

Guidance on the Application of the CLP Criteria

Part 1: General Principles for Classification and Labelling

Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures

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Guidance on the Application of CLP Criteria

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| Version 3.0 | Corrigendum of Part 1: General principles for classification and labelling. The corrigendum includes the following: <ul style="list-style-type: none"> The list of abbreviations was updated. A footnote informing the reader that with effect from 1 September 2013, Directive 98/8/EC had been repealed by Biocidal Products Regulation (EU) No 528/2012 was added. In Part 1, modal verbs 'shall' were replaced with 'must' where appropriate. | November 2013 |
| Version 3.1 | Corrigendum to take account of the end of the transition period of the 4 th ATP (as foreseen in version 4.0 above): <ul style="list-style-type: none"> change the colour of relative legal text boxes from orange to green; in Part 2, to delete section 2.2.1 Flammable gases and section 2.3.1 Flammable Aerosols (outdated text) and renumber sections 2.2.2 Flammable gases (including chemically unstable gases) and 2.3.2 Aerosols accordingly; in Part 3, to delete the "outdated text" in sections 3.7.4.1 and 3.7.5.1 in Reproductive Toxicity. <p>In addition, minor editorial errors were corrected and minor reformatting was made.</p> | June 2015 |
| Version 4.0 | Partial revision of the Guidance to update the content mainly following the 8 th Adaptation to Technical Progress to the CLP Regulation (Commission Regulation (EU) No 286/2011). Revision of few specific additional topics. The update includes the following: (i) Throughout the document: | July 2017 |

| | | |
|-------------|---|---------------|
| | <ul style="list-style-type: none"> • Revision of legal references and legal text quotations. • Renumbering of some sections. • Deletion of sections regarding the reclassification of substances and mixtures previously classified in accordance with the DSD or DPD. <p>(ii) Revision of Part 1:</p> <ul style="list-style-type: none"> • Deletion of reference to pre-CLP legislation and transitional period. • Addition of reference to read-across and grouping in the context of bioavailability. • Removal of quotation of Article 31(3) of REACH. • Clarification about applicability of additivity principle. • Clarification about the application of mixture rules to substances with CMR constituents. • Reduction of section 1.2.3.1 on physical hazards to avoid redundancy with section 2.0.4. <p>Revision of section 1.7 and removal of unnecessary information. Table on additional information using transport classification moved to a new Annex I (Formally, Annex VII).</p> | |
| Version 5.0 | Re-presentation of Part 1 as a stand alone guidance document. No alterations to content. | November 2024 |

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LIST OF ABBREVIATIONS

| Standard term / Abbreviation | Explanation |
|------------------------------|--|
| ADN | European Agreement concerning the International Carriage of Dangerous Goods by Inland Waterways (Accord européen relatif au transport international des marchandises dangereuses par voie de navigation intérieure) ¹ |
| ADR | European Agreement concerning the International Carriage of Dangerous Goods by Road (Accord européen relatif au transport international des marchandises dangereuses par route) ² |
| ATE | Acute Toxicity Estimate |
| ATP | Adaptation to Technical Progress (ATP) to the CLP Regulation |
| C&L | Classification and Labelling |
| CA | Competent Authority |
| cATpE | Converted Acute Toxicity point Estimate |
| CLP | Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures ³ |
| CSA | Chemical Safety Assessment |
| DPD | Directive 1999/45/EC on the classification and labelling of Dangerous Preparations ⁴ |
| DSD | Directive 67/548/EEC on the classification and labelling of Dangerous Substances ⁵ |
| ECHA | European Chemicals Agency, Helsinki (https://echa.europa.eu/) |

¹ European Agreement concerning the International Carriage of Dangerous Goods by Inland Waterways, concluded at Geneva on 26 May 2000, as amended.

² European Agreement concerning the International Carriage of Dangerous Goods by Road, concluded at Geneva on 30 September 1957, as amended.

³ Regulation (EC) No 1272/2008 of the European Parliament and Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC and amending Regulation (EC) No 1907/2006 [OJ L 353, 31.12.2008, p. 1].

⁴ Directive 1999/45/EC of the European Parliament and of the Council of 31 May 1999 concerning the approximation of the laws, regulations and administrative provisions of the Member States relating to the classification, packaging and labelling of dangerous preparations [OJ L 200, 30.7.1999, p. 1].

⁵ Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances [OJ 196, 16.8.1967, p. 1].

| Standard term / Abbreviation | Explanation |
|------------------------------------|---|
| ECVAM | European Centre for the Validation of Alternative Methods (http://ihcp.jrc.ec.europa.eu/our_labs/eurl-ecvam) |
| EN | A European Standard |
| EUH | The hazard statements carried through from DSD and DPD, which are not yet included in the GHS are codified as 'EUH' |
| GCL | General Concentration Limits |
| GHS | Globally Harmonised System of Classification and Labelling of Chemicals ⁶ |
| GLP | Good Laboratory Practice |
| HS (or H statement) | Hazard statement |
| ICAO TI | International Civil Aviation Organization (Technical Instructions for the Safe Transport of Dangerous Goods by Air) |
| IMDG Code | International Maritime Dangerous Goods Code |
| IMO | International maritime Organisation |
| IPCS | International Programme on Chemical Safety (joint programme of WHO, ILO and UNEP) |
| IR&CSA | Guidance on Information Requirements and Chemical Safety Assessment, ECHA (http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_en.htm) |
| ISO | International Organisation for Standardization |
| ITDG | Directive 2008/68 on the Inland Transport of Dangerous Goods ⁷ |
| K _{ow} | The n-octanol/water partition coefficient |
| LD ₅₀ /LC ₅₀ | Median (50%) lethal dose/concentration |
| M-factor | Multiplying factor |

⁶ Globally Harmonised System of Classification and Labelling of Chemicals (GHS), Fifth revised edition, United Nations, New York and Geneva, 2013.

⁷ Directive 2008/68/EC of the European Parliament and of the Council of 24 September 2008 on the inland transport of dangerous goods, implementing the European Agreement concerning the International Carriage of Dangerous Goods by Road (ADR), the Regulations concerning the International Carriage of Dangerous Goods by Rail (RID) and the European Agreement concerning the International Carriage of Dangerous Goods by Inland Waterways (ADN) [OJ L 260, 30.9.2008, p. 13].

| Standard term / Abbreviation | Explanation |
|------------------------------|--|
| MSCA | Member State Competent Authority |
| n.a. | Not available |
| OECD | Organisation for Economic Co-operation and Development |
| OECD TG | OECD Test Guideline All Test Guidelines are available at the OECD homepage (https://www.oecd.org/en/topics/sub-issues/testing-of-chemicals/test-guidelines.html) |
| (Q)SAR | (Quantitative) Structure Activity Relationship |
| REACH | Regulation (EC) No 1907/2006 of the European Parliament and of the Council concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals ⁸ |
| RID | Règlement concernant le transport international ferroviaire de marchandises dangereuses (Regulations concerning the International Carriage of Dangerous Goods by Rail) ⁹ |
| SCL | Specific Concentration Limit |
| SDS | Safety Data Sheet |
| STOT-SE | Specific Target Organ Toxicity - Single Exposure |
| STOT-RE | Specific Target Organ Toxicity - Repeated Exposure |
| UN | United Nations |
| UN RTDG Model Regulations | UN Recommendations on the Transport of Dangerous Goods - Model Regulations. It covers all modal transport regulations (ADR, RID, ADN, IMDG and ITDG). It is regularly updated and amended every two years. More information and the latest revision are available at: http://www.unece.org/trans/danger/publi/unrec/rev13/13nature_e.html |

⁸ Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and omission of Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC. [OJ L 396, 30.12.2006 p.1.] [Corrigendum: OJ L 136, 29.5.2007 p.3].

⁹ Regulations concerning the International Carriage of Dangerous Goods by Rail, appearing as Appendix C to the Convention concerning International Carriage by Rail (COTIF) concluded at Vilnius on 3 June 1999, as amended.

| Standard term / Abbreviation | | Explanation |
|------------------------------|-----|---|
| UNSCGHHS SCEGHS) | (or | United Nations SubCommittee of Experts on the Globally Harmonised System (http://www.unece.org/trans/danger/publi/ghs/ghs_welcome_e.html) |
| UNSCETDG SCETDG) | (or | United Nations SubCommittee of Experts on the Transport of Dangerous Goods (http://www.unece.org/trans/danger/danger.htm) |
| WAF | | Water Accommodated Fraction |

 **NOTEs to the reader:**

In this document, text cited from Regulation (EC) No 1272/2008 is indicated in **green boxes** in *italic* font.

 This symbol highlights text to be noted.

1. PART 1: GENERAL PRINCIPLES FOR CLASSIFICATION AND LABELLING

1.1. INTRODUCTION

1.1.1. The objective of the guidance document

This document is a comprehensive technical and scientific guidance on the application of Regulation (EC) No 1272/2008 on the classification, labelling and packaging of substances and mixtures¹⁰, hereafter referred to as CLP.

CLP amended the Dangerous Substance Directive 67/548/EEC¹¹ (DSD), the Dangerous Preparations Directive 1999/45/EC¹² (DPD) and Regulation (EC) No 1907/2006¹³ (REACH), and repealed DSD and DPD from 1 June 2015 (CLP Article 61). CLP was implemented based on the United Nations' Globally Harmonised System of Classification and Labelling of Chemicals (UN GHS) without lowering the protection of human health and the environment, compared to the classification, labelling and packaging system in DSD and DPD. The implementation of GHS into CLP followed various declarations made by the Community to confirm its intention to contribute to GHS development and to implement GHS into EU law.

A core principle of CLP is self-classification of a substance or mixture by the manufacturer, importer or downstream user (CLP Article 4(3) and Recital 17), which involves identification of the hazards of the substance or mixture followed by classification as a result of the comparison of the hazard information with the criteria in CLP. This guidance will enable industry to self-classify chemicals and to provide appropriate hazard communication information to the target populations potentially handling the substance or mixture or exposed to it. For substances of particular concern (carcinogens, mutagens, substances toxic for reproduction (CMRs) and respiratory sensitisers) or for other substances where EU-wide action is needed, CLP sets out a system for formal harmonisation of classifications at EU level.

Given that many provisions under REACH are linked to classification, the implementation of REACH and CLP is interlinked and should be planned and applied in tandem. General advice on the implementation of CLP is available in the ECHA's *Introductory Guidance on the CLP Regulation*, available on the ECHA website (<http://echa.europa.eu/web/guest/guidance-documents/guidance-on-clp>).

The objective of this document is to provide detailed guidance on the application of the CLP criteria for physical, health and environmental hazards.

¹⁰ Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006 [OJ L 353, 31.12.2008, p. 1].

¹¹ Council Directive 67/548/EEC relating to the classification, packaging and labelling of dangerous substances, as amended [OJ 196, 16.8.1967, p. 1].

¹² Directive 1999/45/EC as of 30 July 2002 of the European Parliament and of the Council relating to the classification, packaging and labelling of dangerous preparation, as amended [OJ L 200, 30.7.1999, p.1].

¹³ Regulation (EC) No 1907/2006 of the European Parliament and of the Council concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and omission of Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC. [OJ L 396, 30.12.2006 p.1.] [Corrigendum: OJ L 136, 29.5.2007 p.3].

1.1.2. Background

The aim of classification and labelling is to identify the hazardous properties of a substance or a mixture by applying specific classification criteria to the available hazard data, and then to provide appropriate hazard labelling and information on safety measures.

The EU has had a comprehensive system for the classification and labelling of dangerous substances and mixtures for over 40 years, in the past mainly DSD and DPD. In addition, the Safety Data Sheet (SDS) Directive 91/155/EEC¹⁴ required suppliers to provide more detailed information for professional users. These directives contributed to a single market in chemicals in the EU, based on a high level of protection of human safety and health and the environment.

The GHS was developed worldwide to minimise differences between systems of different jurisdictions for classification and labelling of substances and mixtures. The GHS aims to contribute towards global efforts to provide protection from hazardous effects of chemicals and to facilitate trade.

The GHS criteria for classifying hazardous substances and mixtures were developed taking into account existing systems for hazard classification, such as the EU supply and use system, the Canadian and US Pesticide systems, GESAMP¹⁵ hazard evaluation procedure, IMO¹⁶ Scheme for Marine Pollutants, the UN Recommendations on the Transport of Dangerous Goods (UN/RTGD), and the US Land Transport. These systems include supply and subsequent use of chemicals, the sea transport of chemical substances as well as transport of chemical substances by road and rail. The harmonised criteria are therefore intended to identify hazardous chemicals in a common way for use throughout all these systems.

The GHS provides a basis for an internationally uniform information system on hazardous substances and mixtures. It provides harmonised criteria for classification and hazard communication measures for different target audiences, including consumers, workers and emergency responders, and in transport. It follows a 'building block' approach to enable jurisdictions to adopt the system according to the needs of their law and the various target audiences. However, although the final aim of GHS is to have a fully harmonised classification and labelling system worldwide, it is recognised that differences may persist between sectors (e.g. transport, supply and use), but should not occur within a sector globally (section 1.1.3.1.5, UNSCEGHS, 6th revision).

The GHS was agreed by the UN Committee of Experts on the Transport of Dangerous Goods and the Globally Harmonized System of Classification and Labelling of Chemicals (CETDG/GHS). It was formally approved by the UN Economic and Social Council (UN ECOSOC) in July 2003 and published further in 2003 after a decade of negotiations. It is updated biannually. The changes in GHS are not automatically reflected in the CLP Regulation. The latter is adapted and updated by the Commission via Adaptations to Technical Progress (ATPs - see Article 53(1) of CLP).

1.1.3. Hazard classification

Hazard classification is a process involving the identification of information on the physical, health, environmental or other hazards of a substance or a mixture as set out in Annex I to CLP. This is followed by the comparison of the hazard information (including the *severity of hazard*) with defined criteria, in order to determine the *classification* of the substance or mixture. Thus, under

¹⁴ Council Directive 91/155/EEC relating to defining and laying down the detailed arrangements for the system of specific information relating to dangerous preparations and dangerous substances, as amended [OJ L 076, 22.03.1991, p. 35], repealed and replaced by Regulation (EC) No 1907/2006 as of 1 June 2007.

¹⁵ Group of Experts on the Scientific Aspects of Marine Environmental Protection.

¹⁶ International Maritime Organisation.

CLP, a manufacturer, importer or downstream user will apply the following steps to arrive at a self-classification of a substance or a mixture:

- identification of relevant available information regarding the potential hazards (including *severity of hazard*) of a substance or mixture;
- examination of the information gathered to assess whether it is relevant, reliable and sufficient for classification purposes;
- evaluation of the information (data) by applying the classification criteria in Annex I, CLP for each hazard class and differentiation; and
- decision on whether the hazard information for the substance or mixture meets the criteria for one or more hazard classes or differentiations and therefore decision on the classification of the substance or mixture as hazardous in relation to these hazard classes or differentiations (assignment of hazard categories, SCL(s), M-factor(s) and hazard statement(s) according to the provisions in Annex I, CLP).

Preliminary information on identification of relevant data is provided in section [1.1.6](#) of this guidance document, while guidance on available test methods is provided in Part B of the ECHA *Guidance document on Information Requirements and Chemical Safety Assessment* (Chapters R.2 to R.4, IR&CSA), available on the ECHA Website (<http://echa.europa.eu/web/guest/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment>). Chapters R.7a/b/c of the same Guidance provide more detailed information and endpoint-specific guidance.

Classification according to CLP is based on *intrinsic* hazards, i.e. the basic properties of a substance or mixture as determined in standard tests or by other means designed to identify hazards. It should be noted that for some hazard classes the intrinsic properties of a substance or mixture are not always the only aspects relevant for classification, e.g. explosives or aerosols for which classification is also package dependent, or aspiration hazard which may not be relevant for certain package types. As CLP is hazard-based, it does not take exposure into consideration in arriving at a classification. It should further be noted that classification of substances and mixtures may be required even when placed on the market in forms that are not hazardous. E.g. metals in massive form, alloys, mixtures containing polymers or elastomers, should be classified according to the criteria for e.g. toxic effects by inhalation but may not need to be labelled.

1.1.4. Who is responsible for the hazard classification

CLP and REACH place the responsibility for hazard classification and related provisions such as packaging, hazard communication and SDS on the suppliers of substances and mixtures. Both *substances and mixtures* must be classified, labelled and packaged in accordance with CLP before placing them on the market.

1.1.5. Which substances and mixtures should be classified

Substances and mixtures placed on the market fall within the scope of classification under CLP and should be evaluated in order to reach a decision as to whether or not the criteria are met and therefore if they should be classified. Substances are also subject to classification where they are subject to registration or notification under REACH, even if they are not placed on the market.

However, a number of substances and mixtures are exempted from the requirements of the CLP Regulation as a whole (CLP Article 1):

- radioactive substances and mixtures (Directive 96/29/Euratom¹⁷);

¹⁷ Council Directive 96/29/Euratom of 13 May 1996 laying down basic safety standards for the protection of the health of workers and the general public against the dangers arising from ionizing radiation [OJ L 159, 29.6.1996, p. 1].

- substances and mixtures which are subject to customs supervision, provided that they do not undergo any treatment or processing, and which are in temporary storage, or in a free zone or free warehouse with a view to re-exportation, or in transit;
- non-isolated intermediates;
- substances and mixtures used in scientific experimentation, analysis or chemical research, provided they are not placed on the market and they are used under controlled conditions in accordance with EU workplace and environmental legislation;
- waste, as defined in Directive 2006/12/EC¹⁸; and
- certain substances or mixtures in the finished state, intended for the final user:
 - medicinal products, as defined in Directive 2001/83/EC¹⁹,
 - veterinary medicinal products, as defined in Directive 2001/82/EC²⁰,
 - cosmetic products, as defined in Directive 76/768/EEC²¹,
 - medical devices as defined in Directive 90/385/EEC²² (active implantable medical devices) and 93/42/EEC²³ (medical devices in general), which are invasive or used in direct physical contact with the human body, and in vitro diagnostic medical devices (Directive 98/79/EC²⁴), and
 - food or feeding stuffs as defined in Regulation 178/2002²⁵, including when they are used as food additives within the scope of Directive 89/107/EEC²⁶, as a flavouring in foodstuffs within the scope of Directive 88/388/EEC and Decision 1999/217/EC²⁷,

¹⁸ Directive 2006/12/EC of the European Parliament and of the Council of 5 April 2006 on waste [OJ L 114, 27.4.2006, p. 9].

¹⁹ 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].

²⁰ Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products [OJ L 311, 28.11.2001, p. 1].

²¹ Council Directive 76/768/EEC of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products [OJ L 262, 27.9.1976, p. 169].

²² Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices [OJ L 189, 20.7.1990, p. 17].

²³ Council Directive 93/42/EEC of 14 June 1993 concerning medical devices [OJ L 169, 12.7.1993, p. 1].

²⁴ Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices [OJ L 331, 7.12.1998, p. 1].

²⁵ Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety [OJ L 31, 1.2.2002, p. 1].

²⁶ Council Directive 89/107/EEC of 21 December 1988 on the approximation of the laws of the Member States concerning food additives authorized for use in foodstuffs intended for human consumption [OJ L 40, 11.2.1989, p. 27].

²⁷ 1999/217/EC: Commission Decision of 23 February 1999 adopting a register of flavouring substances used in or on foodstuffs drawn up in application of Regulation (EC) No 2232/96 of the European Parliament and of the Council of 28 October 1996 [OJ L 84, 27.3.1999, p. 1].

as an additive in feeding stuffs within the scope of Regulation (EC) 1831/2003²⁸, and in animal nutrition within the scope of Directive 82/471/EEC²⁹.

In addition, Member States may exempt certain substances or mixtures in specific cases where necessary for the purpose of national defence.

Although CLP does not apply to the transport of dangerous goods by air, sea, road, rail or inland waterways (CLP Article 1(6)), the criteria for classification are normally intended to be the same in the two systems. Thus, a substance or mixture classified in a hazard class which is common to both CLP and the transport legislation will normally be classified the same in both systems. However, the transport classifications do not include all of the GHS categories, so the absence of a transport classification does not mean the substance or mixture should not be classified under CLP. The relation between transport and CLP classification regarding physical hazards is detailed in Annex I to Part 2 of the CLP guidance.

1.1.6. What information is needed for classification

1.1.6.1. Information for the classification of substances

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.

CLP does not require new testing for the purpose of classification for health or environmental hazards; testing for physical hazards is required unless adequate and reliable information is already available (CLP Article 8(2)). However, a substance placed on the market for research and development (R&D) purposes may have been manufactured or imported in quantities that are too small to perform physical hazard testing. In these cases it would not be proportionate to request the respective manufacturer, importer or downstream user to perform the tests required in Part 2 of Annex I to CLP.

Although data may be provided through the application of REACH, it should be recognised that the data set required by REACH (particularly at lower tonnages) will not necessarily enable the comparison with the criteria for all hazard classes. Information may also be available from other EU legislation for which there are specific requirements for test data to be generated, such as legislation on plant protection products (Regulation (EC) No 1107/2009³⁰ and Directive

²⁸ Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 on additives for use in animal nutrition [OJ L 268, 18.10.2003, p. 29].

²⁹ Council Directive 82/471/EEC of 30 June 1982 concerning certain products used in animal nutrition [OJ L 213, 21.7.1982, p. 8].

³⁰ Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market repeals Council Directives 79/117/EEC and 91/414/EEC with effect from 14 June 2011. However Article 80 of Regulation (EC) No 1107/2009 specifies that directive 91/414/EEC shall continue to apply with respect to active substances included in Annex I to that Directive for certain transitional periods.

91/414/EEC³¹) and on biocidal products (Regulation (EU) No 528/2012³² and Directive 98/8/EC³³), or from various non-EU programmes. Finally, the supplier may decide to conduct new testing in order to fill data gaps, provided that he has exhausted all other means of generating information. Testing on animals must be avoided wherever possible and alternative methods (including *in vitro* testing, the use of (Q)SARs, read-across and/or grouping approaches) must always be considered first, provided they are scientifically validated, sufficiently adequate and reliable.

In the case of a substance containing impurities, additives or other constituents, the classification of the substance should, similar to mixtures, preferably be based on available information (including test data) on the substance except when classifying for CMR properties or when evaluating the bioaccumulation and degradation properties within the 'hazardous to the aquatic environment' hazard class (referred to in sections 4.1.3.3.2 and 4.1.2.9 of Annex I to CLP). In such cases it is strongly recommended that the classification of the substance, similar to mixtures (Articles 6(3), 6(4) and 10 of CLP), is based on information of known CMR constituent(s) as there is no toxicological difference between a mixture and a substance containing other constituent substances³⁴. In exceptional cases, data on the substance itself might show relevant effects for classification for CMR and/or bioaccumulation or degradation properties which have not been identified from the information on the constituent substances. These data should then be used, if available.

If, for the purpose of CLP, it is required or decided to generate new data, certain test methods and quality conditions must be met. Studies must be conducted in accordance with the EU test methods (Regulation (EC) 440/2008)³⁵ or other international test methods validated according to international procedures such as those of the OECD. For physical hazards new tests must be carried out in compliance with a relevant recognised quality system or by laboratories complying with a relevant recognised standard, and for health and environmental hazards in compliance with the principles of Good Laboratory Practice (GLP)³⁶. Animal tests must comply with the Directive 86/609/EEC³⁷. Tests on non-human primates are prohibited for the purposes of CLP. Tests on humans must not be performed for the purpose of CLP. However, existing data obtained from other sources, such as accident records and epidemiological and clinical studies, can be used.

1.1.6.2. Information relevant for the classification of mixtures

For mixtures, classification for physical hazards should normally be based on the results of tests carried out on the mixtures themselves (unless, as for substances, a mixture placed on the market

³¹ Council Directive 91/414/EEC of 15 July 1991 concerning the placing of plant protection products on the market, as amended [OJ L 230, 19.8.91, p. 1].

³² Regulation (EU) No 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products. It should be noted that with effect from 1 September 2013, Biocidal Products Regulation (EU) No 528/2012 repealed Directive 98/8/EC.

³³ Directive 98/8/EC of the European Parliament and of the Council of 16 February 1998 concerning the placing of biocidal products on the market, as amended [OJ L 123, 24.4.98, p. 1].

³⁴ Please note that there is a case still pending before the Court of Justice on the classification of an UVCB substance based on information on its constituents: Case C-691/15 P.

³⁵ Council Regulation (EC) No 440/2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 of the European Parliament and of the Council concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)[OJ L 142, 31.5.2008, p. 1].

³⁶ More information on the GLP principles and related requirements is available in the Q&As section on the ECHA website at <https://www.echa.europa.eu/web/guest/support/qas-support/qas>.

³⁷ Directive 86/609/EEC regarding the protection of animals used for experimental and other scientific purposes, [OJ L 358, 18.12.1986, p. 1].

for R&D purposes has been manufactured or imported in quantities that are too small to perform physical hazard testing). New tests for physical hazards must be carried out in compliance with a relevant recognised quality system or by laboratories complying with a relevant recognised standard.

When considering health and environmental hazards, the classification should preferably be based on information (including test data) on the mixture itself, if available, except when classifying for e.g. CMR effects or when evaluating the bioaccumulation and degradation properties within the 'hazardous to the aquatic environment' hazard class referred to in sections 4.1.2.8 and 4.1.2.9 of Annex I to CLP. In these cases, classification of the mixtures must be based on the information on the substances.

New tests for the purpose of classification and labelling for health or environmental hazards of substances and mixtures, may only be performed when the manufacturer, importer or downstream user has exhausted all other means of generating information according to Article 8 of CLP. According to this article, this includes application of the general rules provided in section 1 of Annex XI to REACH which refers to possible alternative methods/approaches to animal testing of a substance when required in REACH, i.e. the use existing data, weight of evidence, (Q)SARs, *in vitro*, grouping of substances and read-across, provided they are considered adequate for the purpose of classification and labelling. In the case of mixtures (and multiconstituent substances), it has to be re-assured that the method is relevant and reliable for the mixture (see specific guidance for each hazard class).

Thus, if no *in vivo* test data are available on a mixture, such data should normally not be generated; rather, all available information on the ingredients³⁸ of the mixture should be used to derive a classification.

Annex I to CLP specifies 'bridging principles' which enables suppliers to derive health or environmental classifications of their mixtures based on available data on similar tested mixtures and on the ingredient substances. Annex I also provides specific rules for the classification of mixtures based on the classification of the individual substances in the mixture.

1.1.7. Data evaluation and reaching a decision on classification

1.1.7.1. Classification of substances

After the available information has been assembled, a systematic evaluation of this information is necessary in order to derive a classification. 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. The substance is then assigned the appropriate hazard communication elements.

In some cases the classification decision may be straightforward, requiring only an evaluation of whether the substance gave a positive or negative result in a specific test that can be directly compared with the classification criteria. In other cases, scientific judgements must be made (e.g. on dose-response relationships, equivocal results and non-standardised tests) in a weight of evidence determination when applying the criteria. Expert judgement may therefore be needed to decide whether the results of a particular test or the available information in a Weight of evidence assessment meet the criteria laid down in Annex I.

³⁸ Note that the term "ingredient" is used in this guidance with the same meaning of "component" to indicate a substance in a mixture.

1.1.7.2. Influence of impurities, additives or individual constituents on the classification of a substance

Substances may contain impurities, additives, or other constituents while still meeting the substance definition in CLP. This applies to both mono-constituent, multi-constituent (e.g. reaction masses) and UVCB substances. The classification of such impurities, additives or individual constituents may influence the classification of the substance, in addition to the other hazardous properties. If data on the substance with its components are not available (or for CMRs, see section 1.1.6.1), in principle, the same classification and labelling rules as for mixtures should apply also for such substances³⁹.

1.1.8. Updating of hazard classifications

Updating of classifications may be necessary if, for example, new information is obtained or if the criteria in CLP are amended. When manufacturers, importers or downstream users become aware of new information or an amendment to CLP or when a change is introduced in a substance or mixture, they must reconsider the classification of the substance or mixture. Note that “new” here refers to information not previously considered (or even new interpretation of old data), not necessarily newly produced data. A downstream user may use the classification derived in accordance with the criteria by his supplier; this does not relieve the downstream user from the obligation to share new information with the supplier to allow him to meet the requirements.

Please, see also Section [1.1.10](#) addressing changes in harmonised classifications.

1.1.9. The interface between hazard classification and hazard communication

CLP provides an integrated system of hazard communication elements on the label including hazard pictograms, signal words, hazard statements and precautionary statements. Provision of this information to the end user is obligatory, irrespective of conditions of use and risk. While the Chemical Safety Assessment (CSA) on a particular substance performed for the purpose of REACH may indicate ‘safe use’, a situation resulting in unforeseen exposure may occur, such as in an accident. In such a situation, workers, managers and emergency personnel will need information on the hazard profile of the substance, which will be provided by the label and the SDS. These sources of information will also provide useful information to the worker on the safe handling of the chemical.

It is recognised that the hazard communication needs of the various end users may differ. Consumers are primarily dependent on the label of a substance or a mixture as a source of hazard and precautionary information, while the requirement for provision of an SDS is primarily applicable to professional users. Thus, the label facilitates communication of key hazard information on a substance or a mixture and additional safety advice (precautionary statements) to consumers, as well as to workers.

1.1.10. The interface between self-classification and harmonised classification, and the list of harmonised classifications

CLP places emphasis on self-classification by industry of the substances or mixtures they supply. In some cases, substances are subject to harmonised classification at EU level, while mixtures must always be self-classified, except for pesticidal and biocidal products where the Member State competent authorities (MSCAs) decide on the classification as part of the national authorisation scheme (CLP Article 36(2)).

If a substance has a harmonised classification as provided in Annex VI to CLP, this classification must always be used by a manufacturer, importer or downstream user, except for the minimum

³⁹ Please note that a case is still pending before the Court of Justice on the classification of a UVCB based on information on its constituents: Case C-691/15 P.

classifications indicated with an asterisk (*) in Table 3.1. The use of the minimum classification is explained in section 1.2.1 of Annex VI. For such minimum classifications, when available data exists to justify a more stringent category than the given minimum, the more stringent category must be used. It should be noted that where some but not all hazard classes or differentiations within a hazard class have been harmonised, the remaining hazards must be evaluated and self-classified to complete the classification (according to CLP Article 4(3) and CLP Recital 17). Note that the presence of an impurity/additive/constituent which leads to classification in a more severe hazard classification than the harmonised classification of the substance (in Annex VI, CLP) should be taken into account in the classification of the substance. (As for substances in Annex VI, the name of the substance to be put on the label should include also the name of the impurity/additive/constituent (i.e. substance name followed by “containing $\geq x\%$ name of impurity”) in cases where they contribute significantly to the classification of the substance as in the case above (see 1.1.1.4, Annex VI, CLP)).

Under CLP, the harmonised classification and labelling of substances normally aims to cover properties of the highest concern (CMR and respiratory sensitisation) but CLP also allows harmonisation for other properties if there is a need for such an action at EU-level. Decisions on harmonised classification are taken by the European Commission through comitology (CLP Article 37(5)), following a proposal submitted to ECHA and an opinion developed by ECHA's Risk Assessment Committee (RAC) on the proposal (CLP Article 37(4)). Whenever a manufacturer, importer or downstream user has new information which may affect a harmonised classification, he must submit a proposal for a change to the member State Competent Authority where the substance is placed on the market.

Substances regulated under the Biocidal Products Regulation (EU) No 528/2012 or under the Plant Protection Products Regulation (EC) No 1107/2009 will normally be subject to harmonised classification and labelling for all hazardous properties. These proposals for harmonised classification and labelling are prepared by MSCAs only (CLP Article 36(2)). However, in general proposals for harmonised classification for a particular substance to be added in Annex VI to CLP can be made by both MSCAs and by manufacturers, importers and downstream users (CLP Article 37). Only MSCAs can propose a revision of an existing harmonised classification and labelling to ECHA (CLP Article 37(6)).

A new or revised harmonised classification of a substance set out in Annex VI to CLP must be applied from the date specified in the respective ATP, although suppliers may use this classification before that date.

When a supplier decides not to apply the harmonised C&L of a substance before this date, they must identify and examine all available information for the self-classification. Thus they should take into consideration the opinion adopted by the ECHA Risk Assessment Committee (RAC) on the harmonised C&L for that substance.

If the C&L of a substance is already harmonised in the same hazard class, compliance with the existing harmonised C&L is legally required until it is formally changed in an ATP to CLP. The new harmonised C&L may be voluntarily applied as soon as the respective ATP enters into force. At the date of applicability, as provided for in the respective ATP, the suppliers are obliged to comply with the new harmonised C&L.

Harmonised classification and labelling of a substance provides for a high level of protection of human health and the environment, and provides legal clarity for different suppliers of the same substance of high concern (i.e. manufacturers of substances, importers of substances or mixtures, producers of specific articles, downstream users (including manufacturers of mixtures) and distributors).

Part 3 of Annex VI to CLP contains the list of harmonised classifications and labellings (except precautionary statements). All harmonised classifications previously adopted under DSD and listed in Annex I to DSD were translated to CLP classifications and carried over to the list of harmonised classifications in Annex VI to CLP also including the Notes assigned to the entries as

referred to in the DSD. This was done to maintain the same level of protection under CLP as under DSD. The harmonisation of classification of substances is a continuous process building on all efforts already done within the EU so far to evaluate hazards of substances that caused concern.

Annex VI contains a number of entries indicated with Note B. The note relates to substances (acids, bases, etc.) that are placed on the market in aqueous solutions. The required classification and labelling may be different at different concentrations. These entries have a general designation of the following type: 'nitric acid ... %'. These entries give the classification of the substance in a water solution above the GCL or SCL. The GCLs or SCLs are applied as usual in the classification of any mixture containing the substance. Thus, the concentration of the undiluted substance is compared with the GCL or SCL, as appropriate. For example, when diluted 75% phosphoric acid is added to a mixture to make up 10% of the mixture, the final concentration of phosphoric acid in the final mixture is 7.5%. As for this substance the SCL for skin and eye irritation is 10%, the final mixture does not require classification for these hazard classes based on phosphoric acid. The presence of Note B specifies that the supplier of an aqueous solution of such a substance must state the percentage concentration of the solution on the label.

Note that the pure substance, i.e. not in water solution, may have different hazards. If there is no entry in Annex VI covering the anhydrous form, a classification would need to be derived based on available information. As the human body contains water, it is likely that the hazards of the aquatic solution still apply. Additional hazards may however occur, for example, hydrogen cyanide is Flam. liq.1 when it is pure but not in solution.

1.1.11. The Classification and Labelling Inventory (C&L Inventory)

Manufacturers and importers are required to notify ECHA of the classification and labelling of hazardous substance(s) placed on the market as such or in a mixture (above a certain concentration leading to the classification of the mixture) and of substances subject to registration in accordance with the REACH Regulation. ECHA will then include the information in the classification and labelling inventory in the form of a database. Substances require notification within one month after their placing on the market. There is no need to notify the substance if the same information has already been submitted as part of a registration under REACH by the same actor, as the classification and labelling, when part of the registration package, will automatically be added to the C&L Inventory (CLP Article 40(1)). Further guidance on what should be included in a notification and how to do it is available on the ECHA website <http://echa.europa.eu/web/guest/regulations/clp/cl-inventory/notification-to-the-cl-inventory>.

ECHA makes certain information from the C&L Inventory publicly available on its website, including the substance name, the classification, labelling and any relevant specific concentration limit or M-factor(s). It is indicated in the Inventory if there is a harmonised classification for the entry, or if it is an agreed entry between manufacturers or importers. Multiple notifications of the same substance can be submitted by different manufacturers or importers, with potential differences in the notified classifications. Notifiers and registrants are required to make every effort to come to an agreed entry.

The information in the C&L Inventory comes from registrations and C&L notifications. This information has not been reviewed or verified by the Agency or any other authority.

1.1.12. Relation of classification to other EU legislation

A network of EU legislation relies on classification in one way or the other (see section 22 of the *Introductory Guidance on the CLP Regulation* for a detailed list of the laws concerned). This downstream legislation includes laws protecting consumers and workers, as well as rules on transport, biocides, pesticides, cosmetics and waste. Therefore, apart from the important hazard communication on the label and in the SDS, there are significant downstream consequences of classification in that it also has a direct effect on risk management measures under REACH and other legislation.

1.1.12.1. REACH

Classification plays a key role in REACH; it must be included in the registration dossier for a substance and it triggers certain provisions such as the performance of an exposure assessment and risk characterisation as part of the CSA and the obligation to provide an SDS. Classification of a substance as mutagenic, carcinogenic or toxic to reproduction (CMR) may also lead to restrictions and the need to apply for authorisations ((EC) No 1907/2006).

1.1.12.2. Plant Protection Products and Biocides

Active substances as well as any plant protection products or biocidal products containing them must be classified in accordance with the CLP Regulation.

Regarding plant protection products, it should be noted that with effect from 14 June 2011, Directive 91/414/EEC has been repealed by Regulation (EC) 1107/2009, which concerns their placing on the market. This means that references to the repealed Directive must now be construed as references to the new Regulation. Nevertheless, Article 80 of the new Regulation specifies that Directive 91/414/EEC must continue to apply with respect to active substances included in Annex I to that Directive for certain transitional periods.

Regarding biocidal products, it should be noted that with effect from 1 September 2013, Directive 98/8/EC has been repealed by Regulation (EU) 528/2012, which concerns their making available on the market and use. This means that references to the repealed Directive must now be construed as references to the new Regulation. Nevertheless, Articles 89 – 95 of the new Regulation specifies the transitional measures which must continue to apply.

In relation to classification, the new Regulations, bring about some changes, e.g. certain classifications (e.g. CMR, Cat. 1A and 1B) may now preclude approval of the respective substance as an active substance, safener, or synergist in plant protection products or biocidal products.

1.1.12.3. Transport legislation

Many of the GHS criteria (by hazard class) are already implemented through the UN Model Regulations for Transport of Dangerous Goods and related legal instruments (ADR, RID, ADN, IMDG Code and ICAO TI).

Available transport classifications can be a source of information for the classification and labelling of substances and mixtures under CLP, especially for physical hazards, see also Section 2 of this document.

1.2. THE SIGNIFICANCE OF THE TERMS 'FORM OR PHYSICAL STATE' AND 'REASONABLY EXPECTED USE' WITH RESPECT TO CLASSIFICATION ACCORDING TO CLP

1.2.1. 'Form or physical state' and 'reasonably expected use'

CLP refers to the terms 'form or physical state' and 'reasonably expected use' in the following Articles:

Article 5(1) *Manufacturers, importers and downstream users of a substance shall identify the relevant available information for the purposes of determining whether the substance entails a physical, health or environmental hazard as set out in Annex I*

[...]

The information shall relate to the forms or physical states in which the substance is placed on the market and in which it can reasonably be expected to be used.

Article 6(1) *The information shall relate to the forms or physical states in which the mixture is placed on the market and, when relevant, in which it can reasonably be expected to be used.*

Article 8(6) *Tests that are carried out for the purposes of this Regulation shall be carried out on the substance or on the mixture in the form(s) or physical state(s) in which the substance or mixture is placed on the market and in which it can reasonably be expected to be used.*

Article 9(5) *When evaluating the available information for the purposes of classification, the manufacturers, importers and downstream users shall consider the forms and physical states in which the substance or mixture is placed on the market and in which it can be reasonably be expected to be used.*

The objective of hazard classification is to identify the intrinsic physical, health and environmental hazards of substances and mixtures taking into account all uses that can be reasonably expected.

In this context, the intention of the UN GHS should be kept in mind:

The GHS (subsection 1.3.2.2.1) uses the term 'hazard classification' to indicate that only the **intrinsic hazardous properties** of substances or mixtures are considered.

The following guidance is intended to clarify the references to 'reasonably expected use' and 'form or physical state' in this context.

1.2.2. The term 'reasonably expected use' in relation to hazard classification

Hazard classification is based on the intrinsic properties of a substance or mixture and does not take into account exposure. Reasonably expected use summarises all physical forms and states of a substance or mixture that may occur during intended use or reasonably foreseeable conditions of misuse.

Reasonably expected use of a substance or mixture is as follows:

- Any process, including production, handling, maintenance, storage, transport or disposal.
- All technical operations/manufacturing activities like e.g. spraying, filing, and sawing.
- Any putative consumer contact through e.g. do-it-yourself or household chemicals.
- All professional and non-professional uses including reasonably foreseeable accidental exposure, but not abuse such as criminal or suicidal uses.

Reasonably expected use is also related to any consumer disposal or any work in which a substance or mixture is used, or intended to be used irrespective of its present limited use or use pattern. Thus, use should not be mixed up with usage category.

1.2.3. The term 'form or physical state' in relation to hazard classification

Depending on different prerequisites, form or physical state is taken into account differently in the practice of testing and classification for physical, health, and environmental hazards which is described in the following paragraphs.

It should be noted that in some cases a substance may autoxidise (in contact with air) or decompose to a more hazardous form. This may warrant classification of the substance even though it in itself is not or is less hazardous. A case-by-case evaluation should be done considering available hazard information on humans or animals and/or the rate and extent of autoxidation or decomposition. The case-by-case evaluation should also consider how the substance can be reasonably expected to be used.

1.2.3.1. Physical hazards

Different forms or physical states of a substance or mixture may result in different physical properties and hazards with possible consequences for the hazard classification of a substance or

mixture. Putative forms comprise properties such as crystal structure, particle size, homogeneity (e.g. emulsions) and texture (e.g. viscosity or tablet form). Examples of physical state factors are: surface treatment (e.g. coating), state of aggregation, moisture content, residual solvent, activation or stabilisation.

The classification of a substance or mixture relates to the tested form and physical state. If the form and / or physical state is changed it has to be evaluated whether this might affect the classification and whether re-testing is necessary. For example, a hazardous phase separation may occur due to a temperature change under conditions of storage, or a solid substance may be molten to bring it into the liquid phase (e.g. for pumping).

General considerations

The test sample should be representative for the substance or mixture placed on the market. This is especially important in case of small 'batch' production. Mixtures might for example contain inert components which, if they are over-represented in the test sample, will lead to incorrect hazard classification.

Specific requirements of certain test methods

Some test methods for the classification of physical hazards have specific requirements regarding the form / particle size of the sample to be tested. In these cases, the specific requirements of the test methods prevail. Examples of tests which have specific requirements regarding the form/particle size of the sample to be tested include those used to determine the classification of explosives and of substances which in contact with water emit flammable gases.

In other test methods, there are no specific requirements regarding the particle size but it is stated explicitly that the particle size may have a significant effect on the test result. Therefore, these properties should be mentioned in the test report (i.e. testing of oxidising solids).

Section 2.0.4 of Part 2 provides further details about the relevance of the physical state for testing purposes.

1.2.3.2. Human health hazards

Also for human health, different forms (e.g. particle sizes, coating) or physical states may result in different hazardous properties of a substance or mixture in use. However, due to test complexity, not every form or physical state can be tested for each health hazard. In general, testing should be performed on the smallest available particle size and the default approach is to test for different routes of exposure (oral, dermal, inhalation). Again, due to test complexity, mostly the data for only one exposure route are available.

In general, the assumption is made that the testing conditions of valid animal assays reflect the hazards to man and these data must be used for classification. Moreover, it is assumed that classification for human health hazards takes into account all the potential hazards which are likely to be faced for all forms or physical states in which the substance is placed on the market and can reasonably be expected to be used. It is assumed that it comprises putative accidental exposures. This approach generally, but not necessarily comprehensively, covers the whole range of intrinsic properties of a substance or mixture: in some cases, substances or mixtures have to be transformed into specific forms not mirroring 'real-life' exposures in order that an animal test can be performed. As a consequence, the results of such tests may have to be evaluated taking into account any limitations due to the fact that the specific form of the tested substance or mixture does not or not perfectly represent that to which human exposure may occur during intended, known, or reasonably expected use. Such evaluation has to be performed according to the state of the scientific and technical knowledge. The burden of proof is on the person placing a substance or mixture on the market.

1.2.3.3. Environmental hazards

The environmental hazard classification is principally concerned with the aquatic environment and the basis of the identification of hazard is the aquatic toxicity of the substance or mixture, and information on the degradation and bioaccumulation behaviour.

The system of classification is designed to ensure that a single classification applies to a substance. In general it takes no account of the specific form since this can vary and is not intrinsic to the substance. The form in which the substance is placed on the market is taken into account when deciding what label to apply and various derogations from labelling exist, e.g. for metals in the massive form. In the massive form the hazard may not be present and the substance need not be labelled. The SDS will, however, indicate the classification and intrinsic hazardous properties to warn the user that subsequent transformation of the substance may produce the hazardous form.

For aquatic hazard classification, organic substances are generally tested in the dissolved form. Exceptions to this approach include complex, multi-component substances and metals and their compounds. Examples of alternative approaches include the use of Water Accommodated Fractions (WAF) for complex, multi-component substances where the toxicity cut-off is related to the loading, and a test strategy for metals and their compounds in which the specific form (i.e. particle size) used for testing is standardised and forms or physical states are not further taken into account.

1.3. SPECIFIC CASES REQUIRING FURTHER EVALUATION – LACK OF BIOAVAILABILITY

1.3.1. Definition

Bioavailability is the rate and extent to which a substance can be taken up by an organism and is available for metabolism or interaction with biologically significant receptors. Bioavailability (biological availability) involves both release from a medium (if present) and absorption by an organism (IPCS 2004).

1.3.2. Bioavailability

Article 12

Specific cases requiring further evaluation

Where, as a result of the evaluation carried out pursuant to Article 9, the following properties or effects are identified, manufacturers, importers and downstream users shall take them into account for the purposes of classification:

[...]

(b) conclusive scientific experimental data show that the substance or mixture is not biologically available and those data have been ascertained to be adequate and reliable;

[...]

In general, bioavailability is not explicitly evaluated in hazard classification – the observation of systemic toxicity implicitly demonstrates a degree of bioavailability. On the other hand, when no toxicity is demonstrated in a test, this may be a result of either lack of intrinsic toxicity of the substance or lack of bioavailability in the test system employed. Nevertheless, as indicated in

Article 12 (b) of CLP there may be cases where a specific evaluation of bioavailability is warranted. Bioavailability may also need to be considered for grouping and read-across.

In general terms, for a substance or mixture to have an effect on a biological or environmental system, there must be some degree of bioavailability. Therefore, it follows that a substance or mixture need normally not be classified when it can be shown by conclusive experimental data from internationally acceptable test methods, e.g. from the Test Method Regulation (EC) No 440/2008, that the substance or a substance in a mixture is not biologically available (UN GHS 1.3.2.4.5.1). A non bioavailable substance may, however, react with e.g. other components in a mixture to transform to soluble available forms. The rate and extent at which this process, known as 'transformation' for the purposes of the classification guidance, takes place can vary extensively between different substances, and can be an important factor in determining the appropriate hazard category (see Annex IV, Section IV.1 of Part 4 and 5 of the CLP Guidance). Note that a substance which is inert and insoluble may still pose a hazard requiring classification, e.g. asbestos fibers. Further, it is important to note that bioavailability is not limited to systemic bioavailability but also includes local bioavailability for example for local effects like irritation and sensitisation.

When considering the non-bioavailability of a substance or a mixture, the evaluation should be based on data for all relevant constituents of a substance or ingredients of the mixture. Further, one should consider potential interaction of the ingredients that could influence the bioavailability of the mixture as such or one of its components.

Bioavailability considerations are only relevant with respect to classification for health and/or environmental hazards and not for physical hazards.

1.3.2.1. Human health hazards

The assumption is that all substances and mixtures are considered to be bioavailable to some extent. However, there are a few specific cases in which bioavailability may have an influence on hazard classification. For instance in the case of some metals and polymers, the nature of the physical form (metals in solid form) and the molecular size (polymers are very large molecules), or their physico-chemical properties may limit absorption. Where a supplier proposes derogation from hazard classification on the basis of bioavailability, he has to provide adequate and robust data to support the conclusion of lack of bioavailability. It is possible that a substance is bioavailable by one route but not another (e.g. absorbed following inhalation but not absorbed through the skin). In such cases the lack of bioavailability may derogate classification for the relevant route.

In general, a prediction of lower bioavailability must be supported by robust evidence and a weight of evidence determination using expert judgment must be applied.

Information on bioavailability is usually obtained from adequate, reliable, and conclusive toxicokinetic studies for all relevant routes of exposure and all relevant forms or physical states where the substance and/or metabolite(s) of the substance have been quantified in body fluids and/or target organs. At present (2016), *in vitro* tests for release of moieties in biological fluids are being developed, but have not yet been agreed by OECD. It should be noted that concluding that there is lack of or reduced bioavailability has a high burden of evidence and needs to be supported by robust data and expert evaluation.

Bioavailability of a substance or a substance in mixtures is normally assumed if there are *in vitro* studies available which show the solubility of a substance or mixture in body fluids or artificial simulated body fluids. Furthermore, conclusions on bioavailability of a substance or a mixture may be based on considerations of the physical properties of a substance or derived from Structural Activity Relationships (SAR). Note also that bioavailability is not limited to solubility, local bioavailability and the uptake of (nano)particles also has to be taken into account. Further, a substance or mixture can be transformed, e.g. by gastric fluid so that the substance absorbed may differ from the substance delivered. In certain exceptional circumstances it may be possible

that a substance on its own or in a mixture can be considered to be non-bioavailable, based on either appropriate *in vitro* data, e.g. from skin absorption models, SAR considerations or consideration of the physical properties of the substance, if the respective requirements described above have been taken into account in an adequate analysis.

1.3.2.2. Environmental hazards

The hazard classification for the aquatic environment is based on the three elements aquatic toxicity, bioaccumulation and degradation. The measurement of toxicity to aquatic organisms and its use within a hazard classification system introduces a number of compounding problems. The substance is not dosed directly into the organism but rather into water in which the organism lives. While this reflects more accurately the manner in which the organism will receive the dose in the environment, it does not allow the direct control of the dose which is an important part of much mammalian toxicity testing. The dose is limited by the bioavailability of the substance, the maximum dose being determined by the level of water solubility.

It is usually assumed that toxic effects are only measured following exposure to the dissolved fraction, i.e. organisms are exposed to substances dissolved in water. It is assumed that the substances will either be absorbed by the organisms through passive diffusion or taken up actively by a specific mechanism. Bioavailability may, therefore, vary between different organisms. In the case of bioaccumulation, oral exposure could also be considered for substances with high Log K_{ow} . Further guidance of the impact of bioavailability caused by the size of the molecule and how this is considered for aquatic hazard classification can be found in Annex [III](#) to Part 4 and 5 of the CLP Guidance.

In general, there are no specific environmental test methods developed to measure biological availability of substances or mixtures. This aspect is built into the testing methodology for toxicity and if adverse effects are identified the substance should be classified accordingly. Substances which lack bioavailability would not be absorbed by the exposed organisms and therefore due to lack of toxic effects these substances would not be classified, unless they are known to degrade or transform to hazardous products. For example see the strategy for metals classification in Annex [IV](#) to Part 4 and 5 of the CLP Guidance.

1.4. USE OF SUBSTANCE CATEGORISATION (READ-ACROSS AND GROUPING) AND (Q)SARS FOR CLASSIFICATION AND LABELLING

Article 5(1) *Manufacturers, importers and downstream users of a substance shall identify the relevant available information for the purposes of determining whether the substance entails a physical, health or environmental hazard as set out in Annex I, and, in particular, the following:*

[...]

(c) any other information generated in accordance with section 1 of Annex XI to Regulation (EC) No 1907/2006;

Article 6(1) *Manufacturers, importers and downstream users of a mixture shall identify the relevant available information on the mixture itself or the substances contained in it for the purposes of determining whether the mixture entails a physical, health or environmental hazard as set out in Annex I, and, in particular, the following:*

[...]

(c) any other information generated in accordance with section 1 of Annex XI to Regulation (EC) No 1907/2006 for the mixture itself or the substances contained in it;

Article 9(1) *Manufacturers, importers and downstream users of a substance or a mixture shall evaluate the information identified in accordance with Chapter 1 of this Title by applying to it*

the criteria for classification for each hazard class or differentiation in Parts 2 to 5 of Annex I, so as to ascertain the hazards associated with the substance or mixture

Article 9(3) *Where the criteria cannot be applied directly to available identified information, manufacturers, importers and downstream users shall carry out an evaluation by applying a weight of evidence determination using expert judgement in accordance with section 1.1.1 of Annex I to this Regulation, weighing all available information having a bearing on the determination of the hazards of the substance or the mixture, and in accordance with section 1.2 of Annex XI to Regulation (EC) No 1907/2006.*

Article 13 *If the evaluation undertaken pursuant to Article 9 and Article 12 shows that the hazards associated with the substance or mixture meet the criteria for classification in one or more hazard classes or differentiations in Parts 2 to 5 of Annex I, manufacturers, importers and downstream users shall classify the substance or mixture in relation to the relevant hazard class or classes or differentiations by assigning the following:*

(a) one or more hazard categories for each relevant hazard class or differentiation;

(b) subject to Article 21, one or more hazard statements corresponding to each hazard category assigned in accordance with (a).

Section 1 of Annex XI to REACH provides a list of data that can be used instead of testing when standard data are missing. This Annex specifies the conditions under which results of (Q)SARs, read-across and grouping may be used in order to fulfil the information requirements under REACH and refers to the adequacy of the information for the purpose of classification of substances. It states e.g. that results of (Q)SARs may be used instead of testing when the (Q)SAR models have been scientifically validated, 'the substance falls within the applicability domain', the 'results are adequate for the purpose of classification and labelling' and 'adequate and reliable documentation of the applied method is provided'. Results generated by read-across and grouping may, according to the same principles, be used for classification and labelling if they are 'adequate for classification and labelling', 'have adequate and reliable coverage of the key parameters addressed in the corresponding test method', 'cover an exposure duration comparable to or longer than the corresponding test method', and 'adequate and reliable documentation of the applied method' is provided.

According to CLP Article 9(3), a weight of evidence determination using expert judgement has to be applied where the criteria cannot be applied directly to the available data. This determination is further described in CLP Annex I, 1.1.1.

It is important to note that most of the criteria for classification are directly related to specific test methods. Thus, the adequacy of results of (Q)SARs, read-across and grouping should be evaluated against the criteria taking into account that normally the individual method attempts to estimate the same hazard as the criterion. Nevertheless, when grouping, read-across and (Q)SARs are being used alone or as a part of the basis for classification, it is normally necessary to do so employing weight of evidence and expert judgement in order to be able to apply the criteria to the information leading to a decision on the classification when the criteria are met (Article 13, CLP).

CLP Annex I, 1.1.1.3 refers to the consideration of any information that is relevant for the determination of a hazard including the category approach. The latter encompasses grouping and read-across to help in a weight of evidence determination which is needed when the application of the criteria is not straightforward and cannot be applied directly to the available information (Article 9(1)(3), recital (33)).

Annex I: 1.1.1.3. *A weight of evidence determination means that all available information bearing on the determination of hazard is considered together, such as the results of suitable in vitro tests, relevant animal data, information from the application of the category approach (grouping, read-across), (Q)SAR results, human experience such as occupational data and*

data from accident databases, epidemiological and clinical studies and well documented case reports and observations. The quality and consistency of the data shall be given appropriate weight. Information on substances or mixtures related to the substance or mixture being classified shall be considered as appropriate, as well as site of action and mechanism or mode of action study results. Both positive and negative results shall be assembled together in a single weight of evidence determination.

IR&CSA, Chapter R.6 provides extensive advice on the use of (Q)SARs and grouping of substances including guidance on read-across, for developing the data set for hazard evaluation. Guidance on the use of (Q)SAR and grouping for specific hazard classes is given in IR&CSA, Chapter R.7.

In general, read-across, grouping and use of (Q)SARs as the sole information elements to obtain data on basic physical-chemical properties is not recommended, since reliable data should normally be available or is easily obtainable through testing. However, there may occasionally be practical problems with testing of substances for physical-chemical properties, especially for UVCBs where the properties may be dependent on the variable composition. Therefore, the appropriateness of using read-across, categorisation and (Q)SARs for physical-chemical assessment should be considered on a case by case basis. This should also be the case when such data are considered for the evaluation of health and environmental hazards in order to apply the criteria for classification.

Given the availability of extensive guidance only a brief overview of each approach is presented below. For classification of mixtures see Section [1.6](#) of this document.

1.4.1. (Q)SAR

Structure Activity Relationships and Quantitative Structure Activity Relationships, collectively referred to as (Q)SARs, are defined in IR&CSA, Chapter R.6.1.1 as theoretical models that can be used to predict in a qualitative or quantitative manner the physico-chemical, biological (e.g. toxicological) or environmental fate properties of compounds from knowledge of their chemical structure.

It should be noted that the use of (Q)SAR results requires the user to be sufficiently skilled to understand the applicability of the selected (Q)SAR and to interpret the results in terms of reliability and adequacy for the purpose of classification and labelling.

Extensive guidance on the use of (Q)SAR for hazard identification is given in IR&CSA, Chapter R.6.1. Guidance on the use of (Q)SARs for classification and labelling is also given in IR&CSA, Chapter R.6.1.4.2. This guidance is directly applicable to CLP. It should be noted that the (Q)SAR approach is not directly applicable to inorganic substances.

1.4.2. Grouping

Guidance on grouping of substances for the purpose of hazard evaluation is given in IR&CSA, Chapter R.6.2. Annex XI to REACH opens the possibility of evaluating substances not on a one-by-one basis, but by grouping substances in categories. A substance category is a group of substances whose physico-chemical, human health, environmental and/or environmental fate properties are expected to be similar or to follow a regular pattern as a result of structural similarity.

The use of grouping for hazard evaluation in the grouping approach means that not every substance needs to be tested for every hazard. Read-cross by interpolation can be used to fill data gaps, as well as trend analysis and (Q)SAR, and in addition the overall data for that category must prove adequate to support the hazard assessment.

In some cases it is necessary to create sub-groups within a category of substances, e.g. when there is a consistent trend within a group with regard to the potency of an effect which may justify different classifications or setting of SCLs (see also IR&CSA, R.6.2.1.2).

1.4.3. Read-across

Read-across is the use of hazard specific information for one substance ('source') to predict the same hazard for another substance ('target'), which is considered to have similar physico-chemical, human health, environmental fate and/or (eco)toxicological properties. This can be based on structural similarity with a parent substance or its transformation products, and their bioavailability, bioaccessibility, or known physico-chemical properties such as water solubility. For certain substances without test data, the formation of common significant metabolites or information on metabolites of tested substances or information from precursors, may be valuable information (IR&CSA, Chapter R.6.2.5.2 and OECD 2004). For any hazard, read-across may be performed in a qualitative or quantitative manner. Extensive guidance on the use of read-across is given in IR&CSA, Chapter R.6.2.2.1.

Specific guidance for certain types of substances such as reaction products and multi-constituent substances, complex substances, isomers, metals and metal compounds and other inorganic compounds is given in IR&CSA, Chapter R.6.2.5.

1.5. SPECIFIC CONCENTRATION LIMITS AND M-FACTORS

1.5.1. Specific concentration limits

Article 10(1) *Specific concentration limits and generic concentration limits are limits assigned to a substance indicating a threshold at or above which the presence of that substance in another substance or in a mixture as an identified impurity, additive or individual constituent leads to the classification of the substance or mixture as hazardous.*

Specific concentration limits shall be set by the manufacturer, importer or downstream user where adequate and reliable scientific information shows that the hazard of a substance is evident when the substance is present at a level below the concentrations set for any hazard class in Part 2 of Annex I or below the generic concentration limits set for any hazard class in Parts 3, 4 and 5 of Annex I.

In exceptional circumstances specific concentration limits may be set by the manufacturer, importer or downstream user where he has adequate, reliable and conclusive scientific information that a hazard of a substance classified as hazardous is not evident at a level above the concentrations set for the relevant hazard class in Part 2 of Annex I or above the generic concentration limits set for the relevant hazard class in Parts 3, 4 and 5 of that Annex.

Article 10(3) *Notwithstanding paragraph 1, specific concentration limits shall not be set for harmonised hazard classes or differentiations for substances included in Part 3 of Annex VI.*

The specific concentration limit (SCL) concept allows a fine tuning of the contribution of certain hazardous substances to the classification of mixtures based on the potency of the substances, as well as a classification of other substances containing these substances as impurities, additives or individual constituents. The SCL concept is generally only applicable to health hazards. For physical hazards, classification must normally be established on the basis of test data for the respective mixture, where applicable.

The procedure of derivation of SCLs is different for every health hazard class and therefore guidance on how to set SCLs is provided in the respective chapters of the different health hazard classes. A general overview on the applicability of SCLs and guidance availability for setting SCLs for health hazards is illustrated by Table [1.1](#) below.

SCLs should take precedence over the generic concentration limits (GCLs) given in the relevant health hazard sections of Annex I to CLP. In case specific concentration limits have been set in Annex VI to CLP, these must be applied. Moreover, manufacturers, importers or downstream

users may not set their own SCLs for hazards subject to harmonised classifications in Annex VI to CLP.

However, if a hazard class is not included in Annex VI and adequate and reliable data exist showing a hazard below the GCL, SCLs must be set by a manufacturer, importer or downstream user in accordance with CLP and be available in the C&L Inventory. SCLs should be communicated via the SDS.

Table 1.1 Possibilities for setting SCL for health hazards addressed in relevant sections of the guidance

| Hazard class | Category | Lower than GCL | SCL | Higher SCLs than GCL (in exceptional circumstances) | Guidance |
|-------------------------------|------------|-----------------|-----|---|---|
| Acute toxicity | all | not applicable | | not applicable | not necessary |
| Skin corrosion/irritation | all | yes | | yes | available in Part 3, Section 3.2 |
| Serious damage/eye irritation | eye all | yes | | yes | available in Part 3, Section 3.3 |
| Respiratory sensitisation | all | yes* | | yes* | see Part 3, Section 3.4 *currently not available; |
| Skin sensitisation | all | yes | | yes* | available in Part 3, Section 3.4 *currently not available |
| Germ cell mutagenicity | all | yes* | | yes* | see Part 3, Section 3.5 *currently not available |
| Carcinogenicity | all | yes | | yes | available in Part 3, Section 3.6 |
| Reproductive toxicity | all | yes | | yes | available in Part 3, Section 3.7 |
| STOT-SE | 1 | yes | | no | available in Part 3, Section 3.8 |
| | 2 | no | | no | see Part 3, Section 3.8 |
| | 3 | yes | | yes | available in Part 3, Section 3.8 |
| STOT-RE | 1 | yes | | no | available in Part 3, Section 3.9 |
| | 2 | no | | no | see Part3 , Section 3.9 |
| Aspiration hazard | 1 | not appropriate | | not appropriate | not necessary |

1.5.2. Multiplying factors (M-factors)

Article 10(2) *M-factors for substances classified as hazardous for the aquatic environment, acute category 1 or chronic category 1, shall be established by manufacturers, importers and downstream users.*

Article 10(4) *Notwithstanding paragraph 2, M-factors shall not be set for harmonised hazard classes or differentiations for substances included in Part 3 of Annex VI for which an M-factor is given in that Part.*

However, where an M-factor is not given in Part 3 of Annex VI for substances classified as hazardous to the aquatic environment, acute category 1 or chronic category 1, an M-factor based on available data for the substance shall be set by the manufacturer, importer or downstream user. When a mixture including the substance is classified by the manufacturer, importer or downstream user using the summation method, this M-factor shall be used.

For the hazard class 'Hazardous to the Aquatic Environment', SCLs are not applicable. Instead the M-factors concept is used.

The M-factors are used in the application of the summation method for classification of mixtures containing substances that are classified as very toxic. The concept of M-factors has been established to give an increased weight to very toxic substances when classifying mixtures. M-factors are only applicable to the concentration of a substance classified as hazardous to the aquatic environment (categories Acute 1 and Chronic 1) and are used to derive by the summation method the classification of a mixture in which the substance is present. They are, however, substance-specific and it is important that they are being established already when classifying substances.

For further guidance on how to establish the M-factor see Section 4.1.3.3.3 of Part 4.

M-factors should have been established in accordance with Article 10 of CLP and be available in the C&L Inventory.

For the harmonised classifications in Annex VI to CLP, M-factors must be set by the manufacturer, importer or downstream user in case there is no M-factor provided, in accordance with CLP Article 10(4).

1.5.3. Harmonised ATE values

From 2016 harmonised Acute Toxicity Estimates (ATE) may be included in annex VI of CLP. These values have to be used, just as any other harmonised item. ATEs are one way of expressing acute toxicity (see Annex I to CLP, 3.1.2.1).

1.6. MIXTURES

1.6.1. How to classify a mixture

The classification of mixtures under CLP is for the same hazards as for substances. As a general rule and as is the case with substances, available relevant data on the mixture as a whole should primarily be used to determine classification where applicable, also considering the validity and suitability of the used test method, with regard to testing mixtures in general and the specific mixture of concern. Not all the test methods relevant for substances may be suitable for (all) mixtures and for this reason care has to be taken. Note that for skin sensitisation, care has to be taken so that the doses used do not render the results unreliable. If this cannot be done, further approaches to mixture classification may be applied. When evaluating CMR hazards and biodegradation and bioaccumulation properties, classification of the mixture should according to

Article 6(3) and (4) always be based on the ingredient substances for these particular hazard classes. However, if data on a mixture show CMR properties even in absence of data on possible CMR ingredients, the mixture has to be classified appropriately following Article 6(3).

It is important to choose the most appropriate method to determine the classification for a mixture for each hazard class, differentiation or category. The method will depend on whether the mixture is being assessed for physical, health or environmental hazards and on the type and quality of information that is available (see also Section [1.2.3](#) of this document on form or physical state).

It is important to get a clear picture on which substances and mixtures are contained in a mixture. Basic information on substances would include the substance identity, its classification and any assigned SCLs or M-factors, and concentration in the mixture and, where relevant, details of any impurities and additives including their identity, classification and concentration. Where an ingredient in a mixture is itself a mixture, it is necessary to get information on the ingredient substances of that mixture together with their concentrations, classifications and any applied SCLs or M-factors.

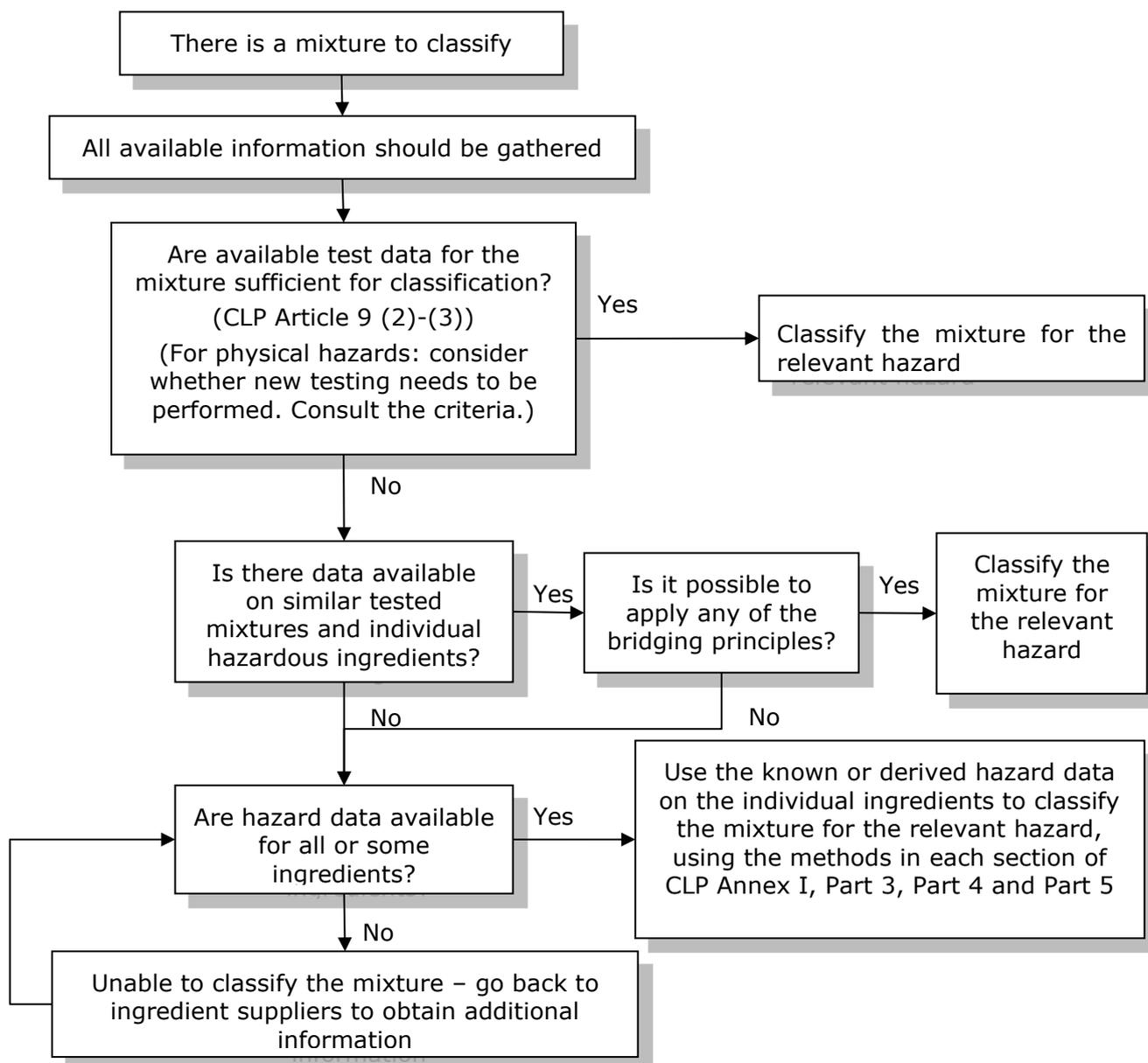
Useful sources for such information are the SDS from the supplier of the substance or the mixture, and the C&L Inventory provided by ECHA, which also includes the harmonised classifications of substances listed in Annex VI to CLP. Also data from registration dossiers are a valuable source of information.

It should be noted that an SDS should also be provided in some cases when the mixture does not meet the criteria for classification but certain specific criteria are met (see Article 31(3) of REACH).

Further dialogue with the supplier may be necessary to obtain additional information. For example on compositional information for the mixture supplied.

The classification of mixtures follows the sequence displayed in Figure [1.1](#), for each hazard class independently (except for CMR and when evaluating biodegradation and bioaccumulation properties):

Figure 1.1 How to classify a mixture



⚠ Note: The principles for using expert judgement and weight of evidence determination (CLP Article 9(3) and (4)) and Annex I, section 1.1.1.) should be taken into account.

1.6.2. Classification for physical hazards

The majority of the physical hazards of mixtures should be determined through testing based on the methods or standards referred to in CLP Annex I, Part 2. In a few cases, the classification of mixtures can also be derived through a calculation, if sufficient appropriate data are available (see CLP Annex I 2.2.4.1 and ISO 10156 for flammable gases, CLP Annex I 2.4.4 and ISO 10156 for oxidizing gases and CLP Annex I, 2.6.4.2 and 2.6.4.3 for flammable liquids).

Test methods for physical hazards are referred to in each physical hazard class chapter of CLP. Most of these test methods can be found in the UN Manual of Tests and Criteria, see the website http://www.unece.org/trans/danger/publi/manual/manual_e.html. A few of these test methods are contained in standards which are also referred to in CLP (see particularly flammable gases,

oxidizing gases and flammable liquids). When test result, based on other methods or standards (which are not referred to in CLP) are available, then these data may still be used, provided they are adequate for the purpose of hazard determination. Expert judgement is necessary to conclude whether there is sufficient documentation to assess the suitability of the test used, and whether the test was carried out using an acceptable level of quality assurance and thus on the adequacy of such data for the purposes of classification according to CLP.

Please note that in practice the physical hazards of a substance or mixture may differ from those shown by tests, e.g. in case of certain ammonium-nitrate-based compounds (explosive / oxidising properties) and certain halogenated hydrocarbons (flammable properties). Such experience must be taken into account for the purpose of classification (CLP Article 12(a)).

The information available or generated must be checked to determine if it is directly comparable to the respective hazard criteria and if it is, then it can be used to derive the classification immediately. Where the criteria cannot be directly applied to the available data, expert judgement should be used for the evaluation of the available information in a weight of evidence determination (CLP Article 9(3) and CLP Annex I, 1.1.1.).

1.6.3. Health and environmental hazards

For the purpose of classification for health or environmental hazards, for each hazard check whether or not there is information:

- on the mixture itself;
- on similar tested mixtures and ingredient substances; or
- on the classification of ingredient substances and their concentrations in the mixture.

As pointed out in the introduction to this chapter, the supplier should be contacted if it is considered that the information on the substances or mixtures supplied is not sufficient for classification purposes.

The information available on the hazard under consideration, will determine if the mixture should be classified using the approaches below in the following sequence (CLP Article 9):

- a. Classification derived using data on the mixture itself (see Section [1.6.3.1](#) of this document), by applying the substance criteria of Annex I to CLP;
- b. Classification based on the application of bridging principles (see Section [1.6.3.2](#) of this document), which make use of test data on similar tested mixtures and ingredient substances; and
- c. Classification based on calculation or on concentration thresholds, including SCLs and M-factors.

1.6.3.1. Classification derived using data on the mixture itself

Classification derived using data on the mixture itself, by applying the substance criteria of Annex I to CLP, is applicable for all hazards, except: CMR hazards (see CLP Article 6(3)), bioaccumulation and biodegradation properties within the evaluation of the 'hazardous to the aquatic environment' hazard class referred to in sections 4.1.2.8 and 4.1.2.9 of Annex I to CLP (see CLP Article 6(4)).

Article 6(3) *For the evaluation of mixtures pursuant to Chapter 2 of this Title in relation to the 'germ cell mutagenicity', 'carcinogenicity' and 'reproductive toxicity' hazard classes referred to in sections 3.5.3.1, 3.6.3.1 and 3.7.3.1 of Annex I, the manufacturer, importer or downstream user shall only use the relevant available information referred to in paragraph 1 for the substances in the mixture.*

Further, in cases where the available test data on the mixture itself demonstrate germ cell mutagenic, carcinogenic or toxic to reproduction effects which have not been identified from the information on the individual substances, those data shall also be taken into account.

Article 6(4) *For the evaluation of mixtures pursuant to Chapter 2 of this Title in relation to the 'biodegradation and bioaccumulation' properties within the 'hazardous to the aquatic environment' hazard class referred to in sections 4.1.2.8 and 4.1.2.9 of Annex I, the manufacturer, importer or downstream user shall only use the relevant available information referred to in paragraph 1 for the substances in the mixture.*

Where the criteria cannot be directly applied to the available data, expert judgement should be used for the evaluation of the available information in a weight of evidence determination (CLP Article 9(3) and CLP Annex I, 1.1.1). Note that the test method used must be suitable for the mixture tested. If data from test methods other than those indicated in Article 8(3) are used, a comparison with the methods indicated in that article has to be made to verify the effect on the evaluation of the information.

1.6.3.2. Bridging principles

In the case of a classification for health or environmental hazards, relevant information on the mixture itself may not always be available. However, where there are sufficient data on similar tested mixtures and individual hazardous ingredient substances, CLP allows bridging principles to be used to classify the mixture (CLP Annex I, 1.1.3). Only one bridging principle could be applied in the evaluation of a hazard class with the exception of Aerosols, where a mixture classified based on another bridging principle is used in an aerosol container. However, different bridging principles may apply to different hazard classes.

To apply these bridging principles certain conditions should be considered for their application. The conditions are summarised below.

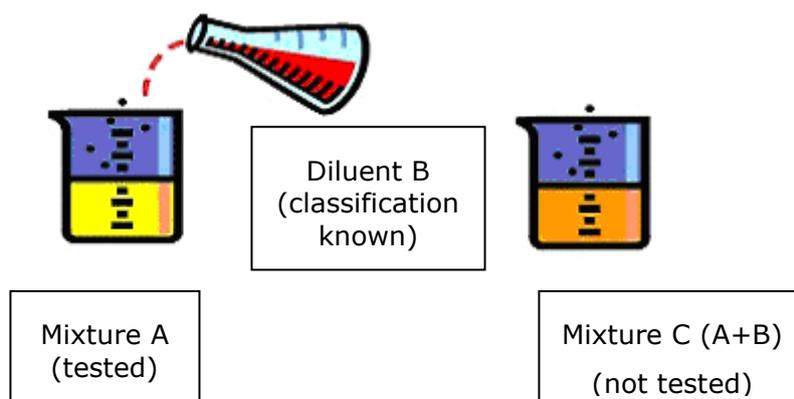
It is necessary to consult Annex I of CLP, Part 3 for health hazards and Part 4 for environmental hazards, before undertaking any of these assessments.

In case it is not possible to classify the mixture by applying bridging principles and a weight of evidence determination using expert judgement by applying the criteria in Annex I to test results of a mixture, then the mixture should be classified using the other methods described in CLP Annex I, Parts 3 and 4.

1.6.3.2.1. Dilution

Where the tested mixture is diluted with a substance (diluent) that has an equivalent or lower hazard category than the least hazardous original ingredient substance, then it can be assumed that the respective hazard of the new mixture is equivalent to that of the original tested mixture. The application of dilution for determining the classification of a mixture is illustrated by Figure [1.2](#).

Figure 1.2 Application of the bridging principle: dilution for determining the acute toxicity classification of a mixture



Example: Mixture A, which has been classified as acute toxic category 2 based on test data, is subsequently diluted with diluent B to form mixture C. If diluent B has an equivalent or lower acute toxicity classification than the least acutely toxic ingredient in mixture A and is not expected to affect the hazard classification of other ingredients, then mixture C may be also classified as acutely toxic category 2. However, this approach may over-classify mixture C, thus the supplier may choose to apply the additivity formula described in CLP Annex I, 3.1.3.6 (see Section [1.6.3.3.1](#) of this document).

Note that also the diluent of the tested mixture is considered a relevant ingredient.

Consider using this particular bridging principle also when, for example,

- diluting an irritant mixture with water,
- diluting an irritant mixture with a non-classified ingredient, or
- diluting a corrosive mixture with a non-classified or irritant ingredient.

In case a mixture is diluted with another mixture, see Section [1.6.4.1](#) of this document.

Within the 'hazardous to the aquatic environment' hazard class, if a mixture is formed by diluting another classified mixture or substance with water or other totally non-toxic material, the toxicity of the mixture can also be calculated from the original mixture or substance (see section 4.1.3.4.3 of Annex I to CLP and mixture example C in Section 4.1.4.7 of Part 4).

1.6.3.2.2. Batching

Where a batch of a tested mixture is produced under a controlled process, then it can be assumed that the hazards of each new batch are equivalent to those of previous batches. This method must not be used where there is reason to believe that the composition may vary significantly, affecting the hazard classification.

1.6.3.2.3. Concentration of highly hazardous mixtures

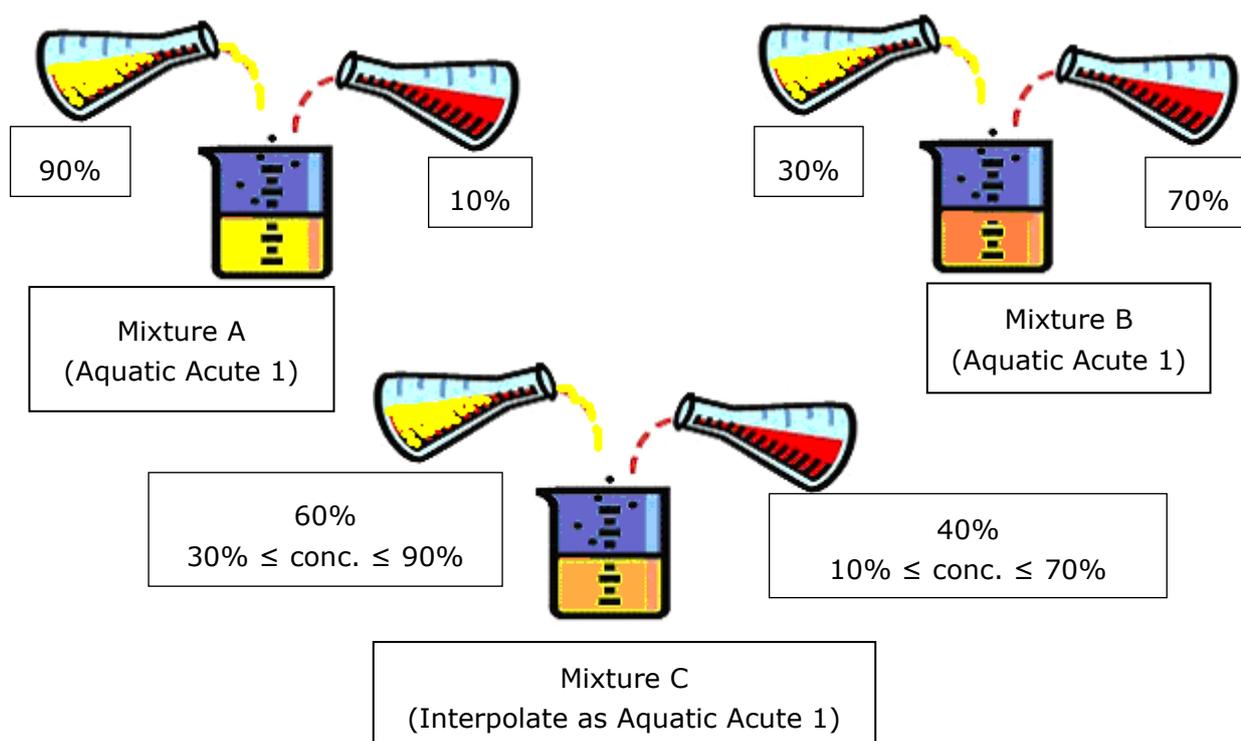
Where a tested mixture is already classified in the highest hazard category or sub-category, an untested mixture which contains a higher concentration of those ingredient substances that are in that category or sub-category should also be classified in the highest hazard category or sub-category (CLP Annex I, 1.1.3.3).

1.6.3.2.4. Interpolation within one hazard category

Assume there are three mixtures (A, B and C) which contain identical hazardous components. If mixtures A and B have been tested and are in the same hazard category, and mixture C is not

tested and has concentrations of those hazardous components intermediate to the concentrations in mixtures A and B, then mixture C is assumed to be in the same hazard category as A and B. The application of interpolation for determining the classification of a mixture is illustrated by Figure 1.3 (CLP Annex I, 1.1.3.4).

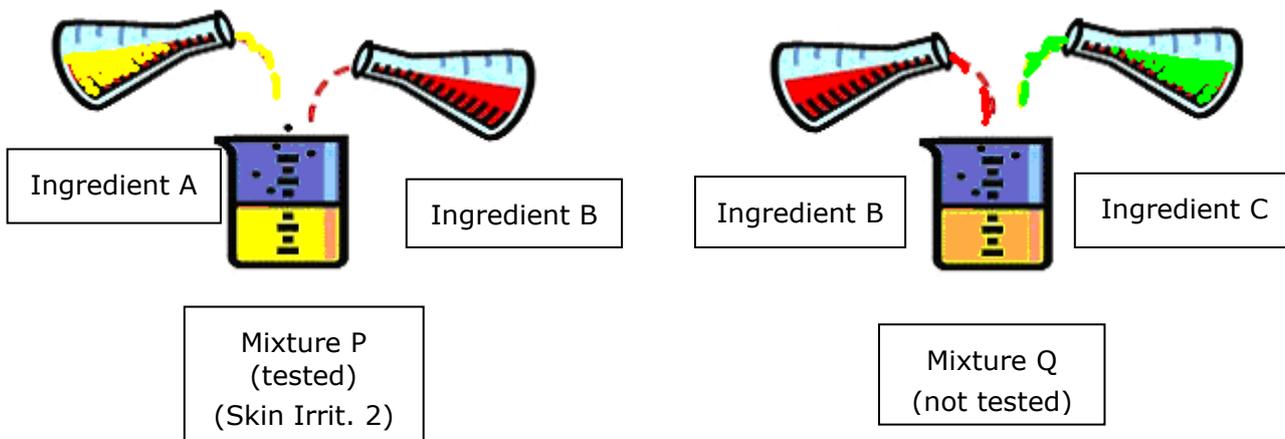
Figure 1.3 Application of the bridging principle: interpolation for determining the aquatic acute hazard classification of a mixture



1.6.3.2.5. Substantially similar mixtures

Two mixtures contain an identical ingredient at the same concentration. Each of the two mixtures contains an additional ingredient which is not identical with each other; however they are present in equivalent concentrations and the hazard category of these two ingredients is the same and neither of them is expected to affect the hazard classification of the other ingredient. If one of the mixtures is classified based on test data it may be assumed that the hazard category of the other mixture is the same. The application of substantially similar mixtures for determining the classification of a mixture is illustrated by Figure 1.4 (CLP Annex I, 1.1.3.5).

Figure 1.4 Application of the bridging principle: substantially similar mixtures for determining the skin irritation classification of a mixture



Example: If the Ingredient C has the same hazard category and the same potency as Ingredient A, then Mixture Q can be classified as Skin Irrit. 2 like Mixture P. Potency may be expressed by, for example, differences in the specific concentration limits of Ingredients A and C. This method should not be applied where the irritancy of Ingredient C differs from that of Ingredient A.

1.6.3.2.6. Review of classification where the composition of a mixture has changed

Article 15(2) Where the manufacturer, importer or downstream user introduces a change to a mixture that has been classified as hazardous, that manufacturer, importer or downstream user shall carry out a new evaluation in accordance with this Chapter where the change is either of the following:

- (a) a change in the composition of the initial concentration of one or more of the hazardous constituents in concentrations at or above the limits in Table 1.2 of Part 1 of Annex I;
- (b) [...]

Annex I: 1.1.3.6 Review of classification where the composition of a mixture has changed

The following variations in initial concentration are defined for the application of Article 15(2)(a):
Table 1.2

Bridging Principle for changes in the composition of a mixture

| Initial concentration range of the constituent | Permitted variation in initial concentration of the constituent |
|--|---|
| $\leq 2,5 \%$ | $\pm 30 \%$ |
| $2,5 < C \leq 10 \%$ | $\pm 20 \%$ |
| $10 < C \leq 25 \%$ | $\pm 10 \%$ |
| $25 < C \leq 100 \%$ | $\pm 5 \%$ |

! NOTE: The guidance below explaining Table 1.2 in the green box relates to a change in the composition of mixtures already classified as hazardous. A change in the composition of non-hazardous mixtures may result in concentration thresholds being reached and a need to

*classify the changed mixture as hazardous. Where the manufacturer, importer or downstream user introduces a change to a mixture **not** classified for a specific hazard, that manufacturer, importer or downstream user must therefore always carry out a new evaluation for that hazard in accordance with Chapter 2 of Title II to CLP (see Article 15(1) of CLP).*

When a manufacturer, importer or downstream user introduces a change in the composition of the initial concentration of one or more of the hazardous constituents of a mixture classified as hazardous, that manufacturer, importer or downstream user must carry out a new evaluation, if the change in concentrations is at or above the limits in Table 1.2 of Part 1 of Annex I to CLP.

However, where the variations of the initial concentrations of the constituents lie within the permitted variation, manufacturer, importer or downstream user does not need to carry out a new evaluation and may use the current classification of the mixture.

The following example is to illustrate what is meant by the permitted variations in Table 1.2.

Example: Mixture A is classified as hazardous based on the initial concentration of two hazardous constituents, substance A and substance B. The initial concentrations in the mixture of substance A and substance B are 2 % and 12 %, respectively. The permitted variation according to Table 1.2 is for substance A ± 30 % of the initial concentration and for substance B ± 10 % of the initial concentration. This means that the concentration in the mixture may for substance A vary between 1.4 % and 2.6 % and for substance B between 10.8 % and 13.2 %, without having to carry out a new evaluation in accordance with Chapter 2 of Title II to CLP:

Substance A: $2 \times \pm 0.3 = \pm 0.6 \rightarrow 1.4 - 2.6$

Substance B: $12 \times \pm 0.1 = \pm 1.2 \rightarrow 10.8 - 13.2$

1.6.3.2.7. Aerosols (some health hazards only)

A mixture in aerosol form is considered to have the same classification as the non-aerosolised form of a mixture, provided that the propellant used does not affect these hazards upon spraying and data demonstrating that the aerosolised form is not more hazardous than the non-aerosolised form is available (see CLP Annex I, 1.1.3.7.).

1.6.3.3. Classification based on calculation or concentration thresholds

In most cases, test data on the mixture itself or similar mixtures will not be available, therefore bridging principles and weight of evidence determination using expert judgement for all of the necessary health and environmental hazard assessments may not be applied. In these cases, classification must be based on calculation or on concentration thresholds referring to the classified substances present in the mixture.

In the case where one or more mixtures are added to another mixture, the same requirement applies: it is necessary to know all ingredient substances, their hazard classifications and their concentrations to be able to derive a correct hazard classification of the final mixture. For further details see Section [1.6.4](#) of this document.

1.6.3.3.1. Classification based on calculation

More detailed guidance on the selection of the most appropriate method is provided in the specific section for each hazard class.

An example is the hazard class acute toxicity where a calculation formula is used which is based on acute toxicity estimates and concentrations, and a modified formula for determining the classification of a mixture containing substances of unknown acute toxicity.

Annex I: 3.1.3.6.1.

[...]

The ATE of the mixture is determined by calculation from the ATE values for all relevant ingredients according to the following formula for Oral, Dermal or Inhalation Toxicity:

$$\frac{100}{ATE_{\text{mix}}} = \sum_n \frac{C_i}{ATE_i}$$

where:

C_i = concentration of ingredient i (% w/w or % v/v)

i = the individual ingredient from 1 to n

n = the number of ingredients

ATE_i = Acute Toxicity Estimate of ingredient i .

Annex I: 3.1.3.6.2.3. If the total concentration of the ingredient(s) with unknown acute toxicity is ≤ 10 % then the formula presented in section 3.1.3.6.1 shall be used. If the total concentration of the ingredient(s) with unknown toxicity is > 10 %, the formula presented in section 3.1.3.6.1 shall be corrected to adjust for the total percentage of the unknown ingredient(s) as follows:

$$\frac{100 - (\sum C_{\text{unknown}} \text{ if } > 10\%)}{ATE_{\text{mix}}} = \sum_n \frac{C_i}{ATE_i}$$

For more information on the CLP calculation formulae for this hazard, please see Section 3.1.3.3.3 of this document.

Another example is provided by hazard class 'hazardous to the aquatic environment', namely the additivity formula:

Annex I: 4.1.3.5.2. Mixtures can be made of a combination of both components that are classified (as Acute Category 1 and/or Chronic Category 1, 2, 3 or 4) and others for which adequate toxicity test data are available. When adequate toxicity data are available for more than one component in the mixture, the combined toxicity of those components is calculated using the following additivity formulas(a) and (b), depending on the nature of the toxicity data:

(a) Based on acute aquatic toxicity:

$$\frac{\sum C_i}{L(E)C_{50m}} = \sum_{\eta} \frac{C_i}{L(E)C_{50i}}$$

where:

C_i = concentration of component i (weight percentage)

$L(E)C_{50i}$ = (mg/l) LC_{50} or EC_{50} for component i

η = number of components

$L(E)C_{50m}$ = $L(E)C_{50}$ of the part of the mixture with test data

The calculated toxicity may be used to assign that portion of the mixture a short-term (acute) hazard category which is then subsequently used in applying the summation method;

(b) Based on chronic aquatic toxicity:

$$\frac{\sum C_i + \sum C_j}{Eq\ NOEC_m} = \sum_n \frac{C_i}{NOEC_i} + \sum_n \frac{C_j}{0,1x\ NOEC_j}$$

Where:

C_i = concentration of component i (weight percentage) covering the rapidly degradable components

C_j = concentration of component i (weight percentage) covering the non-rapidly degradable components

$NOEC_i$ = NOEC (or other recognised measures for chronic toxicity) for component i covering the rapidly degradable components, in mg/l;

$NOEC_j$ = NOEC (or other recognised measures for chronic toxicity) for component i covering the non-rapidly degradable components, in mg/l;

n = number of components, and i and j are running from 1 to n ;

$EqNOEC_m$ = Equivalent NOEC of the part of the mixture with test data;

[...]

 NOTE: The full use of this approach requires access to the whole aquatic toxicity data set and the necessary knowledge to select the best and most appropriate data. CLP has limited the use of the additivity formulae to those circumstances where the substance hazard category is not known, although the acute and/or chronic toxicity data are available. With the aquatic toxicity data at hand the ingredient substance classification and M-factor(s) could easily be gained by a direct comparison with the substance criteria, which then could be fed straight into the summation method. It will therefore usually not be necessary to use the additivity formulae.

For more information on the CLP calculation formulae for this hazard please see Section 4.1.4.3 of this document.

1.6.3.3.2. Classification based on concentration thresholds

Generic concentration thresholds

For most hazard classes or differentiations, classification based on concentration thresholds may be applicable. CLP distinguishes between two different kinds of generic concentration thresholds:

- Generic cut-off values: these values are the minimum concentrations for a substance to be taken into account for classification purposes. These substances are also referred to as relevant ingredients in some hazard classes (see Sections 3.1, 3.2, and 3.3 of Part 3). When a classified substance is present in a concentration above the generic cut-off value it contributes to the mixture classification even if it does not trigger classification of the mixture directly. The generic cut-off values are defined for some hazard classes and categories only and are listed in Table 1.1 of Annex I to CLP;
- Generic concentration limits (GCL): these values are the minimum concentrations for a substance which trigger the classification of a mixture if exceeded by the individual concentration or the sum of concentrations of relevant substances (where the individual substance concentrations can be 'added' to each other in a straight forward way); they are set out in parts 2-5 of Annex I for those hazard classes where they apply.

Generic concentration thresholds are generic for a hazard class, differentiation or category. The difference between a generic cut-off value and a generic concentration limit is demonstrated through the example of the skin irritation hazard: while Table 1.1 of Annex I to CLP defines the generic cut-off value to be 1 % for a skin irritant substance which is present in a mixture, Table 3.2.3 of Annex I to CLP shows that a GCL of the skin irritant substance above or equal to the concentration limit of 10% triggers classification of the mixture for skin irritation. However, at $\geq 1\%$ and below 10 %, the substance may still contribute to the classification of the mixture as skin irritant. This because the concentration would be taken into account if other skin corrosive/irritant substances are present in the mixture below the relevant generic concentration

limits. If additivity applies, classification as provided by the summation in CLP Annex I, Table 3.2.3 may be applicable, i.e.:

$(10 \times \text{Skin Corrosive Categories 1A, 1B, 1C}) + \text{Skin Irritant Category 2}$ should be $\geq 10\%$

Specific concentration thresholds

In contrast to generic thresholds, 'Specific Concentration Limits' (SCLs) and/or specific cut-off values may be established for individual substances:

- SCLs are described in section 1.5.1 of this document and where they have been established they are included in Table 3.1 of Annex VI to CLP⁴⁰ and/or in the C&L Inventory (CLP Article 42). For 'hazardous to the aquatic environment' the Multiplying factors (M-factors) concept⁴¹ is used instead of SCLs, see section 1.5.2 of this guidance. SCLs and M-factors included in Tables 3.1 must be used where applicable and, for classifications not included in Annex VI, SCLs and M-factors notified to the C&L Inventory can be considered and used where applicable.
- Cut-off values that may be different from the generic values and that are to be used in specific cases are given in 1.1.2.2.2(a) and (b) of Annex I to CLP. For example concerning aquatic hazard, for a substance with an established M-factor, the cut-off value is always the generic cut-off value divided by the M-factor; hence, $(0.1/M)\%$ (see 1.1.2.2.2(b) and 4.1.3.1 of Annex I to CLP).

1.6.3.3.3. Additivity Vs. non additivity of hazards

For some hazard classes additivity concepts are normally not applicable. In these cases, the general approach is that if a substance or mixture contains two substances each present at a concentration below the GCL defined for that hazard class or differentiation, even if the sum of the substances' concentrations is above this limit, the mixture will not be classified, as far as no lower SCL has been set.

Additivity is normally not applied for the following hazard classes:

- a. skin and respiratory sensitisation;
- b. germ cell mutagenicity;
- c. carcinogenicity;
- d. reproductive toxicity;
- e. specific target organ toxicity, single and repeated exposure, categories 1 and 2;
- f. skin corrosion/irritation in certain cases (see CLP Annex I, 3.2.3.3.4); and
- g. serious eye damage/eye irritation in certain cases (see CLP Annex I, 3.3.3.3.4).

However, in certain cases for these hazard classes additivity may be scientifically justified. Expert judgement is needed.

If the mode of action (MoA) of two substances is the same, additivity can reasonably be assumed. Examples of cases where additivity applies is reprotoxicity of anticoagulant rodenticides (a group

⁴⁰ Please note that Table 3.2 of Annex VI to CLP is deleted from 1 June 2017 by Commission Regulation (EU) 2016/1179 (9th ATP) amending CLP.

⁴¹ M-factors are used to derive, by means of the summation method, the classification of a mixture in which the substance is present for which the M-factor has been established. For further guidance on how to establish and use M-factors see sections 4.1.3.3.2 and 4.1.4.5, respectively.

of substances affecting the same enzyme in the same way), reprotoxicity of substances releasing boron ions, skin sensitisation by nickel substances and carcinogenicity and mutagenicity of formaldehyde releasers. For the latter group of substances there are notes⁴² in Annex VI stating that the levels of releasable formaldehyde from different components of a mixture must be added. This applies regardless whether the substances have a harmonised classification or not, whether the purpose of the substance is to act as a formaldehyde releaser or not and it includes formaldehyde itself.

When the MoA is different, there may be some cases where it is deemed appropriate to assume additive or synergistic effects. In other cases, there may be no cause for additivity.

For STOT SE-RE 1 and 2 additivity may be assumed for substances with the same target organ, especially if the MoAs are similar. Again, in other cases there may be no reason to assume additivity.

Additivity is used for the following hazard classes or differentiations:

- a. Acute toxicity (according to specific formula);
- b. skin corrosion/irritation (besides the cases mentioned in CLP Annex I, 3.2.3.3.4);
- c. serious eye damage/eye irritation (besides the cases mentioned in CLP Annex I, 3.3.3.3.4);
- d. specific target organ toxicity, single exposure Category 3 (respiratory tract irritation);
- h. specific target organ toxicity, single exposure Category 3 (narcotic effects);
- e. aspiration hazard (plus consideration of viscosity of the final mixture);
- f. short-term (acute) and long-term (chronic) aquatic toxicity and
- g. Hazardous for the ozone layer.

In these cases, as well as in the specific cases described above when additivity may be scientifically justified, if the sum of the concentrations of one or several substances classified for the same hazard class/category in the mixture equals or exceeds the GCL set out for this hazard class/category, the mixture must be classified for that hazard. For substances that have an SCL or M-factor(s), these should be taken into account when applying the summation methods. The method described in section 3.2.3.2.3.2 can be used when one or more substances in a mixture have SCLs.

If the sum of $(\text{ConcA} / \text{clA}) + (\text{ConcB} / \text{clB}) + \dots + (\text{ConcZ} / \text{clZ})$ is ≥ 1 then the mixture needs to be classified for the hazard class in question.

Where ConcA = the concentration of substance A in the mixture;

clA = the concentration limit (either specific or generic) for substance A;

ConcB = the concentration of substance B in the mixture;

clB = the concentration limit (either specific or generic) for substance B; etc.

⁴² The 10th ATP added the following notes in Annex I to CLP:

"Note 8: The classification as a carcinogen need not apply if it can be shown that the maximum theoretical concentration of releasable formaldehyde, irrespective of the source, in the mixture as placed on the market is less than 0,1%."

"Note 9: The classification as a mutagen need not apply if it can be shown that the maximum theoretical concentration of releasable formaldehyde, irrespective of the source, in the mixture as placed on the market is less than 1%."

An example is provided for the hazard class serious eye damage /eye irritation: in case there are only substances classified as eye irritation Category 2 present in a mixture, then their sum must be equal to or exceed the generic concentration limit of 10 % in order for the mixture to be classified in Category 2 as well. Note that only relevant substances (i.e. for eye irritants, above the generic cut-off value of 1%) should be summed up and contribute to mixture classification. Further guidance on the application of SCLs when using the summation method to derive conclusions on skin corrosion / irritation or serious eye damage/eye irritation hazards can be found in Sections 3.2 and 3.3 of Part 3.

1.6.4. Classification of mixtures in mixtures

For physical hazards, an adequate hazard classification is generally derived by testing. To determine the classification of a mixture for health or environmental hazards using the additivity or summation methods, information on all the component substances, including their individual hazard classification and concentration, is generally required. In the case where one or more mixtures are added to another mixture, the same requirement applies: it is generally necessary to know all component substances, their hazard classifications and their concentrations to be able to derive a correct hazard classification of the final mixture. It is generally not possible to derive the correct hazard classification for the final mixture by using only the hazard classification(s) of the mixtures that were combined to make it. For example, a mixture containing 1% of a Carc. Cat. 1B substance would be classified as Carc. Cat. 1B. Taking 1% of this mixture into another mixture would lead to a concentration of the ingredient causing the carcinogenic classification of 0.01%, i.e. below the GCL. The same situation may occur also for substances classified due to an impurity.

However, there is one exception. If the acute toxicity estimate (ATE) of a mixture is known (either actual or derived), this value can be used to derive a correct classification for acute toxicity if this mixture is added to another mixture.

Thus, it is very important that suppliers of mixtures communicate the necessary information listed above on component substances (including their individual hazard classification and concentration) down the supply chain, normally in the SDS, to enable a correct classification to be established by downstream users formulating new mixtures from their products. However, the information provided in the SDS may not be sufficient, for example where only a concentration range is quoted for a particular substance or where the mixture contains other substances classified as hazardous but which are present below the concentration which triggers the obligation to indicate the substance in the SDS. Thus further dialogue with the supplier of the mixture may be necessary to obtain additional information on the constituent substances to ensure correct classification and labelling of the new mixture.

In situations, where tested mixtures are added to other tested or untested mixtures, an adequate hazard classification can only be derived by taking account of the test data as well as the knowledge on all ingredient substances, their hazard classifications, and their concentrations in these mixtures. Such an approach is a case-by-case analysis and requires expert judgement.

1.6.4.1. Example: Classification of Mixture A

Note that the example only addresses health hazards. For compositional details see Table [1.2](#) and Table [1.3](#) below.

Mixture A is a water solution containing a surfactant, a thickening agent dye and a fragrance mixture. Classification of components and composition of the fragrance mixture are known.

No test data are available on Mixture A and it is not possible to apply bridging principles due to lack of data on similar tested mixtures. Therefore it is necessary to identify the ingredients in Mixture A (including their % w/w and classification).

Mixture A does not contain any ingredients classified as a respiratory sensitiser, CMR, STOT or aspiration hazard. Therefore it is possible to conclude that Mixture A will not be classified as hazardous for these particular hazard classes.

Acute toxicity

As indicated in CLP Annex I, point 3.1.3.3(b), there are two options to calculate the acute toxicity of Mixture A: (i) treat the 'fragrance mixture' as an ingredient when calculating the ATE for Mixture A, or (ii) break the 'fragrance mixture' down into its component ingredients and only take over the relevant ingredients (CLP Annex I, 3.1.3.3(a) and 3.1.3.6.1) into the calculation for the ATE of Mixture A.

Following option (i) it is first necessary to calculate ATE_{mix} of the 'fragrance mixture' (see Table 1.3) taking into account 'FM component 1' and 'FM component 2' (other components can be excluded as their LD_{50} values are > 2000 mg/kg):

$$\frac{100}{ATE_{mix}} = \sum_n \frac{C_i}{ATE_i} \rightarrow$$

$$ATE_{mix} = \frac{100}{\sum_n \frac{C_i}{ATE_i}} \rightarrow$$

$$ATE_{mix} = \frac{100}{\frac{35.2}{1230} + \frac{17.0}{500}} = 1597 \text{ mg/kg}$$

The ATE_{mix} for the 'fragrance mixture' can then be included in the calculation of the ATE_{mix} for Mixture A:

$$ATE_{mix} = \frac{100}{\frac{8.0}{1800} + \frac{5.0}{1597}} = 13300 \text{ mg/kg}$$

Following option (ii) it is only necessary to include 'FM component 1' from the 'fragrance mixture' (present in Mixture A at 1.76 %), as 'FM component 2' is present in a concentration $< 1\%$). Calculation of the ATE_{mix} for Mixture A according to option (ii):

$$ATE_{mix} = \frac{100}{\frac{8.0}{1800} + \frac{1.76}{1230}} = 17200 \text{ mg/kg}$$

Both options indicate that the calculated ATE_{mix} of Mixture A is > 2000 mg/kg thus mixture A is not classified as hazardous for acute toxicity by the oral route.

 NOTE: If an acute oral toxicity test (i.e. an actual LD_{50} value) was available for the fragrance mixture, then this should be used in the calculation for the ATE of Mixture A.

Skin corrosion/irritation

Work out the actual levels of the 'fragrance mixture' ingredients in Mixture A and carry out the summation method (CLP Annex I, Table 3.2.3) using the relevant ingredients.

Mixture A does not contain any ingredient classified as Skin Corr. 1A, B or C. Therefore Mixture A is not classified as Skin Corr. 1A, B or C.

The 'fragrance mixture' contains ingredients classified as Skin Irrit. 2, but these are all present in Mixture A at concentrations < 1 % and can be disregarded (generic cut-off values to be taken into account, CLP Annex I, Table 1.1). Mixture A does also contain 8 % of the 'anionic surfactant' classified as Skin Irrit. 2, but as the concentration of the 'anionic surfactant' < 10 % (GCL, CLP Annex I, Table 3.2.3), Mixture A is not classified as Skin Irrit. 2.

Serious eye damage/eye irritation

Work out the actual levels of the 'fragrance mixture' ingredients in Mixture A and carry out the summation method (CLP Annex I, Table 3.3.3) using the relevant ingredients:

Mixture A contains 8 % of an ingredient classified as Eye Dam. 1, thus Mixture A must also be classified as Eye Dam. 1 (i.e. the relevant ingredient is present in a concentration above the GCL of 3 %). The 'fragrance mixture' also contains an ingredient classified as Eye Dam. 1, but this is present in Mixture A at a concentration < 1 % and can be disregarded.

Skin sensitisation

The 'fragrance mixture' contains four ingredients classified as skin sensitisers (cat 1) but their actual levels in Mixture A are below the GCL of 1 % thus Mixture A is not classified as a skin sensitiser. However, the four skin sensitiser ingredients are present above 0.1 %, thus additional labelling information EUH208 (CLP Annex II, 2.8) would be required on the label for Mixture A.

In summary, mixture A is classified as Eye Dam.1 and additional labelling information is needed on the label. EUH208 – 'Contains (name of sensitising substance). May produce an allergic reaction'.

Table 1.2 Ingredients in Mixture A

| Ingredient | % w/w | Oral LD ₅₀ (rat) | Classification |
|--|---------------|-----------------------------|---|
| Anionic surfactant | 8.00 | 1800 mg/kg | Acute Tox. 4 (oral) Eye Dam. 1 Skin Irrit. 2 |
| Thickening agent | 0.80 | > 5000 mg/kg | Not classified |
| Dye | 0.05 | > 5000 mg/kg | Not classified |
| Fragrance mixture (see list of ingredients below) | 5.00 | not tested | Acute Tox. 4 (inhalation, oral) Skin Sens. 1 Eye Dam. 1 Skin Irrit. 2 Aquatic Chronic 2 |
| Water | 86.15 | | Not classified |
| Total: | 100.00 | | |

Table 1.3 Ingredient 'Fragrance mixture'

| Ingredient | % w/w | % in Mixture A | Oral LD ₅₀ (rat) | Classification |
|----------------|---------------|----------------|----------------------------------|--|
| FM component 1 | 35.20 | 1.76 | 1230 mg/kg | Acute Tox. 4 (inhalation, oral) |
| FM component 2 | 17.00 | 0.85 | not available (use cATpE 500) | Acute Tox. 4 (oral) Skin Sens. 1 |
| FM component 3 | 16.00 | 0.8 | 3600 mg/kg | Skin Sens. 1 Skin Irrit. 2 |
| FM component 4 | 13.40 | 0.67 | 3100 mg/kg | Skin Sens. 1 |
| FM component 5 | 7.00 | 0.35 | > 2000 mg/kg | Eye Dam. 1 Aquatic Chronic 2 |
| FM component 6 | 6.00 | 0.3 | 4400 mg/kg | Flam. Liq. 3 Skin Sens. 1 Skin Irrit. 2 Aquatic Chronic 1 |
| FM component 7 | 2.80 | 0.14 | > 5000 mg/kg | Not classified |
| FM component 8 | 2.60 | 0.13 | > 5000 mg/kg | Aquatic Chronic 1 |
| Total: | 100.00 | 5.00 | | |

1.6.4.2. Example: Classification of Mixture B

Note that the example only addresses health hazards.

Mixture B is a powder form detergent containing a base powder, silicates, carbonate and inorganic processing aid. The compositional details including the %w/w and classification of the ingredients are provided in Table 1.4 and Table 1.5 below.

No test data are available on Mixture B and it is not possible to apply bridging principles due to lack of data on similar tested mixtures.

Mixture B does not contain any ingredients classified as a skin sensitiser, CMR or aspiration hazard. Therefore it is possible to conclude that Mixture A will not be classified as hazardous for these particular hazard classes.

Acute toxicity

As indicated in CLP Annex I, 3.1.3.3(b), there are two options to calculate acute toxicity of Mixture B: (i) treat the 'base powder' as an ingredient when calculating the ATE for Mixture B, or (ii) break the 'base powder' down into its component ingredients and only take over the relevant ingredients (CLP Annex I, 3.1.3.3(a) and 3.1.3.6.1) into the calculation for the ATE of Mixture B.

Following option (i) it is first necessary to calculate the ATE_{mix} of the 'base powder' taking into account the non-ionic surfactant (other components can be excluded as LD₅₀ values are > 2000 mg/kg):

$$\frac{100}{ATE_{mix}} = \sum_n \frac{C_i}{ATE_i} \rightarrow$$

$$ATE_{mix} = \frac{100}{\sum_n \frac{C_i}{ATE_i}} \rightarrow$$

$$ATE_{mix} = \frac{100}{\left(\frac{18.0}{500}\right)} = 2778\text{mg/kg}$$

The ATE_{mix} for the 'base powder' can then be used for the calculation of the ATE_{mix} for Mixture B:

$$ATE_{mix} = \frac{100}{\frac{20.0}{2778} + \frac{18.0}{770} + \frac{8.0}{1800}} = 2860\text{mg/kg}$$

Following option (ii) it is only necessary to include the non-ionic surfactant from the 'base powder' (present in Mixture B at 3.6%). Other ingredients in the 'base powder' can be excluded as $LD_{50} > 2000$ mg/kg for all of them. The calculation of the ATE_{mix} for Mixture B applying option (ii):

$$ATE_{mix} = \frac{100}{\frac{3.6}{500} + \frac{18.0}{770} + \frac{8.0}{1800}} = 2860\text{mg/kg}$$

Both options indicate that the calculated ATE_{mix} of Mixture B is > 2000 mg/kg. Therefore Mixture B is not classified as hazardous for acute toxicity by the oral route.

 NOTE: If an acute oral toxicity test (i.e. an actual LD_{50} value) was available for the 'base powder' then this should be used in the calculation for the ATE of Mixture B.

Skin corrosion/irritation

Additivity is considered to apply. Work out the actual levels of the 'base powder' ingredients in Mixture B and carry out the summation method (CLP Annex I, Table 3.2.3) using the relevant ingredients:

Mixture B does not contain any ingredients classified as Skin Corr. 1A, B or C thus Mixture B is not classified as Skin Corr. 1A, B or C.

Mixture B does however contain 23 % ingredients classified as Skin Irrit. 2 (11% silicates, 8% anionic surfactant and 4% anionic surfactant from the 'base powder'), as the content of classified ingredients are $> 10\%$ also Mixture B is classified as Skin Irrit. 2.

Serious eye damage/eye irritation

Work out the actual levels of the 'base powder' ingredients in Mixture B and carry out the summation method (CLP Annex I, Table 3.3.3) using the relevant ingredients:

Mixture B contains 40.6 % ingredients classified as Eye Dam.1 (18% substance X, 11% silicates, 8 % anionic surfactant and 3.6 % non-ionic surfactant), thus Mixture B is also classified as Eye Dam.1.

Respiratory sensitisation

Mixture B contains 0.7% of the ingredient 'enzymes' classified for respiratory sensitisation category 1. However this is below the concentration triggering classification (CLP Annex I, Table 3.4.5) thus Mixture B is not classified as a respiratory sensitiser. However ingredient 'enzymes' trigger additional labelling information EUH208 (CLP Annex II, 2.8).

STOT

Mixture B does not contain any ingredients classified as STOT RE or STOT SE 1 or 2, but it contains 11% of an ingredient classified as STOT SE 3 (respiratory tract irritation). The generic concentration limit is 20 % for extrapolating the classification as STOT SE 3 from an ingredient to the mixture (CLP Annex I, 3.8.3.4.5.), thus Mixture B does not trigger classification as STOT SE 3 (respiratory tract irritation).

In summary, mixture B is classified as Skin Irrit. 2, Eye Dam. 1 and additional labelling information is needed on the label. EUH208 – 'Contains (name of sensitising substance). May produce an allergic reaction'.

Table 1.4 Ingredients in Mixture B

| Ingredient | % w/w | Oral LD ₅₀ (rat) | Classification |
|--|-------|-----------------------------|---|
| Base powder (see list of ingredients below) | 20.00 | not tested | Eye Dam.1 Skin Irrit. 2 |
| Substance X | 18.00 | 770 mg/kg | Ox. Sol. 1 Acute Tox. 4 (oral) Eye Dam. 1 |
| Silicates | 11.00 | 3400 mg/kg | Eye Dam. 1 Skin Irrit. 2 STOT SE 3 (respiratory tract irritation) |
| Carbonate | 7.00 | 4090 mg/kg | Eye Irrit. 2 |
| Inorganic processing aid | 11.30 | > 5000 mg/kg | Not classified |
| Builder | 16.00 | > 5000 mg/kg | Not classified |
| Anionic surfactant | 8.00 | 1800 mg/kg | Acute Tox. 4 (oral) Eye Dam. 1 Skin Irrit. 2 |
| Substance Y | 5.00 | > 5000 mg/kg | Not classified |
| Enzymes | 0.70 | > 2000 mg/kg | Resp. Sens. 1 |

| Ingredient | % w/w | Oral LD ₅₀ (rat) | Classification |
|-----------------|---------------|-----------------------------|----------------|
| Polycarboxylate | 3.00 | > 5000 mg/kg | Not classified |
| Total: | 100.00 | | |

Table 1.5 Ingredients 'base powder'

| Ingredient | % w/w | % in Mixture B | Oral LD ₅₀ (rat) | Classification |
|--------------------------|---------------|----------------|-----------------------------|--|
| Non-ionic surfactant | 18.00 | 3.6 | 500 mg/kg | Acute Tox. 4 (oral) Eye Dam. 1 Aquatic Acute 1 |
| Anionic surfactant | 20.00 | 4.0 | > 2000 mg/kg | Skin Irrit. 2 Eye Irrit. 2 |
| Builder | 50.00 | 10.0 | > 5000 mg/kg | Not classified |
| Carbonate | 8.00 | 1.6 | 4090 mg/kg | Eye Irrit. 2 |
| Inorganic processing aid | 4.00 | 0.8 | > 5000 mg/kg | Not classified |
| Total: | 100.00 | 20.00 | | |

1.7. ANNEX VII TO CLP

Article 61(5) *Where a substance or mixture has been classified in accordance with Directive 67/548/EEC or 1999/45/EC before 1 December 2010 or 1 June 2015 respectively, manufacturers, importers and downstream users may amend the classification of the substance or mixture using the conversion table in Annex VII to this Regulation.*

 NOTE: Article 61 uses the term 'conversion table' and Annex VII uses the term 'translation table'. These terms have the same meaning i.e. the tables in Annex VII to CLP that relate classifications according to DSD or DPD to a classification according to CLP.

The tables contained in Annex VII to CLP show how classifications in accordance with the DSD were converted into the corresponding classification under CLP and included in Table 3.1 of Annex VI to CLP⁴³. The tables also aimed to support translation of existing self-classifications in accordance with DSD into classifications in accordance with CLP.

Although conceptually similar, the coverage of CLP and the DSD or DPD is different. In some cases, the relationship between the category of danger and corresponding R-phrases and the hazard categories and corresponding hazard statements is clear, but in other cases, it is less well defined. Additionally, CLP introduced new hazard classes reflecting hazards that were not covered or were only partly covered by DSD and DPD.

⁴³ Note that the 8th ATP has corrected the Annex VII to CLP. The current Annex VII suggests R34 = Skin Corr. 1 whereas the original translation was to Skin Corr. 1B.

While the tables explicitly point out where no translation was possible or where minimum classification would be applied, they do not identify situations where CLP hazard classes or categories, not covered by the DSD and DPD, are required under CLP. In the particular case of 'no classification' under the DPD, the table would not provide any indication for a reasonable translation to a CLP classification.

As mentioned, the Annex VII (to CLP) translation tables did not always give a direct translation. For certain hazard classes, including acute toxicity and STOT repeated exposure, a translation from DSD to CLP according to Annex VII to CLP, resulted in a recommended minimum classification. This minimum classification is also indicated as such in Table 3.1 in Annex VI, and should only be used if no additional hazard information is available (see also CLP Annex VI, 1.2.1).

It should be noted that whenever data for a substance or mixture is available for a hazard class, the substance or mixture must be classified in accordance with the CLP criteria and the Annex VII (to CLP) tables must no longer be used.

Table 1.6 identifies where no direct translation was possible according to the Annex VII (to CLP) translation tables for substances and mixtures requiring classification under DSD or DPD.

In addition to the differences indicated in Table 1.6, it should be noted that for some hazards, the generic concentration limits to be applied for mixtures, were lowered under CLP as compared to DPD. Lower generic concentration limits were set for skin corrosion (R34 and R35), severe eye damage and eye irritation (R41 and R36), skin irritancy (R38) and reproductive toxicity (R60, R61, R62 and R63).

Table 1.6 Hazard classes where the translation tables in Annex VII to CLP indicate that no direct translation was possible from DSD to CLP

| Classifications under DSD or DPD | Potential translation outcomes | Comments |
|----------------------------------|--|--|
| E, R2 E, R3 | 1) Explosive. 2) Organic peroxide 3) Flammable solid 4) Oxidising solid 5) Self-reactive 6) No classification | Change of classification criteria and method; case-by-case considerations See Annex I to Part 2 of the CLP Guidance for additional information on transport classifications |
| O, R8 (liquid) | Oxidising liquid | All liquid substances or mixtures classified O,R8 are classified as oxidising liquids under CLP. See Annex I to Part 2 of the CLP Guidance for additional information on transport classifications |
| O, R8 (solid) | Oxidising solid | The test methods for oxidising solids in 67/548/EEC and CLP were different. Most solids classified O, R8 are also classified as oxidising solids under CLP. See Annex I to Part 2 of the CLP Guidance for additional information on transport classifications |
| F, R11 (solid) | 1) Flammable solid 1a) Possibly self-heating in addition 2) Self-reactive | Solid substances or mixtures classified F, R11 may be classified as flammable solids or self reactives under CLP. If classified as flammable solids, they may additionally be classified as self-heating. |

| Classifications under DSD or DPD | Potential translation outcomes | Comments |
|---|--|---|
| | | See Annex I to Part 2 of the CLP Guidance for additional information on transport classifications |
| F, R15 | Substance or mixture which, in contact with water, emit(s) flammable gas(es) | See Annex I to Part 2 of the CLP Guidance for additional information on transport classifications |

ANNEX I: COLLECTION OF INTERNET LINKS FOR THE USERS OF THE GUIDANCE

Table I.1 Internet links for users of the guidance

| Reference/Site name | Host | URL |
|---------------------------------------|------|---|
| ECHA website | ECHA | http://echa.europa.eu/web/guest |
| UN GHS | UN | http://www.unece.org/trans/danger/publi/ghs/ghs_welcome_e.html |
| eChemPortal | OECD | http://www.echemportal.org/ |
| REACH guidance | ECHA | http://echa.europa.eu/guidance-documents/guidance-on-reach |
| OECD Series on Testing and Assessment | OECD | http://www.oecd.org/document/30/0,3746,en_2649_34377_1916638_1_1_1_1,00.html |
| EU Test Method Regulation 440/2008 | EC | http://eur-lex.europa.eu/lexuriserv/lexuriserv.do?uri=celex:32008r0440:en:not |
| OECD test guidelines | OECD | http://www.oecd.org/env/ehs/testing/oecdguidelinesforhetestingofchemicals.htm |
| Public C&L Inventory | ECHA | http://www.echa.europa.eu/web/guest/information-on-chemicals/cl-inventory-database |

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