard Assessment

Draft new chapter B.8
Scope of Exposure Assessment

… 2010

Draft Version 2

LEGAL NOTICE

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

PREFACE

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

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

The guidance documents were drafted and discussed within the REACH Implementation Projects (RIPs) led by the European Commission services, involving stakeholders from Member States, industry and non-governmental organisations. After acceptance by the Member States Competent Authorities the guidance documents had been handed over to ECHA for publication and further maintenance. Any updates of the guidance are drafted by ECHA and are then subject to a consultation procedure, involving stakeholders from Member States, industry and non-governmental organisations. For details of the consultation procedure, please see:
http://echa.europa.eu/doc/FINAL_MB_30_2007_Consultation_procedure_on_guidance.pdf

The guidance documents can be obtained via the website of the European Chemicals Agency (http://echa.europa.eu/reach_en.asp). Further guidance documents will be published on this website when they are finalised or updated.

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

1 Corrigendum to Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC (OJ L 396, 30.12.2006); amended by Council Regulation (EC) No 1354/2007 of 15 November 2007 adapting Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) by reason of the accession of Bulgaria and Romania (OJ L 304, 22.11.2007, p. 1).

Convention for citing the REACH regulation

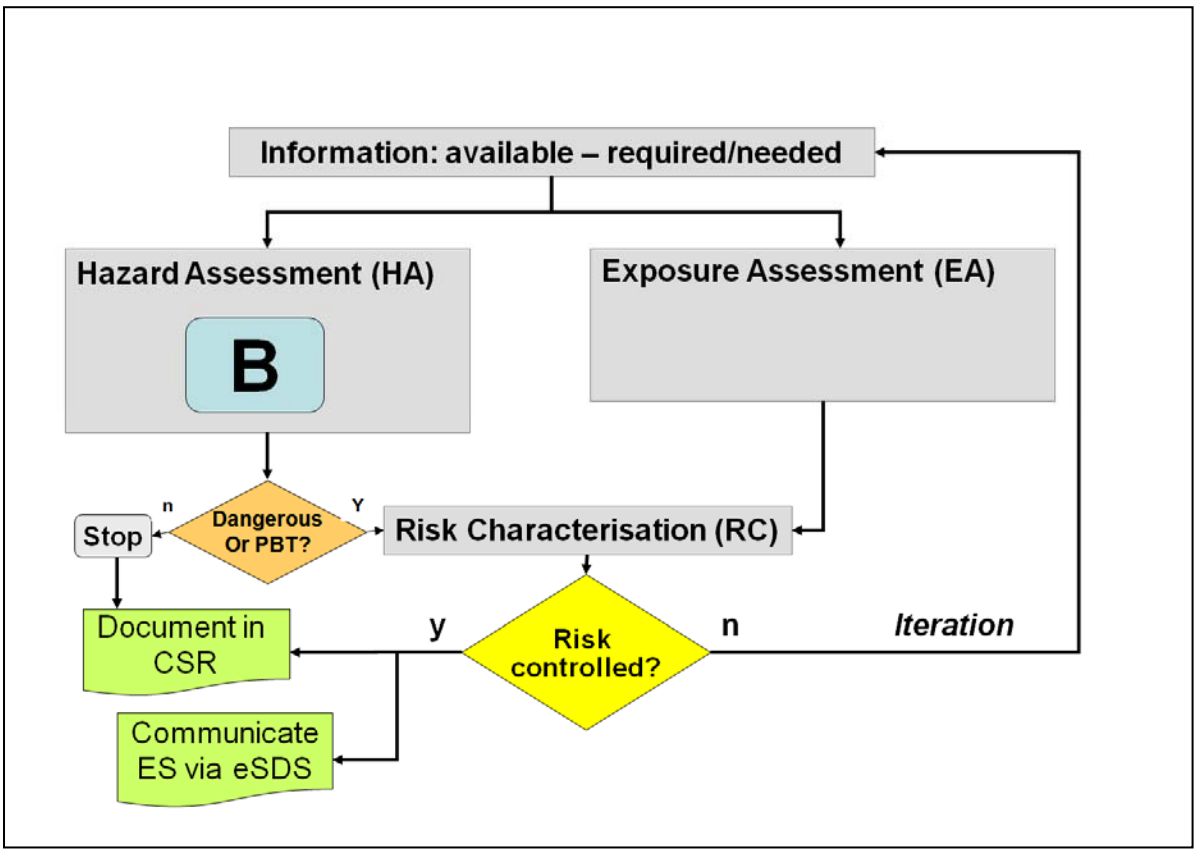
Where the REACH regulation is cited literally, this is indicated by text in italics between quotes.

Table of Terms and Abbreviations

See Chapter R.20

Pathfinder

The figure below indicates the location of Chapter R.4 within the Guidance Document



CONTENTS

B.8 SCOPE OF EXPOSURE ASSESSMENT

B.8.1 Background and General Principles

Article 14(1) of REACH requires that an exposure assessment and a subsequent risk characterisation be carried out for substances manufactured or imported in a quantity equal to or greater than 10 tonnes/year and meeting the criteria for being classified as dangerous under Directive 67/548/EEC (from 1 December 2010, replaced by the criteria for the hazard classes and/or categories specified in Article 58(1)[2] of Regulation (EC) No 1272/2008) or the PBT/vPvB criteria according to Annex XIII to REACH.

REACH further specifies in Annex I that an exposure assessment shall consider all stages of the life-cycle of the substance resulting from the substance's manufacture and its identified uses and shall cover any exposures that may relate to the **identified hazards** during the performed hazard assessment.

REACH requires carrying out an exposure assessment as soon as a substance is classified for at least one physicochemical, toxicological or environmental hazard or is identified as being PBT or vPvB. This means that performing an exposure assessment according to Annex I has also to be considered when the substance is classified for one type of hazard only (e.g. toxicological properties) but not for another type of hazard (e.g. environmental effects) and *vice versa*. In such cases, the registrant should also consider the non classifiable[3] hazards and the corresponding need for exposure assessment and risk characterisation.

Examples illustrating such cases include the following cases:

- No classification criteria are defined for a certain type of hazard (e.g. hazards related to terrestrial ecosystems), nevertheless it may be concluded that there is a risk at a certain level of exposure in the terrestrial system; or
- Classification criteria are defined, but based on relevant available hazard information it is concluded that these are not fulfilled; nevertheless the substance may cause adverse effects in the organism if a certain exposure level is exceeded; or
- Classification criteria are defined, but no relevant data are available allowing a comparison with the criteria (e.g. due to data waiving).

Thus, "no-classification" in a certain type of hazard does not mean that there is no hazard (and subsequently no risk). Consequently, the scope of exposure assessment is not limited to classified endpoints only but has to cover the full scope of exposure assessment laid down in Annex I to REACH.

After the hazard assessment process, however, a registrant will have to decide whether or not the available data suggest that there is no hazard potentially requiring control of risk, with regard to certain categories of toxicological effects or protection targets. Based on this conclusion, certain parts in the exposure assessment according to Annex I may not need to be performed.

[2] Article 58(1) of Regulation (EC) No 1272/2008 refers to the following hazard classes or categories set out in the relevant parts of its Annex I: hazard classes 2.1 to 2.4, 2.6 and 2.7, 2.8 types A and B, 2.9, 2.10, 2.12, 2.13 categories 1 and 2, 2.14 categories 1 and 2, 2.15 types A to F; 3.1 to 3.6, 3.7 adverse effects on sexual function and fertility or on development, 3.8 effects other than narcotic effects, 3.9 and 3.10; 4.1 and 5.1.

[3] Identified hazards not leading to a classification

The purpose of this document is to give guidance on how to identify situations where a registrant may conclude that for some routes, target groups and types of effect an exposure assessment is not needed.

- Regarding ecotoxicological properties, this decision is based on the application of selected hazard-based criteria as presented under section B.8.3.2. These criteria have been used before to identify substances for inclusion in Annex IV to REACH[4]. Such substances are considered to cause *minimal risk* due to their intrinsic properties, and thus control of risks under REACH is not needed. A selection of those criteria can in turn also be used for identifying hazards that may cause a risk which is higher than *minimal risk*, and for which an exposure assessment and a risk characterisation (following Annex I to REACH) would then be necessary. This means in practice that there is a need to define *minimal risk* based on intrinsic properties and to use these criteria to drive the scope of exposure assessment.

- For toxicological properties as described under section B.8.3.1 the decision making process on which exposure assessment needs to be performed for the different populations, types of effects and duration of exposure is based on the principles already described in Part E (Risk Characterisation) and Chapter R.8 (Dose [Concentration]-Response regarding Human Health) of the IR/CSA Guidance.

B.8.2 Scope of exposure assessment

The scope of exposure assessment is defined according to REACH as 'the assessment shall consider all stages of the life-cycle of the substance resulting from the manufacture and identified uses and shall cover ***any exposures that may relate to the hazards identified in section 1 to 4'*** (cf. section 5.0 of Annex I to REACH).

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

- The substance is not classified at all, in particular neither for physicochemical, human health or environmental hazards nor is it identified as PBT/vPvB substance; or
- The substance is classified for physicochemical, human health and the environment and/or is identified as being PBT/vPvB; or
- The substance is classified for physicochemical hazards only but not for human health or the environment and is not identified as PBT/vPvB substance; or
- The substance is classified either for human health but not for physicochemical and/or the environment and is not identified as PBT/vPvB substance, or *vice versa*.

This guidance will focus on the last scenario and provide support to registrants in their decision making process on the need to perform an exposure assessment according to Annex I. The guidance can also be applied for the third scenario.

[4] The whole set of these criteria is defined in a document by the Commission (Criteria for inclusion of substances in Annex IV of Regulation (EC) No 1907/2006 concerning Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)), which was endorsed by the REACH Competent Authorities on 19 October 2007, constituting a first step in the review of inclusion for deletion of substances from Annex IV.

B.8.3 Decision on the need to perform an exposure assessment

The registrant does not need to consider performing an exposure assessment and risk characterisation for human health and/or the environment as long as he can demonstrate that no hazard (potentially requiring control of risk) can be identified for either of these target groups. This can be demonstrated by comparison of available hazard information (i.e. dose descriptors, such as L(E)C_{50}, NOECs, absence of C&L for acute toxicity) with the criteria listed in sections B.8.3.1 and B.8.3.2, respectively. As a result of the comparison of the available hazard information[5] of a given substance with the criteria, it can be decided whether an exposure assessment for a specific target group, type of effect and duration of exposure and a subsequent risk characterisation according to Annex I to REACH is required. As soon as one criterion is not met for which effects data are available, an exposure assessment with focus on the risk driving endpoints has to be performed, taking into account any exposure that may relate to those hazard(s) identified.

B.8.3.1 Toxicological properties

Exposure assessment is necessary to derive exposure levels to compare with the qualitative or quantitative (DN(M)EL) hazard information for systemic and local effects that are observed in toxicity studies to cover short term and long term exposure.

The decision on whether to conduct an exposure assessment relating to human populations (workers and general population) should be based on available and relevant toxicological studies. Figure 1 presents in a schematic diagram the decision making process for considering exposure assessment needs for human health related endpoints.

Exposure assessment for human populations needs to be considered, even if the available data do not lead to classification for human health. This is due to the fact that the absence of classification for human health endpoints does not necessarily mean the absence of risk. In particular in the case of systemic effects it cannot be concluded *a priori* whether a potential risk can be controlled or not without having exposure estimates to compare against the relevant DN(M)ELs.

The following cases can be identified where an exposure assessment can be omitted for the purposes of the CSA and the preparation of the CSR.

- **Acute systemic effects (inhalation, dermal and oral route)**

For both workers and general population exposure assessment for short term duration (short term event, peak exposure) will not need to be conducted in the case where an acute toxicity hazard (leading to C&L) has not been identified.

- **Local Effects (acute and long term; dermal and inhalation route)**

For both workers and the general population, an exposure assessment (qualitative and/or quantitative) for local effects does not need to be performed if the substance is not classified for irritation, corrosion and sensitization.

[5] "Available hazard information" means information available to the registrant after having carried out the hazard assessment according to Annex I.

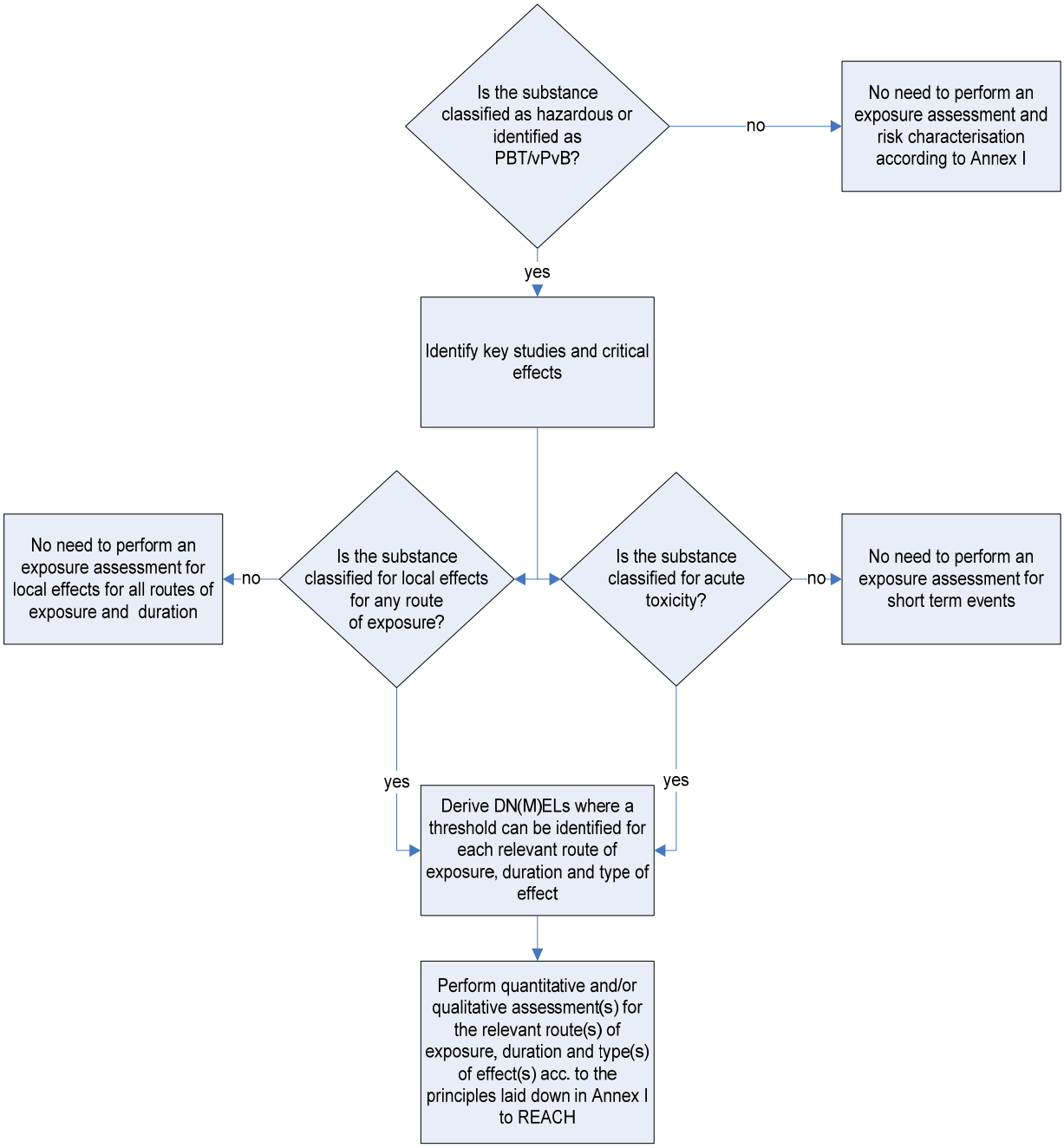


Figure 1: Overview on the decision making process leading to the need to perform an exposure assessment for human health related endpoints.

B.8.3.2 Ecotoxicological properties

The decision on whether to conduct an exposure assessment relating to environmental protection targets should be based on available and relevant ecotoxicological studies. The environmental exposure assessment may need to be considered, even if the substance is not classified for the environment. However, if all the following criteria are met, it may be assumed that there are no hazards potentially requiring control of risk, and thus it can be justified to omit exposure assessment and risk characterisation according to Annex I to REACH.
Figure 2 illustrates the decision making process for considering exposure assessment needs for environmental protection targets.

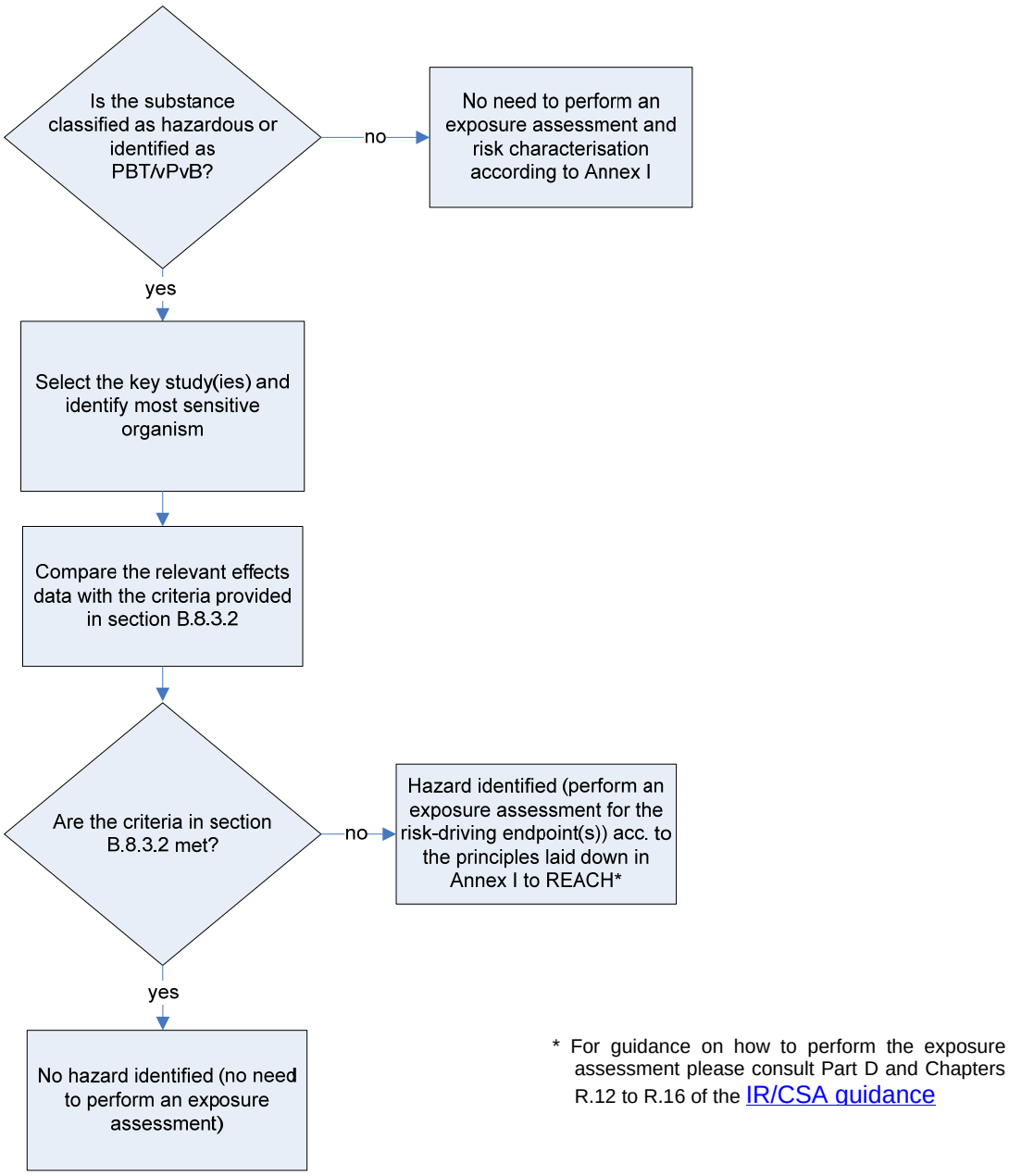


Figure 2: Overview on the application of the criteria for the identification of hazards leading to the need to perform an exposure assessment.

Absence of significant ecotoxicological effects (and thus "no hazard") may be concluded if all of the following criteria are met:

- The intrinsic properties of the substance are well below the criteria for classification as dangerous (hazardous) in accordance with Directive 67/548/EEC (or Regulation (EC) No 1272/2008), using all available data. i.e.:
  - the substance has a very low potential to bioaccumulate in aquatic species (e.g. fish) i.e. experimentally determined BCF < 10. For organic substances an alternative criterion, log Kow < 2.0 can be applied
  - the substance is readily biodegradable (this criterion does not apply to inorganic substances)
  - the aquatic toxicity has to fulfil both of the following criteria:
    - acute, short-term E(L)C_{50} > 1000 mg/l **or** > water solubility, **or** no significant adverse effects recorded at 100 mg/l in acute, short-term aquatic toxicity tests **and** validated QSAR data showing acute effects (E(L)C_{50}) > 1000 mg/l
    - chronic long-term NOEC (or equivalent ECx; e.g. EC_{10}) > 10 mg/l
- The substance shall not have adverse effects on terrestrial organisms, meaning that no adverse effects are reported in any of the tests required under Annex IX of REACH at the maximum test concentrations prescribed by the respective OECD guidelines.

  It might be the case that no studies on terrestrial organisms are available based on considerations that direct and indirect exposure of the soil compartment is unlikely. If a registrant has adapted the standard information requirements, this has to be well documented and justified in the registration dossier. Thus, the justification given for waiving the tests should either refer either to exposure considerations or it should be based on relevant substance properties, such as partitioning behaviour.
- The substance shall not be identified as having or be suspected to have endocrine activity from *in vivo* or *in vitro* tests, nor from the application of relevant (Q)SAR models or other structural alerts which may give rise any concern for endocrine-disrupting properties (DG Environment, ENV.D4./ETU/2005/0028r; http:/ec.europa.eu/ environment/endocrine/documents/final_report_2007.pdf).

Concluding that there are no hazards potentially requiring control of risk related to environmental endpoints would also support the conclusion that there is no need to assess the exposure of **man via the environment** through the oral route. However, this does not apply for exposure of man via ambient air (e.g. in the neighbourhood of sites where a substance is manufactured or used). Short and long term exposure via inhalation needs to be considered here, regardless of whether the above criteria are fulfilled or not.

APPENDIX I Examples

The examples provided in this Appendix are intended to illustrate 'real case' situations where a risk has been identified for (a) particular protection target(s) even though the available information did not lead to classification for that hazard[6]. Hence, they demonstrate why exposure assessment might be required for identification of risks to be controlled even in the absence of classification for that hazard.

The first three examples illustrate cases where the substances are not classified for the environment but where a risk has been identified for at least one environmental compartment. The fourth example deals with the case in which the results of the available tests for different toxicological endpoints did not lead to classification of the substance at the time of the evaluation. Nevertheless, adverse effects are identified in repeated dose studies illustrating the need to carry out an exposure assessment even if classification was not warranted for any of the health related endpoints.

Example 1 Hydrogen fluoride (HF) (EC 231-634-8)

The harmonised classification of the substance listed in table 3.2 of Annex VI to Regulation (EC) No 1272/2008 does not cover environmental hazards. However, the comprehensive risk assessment performed under Council Regulation 793/93/EC (EU RAR Hydrogen fluoride, 2001) identified a risk for at least one environmental protection target.

Classification for human health hazards[7]

T+; R26/27/28 Very toxic by inhalation, in contact with skin and if swallowed

C; R35 Causes severe burns

Classification for environmental hazards[8]

N.C. No classification for environment

The classification of HF covers health hazards only[9]. However, the conclusions of the evaluated risks have identified the need for specific measures to limit the risks for the environment. These measures are related to concerns for effects on local aquatic and atmospheric environmental spheres as a consequence of exposure arising from some production and use sites of the substance.

Relevant hazard information on the substance

Effects Assessment (hazard identification and dose (concentration) – response (effect) assessment) - aquatic compartment:

- acute toxicity to fish – lowest 96-hour LC_{50} value (*Oncorhynchus mykiss*) 51 mg/l
- long-term toxicity – lowest 21-day LC_5 value 4 mg/l

[6] The information on effects and identified risks provided in the examples is taken from the comprehensive Risk Assessment Reports (RAR) as well as the summaries thereof, which can be found on the internet site of the ex-European Chemicals Bureau (ex-ECB): http://ecb.jrc.ec.europa.eu/ esis/index.php?PGM=ora

[7] According to the entry in table 3.2 of Annex VI to Regulation (EC) No 1272/2008 (CLP Regulation).

[8] See FN 6

[9] No environmental classification. The decision taken by the Technical Committee on environmental C&L (TC C&L) not to classify the substance as dangerous for the environment is based on data.

(*Oncorhynchus mykiss*)

- acute toxicity to aquatic invertebrates – lowest 48-hour EC_{50} value (*Daphnia magna*) — 97 mg/l
- 21-day long-term NOEC (*Daphnia magna*; calculated arithmetic mean) — 8.9 mg/l
- acute toxicity to aquatic plants – lowest 96-hour EC_{50} value for algae (*Scenedesmus* sp.) — 43 mg/l
- long-term toxicity – lowest 7-day NOEC for algae — 50 mg/l

$PNEC_{aquatic}$ 0.9 mg/l (extrapolated from the calculated mean NOEC-value for daphnids of 8.9 mg/l using an Assessment factor of 10).

Effects Assessment (hazard identification and dose (concentration) – response (effect) assessment) - terrestrial compartment and atmosphere:

- toxicity to soil micro-organisms – lowest NOEC (NO_3 mineralisation); 63-day study — 106 mg/kg
- toxicity to plants – lowest NOEC for highly sensitive plant species (7 month exposure in fumigation experiments) — 0.2 mg/m^3

$PNEC_{soil}$ 11 mg/kg (based on the lowest available NOEC for nitrification and Assessment factor of 10)

$PNEC_{plant\text{-}air}$ 0.2 µg/m^3 (most important exposure route of HF for plants is uptake from the atmosphere)

Bioaccumulation

BCF values for fish (freshwater): 53-58 (d.w.) and < 2 (w.w.)

BCF values for fish (sea water): 149

BCF values for crustacea (freshwater): < 1 ((d.w.); based on whole body fluoride contents)

BCF values for crustacea (sea water): 27 - 62

BCF values for mollusca and aquatic macrophyta (freshwater): 3.2 – 7.5 (w.w.)

Relevant physicochemical properties

Partition coefficient N-octanol/water (log Kow): -1.4

Comparison with criteria for determination of minimum risk due to ecotoxicological properties (cf. section B.8.3.2 of this document)

A comparison of the available information (environmental effects data) for hydrogen fluoride with the criteria for ecotoxicological properties specified in section B.8.3.2 reveals the need to perform

an exposure assessment[10] for environmental protection target(s) and subsequent risk characterisation, based on the following identified hazards:

- potential to bioaccumulate (reported BCF-values in fish of 53 - 58 [d.w.]);
- reported acute, short-term E(L)C_{50} below 1000 mg/l as well as chronic long-term NOEC below 10 mg/l, respectively;
- reported adverse effects on terrestrial organisms.

[10] According to Section 5.0 of Annex I to REACH, the assessment shall consider all stages of the life-cycle of the substance resulting from the manufacture and identified uses and shall cover any exposures that may relate to the hazards identified. It should focus on populations and environmental compartments likely to be exposed. The decision not to perform the assessment for one population or an environmental compartment should be justified and documented.

Example 2 Acrylamide (EC 201-173-7)

The harmonised classification of the substance listed in table 3.2 of Annex VI to Regulation (EC) No 1272/2008 does not cover environmental hazards. However, the comprehensive risk assessment performed under Council Regulation (EEC) 793/93/EC (EU RAR Acrylamide, 2003) identified a risk to at least one environmental compartment.

Classification for human health hazards[11]

Carc.Cat.2; R45 May cause cancer

Muta.Cat.2; R46 May cause heritable genetic damage

Repr.Cat.3; R62 Possible risk of impaired fertility

T; R25 Toxic if swallowed

T; 48/23/24/25 Toxic: Danger of serious damage on health by prolonged exposure through inhalation, in contact with skin and if swallowed

Xn; R20/21 Harmful by inhalation and in contact with skin

Xi; R36/38 Irritating to eyes and skin

R43 May cause sensitisation by skin contact

Classification for environmental hazards[12]

N.C. No classification for environment

The classification of Acrylamide covers health hazards[13] only. However, the conclusions of the evaluated risks have identified the need for specific measures to limit the risks for the environment. These are related to concerns for the aquatic ecosystem as a consequence of exposure arising from the use of Acrylamide-based grouts in construction applications, and to indirect exposure of other organisms through contaminated water from the same use.

Relevant hazard information on the substance

Effects Assessment (hazard identification and dose (concentration) – response (effect) assessment) - aquatic compartment:

- acute toxicity to fish – lowest 96-hour LC_{50} value (*Lepomis macrochirus*) 100 mg/l
- acute toxicity to aquatic invertebrates – lowest 48-hour EC_{50} value (*Daphnia magna*) 98 mg/l
- long-term toxicity – lowest 28-day NOEC (*Mysidopsis bahia*) 2.04 mg/l

[11] See FN 6

[12] See FN 6

[13] No environmental classification. The decision taken by the TC C&L not to classify the substance as dangerous for the environment is based on data.

- acute toxicity to aquatic plants – lowest 72-hour EC_{50} for algae (*Selenastrum capricornutum*) 33.85 mg/l
- long-term toxicity – lowest 72-hour NOEC for algae (Selenastrum capricornutum) 2.16 mg/l

$PNEC_{aquatic}$ 20.4 µg/l (derived using all available data and an Assessment factor of 100).

Effects Assessment (hazard identification and dose (concentration) – response (effect) assessment) – terrestrial compartment:

- short-term toxicity – lowest EC_{50} value based upon root elongation of plant seedlings 220 mg/l

$PNEC_{soil}$ 220 µg/l (derived using an Assessment factor of 1000 but based on only one terrestrial toxicity result).

Environmental fate

Biodegradation – considered as readily biodegradable (OECD 301D)

Bioaccumulation – BCF values reported to be < 1

Relevant physicochemical properties

Partition coefficient N-octanol/water (log Kow): -1.65 (calculated) to -0.67 (measured)

Comparison with criteria for determination of minimum risk due to ecotoxicological properties (cf. section B.8.3.2 of this document)

The comparison of Acrylamide with the criteria specified in section B.8.3.2 reveals the need to perform an exposure assessment for environmental protection target(s) and subsequent risk characterisation, based on the following identified hazards:

- reported acute, short-term E(L)C_{50} below 1000 mg/l as well as chronic long-term NOEC below 10 mg/l, respectively
- reported adverse effects on terrestrial organisms

Example 3 Toluene (EC 203-625-9)

The harmonised classification of the substance listed in table 3.2 of Annex VI to Regulation (EC) No 1272/2008 does not cover environmental hazards. However, the comprehensive risk assessment performed under Council Regulation (EEC) 793/93/EC (EU RAR Toluene, 2003) identified a risk to at least one environmental compartment.

Classification for human health hazards[14]

F; R11 Highly flammable

Repr.Cat.3; R63 Possible risk of harm to the unborn child

Xn; R48/20-65 Harmful: danger of serious damage to health by prolonged exposure through inhalation. May cause lung damage if swallowed

Xi; R38 Irritating to skin

R67 Vapours may cause drowsiness and dizziness

Classification for environmental hazards[15]

N.C. No classification for environment

The classification of toluene covers physical and health hazards[16] only. However, the risk assessment has identified the need for specific measures to limit the risks for all environmental spheres: aquatic ecosystem, terrestrial ecosystem, atmosphere and micro-organisms in the STP. This conclusion is reached due to following reasons:

- Concerns for the aquatic ecosystem as a consequence of exposure arising from production and combined production and processing of the substance. Concerns for the aquatic and terrestrial ecosystem as a consequence of exposure arising from: processing and the use in basic chemicals industry (including processing aid, "extraction" agent and solvent), processing and formulation, mineral oil and fuel formulation, formulation of polymers, paints and textile processing.
- the contribution of the commercial product toluene to the formation of ozone and other harmful substances, i.e. smog formation.
- sewage treatment plants (STPs) as a consequence of exposure arising from processing of the substance as well as in the use sectors of industry use as basic chemicals.

Relevant hazard information on the substance

Effects Assessment (hazard identification and dose [concentration] – response [effect] assessment) - aquatic compartment:

- acute toxicity to fish – lowest 96-hour LC_{50} value (*Oncorhynchus kisutch*) 5.5 mg/l
- chronic toxicity to fish – lowest NOEC value 1.4 mg/l

[14] See FN 6

[15] See FN 6

[16] No environmental classification. The decision taken by the TC C&L not to classify the substance as dangerous for the environment is based on data.

(*Oncorhynchus kisutch*); extrapolated from lowest chronic fish toxicity LOEC 3.18 mg/l

- acute toxicity to aquatic invertebrates – lowest 48-hour EC_{50} value (*Ceriodaphnia dubia*) — 3.78 mg/l
- long-term toxicity – lowest 7-day NOEC (*Ceriodaphnia dubia*) — 0.74 mg/l

$PNEC_{aquatic}$ 0.074 mg/l (derived using an assessment factor of 10 according to the lowest long-term NOEC of 0.74 mg/l on *Ceriodaphnia* reproduction).

Effects Assessment (hazard identification and dose [concentration] – response [effect] assessment) – terrestrial compartment:

- lowest 28-day NOEC for earthworms (mortality and cocoon production) — between 15 and 50 mg/kg
- long-term study on plants – 28-day study (*Lactuca sativa*) — 1000 mg/l

$PNEC_{soil}$ 0.3 mg/kg (based on two long-term studies on plants and earthworm and an assessment factor of 50).

Environmental fate

Biodegradation – considered as readily biodegradable (respecting the 10-day time window and according to the TGD the first order rate constant for biodegradation in STP (k_{STP}) is set at $1.h^{-1}$ corresponding to a half-life of 0.0289 days)

Bioaccumulation – BCF values in fish reported to range between 8 and 90

Relevant physicochemical properties:

Partition coefficient N-octanol/water (log Kow): 2.65 (measured)

Comparison with criteria for determination of minimum risk due to ecotoxicological properties (cf. section B.8.3.2 to this document)

The comparison of Toluene with the criteria specified in section B.8.3.2 reveals the need to perform an exposure assessment for the environmental protection target(s) and a subsequent risk characterisation, based on the following identified hazards:

- reported BCF-values for fish above 10 as well as log Kow > 2.0
- acute, short-term $E(L)C_{50}$ are below 1000 mg/l (including (Q)SAR calculation) and chronic long-term NOECs are below 10 mg/l, respectively
- reported adverse effects on terrestrial organisms

Example 4 Phenmedipham (EC 237-199-0)[17]

There is no classification for health effects but the substance is classified for effects on the environment as H400, H410 (N; R50-53) in Annex VI to Regulation (EC) No 1272/2008.
The Draft Assessment Report (DAR), which presents the evaluation of phenmedipham as part of the work programme on the Community-wide review for all active substances used in plant protection products within the European Union, lists the following relevant health effects for this active substance.

Endpoint / Test type	Result / Effect	Classification
Acute toxicity		
Rat LD_{50} oral	>8000 mg/kg bw	No
Rat LD_{50} dermal	>2000 mg/kg bw	No
Rat LC_{50} inhalation	>7.0 mg/l/4h	No
Skin irritation	Non-irritant	No
Eye irritation	Non-irritant	No
Skin sensitization	Non-sensitiser (maximisation test)	No
Short term toxicity		
90 day rat study	Effects on red blood cells (methemoglobinemia and hemolytic anemia) and related effects (hemosiderin deposition in spleen, liver and kidneys). NOAEL = 13 mg/kg bw/day	No
Genotoxicity		
Comprehensive battery of *in vitro* and *in vivo* tests	Clastogenic *in vitro*. Non-genotoxic *in vivo*.	No
Long term toxicity and carcinogenicity		
Tests in both rat and mouse	Effects on red blood cells (methemoglobinemia and hemolytic anemia) and related histopathological effects in spleen, liver and kidneys (increased weight, hemosiderosis, extramedullar hematopoiesis). No carcinogenic potential. NOAEL = 3 mg/kg bw/day (2-year rat study)	No
Reproductive toxicity		
Reproduction, rat, 2-generation study	Reduced pup weight at parentally toxic dose levels. NOAEL = 25 mg/kg bw/day)	No
Developmental effects, rat and rabbit	Retarded ossification in rats and rabbits at maternally toxic dose levels. NOAEL = 225 mg/kg bw/day (rabbit)	No

Signs of chemically induced haemolytic anaemia and related effects are consistently shown by the repeated dose studies, with no-adverse-effect-levels (NOAELs) ranging from 3 to 225 mg/kg

[17] The substance is an active substance in plant protection products in the meaning of Directive 91/414/EEC

bw/day, i.e. the adverse effects are expressed also at fairly low dose levels. Some effects on reproduction and developmental effects are also evident, although only at dose levels causing parental toxicity.

The results of the tests for different toxicological endpoints did not lead to classification of the active substance at the time of the evaluation. Nevertheless, adverse effects are identified in repeated dose studies illustrating the need to carry out an exposure assessment even if classification was not warranted for any of the health related endpoints.

Under REACH, for toxicological endpoints that exhibit a threshold for an effect, the NOAELs for these adverse effects would therefore be used for deriving DNELs, and for the selection of the most relevant DNEL as described under Chapter R.8 (Characterisation of dose [concentration]-response for human health) of the IR/CSA Guidance, depending e.g. on the length of the observed or expected exposure.