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Contents

1 Executive summary

This report provides an overview of regulatory toxicological safety requirements of solvents in relation to their production volume and use, with specific emphasis on human health hazards. This overview focusses on relevant European regulation in a global context. All formal requirements for registration, classification and labelling and risk assessment are reviewed and the steps required are summarized. The REACH Regulation and its registration and information requirements are a major driver as also recognized in the recent European standardization Committee standard CEN/TS16766 on bio-based solvents, requirements and test methods. This hazard information gathering may result in identification of substances having dangerous properties that are to be communicated via specific classification and labelling prescriptions.

From the information requirements posed by ECHA to any chemical to be introduced to the European market, REACH requires a standard information package, depending on the chemical's annual production level. Substance identity is an important element of this required information. The substance composition should be well described via molecular and structural formulas, i.e. number of major constituents, as well as any present impurities, or eventual additives. Depending on the annual tonnage level, increasing amounts of information on physico-chemical properties, toxicological properties of these constituents are requested. Of the annual tonnage (tpa) categories, being 1, 10, 100 and 1000, respectively, candidate solvent replacement substances will be expected to exceed the highest level, given the fact that tonnage levels of toluene and *N*-methyl-2-pyrrolidone (NMP) by far exceed this highest level. Therefore, for any of these substitutes the intrinsic properties screening will have to address all human health endpoints.

Both toluene and NMP have undesirable toxicological profiles, showing some serious hazards any replacing substances should clearly fail to show. For toluene the neurotoxic effects are considered most serious, whereas NMP these are reproductive toxicity effects. Of course, the replacing substances ideally should not have any of these hazards, or any of the other intrinsic hazardous properties of these standard solvents, but they also should not introduce other new hazards as intrinsic properties. Therefore, also from this point of view serious candidate replacing substances will have to be screened for all human health endpoints.

2 Introduction

This report provides an overview of regulatory human- and environmental safety requirements of solvents in relation to their production volume and use. This overview focusses on relevant European regulation in a global context. The REACH Regulation[1] and its registration and information requirements are a major driver as also recognized in the recent European standardization Committee standard CEN/TS16766 on bio-based solvents, requirements and test methods. Thus all formal REACH requirements for registration, classification and labelling and risk assessment are reviewed and the steps required are summarized, as far as this is relevant to the objective of this project, i.e. development of safe chemicals derived from non-food carbohydrates that should replace the hazardous solvents toluene and *N*-methyl-2-pyrrolidone (NMP). This report also summarizes the toxicological profiles of these hazardous solvents to set the safety objectives for their substitutes. In addition to these targeted substitutes, requirements of the regulation regarding the impurities and contaminants that may occur depending on the bio-based production process and/or starting material are addressed as well.

It is not the intention of this report to identify the most (cost) efficient procedures for integrated testing as allowed under REACH, as this is the subject of the later reports D4.3. and D4.5.

The next chapter will provide an introduction to relevant regulations, and the focus of this project, while chapter 4 will describe the 2006 REACH Regulation detailing about substance identity, information requirements, the chemical safety report, and any relevant exemptions. Chapter 5 describes the Classification, Labelling and Packaging (CLP) Regulation, that complements the 2006 REACH Regulation, aligns to the Globally Harmonised System (GHS), and describes when to classify substances for dangerous properties, focusing on human health hazards. Chapter 6 describes the toxicological profiles of toluene, and NMP, to set the objectives for any candidates replacing these substance. Finally, chapter 7 summarizes conclusions of the preceding chapters. The Appendices provide relevant definitions, a detailed description of a chemical safety report, and REACH Annexes subjects.

3 Relevant European legislation

REACH is applicable to any (newly) produced or imported substance within the EU. Dependent on the specific use scenario's additional regulatory frameworks may be applicable here, e.g. the General Food Law Regulation[2] or the Cosmetics Regulation[3].

3.1 Focus of hazard assessment in ReSolve

In ReSolve, we aim to use a Green Chemistry approach that includes an early stage screening for potential safety issues. This needs to be rapid and cost effective, while still addressing relevant endpoints and testing requirements that will enable to identify those solvents that are most likely to pass subsequent regulatory testing. Since regulatory testing for a High Production Volume (HPV) chemical is extensive and costly (up to millions of Euros), we need to focus considerably, particularly because of the wish to test a considerable

[1] Regulation (EC) No 1907/2006 of the European Parliament and of the Council (18 December 2006);
[2] Regulation (EC) No. 178/2002;
[3] EU Cosmetics Directive 76/768/EEC, and New EU Cosmetic Products Regulation (EC) No 1223/2009.

number of candidate solvents. For several reasons we will focus on human health hazards, rather than ecotoxicological hazards. A major reason is the importance of human health hazards in risk assessment. We have established a cost effective human cell based screening panel to assess a range of such hazards without using experimental animals. For ecotoxicological testing, often laborious whole animal tests are needed. These tests have simple endpoints such as death of the organism. These acutely toxic effects will to a considerable extent be picked up by the cell-based assay panel. In all cases, stability and bioaccumulation properties are also important to assess.

Beside ecotox testing, the environmental impact of the ReSolve solvents will be assessed using LCA. Furthermore, eco-labelling possibilities for bio-based solvents will be covered in D4.2. In that regard, the labelling criteria are, in general, set up by a group of qualified people (mostly researchers and industry) who investigate and decide which environmental impacts are the most influential ones for a product. Then for these impacts, threshold values are given. These values need to be quantifiable and are usually pass/fail. They need to be adaptable because usually the values get stricter from one round of revision of the criteria to another (at least that is the case with the EU Ecolabel). The most relevant impact categories vary depending on the end application. For some of the typical applications of solvents, there are already EU Ecolabel criteria, e.g. for “rinse-off cosmetics”, “cleaning products” and for “paints and varnishes” (see footnote[4]). These catalogues can be starting points for further analysis. These criteria include:

- minimum share of bio-based raw materials
- sustainability of raw materials
- Greenhouse gas (GHG) footprint
- Volatile Organic Compounds (VOCs)
- excluded or limited substances and mixtures
- biodegradation
- performance / fitness for use

For Ecolabelling, an overview of what the relevant HSE categories are is covered by REACH and by GHS/CLP. Based on these categories, these can be differentiated into labelling criteria and also threshold values later on.

4 REACH legislation

4.1 Introduction

The purpose of the REACH (Registration Evaluation and Authorisation of CHemicals) Regulation is to ensure a high level of protection of human health and the environment. It also aims to promote the use of alternative, non-animal methods for assessment of hazards of substances, as well as the free circulation of substances on the internal market thus enhancing competitiveness and innovation. Where applicable and accessible enough, the formal text of

[4] http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014D0312&from=EN

the REACH regulation is followed rather than a reworded version, in order to avoid misinterpretation.

This Regulation lays down provisions on substances[5] and mixtures[1] that apply to the manufacture, placing on the market or use of such substances on their own, in mixtures or in articles and to the placing on the market of mixtures. This Regulation is based on the principle that it is for manufacturers, importers and downstream users to ensure that they manufacture, place on the market or use such substances that do not adversely affect human health or the environment. Its provisions are underpinned by the precautionary principle.

The REACH Regulation requires registrants to prepare a registration dossier. This is composed of a technical dossier and, where relevant, a chemical safety report, which summarizes the results of a chemical safety assessment. A chemical safety report is only required if the registrant manufactures or imports a substance in quantities of 10 tonnes or more a year.

Before compiling their joint registration dossier, registrants in a substance information exchange forum (SIEF) first need to evaluate all available data on the intrinsic properties of a substance. Only when this data is not adequate to meet the requirements of REACH, may additional testing be needed. However, before testing on vertebrate animals, use of alternative methods and all other options must be considered (Article 13 of REACH).

The standard information requirements are those which are required as a minimum to meet the registration obligations of REACH. They depend on the quantity of the substance that is manufactured or imported into the EU/EEA and are described in annexes to the core text (i.e. Annexes VI to X; see Appendix 8.3 for list of Annexes). These minimum data requirements may be adapted as appropriate. This means that certain tests may be waived.

Registrants of the same substance have to share information which is required for the registration. To avoid unnecessary animal testing and duplication of tests, study results from tests involving vertebrate animals must be shared between registrants.

As a next step in REACH evaluation and authorisation by the competent authority (ECHA) will take place to assure the high level of protection aimed at.

4.2 Safety information requirements

4.2.1 Substances to which REACH applies

The REACH Regulation in fact applies to all substances that are produced within or imported into the EU and to be placed on the market, either on their own, or in mixtures or articles, with a volume greater or equalling 1 tpa. There are, however, some exceptions here. This REACH Regulation does not apply to non-isolated intermediates, or to the extent that a substance is used (a) in medicinal products for human or veterinary use[6], (b) in food or feeding-stuffs[7], as

[5] See Appendix 8.1 for definitions

[6] within the scope of Regulation (EC) No 726/2004, Directive 2001/82/EC of the European Parliament and of Council of 6 November 2001 on the Community code relating to veterinary medicinal products (4) and Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67. Directive as last amended by Regulation (EC) No 1901/2006).

[7] in accordance with Regulation (EC) No 178/2002 including use;

a food additive[8], as a flavouring to food[9] or to food source materials[10], as an additive in feeding-stuffs[11] or in animal nutrition[12]. Also, the following substances shall be exempted for registration and evaluation: (a) substances included in Annex IV to the REACH Regulation, as sufficient information is known about these substances that they are considered to cause minimum risk because of their intrinsic properties; (b) substances covered by Annex V, as registration is deemed inappropriate or unnecessary for these substances and their exemption does not prejudice the objectives of this REACH Regulation; (c) substances on their own or in mixtures, that are already registered. Exemption from the general obligation to register also applies to product and process oriented research and development (PPORD) is also granted for a period of 5 years to a substance manufactured in the Community or imported for the purposes of product and process orientated research and development by a manufacturer or importer or producer of articles, by himself or in cooperation with listed customers and in a quantity which is limited to the purpose of product and process orientated research and development.

4.2.2 General requirements for generation of intrinsic properties of substances

General requirements for generation of information on intrinsic properties of substances entails the following aspects. Please, note that the Annexes referred to will be described in sections 4.2.4 and 4.2.5.

Also, the level of adequacy and certainty of generated information on intrinsic properties of substances referred to in the below description of the REACH Regulation, needs to be satisfied for the final chemicals that are to replace toluene, and NMP in their various application and exposure scenarios. For all candidate chemicals that are to be examined for their suitability to replace toluene, and NMP, approaches outlined in Annex XI will be applied: this Annex is described in section 4.2.5 of this report.

Briefly, this Annex describes that information on intrinsic properties of substances may be generated by means other than tests. In particular for human toxicity, information shall be generated whenever possible by means other than vertebrate animal tests, through the use of alternative methods, for example, in vitro methods or qualitative or quantitative structure-activity relationship models or from information from structurally related substances (grouping or read-across). Testing may also be omitted where justified by information on exposure and implemented risk management measures. This is all described in section 4.2.5 of this report (taken from Annex XI of the REACH Regulation).

These alternative methods will be regularly reviewed and improved by the Agency ECHA with a view to reducing testing on vertebrate animals and the number of animals involved.

Where tests on substances are required to generate information on intrinsic properties of substances, i.e. when other options do not appear feasible, they shall be conducted in accordance with the test methods laid down in a Commission Regulation or in accordance

[8] Council Directive 89/107/EEC;
[9] Council Directive 88/388/EEC;
[10] Commission Decision 1999/217/EC, and Regulation (EC) No 2232/96
[11] Regulation (EC) No 1831/2003
[12] Council Directive 82/471/EEC

with other international test methods recognized by the Commission or the Agency as being appropriate.

Information on intrinsic properties of substances may be generated in accordance with other test methods provided that the conditions set out in Annex XI, section 4.2.5, are met.

Ecotoxicological and toxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice (GLP) provided for in Directive 2004/10/EC or other international standards recognized as being equivalent by the Commission or the Agency and with the provisions of Directive 86/609/EEC, if applicable.

If a substance has already been registered, a new registrant shall be entitled to refer to the study summaries or robust study summaries, for the same substance submitted earlier, provided that he can show that the substance that he is now registering is the same as the one previously registered, including the degree of purity and the nature of impurities, and that the previous registrant(s) have given permission to refer to the full study reports for the purpose of registration.

4.2.3 Substance identity

An important aspect of assessing intrinsic properties of substances is substance identity. For each substance, the information given in this section is considered to be sufficient to enable each substance to be identified. If it is not technically possible or if it does not appear scientifically necessary to give information on one or more of the items below, the reasons shall be clearly stated.

Name or other identifier of each substance:

Name(s) in the IUPAC nomenclature or other international chemical name(s)
Other names (usual name, trade name, abbreviation)
EINECS or ELINCs number (if available and appropriate)
CAS name and CAS number (if available)
Other identity code (if available)

Information related to molecular and structural formula of each substance:

Molecular and structural formula (including SMILES notation, if available)
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)
Molecular weight or molecular weight range

Composition of each substance:

Degree of purity (%)
Nature of impurities, including isomers and by-products
Percentage of (significant) main impurities
Nature and order of magnitude (… ppm, … %) of any additives (e.g. stabilising agents or inhibitors)
Spectral data (ultra-violet, infra-red, nuclear magnetic resonance or mass spectrum)
High-pressure liquid chromatogram, gas chromatogram

Description of the analytical methods or the appropriate bibliographical references for the identification of the substance and, where appropriate, for the identification of impurities and additives. This information shall be sufficient to allow the methods to be reproduced.

Please, note that this detailed identity information requirement is also needed to assess the sameness to substances that are exempted from registration (Annexes IV and V), i.e. including any present impurities, and/or additives.

This identity information requirement is also to be able to classify a substance based on the presence of impurities with dangerous properties, as outlined in the CLP Regulation specifying specific concentration limits for hazardous substances within mixtures (see chapter 5).

4.2.4 Standard information requirements for manufactured or imported substances

In the below Tables the standard information requirements are listed for substances that are to be registered. The information requirements depend on the amount produced per manufacturer or imported per legal entity. Please, note that the below Tables are not as detailed as provided with the REACH Regulation itself.

The standard information requirements apply to non-phase-in substances[13], and to phase-in substances[14] manufactured or imported in the indicated quantities of tpa per manufacturer or importer.

Note that any other relevant physicochemical, toxicological (human health) and ecotoxicological (environmental health) information that already is available shall be provided as well.

For substances to be registered produced or imported between 1 and 10 tpa for which it is predicted (i.e. by the application of in silico tools like quantitative structure activity relationships (QSARs) or other evidence) that they are likely to be hazardous, (i.e. to meet the criteria for category 1A or 1B classification in the hazard classes carcinogenicity, germ cell mutagenicity or reproductive toxicity[15] or the criteria for Persistent Bioaccumulative and Toxic (PBT), very Persistent (vP) or very Bioaccumulative (vB), and for substances which have very dispersive or diffuse use(s) (particularly where such substances are used in consumer mixtures or incorporated into consumer articles) in the CLP Regulation (EC) No 1272/2008), further hazard identification tests are required.

Column 2 of the Tables on standard information requirements in the respective tonnage bands in the REACH Regulation (Annexes VII to X) lists *specific rules* according to which the required standard information may be omitted, replaced by other information, provided at a different stage or adapted in another way. These very detailed specifics are out of the scope of this report and not described here[16]. If the conditions are met under which column 2 allows adaptations, the registrant shall clearly state this fact and the reasons for each adaptation under the appropriate headings in the registration dossier.

[13] see Appendix 8.1 for definition;
[14] see Appendix 8.1 for definition;
[15] see chapter 4, and https://echa.europa.eu/documents/10162/13643/questions_and_answers_clp_20090526_en.pdf
[16] see: REACH Regulation: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32006R1907&from=EN; 2nd column of tables in Annexes VII (p.316) to X.

In addition to these specific rules, a registrant may adapt the required standard information requirements for the respective tonnage bands in the REACH Regulation (Annexes VII to X) according to so-called *general rules*: these are described in the next section 4.2.5 of this report (from Annex XI of the REACH Regulation). In this case as well, the registrant shall clearly state the reasons for any decision to adapt the standard information under the appropriate headings in the registration dossier.

Before new tests are carried out to determine the properties listed in Annexes VII to X, whatever appropriate, all available *in vitro* data, *in vivo* data, historical human data, data from valid (Q)SARs and data from structurally related substances (read-across approach) shall be assessed first (see Annex XI). Prior to testing, further guidance on testing strategies[17] should be consulted in addition to Annexes VII to X.

When, for certain endpoints, information is not provided for other reasons than those mentioned in column 2 of Annex V to X this fact and the reasons shall also be clearly stated.

Table 1. Standard information requirements for the various tonnage bands

Tonnage	Toxicological Information
1 – 10 tpa Annex VII	› *In vitro* skin irritation/corrosion and eye irritation/damage › Skin sensitization *in vitro/in chemico*, and if needed *in vivo* › *In vitro* mutagenicity: gene mutation in bacteria › Acute toxicity (one route, oral)
10 – 100 tpa Annex VIII	› *In vivo* skin and eye irritation/corrosion › *In vitro* mutagenicity: gene mutation, cytogenicity or micronucleus in mammalian cells › Acute toxicity (2nd route, inhalation or dermal) › Sub-acute toxicity (28d; most appropriate route) › Reproductive toxicity screening test (OECD 421 or 422) › Toxico-kinetics (available information)
100 – 1000 tpa Annex IX	› Further *in vivo* mutagenicity tests may be proposed, if appropriate › Sub-chronic toxicity (90d) may be proposed, if appropriate › Reproductive toxicity tests: prenatal developmental (OECD 414) and extended one-generation reproductive toxicity (OECD 433) tests may be proposed, if appropriate
>1000 tpa Annex X	› Further appropriate mutagenicity tests may be proposed, if appropriate › A chronic toxicity test may be proposed, if appropriate › Further reproductive toxicity tests may be proposed, if appropriate › Carcinogenicity test may be proposed, if appropriate

[17] see: endpoint-specific guidance documents: https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment

Tonnage	Ecotoxicological information
1 – 10 tpa Annex VII	› Aquatic toxicity: short-term invertebrates, and growth inhibition plants › Degradation: biotic / biodegradability
10 – 100 tpa Annex VIII	› Short-term toxicity test on fish › Activated sludge respiration inhibition testing › Degradation: abiotic, hydrolysis as a function of pH › Fate and behaviour in the environment: absorption/desorption screening
100 – 1000 tpa Annex IX	› Aquatic toxicity: long-term invertebrates and fish › Degradation: biotic (simulation testing surface water, soil, sediment), identification degradation products › Fate and behaviour in the environment: further information on absorption/desorption; bioaccumulation in aquatic species, absorption › Effects on terrestrial organisms: short-term invertebrates, soil organisms, plants
>1000 tpa Annex X	› Degradation: biotic, further testing if needed › Fate and behaviour in the environment: further testing if needed › Effects on terrestrial organisms: long-term toxicity testing on invertebrates, and plants shall be proposed, if appropriate › Long-term toxicity to sediment organisms shall be proposed, if appropriate › Long-term toxicity or reproductive toxicity to birds shall be proposed, if appropriate

Also, tonnage-triggered physical chemical information requirements are described in these annexes, as follows:

Tonnage	Physico-chemical properties
1 – 100 tpa Annex VII & VIII	› Physical state at 20°C and 1 kPa › Melting/Freezing point › Boiling point › Relative density › Vapour pressure › Surface tension › Water solubility › Partition coefficient n-octanol/water › Flash-point › Flammability › Explosive properties

	› Self-ignition temperature › Oxidising properties › Granulometry
>100 tpa Annex IX & X	› Stability in organic solvents and identity of relevant degradation products › Dissociation constant › Viscosity

For tonnage bands >100 tpa a description of the analytical methods shall be provided on request, for the relevant compartments for which studies were performed using the analytical method concerned. If the analytical methods are not available this shall be justified.

4.2.5 General rules for adaptation of the standard information requirements.

In addition to the specific rules set out in column 2 of Annexes VII to X of the REACH Regulation, which are not detailed in this report (considered outside the scope of this report), a registrant may adapt the standard testing regime in accordance with the general rules described here (and in Annex XI of REACH Regulation). Under dossier evaluation the Agency may assess these adaptations to the standard testing regime.

4.2.5.1 Testing does not appear scientifically necessary

Use of existing data

Data on physical-chemical properties from experiments not carried out according to GLP or the test methods referred to in Article 13(3)[18]

Data shall be considered to be equivalent to data generated by the corresponding test methods if the following conditions are met:

(1) adequacy for the purpose of classification and labelling and/or risk assessment;

(2) sufficient documentation is provided to assess the adequacy of the study; and

(3) the data are valid for the endpoint being investigated and the study is performed using an acceptable level of quality assurance.

Data on human health and environmental properties from experiments not carried out according to GLP or the test methods referred to in Article 13(3)

Data shall be considered to be equivalent to data generated by the corresponding test methods referred to in Article 13(3) if the following conditions are met:

(1) adequacy for the purpose of classification and labelling and/or risk assessment;

[18] Where tests on substances are required to generate information on intrinsic properties of substances, they shall be conducted in accordance with the test methods laid down in a Commission Regulation or in accordance with other international test methods recognized by the Commission or the Agency as being appropriate. The Commission shall adopt that Regulation, designed to amend the non-essential elements of this Regulation by supplementing it, in accordance with the procedure referred to in Article 133(4).

(2) adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3);
(3) exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3) if exposure duration is a relevant parameter; and
(4) adequate and reliable documentation of the study is provided.

Historical human data

Historical human data, such as epidemiological studies on exposed populations, accidental or occupational exposure data and clinical studies, shall be considered.

The strength of the data for a specific human health effect depends, among other things, on the type of analysis and on the parameters covered and on the magnitude and specificity of the response and consequently the predictability of the effect. Criteria for assessing the adequacy of the data include:

(1) the proper selection and characterization of the exposed and control groups;
(2) adequate characterization of exposure;
(3) sufficient length of follow-up for disease occurrence;
(4) valid method for observing an effect;
(5) proper consideration of bias and confounding factors; and
(6) a reasonable statistical reliability to justify the conclusion.

In all cases adequate and reliable documentation shall be provided.

Weight of evidence

There may be sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous property, while the information from each single source alone is regarded insufficient to support this notion.

There may be sufficient weight of evidence from the use of newly developed test methods, not yet included in the test methods referred to in Article 13(3) or from an international test method recognized by the Commission or the Agency as being equivalent, leading to the conclusion that a substance has or has not a particular dangerous property.

Where sufficient weight of evidence for the presence or absence of a particular dangerous property is available:
- further testing on vertebrate animals for that property shall be omitted,
- further testing not involving vertebrate animals may be omitted.

In all cases adequate and reliable documentation shall be provided.

Qualitative or Quantitative structure-activity relationship ((Q)SAR)

Results obtained from valid qualitative or quantitative structure-activity relationship models ((Q)SARs) may indicate the presence or absence of a certain dangerous property. Results of (Q)SARs may be used instead of testing when the following conditions are met:
— results are derived from a (Q)SAR model whose scientific validity has been established,
— the substance falls within the applicability domain of the (Q)SAR model,
— results are adequate for the purpose of classification and labelling and/or risk

assessment, and

— adequate and reliable documentation of the applied method is provided.

The Agency in collaboration with the Commission, Member States and interested parties shall develop and provide guidance in assessing which (Q)SARs will meet these conditions and provide examples.

***In vitro* methods**

Results obtained from suitable *in vitro* methods may indicate the presence of a certain dangerous property or may be important in relation to a mechanistic understanding, which may be important for the assessment. In this context, 'suitable' means sufficiently well-developed according to internationally agreed test development criteria (e.g. the European Centre for the Validation of Alternative Methods (ECVAM)) criteria for the entry of a test into the pre-validation process). Depending on the potential risk, immediate confirmation requiring testing beyond the information foreseen in Annexes VII or VIII or proposed confirmation requiring testing beyond the information foreseen in Annexes IX or X for the respective tonnage level may be necessary.

If the results obtained from the use of such *in vitro* methods do not indicate a certain dangerous property, the relevant test shall nevertheless be carried out at the appropriate tonnage level to confirm the negative result, unless testing is not required in accordance with Annexes VII to X or the other rules in this Annex.

Such confirmation may be waived, if the following conditions are met:

(1) results are derived from an *in vitro* method whose scientific validity has been established by a validation study, according to internationally agreed validation principles;
(2) results are adequate for the purpose of classification and labelling and/or risk assessment; and
(3) adequate and reliable documentation of the applied method is provided.

Grouping of substances and read-across approach

Substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as a group, or 'category' of substances. Application of the group concept requires that physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group (read- across approach). This avoids the need to test every substance for every endpoint. The Agency, after consulting with relevant stakeholders and other interested parties, has provided guidance on technically and scientifically justified methodology for the grouping of substances.

The similarities may be based on:

(1) a common functional group;
(2) the common precursors and/or the likelihood of common breakdown products via physical and biological processes, which result in structurally similar chemicals; or

(3) a constant pattern in the changing of the potency of the properties across the category.

If the group concept is applied, substances shall be classified and labelled on this basis.

In all cases results should:

- be adequate for the purpose of classification and labelling and/or risk assessment,
- have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3),
- cover an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3) if exposure duration is a relevant parameter, and
- adequate and reliable documentation of the applied method shall be provided.

4.2.5.2 Testing is technically not possible

Testing for a specific endpoint may be omitted, if it is technically not possible to conduct the study as a consequence of the properties of the substance: e.g. very volatile, highly reactive or unstable substances cannot be used, mixing of the substance with water may cause danger of fire or explosion or the radio-labelling of the substance required in certain studies may not be possible or when the substance is e.g. identified or predicted as being corrosive. The guidance given in the test methods referred to in Article 13(3), more specifically on the technical limitations of a specific method, shall always be respected.

4.2.5.3 Substance-tailored exposure-driven testing

Testing in accordance with Annex VIII and in accordance with Annex IX and Annex X may be omitted, based on the exposure scenario(s) developed in the Chemical Safety Report.

In all cases, adequate justification and documentation shall be provided. The justification shall be based on a thorough and rigorous exposure assessment in accordance with section 5 of Annex I and shall meet any one of the following criteria:

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

(i) the results of the exposure assessment covering all relevant exposures throughout the life cycle of the substance demonstrate the absence of or no significant exposure in all scenarios of the manufacture and all identified uses as referred to in Annex VI section 3.5;

(ii) a derived- or predicted no effect level (DNEL or PNEC)[19] can be derived from results of available test data for the substance concerned taking full account of the increased uncertainty resulting from the omission of the information requirement, and that DNEL or PNEC is relevant and appropriate both to the information requirement to be omitted and for risk assessment purposes;

[19] see Appendix 8.1 for definitions;

(iii) the comparison of the derived DNEL or PNEC with the results of the exposure assessment shows that exposures are always well below the derived DNEL or PNEC;

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

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

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

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

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

The specific conditions of use must be communicated through the supply chain.

4.2.6 Exemptions from Registration obligation

Any candidate substance that is to potentially replace toluene or NMP may turn out to be an already exempted or even registered chemical. Clearly, if it is already registered under REACH, data-sharing is the next step, and any hazard identification testing is to be tuned to the completeness of the submitted dossier, and may thus well turn out to be redundant and unneeded. If on the other hand the tonnage band of this registered substance is below the one anticipated for the replacing candidate, additional testing is very likely needed. Consulting the ECHA website[20] will clarify the registration status of such candidate substances. In addition, Annex IV of the REACH Regulation lists around 40 substances and substance groups (like glucitol, sucrose, d-mannitol, etc.) that are considered safe for any application and for which registration is not obliged. Annex V of the REACH Regulation describes another set of substances that are exempted from registration: for example, substances which result from a chemical reaction that occurs incidental to exposure of another substance or article to environmental factors such as air, moisture, microbial organisms or sunlight, or from a chemical reaction that occurs incidental to storage of another substance, mixture or article, or, finally from a chemical reaction occurring upon end use of other substances, mixtures or articles and which are not themselves manufactured, imported or placed on the market. The full listing of these substances lists clearly is outside the scope of this report, and they can be found within Annexes IV and V of the REACH Regulation.

[20] https://echa.europa.eu/information-on-chemicals/registered-substances

4.3 Chemical safety report

The purpose of a chemical safety assessment is to set out how to assess and document that the risks arising from the substance are adequately controlled during manufacture and the manufacturer's own use(s) and that others further down the supply chain can adequately control the risks.

The chemical safety assessment shall be prepared by one or more competent person(s) who have appropriate experience and received appropriate training, including refresher training.

The chemical safety assessment of a manufacturer or importer shall address the manufacture of a substance and all the identified uses of his substance. The chemical safety assessment shall consider the use of the substance on its own (including any major impurities and additives), in a mixture and in an article, as defined by the identified uses. The assessment shall consider all stages of the life-cycle of the substance resulting from the manufacture and identified uses. The chemical safety assessment shall be based on a comparison of the potential adverse effects of a substance with the known or reasonably foreseeable exposure of man and/or the environment to that substance taking into account implemented and recommended risk management measures and operational conditions.

The chemical safety assessment shall be based on the information on the substance contained in the technical dossier and on other available and relevant information.

Thus the information to be considered includes information related to the hazards of the substance, the exposure arising from the manufacture or import, the identified uses of the substance, operational conditions and risk management measures applied or recommended to downstream users to be taken into account.

A chemical safety assessment performed by a manufacturer or an importer for a substance includes the following steps 1 to 4, as further detailed below.

1. Human health hazard assessment.
2. Human health hazard assessment of physicochemical properties.
3. Environmental hazard assessment.
4. PBT and vPvB assessment.

In the cases a substance fulfils the criteria for any of the below further detailed classification for hazard, the chemical safety assessment needs also to include the following steps 5 and 6:

5. Exposure assessment.
6. Risk characterisation.

The criteria for hazard classes or categories, and for PBT or vPvB classification are set out in Annex I to Regulation (EC) No 1272/2008; these are partly described in the next chapter. A more detailed description of the chemical safety assessment is provided in Appendix 8.2.

4.4 Conclusions

For any chemical to be introduced to the European market REACH and CLP regulations require a standard information package, depending on the chemicals annual production level.

REACH is about 'substances' (not chemicals), and substance identity is an important element of this information package. REACH identifies so-called mono-constituent substances, or multi-constituents substances, where a single or multiple constituents characterize the substance. Any impurities, or eventual additives should be described as well. Molecular and structural formulas of the main constituent(s), their percental content etc. should be indicated; this also holds for the impurities, and additives. Depending on the annual tonnage level, increasing amounts of information on physico-chemical properties, toxicological, and ecotoxicological properties of these constituents are requested; identified annual tonnage levels (tpa) are 1, 10, 100 and 1000. Given the fact that tonnage levels of toluene and NMP by far exceed this highest level, information requirements for any substitutes for these substances, though perhaps replacing not all applications, will be expected to easily exceed this 1000 tpa level as well. For human health endpoints, as an example, this implies that all endpoints are to be addressed for the candidate substituting substances. This means that the information and testing requirements therefore cover all those mentioned in Table 1.

5 Classification, Labelling and Packaging Regulation

5.1 Introduction

In this chapter we will shortly outline the classification criteria for chemical substances[21]. Subsequently, in chapter 6, we will describe the toxicological profiles of toluene and NMP, as to have objectives for any candidates replacing these substance with regard to their toxicity profiles.

The classification of substances is described in the EU legislation on classification, labelling and packaging[22]. This regulation aims to ensure a high level of protection of human health and the environment and the functioning of the internal market by laying down EU-wide criteria that must be applied to determine whether a substance which is manufactured or imported into the European market has properties which could damage human health or the environment. In cases where the substance meets these so-called "classification criteria", i.e. if it has certain hazardous properties, the substance must be classified accordingly. Suppliers must then communicate the identified hazards of these substances to their customers, including to consumers. The most common tool for hazard communication is the labelling on the packaged substance, but also the Safety Data Sheet which is provided to other companies in the supply chain.

The decision on a particular classification for a substance is mostly taken by the supplier of the substance ("self-classification"). In certain cases the decision on the classification of a substance is taken at Community level – called a "harmonised classification". A harmonised classification must be applied by default by the suppliers of the respective substance. The

[21] note: all this is equally valid for mixtures.

[22] The EU legislation on classification, labelling and packaging consists of three acts: The Dangerous Substances Directive (Directive 67/548/EEC, "DSD"), the Dangerous Preparations Directive (Directive 1999/45/EC, "DPD") and the new Regulation on classification, labelling and packaging of substances and mixtures, Regulation (EC) No 1272/2008 ("CLP Regulation" or "CLP"), which entered into force on 20th January 2009.

classifications of about 8,000 substances that have been harmonised at Community level in the past decades are listed in Annex VI to CLP.

CLP prescribes to notify the classification and labelling of substances when placed on the market to a database established and maintained by ECHA, the so-called Classification & Labelling Inventory.

Hazard labelling allows alerting of the user of a substance to the presence of a hazard and the need to avoid exposure and the resulting risks. Further rules relating to packaging should help to ensure the safe supply of hazardous substances.

It should be noted, that hazard assessment means the assessment of the intrinsic properties of substances. It should not be confused with risk assessment which relates a given hazard to the actual exposure of humans or the environment to the substance displaying this hazard.

5.2 Classification criteria

The classification of a substance reflects the type and severity of the hazards of that substance, i.e. its potential to cause harm to human beings or the environment. A specific classification is expressed through standardised descriptors, e.g. “acute toxicity category 1 (oral)”. It is communicated through standardised phrases and symbols on labels and safety data sheets, e.g. the classification “acute toxicity category 1 (oral)” is communicated through the hazard phrase “Fatal if swallowed”, through the signal word “Danger” and through the skull and crossbones symbol.

The classification of a substance is based on the relevant information available on its hazardous properties. This information can include experimental data generated in tests for physical hazards, toxicological and ecotoxicological tests, historical human data such as accident records or epidemiological studies, or information generated in in vitro tests, (Quantitative) Structure Activity Relationships ((Q)SAR), ‘read-across’, or grouping approaches.

In general, valid data from animal experiments are considered relevant for humans and are used for hazard assessment/classification. However, it is acknowledged that there are cases where animal data are not relevant for humans and should not be used for that purpose. This is the case when there is clear evidence that a substance – induced effect is due to a species-specific mechanism which is not relevant for humans.

The information must be compared with the criteria for classification for each hazard class or differentiation within the hazard class. Differentiation is a distinction depending on the route of exposure or the nature of the effects. A decision should be made as to whether the substance meets the criteria for classification. When this is the case; the classifier should assign one or more hazard categories for each relevant hazard class or differentiation.

Substances, mono-constituent or multi-constituent[23], may contain impurities, additives, or other constituents. The classification of such impurities, additives or individual constituents may influence the classification of the substance, in addition to the other hazardous properties.

[23] a mono-constituent substance is a well-defined substance for which one constituent is present at a concentration of at least 80 % (w/w), named according to the chemical name of that main constituent; a multi-

For each human health endpoint potential classifications are described below.

5.3 Human health endpoint classifications

Substances are to be assessed for classification for the below described human health hazards, though this may depend on the tonnage level. Note that for mixtures, if not tested as mixture, classifications depend on specific concentration limits that are outlined in the referred Guidance sections.

Acute toxicity:

Acute toxicity means those adverse effects occurring following oral or dermal administration of a single dose of a substance or a mixture, or multiple doses given within 24 hours, or an inhalation exposure of 4 hours.

This hazard class is differentiated into acute oral, acute dermal, and acute inhalation toxicity; substances can be allocated to one of four hazard categories 1, 2, 3, and 4, based on acute toxicity LD_{50} (oral, dermal) or LC_{50} (inhalation) values per route.

Acute toxicity category		Oral[1]	Dermal[2]	Inhalation[3]
1	'fatal'	H300, H304	H310	H330
2	'toxic'	H301	H311	H331
3	'harmful'	H302	H312	H332
4	'may be harmful'	H303, H305	H313	H333

[1] 'if swallowed'; [2] 'in contact with skin'; [3] 'if inhaled'

The applied hazard statements are, e.g., H300 to H303, H310 to H313, and H330 to H333 are 'Fatal if swallowed', H311 'Toxic in contact with skin' etc.. Additionally, two other acute oral toxicity hazard statements are H304 'May be fatal if swallowed and enters airways', and H305 'May be harmful if swallowed and enters airways'.

Allocation of substances to hazard categories, and of how to assess mixtures, is according to the numeric criteria described in section 3.1 (p.236) of ECHA Guidance of 2017[24].

Skin corrosion/ irritation:

Skin Corrosion means the production of irreversible damage to the skin; namely, visible necrosis through the epidermis and into the dermis, following the application of a test substance for up to 4 hours. Corrosive reactions are typified by ulcers, bleeding, bloody scabs, and, by the end of observation at 14 days, by discolouration due to blanching of the skin, complete areas of alopecia, and scars. Histopathology shall be considered to evaluate questionable lesions. Skin Irritation means the production of reversible damage to the skin following the application of a test substance for up to 4 hours.

constituent substance is a well-defined substance for which more than one constituent is present at a concentration between 10 % and 80 % (w/w), named as a reaction mass of the main constituents.

[24] Guidance on the Application of the CLP Criteria Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures Version 5.0 July 2017.

This hazard class is differentiated into 2 categories, corrosive substances, category 1, and irritating substances, category 2. Each category is subduided into 3 subcategories, as follows:

Category	1 / corrosion	2 / irritation
A	H314	H315
B	H314	H315
C	H314	H315

The applied hazard statements are H314 'Causes severe skin burns and eye damage', and H315 'Causes skin irritation'. Additionally, there is another hazard statement on skin irritation: H316 'Causes mild skin irritation'.

Allocation of substances to hazard categories, and of how to assess mixtures, is according to the numeric criteria described in section 3.2 (p.271) of ECHA Guidance of 2017[24].

Serious eye damage / eye irritation:

Serious eye damage means the production of tissue damage in the eye, or serious physical decay of vision, following application of a test substance to the anterior surface of the eye, which is not fully reversible within 21 days of application. Eye irritation means the production of changes in the eye following the application of test substance to the anterior surface of the eye, which are fully reversible within 21 days of application.

It should be noted that if a substance or mixture is classified as Skin corrosion Category 1 then serious damage to eyes is implicit as reflected in the hazard statement for skin corrosion (H314: Causes severe skin burns and eye damage). Thus, the corrosive substance or mixture is also classified, but the corresponding hazard statement (H318: Causes serious eye damage) is not indicated on the label to avoid redundancy.

The two hazard classes are differentiated into 2 categories, 1 and 2 as follows:

Category	Serious eye damage	Eye irritation
1	H318	-
2	-	H319

The applied hazard statements are H318 'Causes serious eye damage', and H319 'Causes serious eye irritation'. Additionally, there is another hazard statement on eye irritatoion: H320 'Causes eye irritation'.

Allocation of substances to hazard categories, and of how to assess mixtures, is according to the numeric criteria described in section 3.3 (p.302) of ECHA Guidance of 2017[24].

Respiratory or skin sensitisation:

Respiratory sensitiser means a substance that will lead to hypersensitivity of the airways following inhalation of the substance. Skin sensitiser means a substance that will lead to an allergic response following skin contact.

It is noted that respiratory sensitisation may be induced not only by inhalation but also by skin contact. Sensitisation includes two phases: the first phase is induction of specialised immunological memory in an individual by exposure to an allergen. The second phase is elicitation, i.e. production of a cell-mediated or antibody-mediated allergic response by exposure of a sensitised individual to an allergen. Usually, for both skin and respiratory sensitisation, lower levels are necessary for elicitation than are required for induction.

These hazards are differentiated into 2 categories, 1A, and 1B, as follows:

Category	Respiratory sensitiser	Skin sensitiser
1A	H334	H317
1B	H334	H317

The applied hazard statements are H334 'May cause allergy or asthma symptoms or breathing difficulties if inhaled', and H317 'May cause an allergic skin reaction'.

Allocation of substances to hazard categories, and of how to assess mixtures, is according to the numeric criteria described in section 3.4 (p.331) of ECHA Guidance of 2017[24].

Germ cell mutagenicity:

A mutation means a permanent change in the amount or structure of the genetic material in a cell. The term 'mutation' applies both to heritable genetic changes that may be manifested at the phenotypic level and to the underlying DNA modifications when known (including specific base pair changes and chromosomal translocations). The term 'mutagenic' and 'mutagen' will be used for agents giving rise to an increased occurrence of mutations in populations of cells and/or organisms.

The more general terms 'genotoxic' and 'genotoxicity' apply to agents or processes which alter the structure, information content, or segregation of DNA, including those which cause DNA damage by interfering with normal replication processes, or which in a non-physiological manner (temporarily) alter its replication. Genotoxicity test results are usually taken as indicators for mutagenic effects.

This hazard is differentiated into 2 categories, 1 and 2 as follows:

Category	Heritable mutations	Hazard statement
1A	Known	H340
1B	Regarded as if	H340
2	Causing concern for	H341

The applied hazard statements are H340 'May cause genetic defects' (1A based on human data; 1B based on animal data), and H341 'Suspected of causing genetic defects'.

Allocation of substances to hazard categories, and of how to assess mixtures, is according to the numeric criteria described in section 3.5 (p.362) of ECHA Guidance of 2017[24].

Carcinogenicity:

Carcinogen means a substance or a mixture of substances which induce cancer or increase its incidence. Substances which have induced benign and malignant tumours in well performed experimental studies on animals are considered also to be presumed or suspected human carcinogens unless there is strong evidence that the mechanism of tumour formation is not relevant for humans.

More explicitly, chemicals are defined as carcinogenic if they induce tumours, increase tumour incidence and/or malignancy or shorten the time to tumour occurrence. Benign tumours that are considered to have the potential to progress to malignant tumours are generally considered along with malignant tumours. Chemicals can potentially induce cancer by any route of exposure (e.g. when inhaled, ingested, applied to the skin or injected), but carcinogenic potential and potency may depend on the conditions of exposure (e.g., route, level, pattern and duration of exposure).

Carcinogenic chemicals have conventionally been divided according to the presumed mode of action; genotoxic or non-genotoxic; for risk assessment different methodologies are applied.

This hazard is differentiated into 2 categories, 1 and 2 as follows:

Category	Cancer	Hazard statement
1A	Known	H350
1B	Regarded as if	H350
2	Causing concern for	H351

The applied hazard statements are H350 'May cause cancer' (1A based on human data; 1B based on animal data), and H351 'Suspected of causing cancer'.

Allocation of substances to hazard categories, and of how to assess mixtures, is according to the numeric criteria described in section 3.6 (p.376) of ECHA Guidance of 2017[24].

Reproductive toxicity:

Reproductive toxicity includes adverse effects on sexual function and fertility in adult males and females, as well as developmental toxicity in the offspring. The definitions presented below are adapted from those agreed as working definitions in IPCS/EHC Document N°225, Principles for Evaluating Health Risks to Reproduction Associated with Exposure to Chemicals. For classification purposes, the known induction of genetically based heritable effects in the offspring is addressed in Germ Cell Mutagenicity (section 3.5), since in the present classification system it is considered more appropriate to address such effects under the separate hazard class of germ cell mutagenicity.

In this classification system, reproductive toxicity is subdivided under two main headings:

(a) Adverse effects on sexual function and fertility;

(b) Adverse effects on development of the offspring.

Some reproductive toxic effects cannot be clearly assigned to either impairment of sexual function and fertility or to developmental toxicity. Nonetheless, substances with these effects, or mixtures containing them, shall be classified as reproductive toxicants.

This hazard is differentiated into 3 categories, as follows:

Category	Fertility / Developmental toxicity	Hazard statement
1A	May damage	H360
1B	May damage	H360
2	Suspected of damaging	H361
additional	May cause harm to breast-fed children	H362

The applied hazard statements are H360 'May damage fertility or the unborn child', H361 'Suspected of damaging fertility or the unborn child', and H362 'May cause harm to breast-fed children'. Hazard statements H360 and H361 both have two sub-categories (i.e. H360d/H360f, and H361d/H361f): 'd' meaning 'Suspected of damaging the unborn child', and 'f' meaning 'Suspected of damaging fertility'.

Allocation of substances to hazard categories, and of how to assess mixtures, is according to the numeric criteria described in section 3.7 (p.398) of ECHA Guidance of 2017[24].

Specific Target Organ Toxicity – Single Exposure (STOT-SE):

Specific target organ toxicity (single exposure) is defined as specific, non-lethal target organ toxicity arising from a single exposure to a substance or mixture. All significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed.

There are two hazard classes for single exposure toxicity: 'Acute toxicity' and 'STOT-SE'. These are independent of each other and both may be assigned to a substance or a mixture if the respective criteria are met. Acute toxicity refers to lethality and STOT-SE to non-lethal effects. However, care should be taken not to assign both classes for the same toxic effect, essentially giving a 'double classification', even where the criteria for both classes are fulfilled. In such a case the most appropriate class should be assigned.

This hazard is differentiated into 3 categories, as follows:

Category	Target organ toxicity	Hazard statement
1A	Cause	H370
1B	Cause	H370
2	May cause	H371
3	Transient, lung	H335, H336

The applied hazard statements are H370 'Causes damage to organs' (1A based on human data; 1B based on animal data), H371 'May cause damage to organs', and H335 'May cause

respiratory irritation'. Additionally, there is another hazard statement related to inhalation exposure H336 'May cause drowsiness or dizziness'.

Allocation of substances to hazard categories, and of how to assess mixtures, is according to the numeric criteria described in section 3.8 (p.433) of ECHA Guidance of 2017[24].

Specific Target Organ Toxicity – Repeated Exposure (STOT-RE):

Specific target organ toxicity (repeated exposure) means specific, target organ toxicity arising from a repeated exposure to a substance or mixture. All significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed are included.

Specific toxic effects covered by other hazard classes are not included in STOT-RE. STOT-RE should only be assigned where the observed toxicity is not covered more appropriately by another hazard class. For example specific effects like tumours or effects on the reproductive organs should be used for classification for carcinogenicity or reproductive toxicity, respectively, but not for STOT-RE.

These adverse health effects include consistent and identifiable toxic effects in humans, or, in experimental animals, toxicologically significant changes which have affected the function or morphology of a tissue/organ, or have produced serious changes to the biochemistry or haematology of the organism and these changes are relevant for human health.

This hazard is differentiated into 2 categories, as follows:

Category	Target organ toxicity	Hazard statement
1	Cause	H372
2	May cause	H373

The applied hazard statements are H372 'Causes damage to organs through prolonged or repeated exposure', and H373 'May cause damage to organs through prolonged or repeated exposure'.

Allocation of substances to hazard categories, and of how to assess mixtures, is according to the numeric criteria described in section 3.9 (p.459) of ECHA Guidance of 2017[24].

6 Toxicological profiles of toluene and NMP

A toxicological profile of a chemical as we apply it in this project is the classification profile of a chemical together with the derived DNELs or DMELs for risk assessment. For toluene and NMP these profiles are described below. For any candidate replacement chemicals we will try to predict these profiles on the basis of alternative methodologies that will be described in the deliverable report of this project named D4.3 "Establish an innovative, cost-effective integrated testing strategy to evaluate toxicological safety issues of candidate solvents."

Below the identities and hazard profiles for toluene, and NMP, respectively, are described. These are taken from ECHA's excel table containing all updates to the harmonised

classification and labelling of hazardous substances (that are also available in Table 3 of Annex VI to the CLP Regulation).

The harmonised classification and labelling of hazardous substances is updated through an "Adaptation to Technical Progress (ATP)" which is issued yearly by the European Commission. Following the adoption of the opinion on the harmonised classification and labelling of a substance by the Committee for Risk Assessment (RAC), the European Commission takes a decision and publishes the updated list in an ATP. The below data are from the 10th ATP[25] .

6.1 Toluene [26]

Identifiers: EC Number: 203-625-9
CAS Number: 108-88-3

Human health hazards:

Human health endpoint	Classifications
Acute toxicity	Asp.Tox.1 / H304
Skin corrosion / irritation	Skin irr.2 / H315
Serious eye damage / eye irritation	-
Respiratory or skin sensitisation	-
Germ cell mutagenicity	-
Carcinogenicity	-
Reproductive toxicity	Repr.2 / H361d
Specific Target Organ Toxicity - Single Exposure (STOT-SE)	STOT-SE 3 / H336
Specific Target Organ Toxicity - Repeated Exposure (STOT-SE)	STOT-RE 2 / H373

Thus, toluene is classified for the following hazards:

H304: 'May be fatal if swallowed and enters airways',

H315: 'Causes skin irritation',

H336: 'May cause drowsiness or dizziness',

H373: 'May cause damage to organs through prolonged or repeated exposure (central nervous system, via inhalation)', and

H361: 'Suspected of damaging the unborn child (via inhalation)'.

[25] https://echa.europa.eu/information-on-chemicals/annex-vi-to-clp
[26] From: https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/15538

The ECHA site lists quite some 'precautionary' (P) statements as a consequence of these hazards:

'Do not handle until all safety precautions have been read and understood' (P202),

'Do not breathe dust/fume/gas/mist/vapours/spray' (P260),

'Wear protective gloves/protective clothing/eye protection/face protection' (P280),

'IF SWALLOWED: Immediately call a POISON CENTER/doctor' (P301 + P310)

'Do NOT induce vomiting' (P331),

'IF ON SKIN (or hair): Take off immediately all contaminated clothing. Rinse skin with water [or shower]' (P303+P361+P353),

'IF INHALED: Remove person to fresh air and keep comfortable for breathing' (P304+ P340),

'IF exposed or concerned: Get medical advice/attention' (P308+P313).

Because toluene is also classified as a flammable solvent, H225 'Highly flammable liquid and vapour', it is noted at the ECHA website to 'Keep away from heat, hot surfaces, sparks, open flames and other ignition sources; No smoking.' (P210), and to 'Take actions to pevent static discharges.' (P243).

For risk assessment the following DNELs were derived:

For workers:

Inhalation, systemic effects:

Long term exposure: 192 mg/m^3; most sensitive endpoint neurotoxicity
Acute/short term exposure: 384 mg/m^3

Inhalation, local effects:

Long term exposure: 192 mg/m^3; most sensitive endpoint irritation respiratory tract
Acute/short term exposure: 384 mg/m^3

Dermal route, systemic effects:

Long term exposure: 384 mg/kg bw/day
Acute/short term exposure: no information available

Dermal route, local effects:

Long term exposure: no information available
Acute/short term exposure: no information available

For the general population:

Inhalation, systemic effects:

Long term exposure: 56.5 mg/m^3; most sensitive endpoint neurotoxicity
Acute/short term exposure: 226 mg/m^3

Inhalation, local effects:

Long term exposure: 56.5 mg/m^3; most sensitive endpoint irritation respiratory tract
Acute/short term exposure: 226 mg/m^3

Dermal route, systemic effects:

Long term exposure: 226 mg/kg bw/day
Acute/short term exposure: no information available

Dermal route, local effects:

Long term exposure: no information available
Acute/short term exposure: no information available

Oral route, systemic effects:

Long term exposure: 8.13 mg/kg bw/day
Acute/short term exposure: no information available

6.2 NMP [27]

Identifiers: EC Number: 212-828-1
CAS Number: 872-50-4

Human health hazards:

Human health endpoint	**Classifications**
Acute toxicity	-
Skin corrosion / irritation	Skin irr.2 / H315
Serious eye damage / eye irritation	Eye irr.2 / H319
Respiratory or skin sensitisation	-
Germ cell mutagenicity	-
Carcinogenicity	-
Reproductive toxicity	Repr.1B / H360d
Specific Target Organ Toxicity - Single Exposure (STOT-SE)	STOT-SE 3 / H335
Specific Target Organ Toxicity - Repeated Exposure (STOT-SE)	-

Thus, NMP is classified for the following hazards:

H315: 'Causes skin irritation',

H319: 'Causes serious eye irritation',

H335: 'May cause respiratory irritation', and

H360: 'May damage the unborn child'.

The ECHA site lists quite some 'precautionary' statements as a consequence of these hazards:

'Remove affected person from danger area. Remove contaminated clothing. First aid personnel should pay attention to their own safety',

[27] From: https://echa.europa.eu/registration-dossier/-/registered-dossier/15493/1

'IF INHALED: Keep patient calm, remove to fresh air. If breathing difficulties develop, aid in breathing and seek immediate medical attention',

'On skin contact: Wash thoroughly with soap and water',

'On contact with eyes: Immediately wash affected eyes for at least 15 minutes under running water with eyelids held open, consult an eye specialist',

'On ingestion: Rinse mouth and then drink plenty of water'; Indication of any immediate medical attention and special treatment needed; Treatment: Treat according to symptoms (decontamination, vital functions), no known specific antidote'.

For risk assessment the following DNELs were derived:

For workers:

Inhalation, systemic effects:

Long term exposure:	40 mg/m^3 (from 8-h OEL TWA, SCOEL, 2007)
Acute/short term exposure:	80 mg/m^3 (from 15-min OEL STEL, SCOEL, 2007)

Inhalation, local effects:

Long term exposure:	medium hazard (irritation; no threshold derived)
Acute/short term exposure:	medium hazard (irritation; no threshold derived)

Dermal route, systemic effects:

Long term exposure:	19.8 mg/kg bw/day (developmental toxicity)
Acute/short term exposure:	208 mg/kg bw/day

Dermal route, local effects:

Long term exposure:	medium hazard (irritation; no threshold derived)
Acute/short term exposure:	medium hazard (irritation; no threshold derived)
Hazard for the eyes:	medium hazard (no threshold derived)

For the general population:

Substance not allowed in consumer applications due to labelling as reproductive toxicant.

6.3 Conclusions

Both substances toluene and NMP have undesirable toxicological profiles, showing some serious hazards any replacing substances should clearly fail to show. For toluene the neurotoxic effects are considered most serious, whereas this is the reproductive toxicity effects shown by NMP. Of course, the replacing substances ideally should not have any of these hazards, or any of the other intrinsic hazardous properties, but they also should not introduce other new hazards as intrinsic properties, not shown by toluene or NMP.

7 General Conclusions

From the information requirements posed by ECHA to any chemical to be introduced to the European market REACH requires a standard information package, depending on the chemical's annual production level. Substance identity is an important element of this required information. The substance composition should be well described via molecular and structural formulas, i.e. number of major constituents, as well as any present impurities, or eventual additives. Depending on the annual tonnage level, increasing amounts of information on physico-chemical properties, toxicological, and ecotoxicological properties of these constituents are requested. Of the identified annual tonnage levels (tpa) being 1, 10, 100 and 1000, respectively, our candidate substances will be expected to exceed the highest level, given the fact that tonnage levels of toluene and NMP by far exceed this highest level. Therefore, for any of these substitutes the intrinsic properties screening will have to address all human health endpoints.

Both toluene and NMP have undesirable toxicological profiles, showing some serious hazards any replacing substances should clearly fail to show. For toluene the neurotoxic effects are considered most serious, whereas this is the reproductive toxicity effects shown by NMP. Of course, the replacing substances ideally should not have any of these hazards, or any of the other intrinsic hazardous properties of these solvents, but they also should not introduce other new hazards as intrinsic properties, not shown by either toluene or NMP. Therefore, also from this point of view serious candidate replacing substances will have to be screened for all human health endpoints.

8 Appendices

8.1 Definitions

Please note, this below list only depicts definitions of relevance to this project (part of Article 3 of the REACH Regulation; in alphabetical order)).

article: means an object which during production is given a special shape, surface or design which determines its function to a greater degree than does its chemical composition;

DNEL: Derived No Effect Level, is defined as the level of chemical exposure above which humans should not be exposed.

DMEL: Derived minimal Effect Level, is defined as the level of chemical exposure above which humans should not be exposed.

exposure scenario: means the set of conditions, including operational conditions and risk management measures, that describe how the substance is manufactured or used during its life-cycle and how the manufacturer or importer controls, or recommends downstream users to control, exposures of humans and the environment. These exposure scenarios may cover one specific process or use or several processes or uses as appropriate;

identified use: means a use of a substance on its own or in a mixture, or a use of a mixture, that is intended by an actor in the supply chain, including his own use, or that is made known to him in writing by an immediate downstream user;

intermediate: means a substance that is manufactured for and consumed in or used for chemical processing in order to be transformed into another substance (hereinafter referred to as synthesis):

(a) non-isolated intermediate: means an intermediate that during synthesis is not intentionally removed (except for sampling) from the equipment in which the synthesis takes place. Such equipment includes the reaction vessel, its ancillary equipment, and any equipment through which the substance(s) pass(es) during a continuous flow or batch process as well as the pipework for transfer from one vessel to another for the purpose of the next reaction step, but it excludes tanks or other vessels in which the substance(s) are stored after the manufacture;

(b) on-site isolated intermediate: means an intermediate not meeting the criteria of a non-isolated intermediate and where the manufacture of the intermediate and the synthesis of (an)other substance(s) from that intermediate take place on the same site, operated by one or more legal entities;

(c) transported isolated intermediate: means an intermediate not meeting the criteria of a non-isolated intermediate and transported between or supplied to other sites;

manufacturer: means any natural or legal person established within the Community who manufactures a substance within the Community;

manufacturing: means production or extraction of substances in the natural state;

mixture: means a mixture or solution composed of two or more substances.

not chemically modified substance: means a substance whose chemical structure remains unchanged, even if it has undergone a chemical process or treatment, or a physical mineralogical transformation, for instance to remove impurities;

non-phase-in substance: all substances that are not fulfilling of the criteria for phase-in substances are considered non-phase in substances. Non phase-in substances do not benefit from the transitional

regime provided for phase-in substances and need to be registered before they can be manufactured, imported or placed on the market in the EU in a quantity of 1 tonne/year or more, unless they have already been notified under Directive 67/548/EEC.

notified substance: means a substance for which a notification has been submitted and which could be placed on the market in accordance with Directive 67/548/EEC;

phase-in substance**:** means a substance which meets at least one of the following criteria:
(a) it is listed in the European Inventory of Existing Commercial Chemical Substances (EINECS);
(b) it was manufactured in the Community, or in the countries acceding to the European Union on 1 January 1995 or on 1 May 2004, but not placed on the market by the manufacturer or importer, at least once in the 15 years before the entry into force of this Regulation, provided the manufacturer or importer has documentary evidence of this;
(c) it was placed on the market in the Community, or in the countries acceding to the European Union on 1 January 1995 or on 1 May 2004, before entry into force of this Regulation by the manufacturer or importer and was considered as having been notified in accordance with the first indent of Article 8(1) of Directive 67/548/EEC but does not meet the definition of a polymer as set out in this Regulation, provided the manufacturer or importer has documentary evidence of this, including proof that the substance was placed on the market by any manufacturer or importer between 18 September 1981 and 31 October 1993 inclusive;

PNEC: Predicted No Effect Concentration, defined as the concentration of a chemical which marks the limit at which below no adverse effects of exposure in an ecosystem are measured.

PPORD: Product and Process Orientated Research and Development, means any scientific development related to product development or the further development of a substance, on its own, in mixtures or in articles in the course of which pilot plant or production trials are used to develop the production process and/or to test the fields of application of the substance;

registrant: means the manufacturer or the importer of a substance or the producer or importer of an article submitting a registration for a substance;

registrant's own use: means an industrial or professional use by the registrant;

site: means a single location, in which, if there is more than one manufacturer of (a) substance(s), certain infrastructure and facilities are shared;

substance: means a chemical element and its compounds in the natural state or obtained by any manufacturing process, including any additive necessary to preserve its stability and any impurity deriving from the process used, but excluding any solvent which may be separated without affecting the stability of the substance or changing its composition;

substances which occur in nature: means a naturally occurring substance as such, unprocessed or processed only by manual, mechanical or gravitational means, by dissolution in water, by flotation, by extraction with water, by steam distillation or by heating solely to remove water, or which is extracted from air by any means;

use and exposure category: means an exposure scenario covering a wide range of processes or uses, where the processes or uses are communicated, as a minimum, in terms of the brief general description of use;

scientific research and development: means any scientific experimentation, analysis or chemical research carried out under controlled conditions in a volume less than one tonne per year;

use: means any processing, formulation, consumption, storage, keeping, treatment, filling into containers, transfer from one container to another, mixing, production of an article or any other utilisation;

8.2 Chemical Safety Assessment

A chemical safety assessment (CSA) for a substance shall include the following steps:

1. Human health hazard assessment.
2. Human health hazard assessment of physicochemical properties.
3. Environmental hazard assessment.
4. PBT and vPvB assessment.

In the cases a substance fulfils the criteria for any of the classifications for hazard, the chemical safety assessment shall also include:

5. Exposure assessment.
6. Risk characterisation.

Below these steps are further detailed:

1. Human health hazard assessment

The objectives of the human health hazard assessment shall be to determine the classification of a substance in accordance with Regulation (EC) No 1272/2008; and to derive levels of exposure to the substance above which humans should not be exposed. This level of exposure is known as the Derived No-Effect Level (DNEL).

The human health hazard assessment shall consider the toxicokinetic profile (i.e. absorption, metabolism, distribution and elimination) of the substance and the following groups of effects:

(1) acute effects such as acute toxicity, irritation and corrosivity;
(2) sensitization;
(3) repeated dose toxicity; and
(4) CMR effects (carcinogenicity, germ cell mutagenicity and toxicity for reproduction).

Based on all the available information, other effects shall be considered when necessary.

The hazard assessment shall comprise the following four steps:

Step 1: Evaluation of non-human information.
Step 2: Evaluation of human information.
Step 3: Classification and Labelling.
Step 4: Derivation of DNELs.

The first three steps shall be undertaken for every effect for which information is available and shall be recorded under the relevant section of the Chemical Safety Report. For any effect for which no relevant information is available, the relevant section shall contain the sentence: 'This information is not available'. The justification, including reference to any literature search carried out, shall be included in the technical dossier.

Step 4 of the human health hazard assessment shall be undertaken by integrating the results from the first three steps and shall be included under the relevant heading of the Chemical Safety Report and summarized in the Safety Data Sheet.

Step 1: Evaluation of non-human information

The evaluation of non-human information shall comprise:
- the hazard identification for the effect based on all available nonhuman information,
- the establishment of the quantitative dose (concentration)-response (effect) relationship.

When it is not possible to establish the quantitative dose (concentration)- response (effect) relationship, then this should be justified and a semi-quantitative or qualitative analysis shall be included. For instance, for acute effects it is usually not possible to establish the quantitative dose (concentration)-response (effect) relationship on the basis of the results of a test conducted. In such cases it suffices to determine whether and to which degree the substance has an inherent capacity to cause the effect.

All non-human information used to assess a particular effect on humans and to establish the dose (concentration) – response (effect) relationship, shall be briefly presented, if possible in the form of a table or tables, distinguishing between in vitro, in vivo and other information. The relevant test results (e.g. ATE, LD50, NO(A)EL or LO(A)EL) and test conditions (e.g. test duration, route of administration) and other relevant information shall be presented, in internationally recognized units of measurement for that effect.

If one study is available then a robust study summary should be prepared for that study. If there are several studies addressing the same effect, then, having taken into account possible variables (e.g. conduct, adequacy, relevance of test species, quality of results, etc.), normally the study or studies giving rise to the highest concern shall be used to establish the DNELs and a robust study summary shall be prepared for that study or studies and included as part of the technical dossier. Robust summaries will be required of all key data used in the hazard assessment. If the study or studies giving rise to the highest concern are not used, then this shall be fully justified and included as part of the technical dossier, not only for the study being used but also for all studies demonstrating a higher concern than the study being used. It is important irrespective of whether hazards have been identified or not that the validity of the study be considered.

Step 2: Evaluation of human information

If no human information is available, this part shall contain the statement: 'No human information is available'. However, if human information is available, it shall be presented, if possible in the form of a table.

Step 3: Classification and Labelling

The appropriate classification developed in accordance with the criteria in Regulation (EC) No 1272/2008 shall be presented and justified. Where applicable, Specific Concentration limits[28] shall be presented and justified.

The assessment should always include a statement as to whether the substance fulfils or does not fulfil the criteria given in Regulation (EC) No 1272/2008 for classification in the hazard class carcinogenicity category 1A or 1B, in the hazard class germ cell mutagenicity category 1A or 1B or in the hazard class reproductive toxicity category 1A or 1B.

If the information is inadequate to decide whether a substance should be classified for a particular hazard class or category, the registrant shall indicate and justify the action or decision he has taken as a result.

[28] resulting from the application of Article 10 of Regulation (EC) No 1272/2008 and Articles 4 to 7 of Directive 1999/45/EC.

Step 4: Identification of DNEL(s)

Based on the outcomes of steps 1 and 2, (a) DNEL(s) shall be established for the substance, reflecting the likely route(s), duration and frequency of exposure. For some hazard classes, especially germ cell mutagenicity and carcinogenicity, the available information may not enable a toxicological threshold, and therefore a DNEL, to be established. If justified by the exposure scenario(s), a single DNEL may be sufficient. However, taking into account the available information and the exposure scenario(s) it may be necessary to identify different DNELs for each relevant human population (e.g. workers, consumers and humans liable to exposure indirectly via the environment) and possibly for certain vulnerable sub-populations (e.g. children, pregnant women) and for different routes of exposure. A full justification shall be given specifying, inter alia, the choice of the information used, the route of exposure (oral, dermal, inhalation) and the duration and frequency of exposure to the substance for which the DNEL is valid. If more than one route of exposure is likely to occur, then a DNEL shall be established for each route of exposure and for the exposure from all routes combined. When establishing the DNEL, the following factors shall, inter alia, be taken into account:

(a) the uncertainty arising, among other factors, from the variability in the experimental information and from intra- and inter-species variation;

(b) the nature and severity of the effect;

(c) the sensitivity of the human (sub-)population to which the quantitative and/or qualitative information on exposure applies.

If it is not possible to identify a DNEL, then this shall be clearly stated and fully justified.

2. Physicochemical hazard assessment

The objective of the hazard assessment for physicochemical properties shall be to determine the classification of a substance in accordance with Regulation (EC) No 1272/2008.

As a minimum, the potential effects to human health shall be assessed for the following physicochemical properties:

- explosivity,
- flammability,
- oxidising potential.

If the information is inadequate to decide whether a substance should be classified for a particular hazard class or category, the registrant shall indicate and justify the action or decision he has taken as a result.

The assessment of each effect shall be presented under the relevant heading of the Chemical Safety Report.

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.

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

3. Environmental hazard assessment

The objective of the environmental hazard assessment shall be to determine the classification of a substance in accordance with Regulation (EC) No 1272/2008 and to identify the concentration of the

substance below which adverse effects in the environmental sphere of concern are not expected to occur. This concentration is known as the Predicted No Effect Concentration (PNEC).

The environmental hazard assessment shall consider the potential effects on the environment, comprising the (1) aquatic (including sediment), (2) terrestrial and (3) atmospheric compartments, including the potential effects that may occur (4) via food-chain accumulation. In addition, the potential effects on the (5) microbiological activity of sewage treatment systems shall be considered. The assessment of the effects on each of these five environmental spheres shall be presented in the Chemical Safety Report and summarized in the Safety Data Sheet.

For any environmental sphere, for which no effect information is available, the relevant section of the chemical safety report shall contain the sentence: 'This information is not available'. The justification, including reference to any literature research carried out, shall be included in the technical dossier. For any environmental sphere for which information is available, but the manufacturer or importer believes that it is not necessary to conduct the hazard assessment, the manufacturer or importer shall present a justification, with reference to pertinent information in the Chemical Safety Report and in the Safety Data Sheet.

The hazard assessment shall comprise the following three steps, which shall be clearly identified as such in the Chemical Safety Report:

Step 1: Evaluation of information.
Step 2: Classification and Labelling.
Step 3: Derivation of the PNEC.

Step 1: Evaluation of information

The evaluation of all available information shall comprise:
- the hazard identification based on all available information,
- the establishment of the quantitative dose (concentration)-response (effect) relationship.

When it is not possible to establish the quantitative dose (concentration)- response (effect) relationship, then this should be justified and a semiquantitative or qualitative analysis shall be included.

All information used to assess the effects on a specific environmental sphere shall be briefly presented, if possible in the form of a table or tables. The relevant test results (e.g. LC50 or NOEC) and test conditions (e.g. test duration, route of administration) and other relevant information shall be presented, in internationally recognised units of measurement for that effect.

All information used to assess the environmental fate of the substance shall be briefly presented, if possible in the form of a table or tables. The relevant test results and test conditions and other relevant information shall be presented, in internationally recognised units of measurement for that effect.

If one study is available then a robust study summary should be prepared for that study. Where there is more than one study addressing the same effect, then the study or studies giving rise to the highest concern shall be used to draw a conclusion and a robust study summary shall be prepared for that study or studies and included as part of the technical dossier. Robust summaries will be required of all key data used in the hazard assessment. If the study or studies giving rise to the highest concern are not used, then this shall be fully justified and included as part of the technical dossier, not only for the study being used but also for all studies reaching a higher concern than the study being used. For substances where all available studies indicate no hazards an overall assessment of the validity of all studies should be performed.

Step 2: Classification and Labelling

The appropriate classification developed in accordance with the criteria in Regulation (EC) No 1272/2008 shall be presented and justified. Any Mfactor resulting from the application of Article 10 of Regulation (EC) No 1272/2008 shall be presented and, if it is not included in Part 3 of Annex VI to Regulation (EC) No 1272/2008, justified.

If the information is inadequate to decide whether a substance should be classified for a particular hazard class or category, the registrant shall indicate and justify the action or decision he has taken as a result.

Step 3: Identification of the PNEC

Based on the available information, the PNEC for each environmental sphere shall be established. The PNEC may be calculated by applying an appropriate assessment factor to the effect values (e.g. LC50 or NOEC). An assessment factor expresses the difference between effects values derived for a limited number of species from laboratory tests and the PNEC for the environmental sphere (1).

If it is not possible to derive the PNEC, then this shall be clearly stated and fully justified.

4. PBT and vPvB assessment

Introduction

The objective of the PBT and vPvB assessment shall be to determine if the substance fulfils the criteria given in Annex XIII and if so, to characterize the potential emissions of the substance. A hazard assessment in addressing all the long-term effects, and the estimation of the long-term exposure of humans and the environment cannot be carried out with sufficient reliability for substances satisfying the PBT and vPvB criteria. Therefore, a separate PBT and vPvB assessment is required.

The PBT and vPvB assessment shall comprise the following two steps, which shall be clearly identified in the Chemical Safety Report:

Step 1: Comparison with the Criteria.

Step 2: Emission Characterisation.

The assessment shall also be summarised in the Safety Data Sheet.

Step 1: Comparison with the criteria

This part of the PBT and vPvB assessment shall entail the comparison of the available information with the criteria given in Section 1 of Annex XIII and a statement of whether the substance fulfils or does not fulfil the criteria, and an assessment shall be conducted.

Step 2: Emission Characterisation

If the substance fulfils the criteria or it is considered as if it is a PBT or vPvB in the registration dossier an emission characterization shall be conducted. In particular it shall contain an estimation of the amounts of the substance released to the different environmental compartments during all activities carried out by the manufacturer or importer and all identified uses, and an identification of the likely routes by which humans and the environment are exposed to the substance.

5. Exposure assessment

The objective of the exposure assessment shall be to make a quantitative or qualitative estimate of the dose/concentration of the substance to which humans and the environment are or may be exposed. 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. The exposure assessment shall entail the following two steps, which shall be clearly identified as such in the Chemical Safety Report:

Step 1: Generation of exposure scenario(s) or the generation of relevant use and exposure categories.

Step 2: Exposure Estimation.

Where required, the exposure scenario shall also be included in the Safety Data Sheet.

Step 1: Development of exposure scenarios

Step 2: Exposure Estimation

In particular, the exposure estimation shall take account of:

- adequately measured, representative exposure data,
- the quantity in which the substance is produced and/or imported,
- the quantity for each identified use,
- implemented or recommended risk management, including the degree of containment,
- duration and frequency of exposure according to the operational conditions,
- the activities of workers related to the processes and the duration and frequency of their exposure to the substance,
- the activities of consumers and the duration and frequency of their exposure to the substance,
- the duration and frequency of emissions of the substance to the different environmental compartments and the dilution in the receiving environmental compartment,
- the physicochemical properties of the substance,
- transformation and/or degradation products,
- the likely routes of exposure of and potential for absorption in humans,
- the likely pathways to the environment and environmental distribution and degradation and/or transformation (see also Section 3 Step 1),
- scale (geographical) of exposure,
- matrix dependent release/migration of the substance.

6. Risk characterisation

The risk characterisation shall be carried out for each exposure scenario and shall be presented under the relevant heading of the Chemical Safety Report.

The risk characterisation shall consider the human populations (exposed as workers, consumers or indirectly via the environment and if relevant a combination thereof) and the environmental spheres for which exposure to the substance is known or reasonably foreseeable, under the assumption that the risk management measures described in the exposure scenarios have been implemented. In addition, the overall environmental risk caused by the substance shall be reviewed by integrating the results for the overall releases, emissions and losses from all sources to all environmental compartments.

The risk characterisation consists of:

- a comparison of the exposure of each human population known to be or likely to be exposed with the appropriate DNEL,

- a comparison of the predicted environmental concentrations in each environmental sphere with the PNECs, and
- an assessment of the likelihood and severity of an event occurring due to the physicochemical properties of the substance.

For any exposure scenario, the risk to humans and the environment can be considered to be adequately controlled, throughout the lifecycle of the substance that results from manufacture or identified uses, if:

- the exposure levels estimated in Section 6.2 do not exceed the appropriate DNEL or the PNEC, as determined in Sections 1 and 3, respectively, and,
- the likelihood and severity of an event occurring due to the physicochemical properties of the substance as determined in Section 2 is negligible.

For those human effects and those environmental spheres for which it was not possible to determine a DNEL or a PNEC, a qualitative assessment of the likelihood that effects are avoided when implementing the exposure scenario shall be carried out.

For substances satisfying the PBT and vPvB criteria, the manufacturer or importer shall use the information as obtained, Step 2 when implementing on its site, and recommending for downstream users, risk management measures which minimise exposures and emissions to humans and the environment, throughout the lifecycle of the substance that results from manufacture or identified uses.

8.3 REACH Annexes

Below the Annexes of the REACH Regulation referred to in the main text are listed for illustration.

ANNEX I: General provisions for assessing substances and preparing chemical safety reports (CSRs) – conditions under which manufacturers, importers or downstream users may conduct a CSR, the methodologies and documentation process.

ANNEX II: Guide to the compilation of safety data sheets – requirements for a supplier to compile with the safety data sheet for a substance or a mixture in accordance with Article 31.

ANNEX III: Criteria for substances registered in quantities between 1 and 10 tonnes.

ANNEX IV: Exemptions from the obligation to register in accordance with Article 2(7)(a) – list of substances exempted from Registration, Downstream Users and Evaluation as sufficient information is known about these substances that they are considered to cause minimum risk because of their intrinsic properties.

ANNEX V: Exemptions from the obligation to register in accordance with Article 2(7)(b) – list of substances exempted from Registration, Downstream users and Evaluation as registration is deemed inappropriate or unnecessary as these substances do not prejudice the objectives of REACH.

ANNEX VI: Information requirements referred to in Article 10 – details the general information needed for the submission of a registration dossier and evaluation.

ANNEX VII: Standard information requirements for substances manufactured or imported in quantities of one tonne or more.

ANNEX VIII: Standard information requirements for substances manufactured or imported in quantities of 10 tonnes or more.

ANNEX IX: Standard information requirements for substances manufactured or imported in quantities of 100 tonnes or more.

ANNEX X: Standard information requirements for substances manufactured or imported in quantities of 1,000 tonnes or more.

ANNEX XI: General rules for adaptation of the standard testing regime set out in Annexes VII to X – explains the standard conditions for testing under REACH. This may also be used for the Evaluation process by ECHA to ensure compliance to testing methods.

ANNEX XII: General provisions for downstream users to assess substances and prepare chemical safety reports – explains how downstream users are to assess and document that the risks arising from their substance(s) are adequately controlled during use, for a use not covered by the Safety Data Sheet supplied to them.

ANNEX XIII: Criteria for the identification of persistent, bioaccumulative and toxic substances, and very persistent and very bioaccumulative substances.

ANNEX XIV: List of substances subject to authorisation – list of substances that can only be used or placed on the market in the EU if an authorisation is granted (unless exemption applies, the sunset date has not passed or if a valid application is still pending).

ANNEX XV: Dossiers – general principles for preparing dossiers to propose and justify the identification of CMRs, PBTs, vPvBs, or a substance of equivalent concern as well as restrictions of the manufacture, placing on the market or use of a substance within the Community.

ANNEX XVI: Socio-economic analysis – outlines the information that may be addressed when submitting a socio-economic analysis (SEA) with an application for authorisation or in connection with a proposed restriction.

ANNEX XVII: Restrictions on the manufacture, placing on the market and use of certain dangerous substances, mixtures and articles – list of substances restricted for manufacture, import use or presence in articles in the EU and the conditions of the restriction.