Guidance on the Application of the CLP Criteria

Extracts of the document for update/revision:

- **Corrections to Part 1 – General Principles for Classification** **p. 30-75**
- **Revision of Part 4 - Environmental Hazards** **p. 106-171**
- **Revision of the Annexes** **p. 172-248**

Note that the numbering and headlines of the sections that are *not* revised are displayed in this document, to retain the original numbering of the sections as shown in the original Guidance. This will facilitate the comparison of the revised parts with the original.

PREFACE

This document is the Guidance on the Application of the CLP Criteria. It is a comprehensive technical and scientific document on the application of Regulation (EC) No 1272/2008 on the classification, labelling and packaging of substances and mixtures (CLP), which will replace the Dangerous Substances Directive 67/548/EEC (DSD) and the Dangerous Preparations Directive 1999/45/EC (DPD) in a staggered way. CLP is based on the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) and is implementing the provisions of the GHS within the EU. The objective of this document is to provide detailed guidance on the application of the CLP criteria for physical, health and environmental hazards. The guidance is developed to assist primarily manufacturers or importers applying classification and labelling criteria and it also includes practical examples. It is also assumed to be the guidance on classification and labelling for Competent Authorities in the Member States (MS CA), for the Commission services and the European Chemicals Agency (ECHA).

In certain chapters, like for example the ones on carcinogenicity, mutagenicity and reproductive toxicity, the guidance includes to a larger extent scientific advice on how to interpret different data used for classification. This additional guidance is based on experience gained within the EU during the application of the classification criteria under Directive 67/548/EEC, and is written for the experts within the respective fields.

This guidance document was developed as a REACH Implementation Project (RIP 3.6) at the Institute for Health and Consumer Products (IHCP) of the Joint Research Centre in Ispra, with support from working groups consisting of experts on classification and labelling from EU Member States and Industry. The project started in September 2007 and the different working groups had meetings and continuous discussions to discuss and develop the guidance text until spring 2009. Finally all texts were consolidated and edited at the IHCP. RIP 3.6 was financially supported with an administrative arrangement made with Directorate-General Enterprise and Industry. The guidance was handed over to ECHA in summer 2009.

At the time of the hand-over, it was clear that further work was necessary in relation to the guidance chapters on health hazards, on the long-term aquatic hazard and in relation to labelling and packaging. Therefore, further drafting work was done, in close collaboration with European experts, to take account of a range of guidance aspects[1] following the 2nd Adaptation to Technical Progress (ATP) to the CLP Regulation (Commission Regulation (EU) No 286/2011[2]). The results of this update work form the core of the first revision of this guidance document. In relation to labelling and packaging, a new stand-alone guidance document was prepared ("Guidance on Labelling and Packaging in accordance with Regulation (EC) No 1272/2008"), warranting the deletion of Part 5 and of Annex V of the Guidance on the Application of the CLP Criteria. The Guidance on Labelling and Packaging in accordance with Regulation (EC) No 1272/2008 is published on ECHA's guidance website, under http://guidance.echa.europa.eu/guidance_en.htm.

[1] Further guidance on the criteria for respiratory and skin sensitisation and on the aspiration hazard that were revised following the 2nd ATP to the CLP Regulation is not part of this update, but is planned for a future update of the guidance.

[2] Commission Regulation (EU) No 286/2011 of 10 March 2011 amending, for the purposes of its adaptation to technical and scientific progress, Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures.

Note that the Table of contents will be revised at the end of the consultation process only.

1 LIST OF ABBREVIATIONS

ADN	Accord européen relatif au transport international des marchandises dangereuses par voie de navigation intérieure (European Agreement concerning the International Carriage of Dangerous Goods by Inland Waterways)[3]
ADR	Accord européen relatif au transport international des marchandises dangereuses par route (European Agreement concerning the International Carriage of Dangerous Goods by Road)[4]
ANE	Ammonium Nitrate Emulsion
ASTM	American Society for the Testing of Materials
ATE	Acute Toxicity Estimate
BAM	Bundesanstalt für Materialforschung und -prüfung (Federal Institute for Materials Research and Testing)
BCF	Bioconcentration Factor
BCOP	Bovine Corneal Opacity and Permeability test
BfR	German Federal Institute for Risk Assessment
BfR DSS	Decision support system by the German Federal Institute for Risk Assessment
BMF	Biomagnification factor
BP	Boiling point
bw	Body weight
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[5]
CNS	Central Nervous System
CSA	Chemical Safety Assessment
CSR	Chemical Safety Report
DIN	Standard of the German Institute for Standardisation
DNA	Deoxyribonucleic Acid
DOC	Dissolved Organic Carbon
DPD	Directive 1999/45/EC on the classification and labelling of Dangerous Preparations[6]

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

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

[5] 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]

[6] 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]

DSD	Directive 67/548/EEC on the classification and labelling of Dangerous Substances[7]
EC3	Effective Concentration inducting a stimulation index of 3 in the LLNA test
ECB	European Chemicals Bureau
	The formerly known European Chemicals Bureau (ECB) was part of the Institute for Health and Consumer Protection (IHCP), which is one of the seven scientific institutes in the European Commission's Joint Research Centre (JRC). Its mission was to provide scientific and technical support to the conception, development, implementation and monitoring of EU policies on chemicals and consumer products. (http://ecb.jrc.ec.europa.eu/)
ECHA	European Chemicals Agency, Helsinki (http://echa.europa.eu/home_en.asp)
ECVAM	European Centre for the Validation of Alternative Methods (http://ecvam.jrc.it/)
ED	Effective Dose
ESAC	ECVAM Scientific Advisory Committee (http://ecvam.jrc.it/)
f/F	Female
FP	Flash point
GCL	General Concentration Limits
GHS	Globally Harmonised System of Classification and Labelling of Chemicals[8]
GJIC	Gap junction intercellular communication
GLP	Good Laboratory Practice
GnRH	Gonadotropin-releasing hormone
GPMT	Guinea Pig Maximisation Test
GV	Guidance Value
Hb	Haemoglobin
HET-CAM	Hen's Egg Test on Chorio-allantoic Membrane
HS	Hazard statement
HSM	Human skin model
Ht	Hematocrit
IARC	International Agency for Research on Cancer (http://www.iarc.fr/)
IATA(DGR)	International Air Transport Association (Dangerous Goods Regulations Manual)
IBC	Intermediate Bulk Container
ICAO TI	International Civil Aviation Organization (Technical Instructions for the Safe Transport of Dangerous Goods by Air)
ICE	Isolated Chicken Eye
IEC	International Electrotechnical Commission (http://www.iec.ch/)
IMDG	International Maritime Dangerous Goods Code

[7] 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]

[8] Globally Harmonised System of Classification and Labelling of Chemicals (GHS), Second revised edition, United Nations New York and Geneva, 2007

INS	Guidance on Identification and Naming of Substances under REACH, ECHA, 2007 (http://guidance.echa.europa.eu/docs/guidance_document/substance_id_en.pdf)
IPCS	International Programme on Chemical Safety (joint programme of WHO, ILO and UNEP)
IR/CSA	Guidance on Information Requirements and Chemical Safety Assessment, ECHA, 2008 (http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_en.htm)
INS	Guidance on Identification and Naming of Substances under REACH, ECHA, 2007 (http://guidance.echa.europa.eu/docs/guidance_document/ substance_id_en.pdf)
IRE	Isolated Rabbit Eye
ISO	International Standards Organisation
ITDG	Directive 2008/68 on the Inland Transport of Dangerous Goods[9]
ITS	Integrated Testing Strategy
LD_{50}/LC_{50}	Median (50%) lethal dose/concentration
LLNA	Local Lymph Node Assay
LO (A) EL/C	Lowest Observed (Adverse) Effect Level/Concentration
LVET	Low Volume Eye Test
m/M	Male
MetHB	Methaemoglobinaemia
MetHb	Methaemoglobin
MP	Melting Point
MSCA	Member State Competent Authority
MTD	Maximal Tolerated Dose
MW	Molecular weight
n.a.	Not available
NC	No Classification
NE	Narcotic effect(s)
NO(A)EC	No Observed (Adverse) Effect Concentration
NO(A)EL	No Observed (Adverse) Effect Level
ODS	Ozone Depleting Substances
ODP	Ozone Depleting Potential
OECD	Organisation for Economic Co-operation and Development
OECD TG	OECD Test Guideline

[9]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]

	The OECD Guidelines for the Testing of Chemicals are a collection of the most relevant internationally agreed test methods used by government, industry and independent laboratories to determine the safety of chemicals and chemical mixtures, including pesticides and industrial chemicals. All Test Guidelines are available at the OECD homepage: http://www.oecd.org/document/40/0,3343,en_2649_34377_37051368_1_1_1_1,00.html
OP	Oxidising Power
P statement (or PS)	Precautionary statement
PB/PK	Physiologically-based pharmacokinetic
PC	Physico-chemical
PPARα	Peroxisome proliferator-activated receptor-alpha
PS (or P statement)	Precautionary statement
(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[10]
RID	Règlement concernant le transport international ferroviaire de marchandises dangereuses (Regulations concerning the International Carriage of Dangerous Goods by Rail)[11]
RIP	REACH Implementation Project
RTDG	Regulations on the Transport of Dangerous Goods. Generic term that covers all modal transport regulations (ADR, RID, ADN, IMDG and ITDG)
RTI	Respiratory tract irritation
SADT	Self-Accelerating Decomposition Temperature
SCEGHS (or UNSCEGHS)	Sub-Committee of Experts on the Globally Harmonised System (http://www.unece.org/trans/danger/publi/ghs/ghs_welcome_e.html)
SCETDG (or UNSCETDG)	Sub-Committee of Experts on the Transport of Dangerous Goods (http://www.unece.org/trans/danger/danger.htm)
SCL	Specific Concentration Limit
SDS	Safety Data Sheet
SIFT	Skin integrity function test
SSD	Species Sensitivity Distribution
STOT-SE	Specific Target Organ Toxicity - Single Exposure

[10] 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]

[11] 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

STOT-RE	Specific Target Organ Toxicity - Repeated Exposure
SVC	Saturated Vapour Concentration
T25	The daily dose (in mg/kg bodyweight/day) inducing a tumour incidence of 25 % upon lifetime exposure
T95	Inhalation chamber equilibrium (attained at the time t95)
TER	Transcutaneous electrical resistance
TG	Test Guideline
TGD	Technical Guidance Document
TM	Test Method as listed in the Test Methods Regulation
Test Methods Regulation	Regulation (EC) No 440/2008 laying down test methods pursuant to the REACH Regulation[12]
TOPKAT	Mathematical (Q)SAR model for prediction of skin corrosion/irritation
UDP	Uridine 5'-diphosphate
UDPG	Uridine diphosphate glucuronyl
UGT	UDP-glucuronyltransferase
UN	United Nations
UN-MTC	United Nations (2003). Manual of Tests and Criteria. ST/SG/AC.10/11/Rev. 4, as amended: Fourth revised edition of the Manual of Tests and Criteria, containing criteria, test methods and procedures to be used for classification of dangerous goods according to the provisions of Parts 2 and 3 of the United Nations Recommendations on the Transport of Dangerous Goods, Model Regulations, as well as of chemicals presenting physical hazards according to the Globally Harmonized System of Classification and Labelling of Chemicals (http://www.unece.org/trans/danger/publi/manual/manual_e.html).
UNSCEGHS (or SCEGHS)	United Nations SubCommittee of Experts on the Globally Harmonised System (http://www.unece.org/trans/danger/publi/ghs/ghs_welcome_e.html)
UNSCETDG (or SCETDG)	United Nations SubCommittee of Experts on the Transport of Dangerous Goods (http://www.unece.org/trans/danger/danger.htm)
US-FHSA	United States Federal Hazardous Substance Act - 40 Code of Federal Regulations 1500.41
VDI	Verein Deutscher Ingenieure (The Association of German Engineers)
UVCB	Substances of unknown or variable composition, complex reaction products or biological materials
VP	Vapour Pressure
WAF	Water Accommodated Fraction
WoE	Weight of Evidence
WSF	Water soluble fraction

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

[12] Council Regulation (EC) No 440/2008 of 30 May 2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) [OJ L 142, 31.5.2008, p. 1] [Corrigendum: OJ L 143, 3.6.2008, p. 55]

1 PART 1: GENERAL PRINCIPLES FOR CLASSIFICATION

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 mixtures[13], hereafter referred to as CLP.

CLP amends the Dangerous Substance Directive 67/548/EEC[14] (DSD), the Dangerous Preparations Directive 1999/45/EC[15] (DPD) and Regulation (EC) No 1907/2006[16] (REACH), and will replace DSD and DPD from 1 June 2015 (CLP Article 61). CLP is based on the 3rd revision of the United Nations' Globally Harmonised System of Classification and Labelling of Chemicals (UN GHS) and is implementing the provisions of the GHS within the EU, without lowering the protection of human health and the environment, compared to the classification, labelling and packaging system in DSD and DPD.

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 its hazards 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 exposed. 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. Further advice on the implementation of CLP is available in the Agency[17]'s Introductory Guidance on the CLP Regulation, available at ECHA website (http://guidance.echa.europa.eu/docs/guidance_document/clp_introductory_en.pdf).

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

[13] 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]

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

[15] 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]

[16] 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]

[17] 'the Agency' means the European Chemicals Agency established by Regulation (EC) No 1907/2006 (REACH).

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 criteria to the available hazard data (classification), and then to provide any 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, mainly DSD and DPD. In addition, the Safety Data Sheet (SDS) Directive 91/155/EEC[18] 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 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 were developed taking into account existing systems for hazard classification, such as the EU supply and use system, the Canadian and US Pesticide systems, GESAMP[19] hazard evaluation procedure, IMO[20] Scheme for Marine Pollutants, the European Road and Rail Transport Scheme (RID/ADR), 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.

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.

1.1.3 Hazard classification

Hazard classification is a process involving identification of the physical, health and environmental hazards of a substance or a mixture, followed by comparison of those hazards (including *degree of hazard*) with defined criteria in order to arrive at a *classification* of the substance or mixture. Under CLP, a manufacturer, importer or downstream user will apply the following three steps to arrive at a self-classification of a substance or a mixture:

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[18] 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.

[19] Group of Experts on the Scientific Aspects of Marine Environmental Protection

[20] International Maritime Organisation

- identification and examination of relevant available information regarding the potential hazards of a substance or mixture;
- comparison of the information (data) with the classification criteria; and
- decision on whether the substance or mixture shall be classified as hazardous in relation to the hazard classes or differentiations provided in CLP Annex I, and the degree of hazard, where appropriate.

Preliminary information on identification and review of relevant data is provided in section 1.1.6 of this guidance document, while further guidance 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://guidance.echa.europa.eu/guidance_en.htm).

Classification according to CLP is based on *intrinsic* hazards, i.e. the basic properties of a substance as determined in standard tests or by other means designed to identify hazards. As CLP is hazard-based, it does not take exposure into consideration in arriving at either a classification or appropriate labelling, unless for specific exceptions when a chemical can be considered as not being biologically available, such as the derogation not to label a metal in the massive form.

1.1.4 Who is responsible for the hazard classification and what is the timetable

CLP and REACH places the responsibility for hazard classification and related provisions such as packaging, hazard communication and SDS on the suppliers of substances and mixtures.

From 1 December 2010 to 1 June 2015 (CLP Article 61):

Substances shall be classified, labelled and packaged in accordance with CLP, but also classified in accordance with DSD in order to allow these classifications to be used in the classifications of mixtures. Classification and labelling information in accordance with both systems shall be included in SDS (see the Guidance on the compilation of Safety Data Sheets, available on the Agency's website), but classification and labelling information in accordance with DSD shall not appear on the label.

Mixtures shall be classified, labelled and packaged in accordance with DPD. They may also be classified, labelled and packaged in accordance with CLP. In that case they shall not be labelled and packaged according to DPD. When a mixture is classified, labelled and packaged according to CLP, classification and labelling information according to both systems shall be provided in SDS (see the Guidance on the compilation of Safety Data Sheets, available on the Agency's website).

From 1 June 2015 (CLP Articles 60 and 61):

Both *substances and mixtures* shall be classified, labelled and packaged in accordance with CLP. DSD and DPD are repealed from 1 June 2015 and classification according to these directives is not allowed.

However, substances classified, labelled and packaged in accordance with DSD and already placed on the market ("on the shelves") before 1 December 2010, and mixtures classified, labelled and packaged in accordance with DPD and already placed on the market ("on the shelves") before 1 June 2015, do not have to be relabelled and repackaged in accordance with CLP until 1 December 2012 and 1 June 2017, respectively.

1.1.5 Which substances and mixtures should be classified (the scope)

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 they should be classified or not. 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/Euroatom[21]);
- 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/EC[22]; and
- certain substances or mixtures in the finished state, intended for the final user:
    - medicinal products, as defined in Directive 2001/83/EC[23],
    - veterinary medicinal products, as defined in Directive 2001/82/EC[24],
    - cosmetic products, as defined in Directive 76/768/EEC[25],
    - medical devices as defined in Directive 90/385/EEC[26] (active implantable medical devices) and 93/42/EEC[27] (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/EC[28]), and
    - food or feeding stuffs as defined in Regulation 178/2002[29], including when they are used as food additives within the scope of Directive 89/107/EEC[30], as

[21] 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]
[22] 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]
[23] 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]
[24] 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]
[25] 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]
[26] 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]
[27] Council Directive 93/42/EEC of 14 June 1993 concerning medical devices [OJ L 169, 12.7.1993, p. 1]
[28] 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]
[29] 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]

a flavouring in foodstuffs within the scope of Directive 88/388/EEC and Decision 1999/217/EC[31], as an additive in feeding stuffs within the scope of Regulation (EC) 1831/2003[32], and in animal nutrition within the scope of Directive 82/471/EEC[33].

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.

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 category 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 or mixture 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 1107/2009[34] and Directive 91/414/EEC[35]) and on biocidal products (Directive 98/8/EC[36]), or

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[30] 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]

[31] 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]

[32] 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]

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

[34] 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

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 category approaches) must always be considered first, provided they are scientifically validated, sufficiently adequate and reliable.

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 440/2008)[37] or other international test methods validated according to international procedures such as those of the OECD. For physical hazards new tests shall be carried out (at least from January 2014) in compliance with 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). Animal tests must comply with the Directive 86/609/EEC[38]. Tests on non-human primates are prohibited for the purposes of CLP. Tests on humans shall 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.

When considering health and environmental hazards, the classification should preferably be based on available information (including test data) on the mixture itself, except when classifying for e.g. CMR effects or for the evaluation in relation to 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 shall be based on the information on the substances.

If no *in vivo* test data are available on a mixture, such data should normally not be generated; rather, all available information on the ingredients of the mixture should be used to derive a classification. Only when the manufacturer, importer or downstream user has exhausted all other means of generating information, new tests may be performed.

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. It also provides specific rules for the classification of mixtures based on the classification of the individual substances in the mixture.

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.

[35] 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]

[36] 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]

[37] 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]

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

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). Expert judgement may therefore be needed to decide whether the results of a particular test meet the criteria laid down in Annex I.

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.

1.1.8 Updating of hazard classifications

Updating of classifications may be necessary, if 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 mixture, they must reconsider the classification of the substance or mixture (but note that a downstream user can rely on the classification from his supplier, provided he shares the new information with that supplier to allow him to meet the requirements).

1.1.9 The interface between hazard classification and hazard communication

In addition to SDS, CLP provides an integrated system of hazard communication elements (hazard pictograms, signal words, hazard statements and precautionary statements) on the label. 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 and additional safety advice (precautionary statements) to consumers of a substance or a mixture.

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 so-called minimum classifications listed in Table 3.1 that may be amended in accordance with section 1.2.1 of Annex VI. Where some but not all hazard classes or differentiations within hazard classes have been harmonised, the remainder should to be self-classified to complete the classification.

Harmonised classification normally applies to those properties of the highest concern (CMR and respiratory sensitisation) and may also apply for other properties if there is a need for a EU-level action. Decisions on harmonised classification are taken by the European Commission through comitology (CLP Article 37(5)), following a proposal submitted to the Agency and an opinion of the Agency's Risk Assessment Committee (RAC) (CLP Article 37(4)).

Substances regulated under the Biocidal Products Directive 98/8/EC[39] 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 to 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 (CLP Article 37(6)).

Harmonised classification and labelling of a substance provides for a high level of protection of health and the environment, and provides legal clarity for 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. All harmonised classifications previously adopted under DSD and listed in Annex I to DSD were 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 work building on all efforts already done within the EU so far to evaluate hazards of substances that caused concern.

[39] 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]

Under DSD, as a rule all hazards for which data were available were evaluated for a substance. While it was in general the objective to obtain a complete (harmonised) classification, some substances (such as complex coal- and oil-derived substances) were exempted. Under CLP the harmonised classifications will be partial in most cases, only cover the hazard classes of particular concern (i.e. CMR and respiratory sensitisation) or any other hazard classes where the need for action at EU level for other hazard classes is justified for the substance. This means that self-classification should be done for non-harmonised hazard classes, according to CLP Article 4(3) and CLP Recital 17.

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

Manufacturers and importers are required to notify the Agency of the classification and labelling of hazardous substance(s) placed on the market and of substances which are placed on the market and subject to registration in accordance with the REACH Regulation. The Agency will then include the information in a classification and labelling inventory in form of a database. Substances placed on the market on or after 1 December 2010 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/clp/inventory_notification_en.asp.

The Agency shall make 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 will be indicated if there is a harmonised classification for the entry, or if it is an agreed entry between manufacturers or importers. While multiple notifications of the same substance may be made by different manufacturers or importers, with the potential for differences in the classifications notified, over time this should provide the stimulus for suppliers to liaise in order to agree on a single entry.

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 23 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 biocides, pesticides and waste. Therefore, the consequences of classification are greater than just a hazard label or an SDS in that it also has a direct effect on the management of associated risks.

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 or biocidal products containing them shall be classified in accordance with the CLP Regulation by the applicable deadlines. On the other hand, and pursuant to Recital 47 of the CLP Regulation, Directive 91/414/EEC on plant

protection products and Directive 98/8/EC on biocidal products "should remain fully applicable to any product within their scope." For example, there are separate provisions for labelling and for updating labels for such substances and mixtures in these acts, and their suppliers must apply these provisions instead of the CLP rules, see e.g. CLP Article 30(3).

It should be noted that with effect from 14 June 2011, Directive 91/414/EEC has been repealed by Regulation (EC) 1107/2009. This means that references to the repealed Directive shall now be construed as references to the new Regulation. Nevertheless, Article 80 of the new Regulation 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. Furthermore, it specifies that products labelled in accordance with Article 16 of Directive 91/414/EEC may continue to be placed on the market until 14 June 2015.

In relation to classification, the new Regulation brings about some changes, e.g. certain classifications (e. g. CMR, Cat. 1 A and 1B) may now preclude approval of the respective substance as an active substance, safener, or synergist in plant protection 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 1.7 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)

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.

The object 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:

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

1.3.2.2.2 Hazard classification incorporates ... identification of ***relevant*** *data regarding the hazards of a substance or mixture ..."*

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 intrinsic properties of the substance 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 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 misuse, 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.

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 form of a substance or mixture as placed on the market might be such that it is not possible to test it in this form, e.g. if it is in the form of tablets or pellets. In such

circumstances, the physical hazards of the substance or mixture shall be considered for classification especially if they are friable and produce secondary effects due to abrasion or crushing during supply and use. If phase separation does occur, the hazardous properties of the most hazardous phase of the substance or mixture shall be communicated.

The test sample should in any case 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). Moreover, particle size is crucial for several other classes such as explosives, flammable solids, self-reactive substances, pyrophoric solids, self-heating substances, solid organic peroxides and substances which, in contact with water, emit flammable gases.

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 shall 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. the 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.

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 not be classified when it can be shown by conclusive experimental data from internationally acceptable test methods, e.g. from Council Regulation (EC) No 440/2008, that the substance or mixture is not biologically available (UN GHS 1.3.2.4.5.1). A non bioavailable substance may, however, react with the media 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.1of this document).

When considering the non-bioavailability of a mixture, the evaluation should be based on data for all relevant 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.

Information on relative bioavailability (e.g. relative amounts of absorption) within a related group/category of chemicals can be of some use in classification. It is possible that consideration of bioavailability data in a semi-quantitative manner would lead to the classification for the same hazard class but in a different category on the grounds that the extent of bioavailability would be reflected in the relative potency. In general, a prediction of lower bioavailability must be supported by robust evidence and a weight of evidence determination using expert judgment shall 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. 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 mixture 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). 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 considering the physical properties of a 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 this document.

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 this document.

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;

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 for the classification of substances. It states 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. A weight of evidence approach has to be used where the criteria cannot be applied directly to the available data according to CLP Article 9(3). This approach is further worked out in CLP Annex I, 1.1.1.

No specific guidance is given in REACH, Annex XI on when a result obtained with one of the methods is "adequate for the purpose of classification and labelling". However, 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 to decide on the classification.

CLP Annex I, 1.1.1.3 refers to the consideration of the category approach which encompasses grouping and read-across and (Q)SAR results to help in the weight of evidence determination of the classification category.

Annex 1: 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.

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)SARs for hazard identification is given in IR/CSA, Chapter R.6.1. Guidance on the use of (Q)SARs for classification and labelling according to DSD 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 category approach means that not every substance needs to be tested for every hazard. Read across 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.

Classification of all substances within an initially considered category may be inappropriate as substances may fall into more than one hazard classification category. Experience has shown that, an effect can be present for some but not all members of an initially considered category. One example is the glycol ethers, where some members of the category show reproductive toxicity whilst other members do not. In other cases, the category may show a consistent trend where the resulting potencies lead to different classifications (IR/CSA, Chapter R.6.2.1.2). In such cases it is proposed to use sub-categories for the different hazard classes where each sub-category receives the most appropriate classification.

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 environmental fate and/or (eco)toxicological properties. This can be based on structural similarity (e.g. (Q)SAR) of a parent substance or its transformation products, and their bioavailability, bioaccessiblity, or known physico-chemical properties such as water solubility. In principle, read across can be applied to characterise physico-chemical properties, environmental fate, human health effects and ecotoxicity. For certain substances without test data the formation of common significant metabolites or information with those 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 class, 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. This is because the concept of substance categories has traditionally been widely used for hazard classification and to some extent also for risk assessment.

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 only applicable to health hazards. For physical hazards, classification shall 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 sections of this document.

For some hazard classes, the potency is considered to be mainly (or mostly) reflected by the dose level causing a certain response of a well defined specific effect. The potency is then compared with a number of potency ranges to which certain SCLs are ascribed. This is the approach taken for setting SCLs for substances classified for sensitization, reproductive toxicity and carcinogenicity.

For certain hazard classes, the dose level is already considered when classifying into a particular hazard category, such as for STOT-SE and STOT-RE, and only a lower SCL can be set. To this end, a defined formula based on potency is used to calculate the SCL.

For some other hazard classes, the setting of SCLs is not appropriate. In particular, for those hazard classes for which the classification criteria are based on physico-chemical properties, it is not appropriate to establish SCLs. For example, the aspiration hazard is primarily a function of viscosity, and to a certain extent of surface tension. Thus the classification criteria refer to kinematic viscosity, hence the approach to assess the aspiration hazard of mixtures is based on test results on the kinematic viscosity of the whole mixture.

For the hazard classes skin corrosion/irritation and serious eye damage/eye irritation, the available data are normally not sufficient to form a basis for developing a general approach. Also, a reliable and conclusive scientific justification for such a method is lacking. Beyond these deficiencies, additional animal testing (of dilutions) of already classified substances is strongly discouraged for the purpose of setting SCLs, especially if there are no suspicions or indications that the general concentration limits are not sufficiently protective for the human health hazard to occur.

An overview of guidance available is also illustrated by Table 1.5.1 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, suppliers may not set own SCLs for harmonised classifications in Annex VI to CLP.

SCLs should be available in the C&L Inventory, and established in accordance with CLP.

Table 1.5.1 *Possibilities for setting SCL for health hazards as addressed in relevant sections of the guidance.*

Hazard class	**Category**	**Lower SCL than GCL**	**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 section 3.2
Serious eye damage/ eye irritation	all	yes	yes	available in section 3.3
Respiratory sensitisation	1	yes	no	to be provided in section 3.4[40]
Skin sensitisation	1	yes	yes	to be provided in section 3.4 (see above)
Germ cell mutagenicity	all	no	no	currently not possible
Carcinogenicity	all	yes	yes	available in section 3.6
Reproductive toxicity	all	yes	yes	available in section 3.7 and in Annex VI
STOT-SE	1	yes	no	available in section 3.8
	2	no	no	see section 3.8
	3	yes	yes	available in section 3.8
STOT-RE	1	yes	no	available in section 3.9

[40] Guidance on the setting of SCLs relating to the revised criteria for respiratory and skin sensitization that are based on the 2nd ATP to the CLP Regulation is planned for a future update of this guidance document.

	2	no	no	see 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 application of 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 in how to establish the M-factor see Section 4.1.3.3.3 of this document.

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 shall be set by the manufacturer, importer or downstream user in case there is no M-factor provided, in accordance with CLP Article 10(4).

1.6 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 data on the mixture as a whole should primarily be used to determine classification where applicable. If this cannot be done, further approaches to mixture classification may be applied.

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 applied 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.

REACH: Article 31(3)

The supplier shall provide the recipient at his request with a safety data sheet compiled in accordance with Annex II, where a mixture does not meet the criteria for classification as dangerous in accordance with Articles 5, 6 and 7 of Directive 1999/45/EC, but contains:

(a) in an individual concentration of ≥ 1 % by weight for non-gaseous mixtures and ≥ 0,2 % by volume for gaseous mixtures at least one substance posing human health or environmental hazards; or

(b) in an individual concentration of ≥ 0,1 % by weight for non-gaseous mixtures at least one substance that is persistent, bio-accumulative and toxic or very persistent and very bio-accumulative in accordance with the criteria set out in Annex XIII or has been included for reasons other than those referred to in point (a) in the list established in accordance with Article 59(1); or

(c) a substance for which there are Community workplace exposure limits.

NOTE: Article 31(3) is amended from 1 June 2015 by CLP Article 59 (2)(b) to read as follows:

The supplier shall provide the recipient at his request with a safety data sheet compiled in accordance with Annex II, where a mixture does not meet the criteria for classification as hazardous in accordance with Titles I and II of Regulation (EC) No 1272/2008, but contains:

(a) in an individual concentration of ≥ 1 % by weight for non-gaseous mixtures and ≥ 0,2 % by volume for gaseous mixtures at least one substance posing human health or environmental

hazards; or

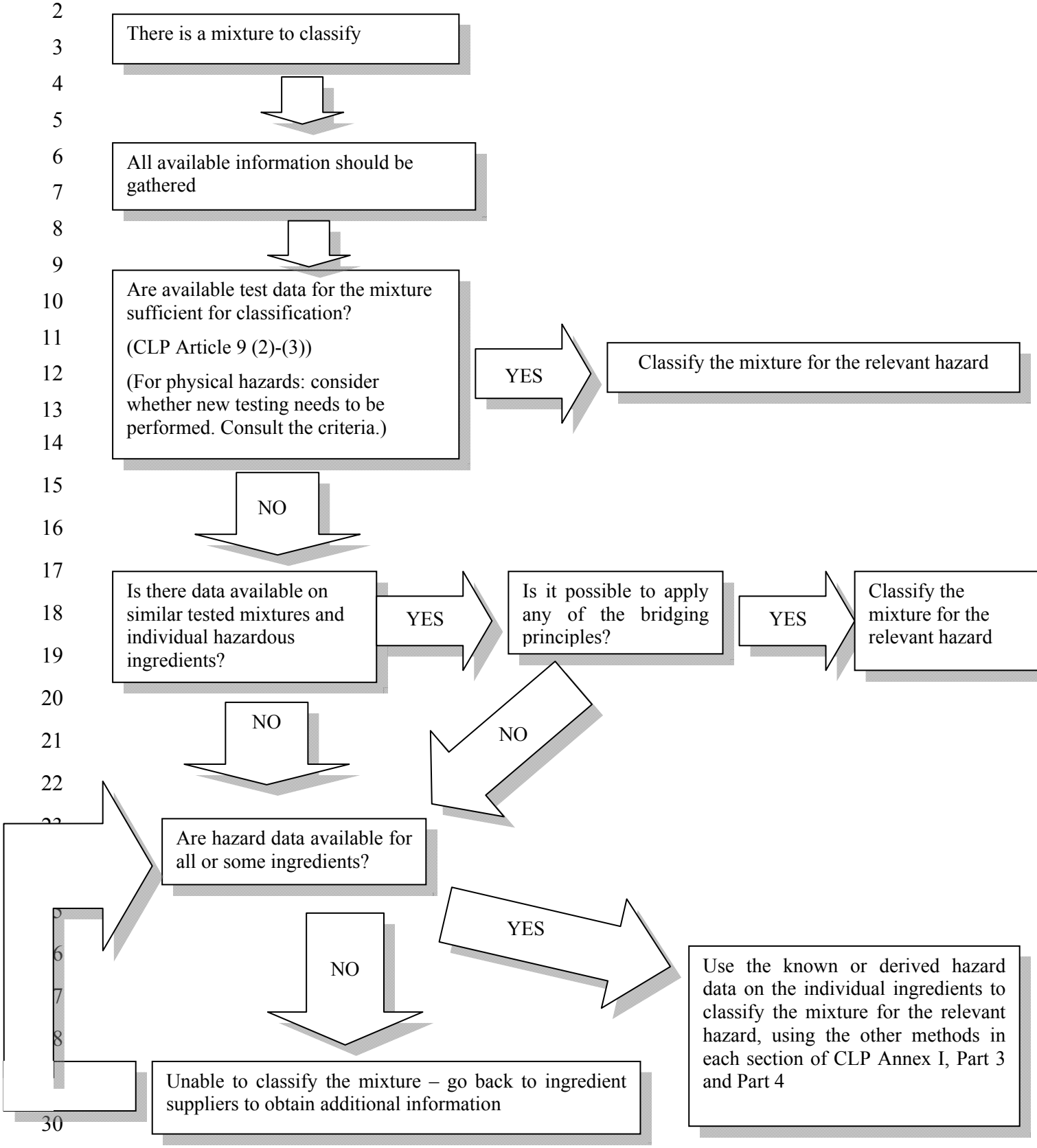
(b) in an individual concentration of ≥ 0,1 % by weight for non-gaseous mixtures at least one substance that is carcinogenic category 2 or toxic to reproduction category 1A, 1B and 2, skin sensitiser category 1, respiratory sensitiser category 1, or has effects on or via lactation or is persistent, bioaccumulative and toxic (PBT) in accordance with the criteria set out in Annex XIII or very persistent and very bioaccumulative (vPvB) in accordance with the criteria set out in Annex XIII or has been included for reasons other than those referred to in point (a) in the list established in accordance with Article 59(1); or

(c) a substance for which there are Community workplace exposure limits.

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 1.6.1, **for each hazard class independently**:

Figure 1.6.1 *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 few cases, such as hazard class "Flammable liquids", the classification of mixtures can also be derived through a calculation, see CLP Annex I, 2.6.4.2 and 2.6.4.3.

The test methods can be found for example in the UN Manual of Tests and Criteria, see the website http://www.unece.org/trans/publications/dg_tests.html, which is normally used to classify substances and mixtures for transport. In cases where test results are available, based on other methods or standards, then these data may still be used, provided they are adequate for the purpose of hazard determination. To conclude on the adequacy the results should be checked by the expert involved to ensure that 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.

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, 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 in many cases. Exceptions are: CMR hazards (see CLP Article 6(3)) bioaccumulation and biodegradation properties and the evaluation 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 (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).

1.6.3.2 Bridging principles

In the case of a classification for health or environmental hazards, 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). To apply these bridging principles certain conditions should be considered for their application which are summarised below.

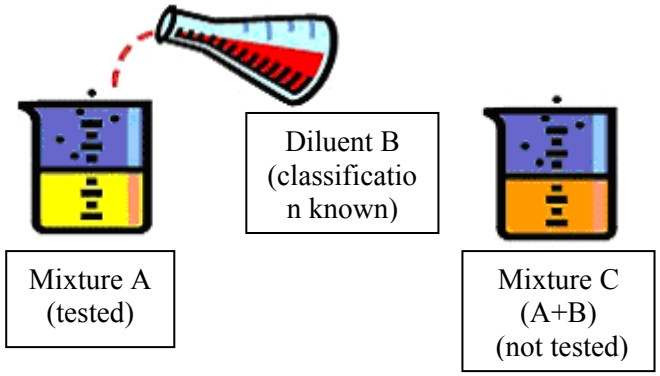
Not all of the bridging principles as described in sections 1.6.3.2.1-1.6.3.2.5 of this document need to be applied when assessing a particular health or environmental hazard. It is necessary to consult Annex I of CLP, Part 3 for health hazards and Part 4 for environmental hazards, before undertaking 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, 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 1.6.3.2.1.

Figure 1.6.3.2.1 *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 1.6.3.4.1 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 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 this document).

1.6.3.2.2 Batching

Where a batch of a 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.

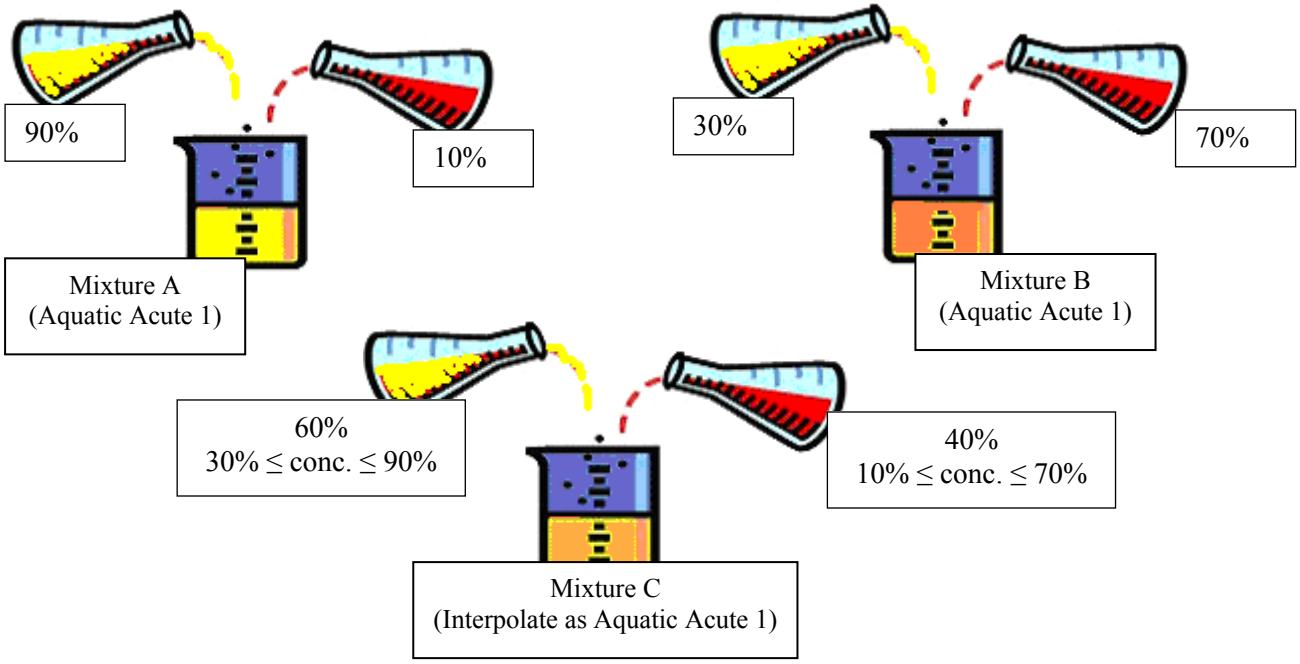
1.6.3.2.3 Concentration of highly hazardous mixtures

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 toxicity 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 1.6.3.2.4. (CLP Annex I, 1.1.3.4).

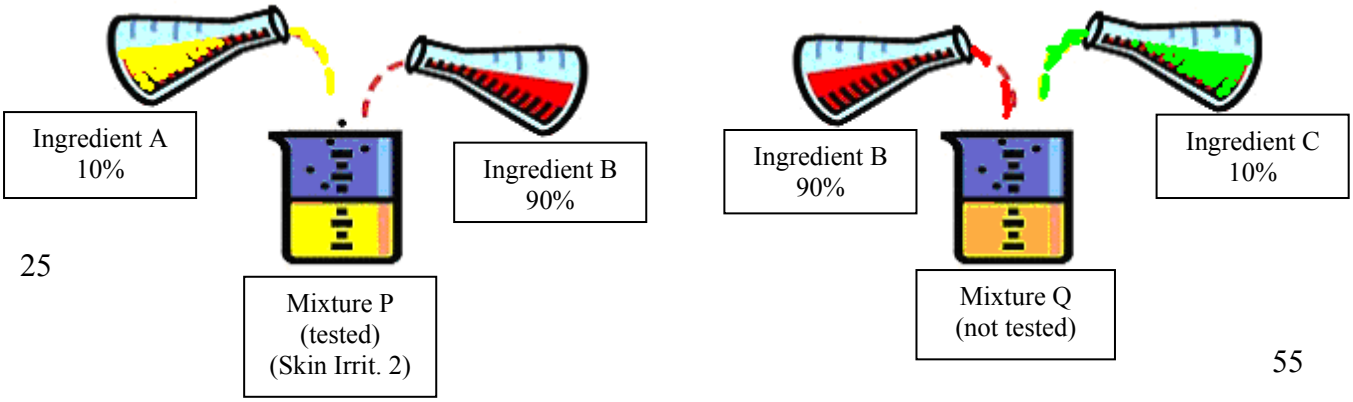
Figure 1.6.3.2.4 *Application of the bridging principle: interpolation for determining the aquatic acute hazard classification of a mixture*



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. 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 1.6.3.2.5. (CLP Annex I, 1.1.3.5).

Figure 1.6.3.2.5 *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
≤ 2,5 %	± 30 %
2,5 < C ≤ 10 %	± 20 %
10 < C ≤ 25 %	± 10 %
25 < C ≤ 100 %	± 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).

Where 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 shall carry out a new evaluation where 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:	$2 \times \pm 0.3 = \pm 0.6$	→	1.4 – 2.6
Substance B:	$12 \times \pm 0.1 = \pm 1.2$	→	10.8 – 13.2

1.6.3.3 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.).

1.6.3.4 Classification based on calculation or concentration thresholds

In most cases, test data on the mixture itself will not be available for a mixture, 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.

1.6.3.4.1 Classification based on calculation

The calculation methods set out under the different chapters of Annex I to CLP mostly differ from those applied under DPD. 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:

$$\frac{100}{ATE_{mix}} = \sum_{n} \frac{C_i}{ATE_i}$$

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:

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

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 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 an acute hazard category which is then subsequently used in applying the summation method;

(b) Based on chronic aquatic toxicity:

$$\frac{\sum C_i + \sum C_j}{\text{Eq NOEC}_m} = \sum_{n} \frac{C_i}{\text{NOEC}_i} + \sum_{n} \frac{C_j}{0{,}1 \text{ x NOEC}_j}$$

Where:

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

C_i = 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;

$NOEC_i$ = 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 ton;

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

NOTE: To make 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.

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

1.6.3.4.2 Classification based on concentration thresholds

Generic concentration thresholds

For some 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). 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: 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 (GCL) 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% a skin irritant substance which is present in a mixture would trigger classification of the mixture as skin irritant if it were present above or equal to the concentration limit of 10% in the mixture, see Table 3.2.3 of Annex I to CLP. However, at ≥ 1% and below 10%, it may still contribute to the classification of the mixture as skin irritant, since the concentration would be taken into account if other skin corrosive/irritant substances are present in the mixture below the relevant generic concentration limits. In some cases, classification as provided by the summation in CLP Annex I, Table 3.2.3 may be applicable, i.e.:

(10 × Skin Corrosive Categories 1A, 1B, 1C) + Skin Irritant Category 2 should be ≥ 10%

Specific concentration thresholds

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

1. SCLs are described in section 1.5.1 of this document and where they have been established they are included in Tables 3.1 and 3.2 of Annex VI to CLP and/or in the C&L Inventory (CLP Article 42). For "hazardous to the aquatic environment" the Multiplying factors (M-factors) concept[41] is used instead of SCLs, see section 1.5.2 of this guidance. SCLs and M-factors included in Tables 3.1 and 3.2 must be used where applicable and, for classifications not included in Annex VI, SCLs and M-factors included in the C&L Inventory shall be used where applicable unless justified otherwise.
2. 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

[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.

for which the M-factor has been established is present. For further guidance in how to establish and use the Mfactor see Sections 4.1.3.3.2 and 4.1.4.5 respectively

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).

Specific concentration thresholds take precedence over generic thresholds. In Annex I to DSD also generic concentration limits were listed in case SCLs were described to a certain entry. However in Tables 3.1 and 3.2 of Annex VI to CLP, these were deleted because under CLP, SCLs and M-factors can be set by the manufacturer or importer and they would then still take precedence to the generic thresholds, why those cannot be defined for specific entries.

1.6.3.4.3 Additivity of hazards

For some hazard classes additivity concepts are not applicable. In these cases, if the mixture contains two substances each below the GCLs defined for that hazard class or differentiation, even if the sum is above this limit, the mixture will not be classified, as far as no lower SCL has been set.

Non-additivity is applied for the following hazard classes:

(a) skin and respiratory sensitisers;

(b) germ cell mutagenicity;

(c) carcinogenicity;

(d) reproductive toxicity;

(e) specific target organ toxicity, single and repeated exposure, categories 1 and 2;

(f) aspiration hazard (plus consideration of viscosity of the final mixture);

(g) skin corrosion/irritation in some special cases (see CLP Annex I, 3.2.3.3.4); and

(h) serious eye damage/eye irritation in some special cases (see CLP Annex I, 3.3.3.3.4).

For example, where there are two ingredient substances classified for specific target organ toxicity - repeated exposure in Category 1 present in the mixture, but none of them is present at or above 10% or below 1 %, then the mixture will not be classified in Category 1 but will be Category 2 (even if the sum would be greater than 10%, because the additivity concept is not applicable).

Additivity is used for the following hazard classes or differentiations:

(a) skin corrosion/irritation (besides the cases mentioned in CLP Annex I, 3.2.3.3.4);

(b) serious eye damage/eye irritation (besides the cases mentioned in CLP Annex I, 3.3.3.3.4);

(c) specific target organ toxicity, single exposure Category 3 (respiratory tract irritation);

(d) specific target organ toxicity, single exposure Category 3 (narcotic effects); and

(e) acute and long-term aquatic hazards.

In these cases, if the sum of the concentrations of one or several classified substances 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.

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 should be summed up and contribute to mixture classification. Further guidance on the application of SCLs when using the summation method to derive skin corrosion / irritation or serious eye damage/eye irritation hazards can be found in sections 3.2 and 3.3 of this document.

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 constituent 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 ingredient 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 with one exception. The exception is that in case 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 constituent substances (including their individual hazard classification and concentration) down the supply chain, for instance 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 for declaration 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 both the test data as well as the knowledge on all 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 1.6.4.1(a) and Table 1.6.4.1(b) below.

No test data are available on Mixture A so 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, 3.1.3.3(b), there are two options to calculate 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 1.6.4.1(b)) 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.

N.B. 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 (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%, 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 (the relevant ingredient is present in a concentration > 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 disregarded.

Skin sensitisation

The 'fragrance mixture' contains four ingredients classified as skin sensitisers but their actual levels in Mixture A are < 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 (CLP Annex II, 2.8) would be required on the label for Mixture A.

Table 1.6.4.1(a) *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 1.6.4.1(b) *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. For compositional details see Table 1.6.4.2(a) and Table 1.6.4.2(b) below.

No test data are available on Mixture B so 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 B (including their % w/w and classification).

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 LD_{50} values are > 2000 mg/kg):

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

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

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

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

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

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):

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

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.

N.B. 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

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% oxygen bleach, 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. However this is below the concentration triggering classification (CLP Annex I, Table 3.4.3) thus Mixture B is not classified as a respiratory sensitiser. However ingredient 'enzymes' trigger additional labelling information (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).

Table 1.6.4.2(a) *Ingredients in Mixture B*

Ingredient	% w/w	Oral LD_{50} (rat)	Classification
Base powder	20.00	not tested	Eye Dam.1

(see list of ingredients below)			Skin Irrit. 2
Oxygen bleach	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
Bleach activator	5.00	> 5000 mg/kg	Not classified
Enzymes	0.70	> 2000 mg/kg	Resp. Sens. 1
Polycarboxylate	3.00	> 5000 mg/kg	Not classified
Total:	**100.00**		

Table 1.6.4.2(b) *Ingredient ' 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 THE APPLICATION OF ANNEX VII

1.7.1 Introduction

In order to assist industry, especially small and medium enterprises (SMEs) to implement CLP, Annex VII to CLP contains translation tables to translate a classification derived in accordance with DSD or DPD into a CLP classification.

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 that relate classifications according to DSD or DPD to a classification according to CLP.

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

While the tables in Annex VII explicitly point out where no translation is possible or where minimum classification can be applied, they do not identify cases where CLP hazard classes or categories, not covered by the DPD and DSD, are required under CLP. In the particular case of "no classification" under DPD, the table should not be used as there is no reasonable indication about a potential translation outcome.

This guidance will help classifiers to identify where translations contained in the tables of Annex VII to CLP may not be precise and also help classifiers to use existing transport classifications to fill some of the gaps.

1.7.2 Use of Annex VII translation tables

Annex VII *Translation table from classification under Directive 67/548/EEC to classification under this Regulation*

This Annex includes a table to assist translation of a classification made for a substance or a mixture under Directive 67/548/EEC or Directive 1999/45/EC, respectively, into the corresponding classification under this Regulation. Whenever data for the substance or mixture are available, an evaluation and classification shall be done in accordance with Articles 9 to13 of this Regulation.

When classifying in accordance with CLP, the use of the tables contained in Annex VII is optional. They can only be used to translate an existing classification provided that:

- the substance was classified according to the DSD before 1st December 2010 or the mixture was classified according to the DPD before 1st June 2015; and
- there is no data (scientific or technical information) for the substance or mixture available for an individual hazard class.

When data for the substance or mixture is available for a hazard class, the substance or mixture must be classified in accordance with CLP criteria; the Annex VII tables must not be used. In practice, this could lead to an approach for a substance/mixture where some hazard classes are re-classified using the Annex VII translation tables and other hazard classes are re-classified in accordance with CLP criteria.

1.7.2.1 Applicability of the Annex VII translation tables

As mentioned in section 1.7.1 of this document, the Annex VII translation tables do not always give a direct translation. For certain hazard classes, including acute toxicity and STOT repeated exposure, there is a recommended minimum classification in CLP, Annex VII

Table 1.1. This minimum classification should only be used if no additional hazard information is available (see also CLP Annex VI, 1.2.1).

Table 1.7.2.1(a) of this document identifies where the use of the Annex VII translation tables for substances and mixtures requiring classification under DSD or DPD, may lead to a classification that differs from one produced using the CLP criteria.

In addition to the differences indicated in Table 1.7.2.1(a), attention is drawn to the fact that for some hazards the DPD generic concentration limits, to be applied for mixtures, were lowered under CLP. 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). Where mixtures containing substances with risk phrases R34 or R41 have been classified on basis of the hazards of individual ingredients, the use of the translation table will lead to an under-classification of the mixture. Therefore, for mixtures with these R-phrases, the use of the translation tables may not be appropriate and re-classification may be done by using the existing data.

It is recommended that classifiers carefully consider the implications of these differences before choosing to use the translation tables. Possible consequences from downstream legislation or Responsible Care® issues need to be considered e.g. if the use of the translation tables increased the severity of the classification compared to using the CLP criteria, this could trigger additional duties under the Seveso Directive or national explosives legislation. Similarly a CLP hazard might not be identified by using the translation table which would have been identified if the CLP criteria had been used, leading to risks or company/product image and reputation issues.

Table 1.7.2.1(b) contains additional translations, using the transport classification that can be used in addition to the translations in Annex VII to improve the quality of the translated classifications. However these translations also have certain restrictions on their applicability.

- The transport classification of named substances or mixtures may be based on experience or certain events that are specific to transport
- The transport classification of named substances or mixtures in the transport regulations have not been systematically reviewed after the transport regulations were adapted to take into account the GHS criteria in particular classes 3 and 6.1. In general the transport classification of named substances or mixtures should be used with caution.
- The transport regulations include the concept of precedence of hazards. CLP does not apply a precedence of hazards and therefore substances or mixtures might need to be classified in additional hazard classes under CLP which are not reflected in the transport classification or are only considered as so-called subsidiary risks. There is usually insufficient information on subsidiary risks to allow a translation to CLP classification to be made.
- Sometimes special provisions are linked to the entries in the Dangerous Goods List which have to be met in order to be classified in the respective class for transport. In these cases the classification for the purposes of supply and use might be different. Sometimes one substance even has two different entries with two different classifications where one of the classifications is linked to one or more special provisions.

If the translation table is used to re-classify a substance or mixture, the new classification remains valid until either new data or change in composition requires the classification to be reviewed.

In deciding whether or not to use the translation table and the additional guidance contained in this document, a classifier should balance the speed and ease of its use against the consequences of the limitations. This judgment will be specific to each situation. This guidance will identify for which hazard classes the use of the translation table will give a different outcome from the direct application of the CLP criteria, and will explain why this is the case. Where possible, the use of an available transport classification as additional information is also described. This will help a classifier to make an informed decision about whether to use the translation tables and additional information contained in this guidance or to re-classify using the CLP criteria.

Table 1.7.2.1(a) *Hazard classes where reclassification using the translation tables gives a different outcome compared to reclassification using CLP criteria*

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; individual treatment See Table 1.7.2.1(b) for additional information using transport classifications
O, R8 (liquid)	Oxidising liquid	All liquid substances or mixtures classified O,R8 are classified as oxidising liquids under CLP. See Table 1.7.2.1(b) for additional information using transport classifications
O, R8 (solid)	Oxidising solid	The test methods for oxidising solids in 67/548/EEC and CLP are different. Most solids classified O, R8 are also classified as oxidising solids under CLP. See Table 1.7.2.1(b) for additional information using 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. See Table 1.7.2.1(b) for additional information using transport classifications
F, R15	Substance or mixture which, in contact with water, emit(s) flammable gas(es)	See Table 1.7.2.1(b) for additional information using transport classifications

Table 1.7.2.1(b) *Additional information using transport classifications*

(Note that within transport, the term "substances" covers also mixtures in CLP terms)

Transport classification		Physical state	CLP-classification		Remarks
Transport class and (sub)division (if applicable)	**Packing group, division, type, group or code**		**Hazard class**	**Hazard category, division, type or group**	
Class 1	Division 1.1 Division 1.2 Division 1.3 Division 1.4 Division 1.5 Division 1.6	Liquid or solid	Explosives	Division 1.1 Division 1.2 Division 1.3 Division 1.4 Division 1.5 Division 1.6	Matching criteria. However, if explosives are un-packed or repacked, they have to be assigned to division 1.1 unless the hazard is shown to correspond to one of the other divisions.
Class 2 - Gases	1 Compressed gas	Gaseous	Gases under pressure	Compressed gas	This translation only applies to the form in which the gas is transported. If it is used in a different form, then the classification has to be amended
	2 Liquefied gas.	Gaseous		Liquefied gas.	
	3 Refrigerated liquefied gas	Gaseous		Refrigerated liquefied gas	
	4 Dissolved gas	Gaseous		Dissolved gas	
	5 Aerosol dispensers, class 2.1	Not relevant (Articles)	Flammable aerosols	Category 1 Category 2	The transport classification does not differentiate between Category 1 and 2 flammable aerosols
	Flammable gases	Gaseous	Flammable gases	Category 1	Category 2 flammable gases cannot be identified using the transport criteria
	Oxidising gases	Gaseous	Oxidising gases	Category 1	
Class 3	Packing group 1	Liquid	Flammable liquid	Category 1	
	Packing group 2	Liquid	Flammable liquid	Category 2	
	Packing group 3	Liquid	Flammable liquid	Category 3	
Class 4.1	Types B-F	Solid or liquid	Self-reactive substances	Types B-F	

Class 4.1 (only readily combustible solids)	Packing group II	Solid	Flammable solids	Category 1	
Class 4.1 (only readily combustible solids)	Packing group III	Solid	Flammable solids	Category 2	
Class 4.2 Pyrophoric substances	Packing group I	Liquid	Pyrophoric liquids	Category 1	
		Solid	Pyrophoric solids	Category 1	
Class 4.2	Packing group II	Solid	Self-heating substances and mixtures	Category 1	
Class 4.2	Packing group III	Solid	Self-heating substances and mixtures	Category 2	
Class 4.3	Packing group I Packing group II Packing group III	Liquid or solid	Substances which in contact with water emit flammable gases	Category 1 Category 2 Category 3	
Class 5.1	Packing group I Packing group II Packing group III	Solid	Oxidising solid	Category 1 Category 2 Category 3	
Class 5.1	Packing group I Packing group II Packing group III	Liquid	Oxidising liquid	Category 1 Category 2 Category 3	
Class 5.2	Types B-F	Solid or liquid	Organic peroxides	Types B-F	
Class 8	Packing group III	Liquid or solid	Corrosive to metals	Category 1	Applies only when the substance or mixture is not classified C; R35 or C;R34

1.7.3 Additional considerations for re-classification due to changes in the classification criteria

Due to changes in the classification criteria, and lowering of several GCLs for mixtures, CLP may trigger classification for certain hazards which were not required by DPD or DSD.

Table 1.7.3 (c) below identifies when a substance or mixture, that does not require classification and labelling according to DSD or DPD, may require classification and labelling according to CLP.

Table 1.7.3(c) *Examples when classification may not be required under DSD and DPD, but may be required under CLP*

Non-classifications under DSD or DPD	Additional hazards under CLP	Comments
Non-classified explosives	Explosive	Certain explosives, not classified as E, R2 or E, R3, which are manufactured with the view to producing a practical explosive or pyrotechnical effect will be classified as explosive under CLP. See Table 1.7.2.1(b) for additional information using transport classifications
Self-reactive substances or mixtures	Self-reactive substance	Self-reactive substances or mixtures may not be identified under the DSD. See Table 1.7.2.1(b) for additional information using transport classifications
Flammable aerosols	Flammable aerosol	Flammable aerosols are not explicitly identified under DSD or DPD. See Table 1.7.2.1(b) for additional information using transport classifications
Gases under pressure	Gas under pressure	Gases under pressure will not be identified as no R phrase for gases under pressure currently exists. The assignment of the correct group of a gas under pressure (compressed, liquefied or dissolved) depends on the physical state in which the gas is packaged or handled. It therefore has to be assigned individually. Note that the transport classification may be different.
Self-heating substances or mixtures	Self-heating substance or mixture	Self-heating substances or mixtures will not be identified as no R phrase for self-heating substances or mixtures currently exists. See Table 1.7.2.1(b) for additional information using transport classifications
Substances or mixtures that are corrosive to metals, but not corrosive to skin	Corrosive to metal	Substances or mixtures that are corrosive to metals, but not corrosive to skin, will not be identified as no R phrase for corrosive to metals currently exists. See Table 1.7.2.1(b) for additional information using transport classifications
Mixtures containing substances with non-additive effects for skin corrosion/irritation and eye damage/irritation	1) Skin corrosive/serious eye damage (Category 1) 2) Skin/eye irritant (Category 2)	The concept of non-additive effects for skin corrosion/irritation and eye damage/irritation is not explicitly considered in the current Directives (see CLP Annex I, Tables 3.2.4 and 3.3.4).
Mixtures containing 1-5% of R34 substances (and thus not classified)	Skin Irritant Category 2	The generic concentration limit is 1% in the CLP but the corresponding limit is 5% in the DPD.

Mixtures containing 10 – 20% of R38 substances (and thus not classified)	1) Skin irritant Category 2	The generic concentration limit is 10% in the CLP but the corresponding limit is 20% in the DPD.
Mixtures containing 1-3% of R41 or R34 substances (and thus not classified)	1) Eye irritant Category 2	The lower generic concentration limit is 1% in the CLP but the corresponding limit is 5% in the DPD.
Mixtures containing 3-5% of R41 or R34 substances (and thus not classified)	1) Serious eye damage Category 1	The generic concentration limit is 3% in the CLP but the corresponding limit is 10% in the DPD.
Mixtures containing 10 – 20% of R36 substances (and thus not classified)	1) Eye irritant Category 2	The generic concentration limit is 10% in the CLP but the corresponding limit is 20% in the DPD.
Mixtures containing 3 - 5% of R62 or R63 substances (and thus not classified)	1) Reproductive toxicant, Category 2	The generic concentration limit is 3% in the CLP but the corresponding limit is 5% in the DPD.
Mixtures containing 0.3-0.5% of R60 or R61 substances (and thus not classified)	1) Reproductive toxicant Category 1A/1B	The generic concentration limit is 0.3% in the CLP but the corresponding limit is 0.5% in the DPD.

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2 PART 2: PHYSICAL HAZARDS

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6 **3.7.3.1.3 When data are not available for the complete mixture: bridging principles**

4 PART 4: ENVIRONMENTAL HAZARDS

4.1 HAZARDOUS TO THE AQUATIC ENVIRONMENT

4.1.1 Introduction

Guidance for the application of the criteria covering effects on the aquatic compartment was developed by OECD and incorporated as Annexes 9 and 10 in the "Globally Harmonised System of classification and labelling of chemicals (UN GHS)" (United Nations GHS (Rev. 3) 2009)).

The text in this chapter, and even more so in some of the Annexes to this chapter, is largely based on the text in UN GHS (Rev. 3, 2009). The guidance given in Annexes 9 and 10 of UN GHS relates to substances, but not mixtures. Some parts have therefore been slightly revised to take into account recent developments and additional guidance documents provided by ECHA. Furthermore guidance on the classification of mixtures has been brought into this chapter as well as classification examples for both substances and mixtures.

4.1.2 Scope

Annex I: 4.1.1.3.1 Classification of substances and mixtures for environmental hazards requires the identification of the hazards they present to the aquatic environment. The aquatic environment is considered in terms of the aquatic organisms that live in the water, and the aquatic ecosystem of which they are part. The basis, therefore, of the identification of acute (short-term) and long-term hazards is the aquatic toxicity of the substance or mixture, although this shall be modified by taking account of further information on the degradation and bioaccumulation behaviour, if appropriate.

The classification scheme has been developed with the objective of identifying those chemicals that present, through their intrinsic properties, a hazard to the aquatic environment covering the aquatic freshwater and marine ecosystems. For most substances, the majority of data available addresses this environmental compartment. The classification scheme is limited in scope in that it does not, as yet, include aquatic sediments, nor higher organisms at the top end of the aquatic food-chain, although these may to some extent be covered by the criteria selected.

Although limited in scope, it is widely accepted that this compartment is vulnerable, in that it is the receiving environment for many harmful substances, and the organisms that live there can be very sensitive. It is also complex since any system that seeks to identify hazards to the environment must seek to define those effects in terms of wider effects on ecosystems rather than on individuals within a species or population. However, for practical reasons a limited set of specific properties has been selected through which the acute (short-term) and long-term hazards, can be best described: acute aquatic toxicity; chronic aquatic toxicity; lack of rapid degradability; and potential or actual bioaccumulation. Relevant definitions for aquatic hazard classification of substances i.e. acute and/or chronic aquatic toxicity, availability and bioavailability to the aquatic environment are outlined in the CLP Regulation, Annex I, Section 4.1.1.1. Some further guidance can be viewed in the IR/CSA[42], Chapter B.6.3. The rationale for the selection of these properties as the means to define the aquatic hazard will be described in more detail in the following sections of this guidance.

[42] IR/CSA … Guidance on Information Requirements and Chemical Safety Assessment (ECHA, 2008).

4.1.3 Classification of substances hazardous to the aquatic environment

4.1.3.1 Information applicable for classification of substances hazardous to the aquatic environment

4.1.3.1.1 Substance properties used for classification

Generally speaking, in deciding whether a substance should be classified, a search of appropriate databases and other sources of data should be made for at least the following substance properties: water solubility, octanol/water partition coefficient (log K_{ow}), acute aquatic toxicity ($L(E)C_{50}$), chronic aquatic toxicity (NOEC or equivalent EC_x[43]), degradation (evidence of rapid degradability, hydrolysis) and bioaccumulation (preferably bioconcentration factor in fish (BCF)). Other information might be considered on a case-by-case basis.

Although not used directly in the criteria, the water solubility and stability data are important since they are a valuable help in the data interpretation of the other properties. However, water solubility may be difficult to determine and is frequently recorded as simply being low, insoluble or less than the detection limit. This may create problems in interpreting aquatic toxicity and bioaccumulation studies (see also Annex III). Hydrolysis data (Test Methods Regulation (EC) N^o 440/2008; OECD Test guideline 111) and information on the hydrolysis products as well as their behaviour in water might be helpful as well. As an example, for substances where the degradation half-life (DT_{50}) is less than 12 hours, environmental effects are likely to be attributed to the hydrolysis products rather than to the parent substance itself (IR/CSA, Chapter R7.8).

4.1.3.1.2 Information and data availability

> **Annex I: 4.1.1.2.2** Preferably data shall be derived using the standardised test methods referred to in Article 8(3). In practice data from other standardised test methods such as national methods shall also be used where they are considered as equivalent. Where valid data are available from non-standard testing and from non-testing methods, these shall be considered in classification provided they fulfil the requirements specified in section 1 of Annex XI to Regulation (EC) No 1907/2006. In general, both freshwater and marine species toxicity data are considered suitable for use in classification provided the test methods used are equivalent. Where such data are not available classification shall be based on the best available data. See also part 1 of Annex I to Regulation (EC) No 1272/2008.

The data used to classify a substance can be drawn from data required for other regulatory purposes as well as the relevant literature. A number of internationally recognised databases exist which can act as a good starting point. Such databases vary widely in quality and comprehensiveness and it is unlikely that any one database will hold all the information necessary for classification to be made. Some databases specialise in aquatic toxicity and others in environmental fate. Information can also be gathered from data submitted under plant protection products and/or biocidal products legislation.

Non-testing information

Information derived from (Q)SAR and read-across, grouping and categorisation can also be used, see also IR/CSA, Chapter R.6.

[43] if available, preference is given to EC_{10}, see OECD 2006

Information sources

IR/CSA Chapter R.3.4.1 specifies a selection of freely available databases and databanks which might be consulted for classification purposes. All ECHA guidance documents are available on the Agency's website (http://guidance.echa.europa.eu/).

Data can also be found through the eChemPortal, which is a global portal to information on chemical substances. The eChemPortal provides access to a number of databases, including the OECD HPV (Existing Chemicals Database) and the SIDS UNEP (Screening Information Dataset for High Volume Chemicals). The eChemPortal is currently hosted by the OECD: (http://www.echemportal.org/)

Further guidance is given in Annex V to this document.

4.1.3.2 Evaluation of available information

4.1.3.2.1 General considerations

The term substance covers a wide range of chemicals (INS[44], Chapter 3) many of which pose challenges to a classification system based on rigid criteria. This section will thus provide some guidance on how these challenges can be dealt with based both on experience in use and clear scientific rationale.

The range of interpretational problems can be extensive and as a result such interpretation will always rely on the ability and expertise of the individuals responsible for classification. However, it is possible to identify some commonly occurring difficulties and provide guidance. Such difficulties can fall into a number of overlapping issues:

(a) The difficulty in applying the current test procedures to some types of substances;

(b) The difficulty in interpreting the data derived both from these "difficult to test" substances and from other substances;

(c) The difficulty in interpretation of diverse datasets derived from a wide variety of sources (e.g. Weight of Evidence).

(d) The difficulty of interpreting 'other' information

Regarding the use of test data, in general, only reliable information (i.e. with a Klimisch reliability score of 1 (reliable without restrictions) or 2 (reliable with restrictions)) should be used for classification purposes. However, good quality data may not always be available for all trophic levels. It will be necessary to consider data of lower quality for those trophic levels for which good quality data are not available. Consideration of such data, however, will also need to consider the difficulties that may have affected the likelihood of achieving a valid result. For larger data sets, preference should be given to information with Klimisch score 1, while information with Klimisch score 2 can be used as supporting information. For more information on the Klimisch reliability scoring system, see IR/CSA, Chapter R.4.2.

4.1.3.2.2 Substances difficult to test

For many organic substances, the testing and interpretation of data present no problems when applying both the relevant Test Methods Regulation (EC) N° 440/2008 and/or OECD Test Guidelines and the classification criteria. There are a number of typical interpretational

[44] INS means Guidance on Identification and Naming of substances in REACH (ECHA, 2007)

problems, however, that can be characterised by the properties of the substance being studied. These are commonly called "difficult substances":

(a) poorly soluble substances: these substances are difficult to test because they present problems in the preparation of a test solution, maintenance of test concentrations and verification of exposure during aquatic toxicity testing. In addition, many available data for such substances have been produced using "solutions" in excess of the water solubility resulting in major interpretational problems in defining the true $L(E)C_{50}$ or $NOEC/EC_x$ for the purposes of classification. Interpretation of the partitioning behaviour can also be problematic where the poor solubility in water and octanol may be compounded by insufficient sensitivity in the analytical method. Water solubility may be difficult to determine and is frequently recorded as simply being less than the detection limit, creating problems in interpreting both aquatic toxicity and bioaccumulation studies. In biodegradation studies, poor solubility may result in low bioavailability and thus lower than expected biodegradation rates. The specific test method or the choice of procedures used can thus be of key importance;

(b) unstable substances: such substances that degrade (or react) rapidly in the test system present both testing and interpretational problems. It will be necessary to determine whether the correct methodology in line with the guidance provided in section 4.1.3.3 has been used, whether it is the substance or the degradation/reaction product that has been tested, and whether the data produced is relevant to the classification of the parent substance;

(c) volatile substances: such substances that can clearly present testing problems when used in open systems should be evaluated to ensure adequate maintenance of exposure concentrations. Loss of test material during biodegradation testing is inevitable in certain methods and will lead to misinterpretation of the results;

(d) complex or multi-constituent[45] substances: such substances, for example, complex hydrocarbons , or other UVCB[46] substances, frequently cannot be dissolved into a homogeneous solution, and the multiple components make monitoring impossible. For organics, consideration therefore needs to be given to using the data derived from the testing of water-accommodated fractions (WAFs) for aquatic toxicity, and the use of such data in the classification scheme[47]. Biodegradation, bioaccumulation, partitioning behaviour and water solubility all present problems of interpretation, where each component of these complex or multi-constituent substances may behave differently;

(e) polymers: such substances frequently comprise a wide range of molecular masses, which individually might have different water solubilities. Special methods are available to determine the water soluble fraction and these data will need to be used in interpreting the test data against the classification criteria;

[45] Further definitions are provided in the Guidance on Identification and Naming of Substances (INS) in REACH (ECHA, 2007).

[46] UVCB means Substances of Unknown or Variable composition, Complex reaction products or Biological materials, see Chapter 4.3 in INS.

[47] Note that the toxicity is sometimes expressed as LL_{50}, related to the lethal loading level. This loading level from the WSF or WAF may be used directly in the classification criteria (see also Annex I.4.5 of this guidance document).

(f) inorganic compounds and metals: such substances, which can interact with the media, can produce a range of aquatic toxicities dependent on factors such as pH, water hardness etc. Difficult interpretational problems also arise from the testing of essential elements that are beneficial at certain levels. For metals and inorganic metal compounds, the concept of degradability as applied to organic compounds has limited or no meaning. Equally the use of bioaccumulation data should be treated with care (see also Annex IV);

(g) surface active substances: such substances can form emulsions in which the bioavailability is difficult to ascertain, even with careful preparation of solutions. Micelle formation can result in an overestimation of the bioavailable fraction even when "solutions" are apparently formed. This presents significant problems of interpretation in each of the water solubility, partition coefficient, bioaccumulation and aquatic toxicity studies;

(h) ionisable substances: such substances can change the extent of ionisation according to the level of counter ions in the media. Acids and bases, for example, will show radically different partitioning behaviour depending on the pH;

(i) coloured substances: such substances can cause problems in the algal/aquatic plant testing because of the blocking of incident light;

(j) impurities: some substances can contain impurities that can change in percentage and in chemical nature between production batches. Interpretational problems can arise where either or both the toxicity and water solubility of the impurities are greater than the parent substance, thus potentially influencing the toxicity data in a significant way. In general, the substance as manufactured including impurities should be tested and the classification should be based on these test results. To asses the sameness of two substances containing the same impurity in different amount (INS, Chapter 5);

(k) essential substances: some substances are essential to life, even though, like any substance, excessive concentrations can be harmful. This can lead to complex concentration/dose-response curves;

(l) substances which can chelate or sequester essential elements, leading to the same problems of interpretation as in (k).

For further details see the OECD Guidance Document on aquatic toxicity testing of difficult substances and mixtures (OECD 2000) and also the IR/CSA Guidance, Chapter R.7b, Appendix 7.8.1 and Annex I to this guidance.

4.1.3.2.3 Interpretation of data for aquatic toxicity, degradation and bioaccumulation

4.1.3.2.3.1 Aquatic toxicity

Annex I: 4.1.2.7.1 Acute aquatic toxicity is normally determined using a fish 96 hour LC_{50}, a crustacea species 48 hour EC_{50} and/or an algal species 72 or 96 hour EC_{50}. These species cover a range of trophic levels and taxa and are considered as surrogate for all aquatic organisms. Data on other species (e.g. *Lemna* spp.) shall also be considered if the test methodology is suitable. The aquatic plant growth inhibition tests are normally considered as chronic tests but the EC_{50}s are treated as acute values for classification purposes (see note 2).

4.1.2.7.2 For determining chronic aquatic toxicity for classification purposes data generated

according to the standardised test methods referred to in Article 8(3) shall be accepted, as well as results obtained from other validated and internationally accepted test methods. The NOECs or other equivalent EC_x (e.g. EC_{10}) shall be used.

Fish, crustacea and algae or other aquatic plants are tested as surrogate species representing a range of trophic levels and taxa, and the test methods are highly standardised (see Annex I for further details). Valid data for short- and long-term tests on other species at the same trophic level shall also be considered, provided they represent equivalent species and test endpoints.

The purpose of classification is to characterise both the acute and long-term hazards in the aquatic environment. The acute and long-term hazards represent distinct types of hazard and should be applied independently.

The lowest available toxicity value(s) between and within the different trophic levels (fish, crustacea, algae/aquatic plants) will normally be used to define the appropriate hazard category(ies), although there may be circumstances where a weight of evidence approach is required (see section 4.1.3.2.4).

Care should be taken when classifying substances like ionisable organic chemicals or organo-metallic substances as the observed results may express different toxicities in freshwater and marine environments and/or poorly soluble substances (water solubility < 1 mg/l), where there is evidence that the acute test does not provide a true measure of the intrinsic toxicity.

Relevant descriptions of the type of acute and/or chronic aquatic toxicity tests have been outlined in detail in Annex I to this guidance and in IR/CSA, Sections R.7.8.3-R.7.8.4. For classification and labelling purposes, tests using organisms outside the specified size (generally smaller) and/or tests with a differing test duration could be used if no other acceptable data are available.

Currently *in vitro* studies are only validated for some human health endpoints and according to IR/CSA, Chapters R.7.8.3-R.7.8.4, there are currently no validated fish cell systems available for use as alternative data to determine acute and long-term hazards within the scope of classification and labelling.

4.1.3.2.3.2 Degradation

Annex I: 4.1.2.9.1 Substances that rapidly degrade can be quickly removed from the environment. While effects of such substances can occur, particularly in the event of a spillage or accident, they are localised and of short duration. In the absence of rapid degradation in the environment a substance in the water has the potential to exert toxicity over a wide temporal and spatial scale.

4.1.2.9.2 One way of demonstrating rapid degradation utilises the biodegradation screening tests designed to determine whether an organic substance is "readily biodegradable". Where such data are not available, a BOD(5 days)/COD ratio ≥ 0,5 is considered as indicative of rapid degradation. Thus, a substance which passes this screening test is considered likely to biodegrade "rapidly" in the aquatic environment, and is thus unlikely to be persistent. However, a fail in the screening test does not necessarily mean that the substance will not degrade rapidly in the environment. Other evidence of rapid degradation in the environment may therefore also be considered and are of particular importance where the substances are inhibitory to microbial activity at the concentration levels used in standard testing. Thus, a further classification criterion is included which allows the use of data to show that the substance did actually degrade biotically or abiotically in the aquatic environment by > 70 % in 28 days. Thus, if degradation is demonstrated under environmentally realistic conditions, then the criterion of "rapid degradability" is met.

The definition of degradation covers both biotic (biodegradation) and abiotic degradation processes. Data on degradation properties of a substance may be available from standardised tests, from other types of investigations, or they may be estimated from the structure of the molecules (see section 1.4). In section II.2 of Annex II to this guidance a general overview of relevant definitions on how to use different (bio)degradability tests and guidance for the interpretation of test data in the context of classification and labelling is given. Additional information on (bio)degradation testing methods can be found in IR/CSA, Chapter R.7.9. The OECD test methods 301A-F (C.4-A to F of the Test Methods Regulation 440/2008), OECD310, or equivalent tests, are commonly used to determine 'ready biodegradability'. Some guidance on the use of QSAR methods for degradability is presented in IR/CSA, Chapter R.7.9.3.1.

The paragraphs below will focus on the guidance for using degradability data for classification & labelling under CLP. It should be noted that the guidance on degradability pertains primarily to individual substances. In the case of complex or multi-constituent substances, the proposed test approaches do not normally allow an unequivocal interpretation of the degradability of the individual components of the substances. Thus, results of biodegradability tests on complex or multi-constituent substances should be carefully evaluated before use for classification purposes is considered.

Annex I: 4.1.2.9.3 Many degradation data are available in the form of degradation half-lives and these can be used in defining rapid degradation provided that ultimate biodegradation of the substance, i.e. full mineralisation, is achieved. Primary biodegradation does not normally suffice in the assessment of rapid degradability unless it can be demonstrated that the degradation products do not fulfil the criteria for classification as hazardous to the aquatic environment.

4.1.2.9.4 The criteria used reflect the fact that environmental degradation may be biotic or abiotic. Hydrolysis can be considered if the hydrolysis products do not fulfil the criteria for classification as hazardous to the aquatic environment.

4.1.2.9.5 Substances are considered rapidly degradable in the environment if one of the following criteria holds true:

(a) if, in 28-day ready biodegradation studies, at least the following levels of degradation are achieved:

(i) tests based on dissolved organic carbon: 70%;

(ii) tests based on oxygen depletion or carbon dioxide generation: 60% of theoretical maximum.

These levels of biodegradation must be achieved within 10 days of the start of degradation which point is taken as the time when 10 % of the substance has been degraded; unless the substance is identified as an UVCB or as a complex, multi-constituent substance with structurally similar constituents. In this case, and where there is sufficient justification, the 10-day window condition may be waived and the pass level applied at 28 days, or

(b) if, in those cases where only BOD and COD data are available, when the ratio of BOD_5/COD is ≥ 0,5; or

(c) if other convincing scientific evidence is available to demonstrate that the substance can be degraded (biotically and/or abiotically) in the aquatic environment to a level > 70 % within a 28-day period.

The following decision scheme may be used as a general guidance to facilitate decisions in relation to rapid degradability in the aquatic environment and classification of chemicals hazardous to the aquatic environment.

A substance is considered to be **not** rapidly degradable **unless** at least one of the following is fulfilled:

(a) The substance is demonstrated to be readily biodegradable in a 28-day test for ready biodegradability. The pass level of the test (70% DOC removal or 60% theoretical oxygen demand) must be achieved within 10 days from the onset of biodegradation, if it is possible to evaluate this according to the available test data (the ten-day window condition may be waived for complex multi-component substances and the pass level applied at 28 days, as discussed in point II.2.3 of Annex II to this document). If this is not possible, then the pass level should be evaluated within a 14 days time window if possible, or after the end of the test; or

(b) The substance is demonstrated to be ultimately degraded in a surface water simulation test with a half-life of < 16 days (corresponding to a degradation of >70% within 28 days); or

(c) The substance is demonstrated to be primarily degraded biotically or abiotically e.g. via hydroysis, in the aquatic environment with a half-life <16 days (corresponding to a degradation of >70 % within 28 days), and it can be demonstrated that the degradation products do not fulfill the criteria for classification as hazardous to the aquatic environment.

When these preferred data types are not available rapid degradation may be demonstrated if one of the following criteria is justified:

(d) The substance is demonstrated to be ultimately degraded in an aquatic sediment or soil simulation test with a half-life of < 16 days (corresponding to a degradation of > 70 % within 28 days); or

(e) In those cases where only BOD_5 and COD data are available, the ratio of BOD_5/COD is greater than or equal to 0.5. The same criterion applies to ready biodegradability tests of a shorter duration than 28 days, if the half-life furthermore is < 7 days; or

(f) A weight of evidence approach based on read-across provides convincing evidence that a given substance is rapidly degradable.

If none of the above types of data are available then the substance is considered as **not** rapidly degradable. This decision may be supported by fulfilment of at least one of the following criteria:

(i) the substance is not inherently degradable in an inherent biodegradability test; or

(ii) the substance is predicted to be slowly biodegradable by scientifically valid QSARs, e.g. for the Biodegradation Probability Program, the score for rapid degradation (linear or non-linear model) < 0.5; or

(iii) the substance is considered to be not rapidly degradable based on indirect evidence, such as knowledge from structurally similar substances; or

(iv) no other data regarding degradability are available.

The percentage degradation reached after 28 days in ready biodegradability tests may be used directly for the assessment of 'rapid degradability' if no specific information on the time window is available or if the data were derived with the MITI 1 test (OECD 301C, 2006 or C.4-E of the Test Methods Regulation 440/2008). In the Closed Bottle test (OECD 301D, or C.4-F of the Test Methods Regulation 440/2008) a 14-day window may be used when

measurements have not been made after 10 days. For some industrial chemicals that in terms of composition can be seen as multi-component substances testing for 'ready biodegradability' can lead to interpretational problems (see Annex II to this guidance).

Selection of test systems

As regards paragraph 4.1.2.9.5 point c in Annex I to CLP, the evaluation of the fulfilment of this criterion should be conducted on a case-by-case basis by expert judgement. Test systems that can be used to demonstrate the occurrence of rapid degradability are listed in Annex II. This includes e.g. simulation tests under realistic conditions, mesocosms and field monitoring.

Inherent- (OECD 302A and B, or C.9 and C.12 of the Test Methods Regulation 440/2008) and sewage treatment simulation (OECD 303, or C.10 of the Test Methods Regulation 440/2008) tests are not normally used in this context, due to the high levels of adapted biomass. Anaerobic degradation tests (OECD 311/ISO 11734 and analogous tests) do not qualify because of the specificity of the anaerobic compartments. Also the newly defined category of 'Enhanced Ready Biodegradation (Screening) Tests' in IR/CSA, Chapter R.7.9 do not qualify for use in classification and labelling, as they are presently not reviewed and internationally standardised.

Use of SARs and QSARs

The estimation of degradation via SARs and/or QSARs for hydrolysis and biodegradation is a rapidly developing field. The predictions from QSAR models may be considered as contributing to a decision on ready or rapid degradation for classification purposes. QSAR models should be used with great care, taking into account the applicability domain and validation of the models. Current practice is to use the outcome of these biodegradation models to predict that a substance is not readily degradable, rather than *vice versa*. This is because models such as BIOWIN tend to predict non-biodegradability more accurately than biodegradability. However, QSAR information can be used as a part of expert judgement and Weight of Evidence practices, for example where very consistent measured and predicted data are available for a structurally analogous compound.

General interpretation problems and substances difficult to test

Both the UN GHS Annex 9 and the INS discuss substances that are inherently difficult to test for biodegradability, and possible adjustments to overcome testing problems. Testing or interpretational problems may occur with e.g. complex multi-constituent substances, surface active agents, highly volatile or insoluble substances, substances that are toxic to micro-organisms at normal test concentrations, and unstable molecules.

4.1.3.2.3.3 Bioaccumulation

Annex I: 4.1.2.8.1 Bioaccumulation of substances within aquatic organisms can give rise to toxic effects over longer time scales even when actual water concentrations are low. For organic substances the potential for bioaccumulation shall normally be determined by using the octanol/water partition coefficient, usually reported as a log K_{ow}. The relationship between the log K_{ow} of an organic substance and its bioconcentration as measured by the bioconcentration factor (BCF) in fish has considerable scientific literature support. Using a cut-off value of log $K_{ow} \geq 4$ is intended to identify only those substances with a real potential to bioconcentrate. While this represents a potential to bioaccumulate, an experimentally determined BCF provides a better measure and shall be used in preference if available. A BCF in fish of ≥ 500 is indicative of the potential to bioconcentrate for classification purposes. Some relationships can be observed between chronic toxicity and bioaccumulation potential, as toxicity is related to the body burden.

The potential for bioaccumulation is an important criterion to determine whether a chemical substance is a potential hazard to the environment. Bioaccumulation of a substance into an organism is not a hazard in itself, but should be considered in relation to potential long-term effects. Chemical concentration and accumulation may result in internal concentrations of a substance in an organism (body burden), which may or may not lead to toxic effects over long-term exposures. Further guidance on bioaccumulation is given in Annex III to this guidance. Bioaccumulation of metals is discussed in Annex IV.

Information on actual bioaccumulation of a substance may be available from standardised tests (e.g. Test Methods Regulation (EC) N^{o} 440/2008, OECD 305: Bioconcentration – Flow through fish test) or information on the bioaccumulation potential, for organic substances, may be estimated from the structure of the molecule.

In general, the potential of an organic substance to bioconcentrate is primarily related to the lipophilicity of the substance. A surrogate measure of lipophilicity is the n-octanol/water partition coefficient (K_{ow}) which, for lipophilic non-ionised organic substances, undergoing minimal metabolism or biotransformation within the organism, is correlated with the bioconcentration factor. Therefore, K_{ow} is often used for estimating the bioconcentration of non-ionised organic substances, based on the empirical relationship between log BCF and log K_{ow}. For those organic substances, estimation methods are available for calculating the K_{ow}. Data on the bioconcentration properties of non-ionised organic substances may thus be

1. experimentally determined
2. estimated from experimentally determined K_{ow}, or
3. estimated from K_{ow} values derived by use of Quantitative Structure Activity Relationships (QSARs)

Experimentally derived BCF values of high quality are ultimately preferred for classification purposes. BCF results from poor or questionable quality studies should not be used for classification purposes if high quality data on log K_{ow} are available. If no BCF is available for fish species, high quality data on the BCF for some invertebrates (e.g. blue mussel, oyster and/or scallop) may be used as a worst case surrogate.

For non-ionised organic substances, experimentally derived high quality K_{ow} values are preferred. If no experimental data of high quality are available validated Quantitative Structure Activity Relationships (QSARs) for log K_{ow} may be used in the classification process. If data are available but not validated, expert judgement should be used. For ionised organic substances problems may occur with e.g. changes in pH which may significantly affect the water solubility and partition coefficient of the substance. Further guidance on how to deal with such difficulties is provided in the OECD Guidance Document on aquatic toxicity testing of difficult substances and mixtures (OECD 2000).

4.1.3.2.4 Using weight of evidence in evaluations in the context of C&L

4.1.3.2.4.1 General aspects of weight of evidence

The weight of evidence approach is described in IR/CSA, Chapter B.4.4 as follows: *"The weight of evidence (WoE) approach is not a scientifically well-defined term or an agreed formalised concept. It involves assessing the relevance, reliability and adequacy of each piece of available information, holding the various pieces of information up against each other and reaching a conclusion on the hazard. This process always involves expert judgement. It is important to document and communicate how the evidence-based approach was used in a reliable, robust and transparent manner."*

Where there is only one experimental data entry per endpoint, classification and labelling decisions are relatively straightforward. However this is often not the case when dealing with data deficient substances or substances for which more than one valid piece of data is available for a given data element. In both situations, available information needs to be evaluated carefully. Data deficiency may occur for substances for which there are no, or limited experimental data with relevance for classification and labelling. This might be the case for substances exempted from REACH such as polymers or substances manufactured in quantities < 1 tonne/annum.

The taxa chosen, fish, crustacea and aquatic plants that represent the "base-set" in most hazard profiles, represent a minimum dataset for a fully valid description of hazard. The lowest of the available toxicity values will normally be used to define the hazard category. Given the wide range of species in the environment, the three taxa tested can only be a poor surrogate and the lowest value is therefore taken for precautionary reasons to define the hazard category. In doing so, it is recognised that the distribution of species sensitivity can be several orders of magnitude wide, and that there will thus be both more and less sensitive species in the environment. Therefore, when data are limited, the use of the most sensitive species tested gives a cautious but acceptable definition of the hazard. There are some circumstances where it may not be appropriate to use the lowest toxicity value as the basis for classification. This will usually only arise where it is possible to define the sensitivity distribution with more accuracy than would normally be possible, such as when large datasets are available. Such large datasets should be evaluated with due caution.

Conversely, as CLP allows the use of expert judgment in employing non-testing information such as QSARs, the classification of data deficient substances could potentially be conducted in the absence of any experimental data.

In applying the WoE approach, the reliability of the experimental information under evaluation needs to be taken into due account. Typically, this information originates from studies which have been ranked according to the Klimisch criteria. The scores assigned to the studies may serve as an indication of the 'weight' that the corresponding information could have in 'weighing the evidence'.

4.1.3.2.4.2 Guidance on WoE for data deficient substances

Either for those substances for which the standard data set of acute aquatic testing in fish, crustacea and algae/aquatic plants is not available or where there are data gaps, REACH introduces the concept of an "Integrated Testing Strategy" (for further guidance see IR/CSA, Chapter R.7B, Figure R.7.8-2). This outlines a stepwise approach on the use of test data and non-testing information, such as reliable QSARs and *in vitro* testing. It outlines how the relevant information is collected and evaluated and in the final step, expert judgement is used to reach an overall assessment of the aquatic toxicity of the substance under evaluation, taking into consideration also metabolites, reaction products, analogues.

For classification purposes, representative species should be chosen which cover a range of trophic levels and taxonomic groups, namely fish, crustacea and primary producers. Annex I to this document also provides guidance on the following where no experimental data are available:

> *QSARs can be relied upon to provide predictions of acute toxicity to fish, crustacea (Daphnia and Mysid) and algae for non-electrolytes, non-electrophilic, and otherwise non-reactive substances. Care should be taken when evaluating the toxicity of poorly water soluble substances, where the quoted toxicity may be greater than the water solubility.*

4.1.3.2.4.3 Guidance on WoE for substances for which more than one valid piece of data is available for a given data element

The best quality data should be used as the fundamental basis for classification. Classification should preferably be based on primary data sources. It is essential that test conditions be clearly and completely articulated.

Where multiple studies for a taxonomic group are available, all studies that are assessed to have sufficient quality should be taken into consideration. The study showing the highest toxicity (e.g. the one with the lowest $L(E)C_{50}$ or NOEC or EC_x) should normally be chosen as key study for aquatic hazard classification for that taxonomic group. However, in a WoE approach, a different weight may be given to studies irrespective the test results. For example: a judgement has to be made on a case-by-case basis whether Klimish 1 studies in a dataset are given more weight than Klimish 2 studies or valid QSAR data available for the same taxonomic group.

Lower quality information showing no or low toxicity should specifically be treated with care, especially where the quality assessment has revealed points of concern regarding methodology and reporting (e.g. maintenance of test concentrations). In addition it should be noted that substances which are difficult to test may yield apparent results that are not indicating the true toxicity. Expert judgement would also be needed for classification in these cases.

Assessment of data quality includes assessment of adequacy of the information for classification purposes and an assessment of both relevance and reliability. Details on the assessment of quality can be found in IR/CSA, Chapter R.4.

Where more than one acceptable test is available for the same taxonomic group, the most sensitive (the one with the lowest $L(E)C_{50}$ or $NOEC/EC_{10}$) is generally used for classification. However, this must be dealt with on a case-by-case basis. When larger data sets (four or more values) are available for the same species, the geometric mean of toxicity values may be used as the representative toxicity value for that species. In estimating a mean value, it is not advisable to combine tests of different species within a taxonomic group or in different life stages or tested under different conditions or duration. This implies that for substances, where four or more ecotoxicity data on the same species and endpoint are available, the data should be grouped, and the geometric mean used as a representative toxicity value for that species.

In case of very large data sets meeting the criteria for applying the Species Sensitivity Distribution (SSD) approach (see IR/CSA, Chapter R.10), statistical techniques (e.g. HC_5 derivation) can be considered to estimate the aquatic toxicity reference value for classification (equivalent to using the lowest EC_{50} or NOEC), in a weight of evidence approach.

4.1.3.2.4.4 Outliers

The WoE approach would also address potential outliers, since as a starting point, all data points for a specific trophic level/taxonomic group would be considered to come from the same sensitivity distribution. Only if a sufficiently large number of data were available, appropriate statistical tests would be performed to confirm or disprove a particular value as an outlier.

The issue of possible 'outliers', which may exist, particularly in large data sets can be tackled according to a proposal in IR/CSA, Chapter R.7.8.4.1.

4.1.3.2.4.5 Weight of evidence in degradation

Where multiple or conflicting datasets exist for a single chemical, the most reliable data should be selected first, and subsequently a "weight of evidence" approach followed based on these data. This implies that if both positive (i.e. above the pass level) and negative results (below pass level) have been obtained for a substance in rapid degradability tests, then the data of the highest quality and the best documentation should be used for determining the rapid degradability of the substance. Thus, given the conservative nature of ready biodegradability tests positive results could be used irrespective of negative results when the scientific quality is good and the test conditions are well documented, i.e. the guideline criteria are fulfilled. See Annex II for further guidance.

4.1.3.2.4.6 Weight of evidence in bioaccumulation

When conflicting bioaccumulation data is available, see Annex III for guidance.

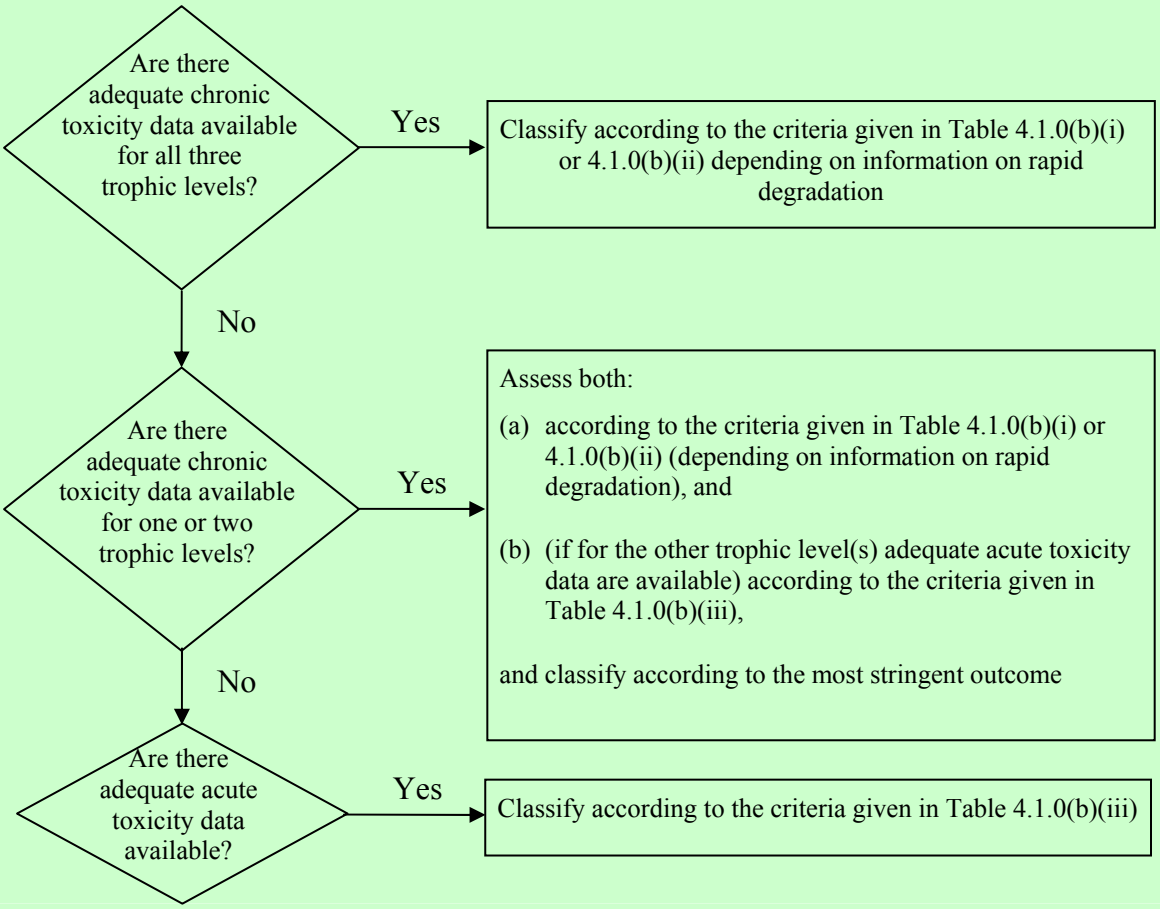
4.1.3.3 Classification categories and criteria

4.1.3.3.1 Outline of the core classification system

Annex I: 4.1.2.2. The core classification system for substances consists of one acute hazard classification category and three long-term hazard classification categories. The acute and the long-term hazard classification categories are applied independently.

Annex I: 4.1.2.3. The criteria for classification of a substance in category Acute 1 are defined on the basis of acute aquatic toxicity data only (EC_{50} or LC_{50}). The criteria for classification of a substance into the categories Chronic 1 to 3 follow a tiered approach where the first step is to see if available information on chronic toxicity merits long-term hazard classification. In absence of adequate chronic toxicity data, the subsequent step is to combine two types of information, i.e. acute aquatic toxicity data and environmental fate data (degradability and bioaccumulation data) (see Figure 4.1.1).

Figure 4.1.1
Categories for substances long-term hazardous to the aquatic environment



4.1.2.1. The system for classification recognises that the intrinsic hazard to aquatic organisms is represented by both the acute and long-term hazard of a substance. For the long-term hazard separate hazard categories are defined representing a gradation in the level of hazard identified. The lowest of the available toxicity values between and within the different trophic levels (fish, crustacean, algae/aquatic plants) shall normally be used to define the appropriate hazard category(ies). There are circumstances, however, when a weight of evidence approach is appropriate.

Where adequate chronic toxicity data exist for the three trophic levels and the lowest chronic toxicity value (that normally would define the appropriate hazard category) is below or equal to 1 mg/l, a long-term hazard classification is warranted. The actual category is also depending on the information on rapid degradation.

While recognising that for packaged goods the long-term hazard represents the principal concern, it must also be recognised that chronic toxicity data are expensive to generate and generally not readily available for most substances. On the other hand, acute toxicity data are more often readily available than chronic toxicity data, or can be generated according to highly standardised test protocols. It is this acute toxicity which has therefore been used as the core property in defining both the acute and the long-term hazard if no adequate chronic

test data are available. Nevertheless, it has been recognised that chronic toxicity data, if available, should be preferred in defining the long-term hazard category.

Chronic toxicity data (ECx or NOEC) would normally override acute data for long-term hazard classification. However, when assessing the adequacy there may be some cases (such as data poor substances) where the chronic data do not represent the species that is considered the most sensitive in available short-term tests. In such cases the classification should be based on the data (acute or chronic) that gives the most strict classification and M-factor.

The combination of chronic toxicity and degradation properties reflects the potential hazard of a substance. Substances that do not rapidly degrade have a higher potential for longer term exposures and therefore should be classified in a more severe category than substances which are rapidly degradable.

A review of the existing adequate appropriate acute toxicity data and environmental fate data (degradability and bioaccumulation) is required for those trophic levels where adequate chronic toxicity data may be absent; to decide if a long-term hazard classification may be warranted.

While recognising that acute toxicity itself is not a sufficiently accurate predictor of chronic toxicity to be used solely and directly for establishing hazard, it is considered that, in combination with either a potential to bioaccumulate (i.e. experimentally determined BCF ≥ 500 or, if absent, the log K_{ow} ≥ 4) or potential longer term exposure (i.e. lack of rapid degradation) it can be used as a suitable surrogate for classification purposes. Substances rapidly degrading that show acute toxicity with a significant degree of bioaccumulation will normally show chronic toxicity at a significantly lower concentration. Equally, substances that do not rapidly degrade have a higher potential for giving rise to longer term exposures which again may result in long-term toxicity being realised.

The hazard categories for acute and chronic aquatic toxicity and their related criteria are set out in CLP, Annex I, Section 4.1, Table 4.1.0.

Annex I: *Table 4.1.0* **Classification categories for hazardous to the aquatic environment**		
(a) Acute (short-term) aquatic hazard		
Category Acute 1: (Note 1)		
96 hr LC_{50} (for fish)	≤ 1 mg/l and/or	
48 hr EC_{50} (for crustacea)	≤ 1 mg/l and/or	
72 or 96 hr ErC_{50} (for algae or other aquatic plants)	≤ 1 mg/l.	(Note 2)

(b) Long-term aquatic hazard

(i) Non-rapidly degradable substances (Note 3) for which there are adequate chronic toxicity data available

Category Chronic 1: (Note 1)

Chronic NOEC or EC_x (for fish)	≤0,1 mg/l and/or
Chronic NOEC or EC_x (for crustacea)	≤0,1 mg/l and/or
Chronic NOEC or EC_x (for algae or other aquatic plants)	≤0,1 mg/l.

Category Chronic 2:

Chronic NOEC or EC_x (for fish)	≤1 mg/l and/or
Chronic NOEC or EC_x (for crustacea)	≤1 mg/l and/or
Chronic NOEC or ECx (for algae or other aquatic plants)	≤1 mg/l.

(ii) Rapidly degradable substances (Note 3) for which there are adequate chronic toxicity data available

Category Chronic 1: (Note 1)

Chronic NOEC or EC_x (for fish)	≤0,01 mg/l and/or
Chronic NOEC or EC_x (for crustacea)	≤0,01 mg/l and/or
Chronic NOEC or EC_x (for algae or other aquatic plants)	≤0,01 mg/l

Category Chronic 2:

Chronic NOEC or EC_x (for fish)	≤0,1 mg/l and/or
Chronic NOEC or EC_x (for crustacea)	≤0,1 mg/l and/or
Chronic NOEC or EC_x (for algae or other aquatic plants)	≤0,1 mg/l

Category Chronic 3:

Chronic NOEC or EC_x (for fish)	≤1 mg/l and/or
Chronic NOEC or EC_x (for crustacea)	≤1 mg/l and/or
Chronic NOEC or ECx (for algae or other aquatic plants)	≤1 mg/l.

(iii) Substances for which adequate chronic toxicity data are not available

Category Chronic 1: (Note 1)

96 hr LC_{50} (for fish)	≤1 mg/l and/or
48 hr EC_{50} (for crustacea)	≤1 mg/l and/or
72 or 96 hr ErC_{50} (for algae or other aquatic plants)	≤1 mg/l. (Note 2)

and the substance is not rapidly degradable and/or the experimentally determined BCF ≥ 500 (or, if absent, the log K_{ow} ≥ 4). (Note 3).

Category Chronic 2:

96 hr LC_{50} (for fish)	>1 to ≤10 mg/l and/or
48 hr EC_{50} (for crustacea)	>1 to ≤10 mg/l and/or
72 or 96 hr ErC_{50} (for algae or other aquatic plants)	>1 to ≤10 mg/l. (Note 2)

and the substance is not rapidly degradable and/or the experimentally determined BCF ≥ 500 (or, if absent, the log K_{ow} ≥ 4). (Note 3).

Category Chronic 3:

96 hr LC_{50} (for fish)	> 10 to ≤ 100 mg/l and/or
48 hr EC_{50} (for crustacea)	> 10 to ≤ 100 mg/l and/or
72 or 96 hr ErC_{50} (for algae or other aquatic plants)	> 10 to ≤ 100 mg/l. (Note 2)

and the substance is not rapidly degradable and/or the experimentally determined BCF ≥ 500 (or, if absent, the log K_{ow} ≥ 4). (Note 3).

NOTE 1: *When classifying substances as Acute Category 1 and/or Chronic Category 1 it is necessary at the same time to indicate then appropriate M-factor(s) (see table 4.1.3).*

NOTE 2: *Classification shall be based on the ErC_{50} [= EC_{50} (growth rate)]. In circumstances where the basis of the EC_{50} is not specified or no ErC_{50} is recorded, classification shall be based on the lowest EC_{50} available.*

NOTE 3: *When no useful data on degradability are available, either experimentally determined or estimated data, the substance should be regarded as not rapidly degradable.*

Classifications may also be made in cases where data are not available on all three trophic levels. In these cases, the classification may be subject to further information becoming available. In general, all the data available will need to be considered prior to assigning a classification. Where good quality data are not available, lower quality data will need to be considered. In these circumstances, a judgement will need to be made regarding the true level of hazard. For example, where good quality data are available for a particular species or taxa, this should be used in preference to any lower quality data which might also be available for that species or taxa. However, good quality data may not always be available for all trophic

levels. It will be necessary to consider data of lower quality for those trophic levels for which good quality data are not available. Consideration of such data, however, will also need to consider the difficulties that may have affected the likelihood of achieving a valid result. For example, the test details and experimental design may be critical to the assessment of the usability of some data, such as that from hydrolytically unstable chemicals, while less so for other chemicals. Such difficulties are described further in Annex I to this guidance.

Normally, the identification of hazard, and hence the classification will be based on information directly obtained from testing of the substance being considered. There are occasions, however, where this can create difficulties or the outcomes do not conform to common sense. For example, some chemicals, although stable in the bottle, will react rapidly (or slowly) in water giving rise to degradation products that may have different properties. Where such degradation is rapid, the available test data will frequently define the hazard of the degradation products since it will be these that have been tested. These data may be used to classify the parent substance in the normal way. However, where degradation is slower, it may be possible to test the parent substance and thus generate hazard data in the normal manner. The subsequent degradation may then be considered in determining whether an acute or long-term hazard category should apply. There may be occasions, however, when a substance so tested may degrade to give rise to a more hazardous product. In these circumstances, the classification of the parent compound should take due account of the hazard of the degradation product, and the rate at which it can be formed under normal environmental conditions.

4.1.3.3.2 The "safety net"

4.1.2.4 The system also introduces a "safety net" classification (referred to as category Chronic 4) for use when the data available do not allow classification under the formal criteria for acute 1 or chronic 1 to 3 but there are nevertheless some grounds for concern (see example in Table 4.1.0).

Annex I: 4.1.2.6. *Table 4.1.0. continued*

"Safety net" classification

Chronic Category 4

Cases when data do not allow classification under the above criteria but there are nevertheless some grounds for concern. This includes, for example, poorly soluble substances for which no acute toxicity is recorded at levels up to the water solubility (Note 4), and which are not rapidly degradable in accordance with Section 4.1.2.9.5 and have an experimentally determined BCF ≥ 500 (or, if absent, a log $K_{ow} \geq 4$), indicating a potential to bioaccumulate, which will be classified in this category unless other scientific evidence exists showing classification to be unnecessary. Such evidence includes chronic toxicity NOECs > water solubility or > 1 mg/l, or other evidence of rapid degradation in the environment than the ones provided by any of the methods listed in Section 4.1.2.9.5.

NOTE 4: *"No acute toxicity" is taken to mean that the $L(E)C_{50}(s)$ is/are above the water solubility. Also for poorly soluble substances, (water solubility < 1 mg/l), where there is evidence that the acute test does not provide a true measure of the intrinsic toxicity.*

Category Chronic 4 is for example triggered in the following cases. For some poorly soluble substances, which are normally considered as those having a water solubility < 1 mg/l, no acute toxicity is expressed in toxicity tests performed at the solubility limit. If for such a substance, however, the BCF ≥ 500, or if absent, the log K_{ow} ≥ 4 (indicating a bio-

accumulating potential) and the substance is also not rapidly degradable, a safety net classification, category Chronic 4 is assigned. For these types of substances the exposure duration in short-term tests may well be too short for a steady-state concentration of the substance to be reached in the test organisms. Thus, even though no acute toxicity has been measured in a short-term (acute) test, it remains a real possibility that such non-rapidly degradable and bioaccumulative substances may exert chronic effects, particularly since such low degradability may lead to an extended exposure period in the aquatic environment.

The precise definitions of the core elements of this system are described in detail in Annexes I-III to this guidance document.

4.1.3.3.3 Setting an M-factor for highly toxic substances

4.1.2.5 Substances with acute toxicities below 1 mg/l or chronic toxicities below 0,1 mg/l (if non-rapidly degradable) and 0,01 mg/l (if rapidly degradable) contribute as components of a mixture to the toxicity of the mixture even at a low concentration and shall normally be given increased weight in applying the summation of classification approach (see Note 1 of Table 4.1.0 and 4.1.3.5.5).

When a substance is classified as category Acute 1 and/or category Chronic 1, (a) multiplying factor(s) (M-factor) has/have to be assigned (as described Article 10 of CLP). Where appropriate, M-factors shall be set for acute and long-term hazards separately. This means that there can be two different M-factors (one for acute and one for long-term hazard) for one substance. It is important to also include the M-factor(s) in the SDS as other users in the supply chain might need it, e.g. for classification of mixtures containing that substance.

The M-factor itself can be taken from the table below and is dependent on the toxicity band of the substances. For a substance with an acute toxicity of 0.005 mg/l for example an M-factor of 100 needs to be assigned. Whereas e.g. with a chronic toxicity of 0.005 mg/l an M-factor of 10 needs to be assigned for non-rapidly degrable substance and an M-factor of 1 to rapidly degradable substances.

Annex I: *Table 4.1.3*

Multiplying factors for highly toxic components of mixtures

Acute toxicity	M factor	Chronic toxicity	M factor	
$L(E)C_{50}$ value		NOEC value	NRD[a] components	RD[b] components
$0,1 < L(E)C_{50} \leq 1$	1	$0,01 < NOEC \leq 0,1$	1	-
$0,01 < L(E)C_{50} \leq 0,1$	10	$0,001 < NOEC \leq 0,01$	10	1
$0,001 < L(E)C_{50} \leq 0,01$	100	$0,0001 < NOEC \leq 0,001$	100	10
$0,0001 < L(E)C_{50} \leq 0,001$	1000	$0,00001 < NOEC \leq 0,0001$	1000	100
$0,00001 < L(E)C_{50} \leq 0,0001$	10000	$0,000001 < NOEC \leq 0,00001$	10000	1000
(continue in factor 10 intervals)		(continue in factor 10 intervals)		

[a] *Non-rapidly degradable*
[b] *Rapidly degradable*

The NOEC value in Table 4.1.3 (Annex I to CLP) refers to both NOEC and EC_x (toxicity values are in mg/l). The first two columns in Table 4.1.3 refer to the classification system in Table 4.1.0 (a)(b, point iii), the last three columns refer to the respective classification system in Table 4.1.0 (b, points i & ii). In cases where chronic data are not available and Table (a)(b, point iii) is used for defining long-term aquatic hazard, the resulting M-factor derived for acute aquatic toxicity is also applied to the chronic classification.

4.1.3.4 Decision on classification: examples for substances

If the evaluation shows that the criteria are fulfilled, one category for acute aquatic hazard and/or one for long-term aquatic hazard should be assigned, as well as (an) M-factor(s) where applicable. For the labelling elements, such as hazard pictograms, signal words, hazard statements and precautionary statements, see section 4.1.6 of this guidance.

Further classification examples specific to metals and metal compounds are given in Annex IV to this guidance document.

The examples in this section are focussed on self-classification based on relevant data available. Mandatory use of harmonised classification for substances included in Table 3.1 of Annex VI, the use of information from the classification and labelling inventory and the use of the translation Table in Annex VII are not taken into account in these examples.

After data collection self-classification starts with evaluation of the adequateness of the data collected and assessment of the results and concluding on endpoints relevant for environmental hazard classification. Where the assessment shows that criteria for environmental classification are fulfilled, one category for acute aquatic hazard and/or one category for long-term aquatic hazards should be assigned and M-factor(s) should be deducted where applicable.

List of the examples on substance classification included in this section:

- Example A: Hydrophilic substance, straightforward classification based on acute and chronic toxicity data;
- Example B: Hydrophilic substance, straightforward classification based on acute data, no chronic toxicity data available;
- Example C: Moderately water soluble substance, straightforward classification based on acute data, chronic toxicity data available for two trophic levels; combined set of QSAR data and experimental data;
- Example D: Substance with several toxicity data for one trophic level;
- Example E: “Safety net” classification category Chronic 4;
- Example F: Substance difficult to test, toxicity above level of water solubility.

Further classification examples specific to metals and metal compounds are given in Annex IV to this guidance.

The examples are presented using a logical format starting with a table listing for all relevant data elements the information available, followed by an aquatic hazard assessment for each data element, a section showing the aquatic hazard classification, a section with the reasoning behind the conclusions and finally a table presenting the applicable labelling elements.

Explanation of data elements used in the examples:

- Physico-chemical properties important for evaluation of aquatic hazards for the purpose of classification: Generally this consists of water solubility (mg/l) and log octanol/water partition coefficient (log K_{ow});
- Acute aquatic toxicity: Generally expressed in terms of LC_{50} or EC_{50} (mg/l);
- Long-term aquatic toxicity: Generally expressed in terms of NOEC or EC_x(mg/l);
- Degradation (evidence of rapid degradation): Generally expressed in terms of biotic or abiotic degradation of organic substances (or transformation of inorganic substances). In case of rapid primary degradation, information shall be given whether the degradation products can be classified as hazardous to the aquatic environment or not;
- Bioaccumulation: Generally expressed in terms of bioconcentration factor in fish

Information on reliability is not taken into account in the exemplification. For the purpose of the examples the reliability score is assumed to be high (e.g. for experimental tests, Klimisch score 1 or 2) unless otherwise stated. Note that assigning a reliability score to studies is important - if a study is assessed as poorly reliable it is normally not usable for classification purposes.

Besides the conclusion from studies on relevant endpoints for classification the following information is presented for each example in a separate column:

- Referral to applicable test method according to the EU Test Methods Regulation (EC) No 440/2008 or OECD test guideline or QSAR model used;
- Some basic information on the test design (pH of the test media, renewal regime of test media (static, semi-static, flow-through);
- Use of measured or nominal test concentrations;
- Compliance of the experiment and reporting with OECD Good Laboratory Practice (GLP) rules;
- Specific information related to the relevant endpoints, as appropriate.

This information plays a crucial role when the adequacy of the data and the assessment of the study results are being evaluated for their applicability in the classification and labelling scheme. However, in these examples this information is included mainly to make the data more realistic.

4.1.3.4.1 Example A: Hydrophilic substance, straightforward classification based on acute and chronic toxicity data

DATA ELEMENTS		Value	Test method ((EC) No. 440/2008) or OECD guideline / remarks
Physico-chemical properties			
Water solubility:		1200 mg/l	A.6. / pH:7.0, non-GLP
Log octanol/water partition coefficient (log K_{ow}):		2.75	A.8. / pH:7.5, GLP
Acute aquatic toxicity			
Fish	*Oncorhynchus mykiss*:	12 mg/l (96 h LC_{50})	C.1. / static, non-GLP
	Lepomis macrochirus:	2.7 mg/l (96 h LC_{50})	C.1. / static, GLP
Crustacea	*Daphnia magna*:	18 mg/l (48 h EC_{50})	C.2. / static, non-GLP
Algae/aquatic plants	*Scenedesmus subspicatus*:	0.056 mg/l (96 h ErC_{50})	C.3. / static, GLP
	Lemna gibba:	0.031 mg/l (7 d ErC_{50})	C.26. / semi-static, GLP
Chronic aquatic toxicity			
Fish:	*Danio rerio*:	1.2 mg/l (21 d NOEC)	OECD 210 / Early Life Stage toxicity test, flow-through, GLP
Crustacea:	*Daphnia magna*:	1.1 mgl (21 d NOEC)	C.20. / semi-static, GLP
Algae/aquatic plants:	*Scenedesmus subspicatus*:	0.01 mg/l (96 h NOEC)	C.3. / static, GLP
Degradation (evidence of rapid degradation)			
Biotic degradation:		86 % in 28 days (10 day-window fulfilled)	C.4-C / pH:7.5, GLP
Abiotic degradation, hydrolysis: (half-life (d)):		No data	
Bioaccumulation			
Bioconcentration factor in fish (BCF)		No data	

Aquatic hazard assessment, conclusions and comments:

Physico-chemical properties:

- The substance is readily soluble. Log K_{ow} < 4, indicating low potential for bioaccumulation, which can be used in absence of BCF data.

Acute aquatic toxicity:

- The acute aquatic toxicity based on the lowest of the available toxicity values is between 0.01 and 0.1 mg/l.

Long-term aquatic toxicity:

- The long-term aquatic toxicity based on the lowest of the available toxicity values is between 0.001 and 0.01 mg/l.

Degradation (evidence of rapid degradation):

- > 70 % degradation in 28 days based on dissolved organic carbon (DOC) fulfils the criteria for rapid degradation.

Aquatic hazard classification and, where applicable, established M-factor(s):

Acute (short-term) aquatic hazard: category Acute 1, M-factor: 10.

Long-term aquatic hazard: category Chronic 1, M-factor: 1.

Reasoning:

Acute aquatic hazard: acute toxicity $L(E)C_{50} \leq 1$ mg/l. M-factor based on $L(E)C_{50}$ between 0.01 and 0.1 mg/l.

Long-term aquatic hazard:

The criteria for classification of a substance into the categories Chronic 1 to 3 follow a tiered approach where the first step is to see if adequate information on long-term toxicity is available allowing long-term hazard classification. In absence of adequate long-term toxicity data for some or all trophic levels, the subsequent step is to combine two types of information, i.e. acute aquatic toxicity data and environmental fate data (degradability and bioaccumulation data). For details see section 4.1.3.3 and Table 4.1.0.

- Adequate long-term toxicity data for all three trophic levels, long-term toxicity NOEC ≤ 0.01 mg/l, rapidly degradable. M-factor based on NOEC between 0.001 and 0.01 mg/l (rapidly degradable).

1 **Labelling elements based on the classification:**

Element	Code
GHS Pictogram	GHS09
Signal Word	WARNING
Hazard Statement	H410[48]
Precautionary statement(s)	P273, P391, P501

2

[48] Note that in accordance with CLP Article 27 the hazard statement H400 may be considered redundant and therefore not included on the label because hazard statement H410 also applies, see section 4.1.6 of this document.

4.1.3.4.2 Example B: Hydrophilic substance, straightforward classification based on acute data, no chronic data available

DATA ELEMENTS		Value	Test method ((EC) No. 440/2008) or OECD guideline / remarks
Physico-chemical properties			
Water solubility:		1200 mg/l	A.6. / pH:7.0, non-GLP
Log octanol/water partition coefficient (log K_{ow}):		2.75	A.8. / pH:7.5, GLP
Acute aquatic toxicity			
Fish	*Oncorhynchus mykiss*:	12 mg/l (96 h LC_{50})	C.1. / static, non-GLP
	Lepomis macrochirus:	2.7 mg/l (96 h LC_{50})	C.1. / static, GLP
Crustacea	*Daphnia magna*:	18 mg/l (48 h EC_{50})	C.2. / static, non-GLP
Algae/aquatic plants	*Scenedesmus subspicatus*:	0.056 mg/l (96 h ErC_{50})	C.3. / static, GLP
	Lemna gibba:	0.031 mg/l (7 d ErC_{50})	C.26. / semi-static, GLP
Chronic aquatic toxicity			
Fish:		No data	
Crustacea:		No data	
Algae/aquatic plants:		NOEC not reported	
Degradation (evidence of rapid degradation)			
Biotic degradation:		86 % in 28days (10 day-window fulfilled)	C.4-C / pH:7.5, GLP
Abiotic degradation, hydrolysis: (half-life (d)):		No data	
Bioaccumulation			
Bioconcentration factor in fish (BCF)		560 l/kg	C.13. / pH: 7.8, GLP, BCF (related to total radioactive residues because data for parent compound not available)

Aquatic hazard assessment, conclusions and comments:

Physico-chemical properties:

- The substance is readily soluble. Log K_{ow} < 4, indicating low potential for bioaccumulation, which can be used in absence of BCF data (see bioaccumulation assessment).

Acute aquatic toxicity:

- The acute aquatic toxicity based on the lowest of the available toxicity values is between 0.01 and 0.1 mg/l.

Long-term aquatic toxicity:

- No adequate chronic toxicity data available for all three trophic levels.

Degradation (evidence of rapid degradation):

- > 70 % degradation based on dissolved organic carbon (DOC) fulfils the criteria for rapid degradation.

Bioaccumulation:

- BCF > 500, hence high potential for bioaccumulation. BCF value overrules the use of logK_{ow} value which in this case is lower than the cut-off value of 4.

Aquatic hazard classification and, where applicable, established M-factor(s):

Acute aquatic hazard: category Acute 1, M-factor: 10.

Long–term aquatic hazard: category Chronic 1, M-factor: 10.

Reasoning:

Acute (short-term) aquatic hazard: acute toxicity L(E)C_{50} ≤ 1 mg/l. M-factor based on L(E)C_{50} between 0.01 and 0.1 mg/l.

Long-term aquatic hazard:

The criteria for classification of a substance into the categories Chronic 1 to 3 follow a tiered approach where the first step is to see if adequate information on long-term toxicity is available allowing long-term hazard classification. In absence of adequate long-term toxicity data for some or all trophic levels, the subsequent step is to combine two types of information, i.e. acute aquatic toxicity data and environmental fate data (degradability and bioaccumulation data). For details see section 4.1.3.3 and Table 4.1.0.

- No adequate long-term toxicity data available (for all three trophic levels);
- Lowest acute toxicity L(E)C_{50} ≤ 1 mg/l;
- Substance is rapidly degradable but the experimentally determined BCF > 500;
- Since the conclusion is based on Table 4.1.0 (b) (iii), therefore the M-factor is based on the acute toxicity between 0.01 and 0.1 mg/l. In this case, the same factor M applies for both acute and long-term hazard.

1 **Labelling elements based on the classification:**

Element	Code
GHS Pictogram	GHS09
Signal Word	WARNING
Hazard Statement	H410[49]
Precautionary statement(s)	P273, P391, P501

[49] Note that in accordance with CLP Article 27 the hazard statement H400 may be considered redundant and therefore not included on the label because hazard statement H410 also applies, see section 4.1.6 of this document.

4.1.3.4.3 Example C: Moderately water soluble substance, straightforward classification based on acute data, chronic data available for two trophic levels only; combined set of QSAR data and experimental data

DATA ELEMENTS		Value	Test method ((EC) No. 440/2008) or OECD guideline / remarks
Physico-chemical properties			
Water solubility:		25 mg/l	A.6. / pH: 7.0, non-GLP
Log octanol/water partition coefficient (log K_{ow}):		5.75 3.9	A.8. / pH: 7.5, GLP QSAR KOWINN, valid, non-GLP
Acute aquatic toxicity			
Fish	*Oncorhynchus mykiss*: *Lepomis macrochirus*:	12.3 mg/l (96 h LC_{50}) 22.5 mg/l (96 h LC_{50})	C.1. / static, non-GLP C.1. / static, GLP
Crustacea	*Daphnia magna*: *Daphnia magna*:	0.79 mg/l (48 h EC_{50}) 1.06 mg/l (48 h EC_{50})	C.2. / static, non-GLP QSAR, ECOSAR, valid, non-GLP
Algae/aquatic plants	*Scenedesmus subspicatus*:	1.53 mg/l (96 h ErC_{50})	C.3. / static, GLP
Chronic aquatic toxicity			
Fish:	*Oncorhynchus mykiss*:	0.56 mg/l (21 d NOEC)	OECD 210 / Early Life Stage toxicity test, flow-through, GLP
Crustacea:		No data	
Algae/aquatic plants:	*Scenedesmus subspicatus*:	0.23 mg/l (96 h NOEC)	C.3. / static, GLP
Degradation (evidence of rapid degradation)			
Biotic degradation: Abiotic degradation, hydrolysis: (half-life (d)):		45 % in 28 days No data	C.4-C / pH: 7.5, GLP
Bioaccumulation			
Bioconcentration factor in fish (BCF):		No data	

Aquatic hazard assessment, conclusions and comments:

Physico-chemical properties:

- The substance is moderately soluble. Log K_{ow} 5.75 based on weight of evidence, valid K_{ow} estimated with QSAR is overruled by valid GLP experimental data.

  Note that use of experimental data and QSAR data for estimation log K_{ow} should be carefully considered on a case by case basis. The validity of data may be dependant on the structure of the chemical. See Annex III, section 2.2 for more details on the use of log K_{ow} data and Annex III, section 3.4.1 for details on chemical classes that need special attention in this respect.

Acute aquatic toxicity:

- The acute aquatic toxicity based on the lowest of the available toxicity values is between 0.1 and 1 mg/l;
- For *Daphnia magna* two valid values are presented. A weight of evidence approach is applied in which the QSAR data are outweighed by the valid experimental data. Hence, the lowest acute toxicity value of 0.79 mg/l is used for crustaceans.

Long-term aquatic toxicity:

- Adequate chronic toxicity data available only for fish and algae/aquatic plants, not for crustaceans;
- The chronic aquatic toxicity based on the lowest of the available toxicity values for fish and algae/aquatic plants is between 0.1 and 1 mg/l.

Since there is adequate chronic toxicity data available for two trophic levels, assess both:

(a) according to the criteria given in Table 4.1.0(b)(i) or 4.1.0(b)(ii) (depending on information on rapid degradation), and

(b) (if for the other trophic level(s) adequate acute toxicity data are available) according to the criteria given in Table 4.1.0(b)(iii),

and classify according to the most stringent outcome.

Degradation (evidence of rapid degradation):

- < 70 % degradation in 28 days based on dissolved organic carbon (DOC), does not fulfil the criteria for rapid degradation.

Bioaccumulation:

- Log K_{ow} 5.75, indicating high potential for bioaccumulation, which can be used in absence of BCF data.

Aquatic hazard classification and, where applicable, established M-factor(s):

Acute aquatic hazard: category Acute 1, M factor: 1.

Long-term aquatic hazard: category Chronic 1, M factor: 1.

Reasoning:

Acute (short-term) aquatic hazard: lowest acute aquatic toxicity $L(E)C_{50} \leq 1$ mg/l. M-factor based on $L(E)C_{50}$ between 0.1 and 1 mg/l.

Long-term aquatic hazard:

The criteria for classification of a substance into the categories Chronic 1 to 3 follow a tiered approach where the first step is to see if adequate information on long-term toxicity is available allowing long-term hazard classification. In absence of adequate long-term toxicity data for some or all trophic levels, the subsequent step is to combine two types of information, i.e. acute aquatic toxicity data and environmental fate data (degradability and bioaccumulation data). In this example the absence of long-term study for the species/trophic level (i.e. Daphnia/Crustacea) with the lowest acute toxicity value supports using the surrogate system. For details see section 4.1.3.3 and Table 4.1.0.

- NOEC-based system (Table 4.1.0 (b)(i): lowest long-term aquatic toxicity NOEC ≤ 1 mg/l, not rapidly degradable, hence category Chronic 2;
- Surrogate system (Table 4.1.0 (b)(iii): lowest acute aquatic toxicity $L(E)C_{50} < 1$ mg/l, not rapidly degradable (and Log $K_{ow}>4$), hence category Chronic 1;
- Conclusion: category Chronic 1 applies following the most stringent outcome;
- Since the conclusion is based on the surrogate system (Table 4.1.0 (b) (iii)) the M-factor is based on the acute aquatic toxicity between 0.1 and 1 mg/l.

Labelling elements based on the classification:

Element	Code
GHS Pictogram	GHS09
Signal Word	WARNING
Hazard Statement	H410[50]
Precautionary statement(s)	P273, P391, P501

[50] Note that in accordance with CLP Article 27 the hazard statement H400 may be considered redundant and therefore not included on the label because hazard statement H410 also applies, see section 4.1.6 of this document.

1 4.1.3.4.4 Example D: Substance with several toxicity data for a trophic level

DATA ELEMENTS		Value	Test method ((EC) No. 440/2008) or OECD guideline / remarks
Physico-chemical properties			
Water solubility:		120 mg/l	A.6. / pH:7.0, non-GLP
Log octanol/water partition coefficient (log K_{ow}):		4.9	A.8. / pH:7.5, GLP
Acute aquatic toxicity			
Fish:	*Lepomis macrochirus*:	108 mg/l (96 h LC_{50})	C.1. / static, GLP
Crustacea[51]:	*Daphnia magna*:	40 mg/l (48 h EC_{50})	C.2. / static, GLP
	Procambarus clarkii:	0.12 mg/l (48 h EC_{50})	Method na. / static, GLP
	Asellus aquaticus:	0.4 mg/l (48 h EC_{50})	Method na. / static, non-GLP
	Mysidopsis bahia:	0.5 mg/l (48 h EC_{50})	Method na. / static, GLP
	Chironomus tentans:	0.8 mg/l (48 h EC_{50})	Method na. / static, GLP
Algae/aquatic plants	*Pseudokirchneriella subcapitata*:	22 mg/l (96 h ErC_{50})	C.3. / static, GLP
Chronic aquatic toxicity			
Fish:	*Pimephales promelas*	1.1 mg/l (21 d NOEC)	OECD 210 / Early Life Stage toxicity test, flow-through, GLP, endpoint: growth
Crustacea:	*Daphnia magna*	1.2 mg/l (21 d NOEC)	C.20. / semi-static, GLP, endpoint: reproduction
Algae/aquatic plants:	*Pseudokirchneriella subcapitata*:	8.5 mg/l (96 h NOEC)	C.3. / static, GLP
Degradation (evidence of rapid degradation)			
Biotic degradation:		No data	
Abiotic degradation, hydrolysis (half-life (d)):		No data	
Bioaccumulation			
Bioconcentration factor in fish (BCF):		No data	

[51] Some species in this trophic level may be representatives of other taxonomic groups than crustecea e.g. the non-biting midge *Chironomus tentans* is a representative of the subphylum Hexapoda (class Insecta).

Aquatic hazard assessment, conclusions and comments:

Physico-chemical properties:

- The substance is water soluble. Log K_{ow} 4.9.

Acute aquatic toxicity:

- The acute aquatic toxicity (based on the lowest of the available toxicity values) is between 0.1 and 1 mg/l. The classification in this example should be based on the most sensitive species which is the crustacean *Procambarus clarkii*;
- Note that in general for substances for which multiple toxicity data is available for a taxonomic group (in this case crustaceans) on a case-by-case basis the toxicity data may be evaluated by weighting the evidence. If for example four or more acute LC_{50} values were available for the same fish species, then a geometric mean may be calculated (see section 4.1.3.2.4.3). In this specific example, acute toxicity data on five separate crustacean species is available and all – except one – are from GLP studies that are weighed equally in a weight of evidence approach. Accordingly, the lowest value is used for classification purposes.

Chronic aquatic toxicity:

- Adequate long-term toxicity data available only for fish and algae/aquatic plants. The chronic aquatic toxicity (based on the lowest of the two available toxicity values) is above 1 mg/l;
- For crustaceans chronic data is available for *Daphnia magna* which based upon the relatively large acute dataset is clearly the least sensitive of the species for which data is available. Hence, the chronic aquatic toxicity data on *Daphnia magna* in this case should be considered not in conformity with the definition of 'adequate chronic data'.

Degradation (evidence of rapid degradation):

- No data available for this substance. In this case the substance is considered as not rapidly degradable (see Table 4.1.0, Note 3).

Bioaccumulation:

- Log K_{ow} 4.9, indicating high potential for bioaccumulation, which can be used in absence of BCF data.

Aquatic hazard classification and, where applicable, established M-factor(s):

Acute aquatic hazard: category Acute 1, M factor: 1.

Long-term aquatic hazard: category Chronic 1, M factor 1.

Reasoning:

Acute aquatic hazard: Acute aquatic toxicity $L(E)C_{50} > 0.001$ and < 0.01 mg/l;

Long-term aquatic hazard:

The criteria for classification of a substance into the categories Chronic 1 to 3 follow a tiered approach where the first step is to see if adequate information on long-term toxicity is available allowing long-term hazard classification. In absence of adequate long-term toxicity data for some or all trophic levels, the subsequent step is to combine two types of information, i.e. acute aquatic toxicity data and environmental fate data (degradability and bioaccumulation data). For details see section 4.1.3.3 and Table 4.1.0.

- Adequate Chronic toxicity data available for two out of three trophic levels (fish and algae/aquatic plants), lowest NOEC above 1 mg/l. Conclusion for these two trophic levels: NOEC-based system (Table 4.1.0 (b)(i): lowest long-term aquatic toxicity NOEC > 1 mg/l, hence not classified;
- Surrogate system (Table 4.1.0 (b)(iii): lowest acute aquatic toxicity $L(E)C_{50}$ < 1 mg/l (0.12 mg/l *Procambarus clarkii*), not rapidly degradable (and log K_{ow} > 4), hence category Chronic 1;
- Conclusion: category Chronic 1 applies following the most stringent outcome;
- Since the conclusion is based on the surrogate system (Table 4.1.0 (b) (iii)) the M-factor is based on the acute aquatic toxicity between 0.1 and 1 mg/l.

Labelling elements based on the classification:

Element	Code
GHS Pictogram	GHS09
Signal Word	WARNING
Hazard Statement	H410[52]
Precautionary statement(s)	P273, P391, P501

[52] Note that in accordance with CLP Article 27 the hazard statement H400 may be considered redundant and therefore not included on the label because hazard statement H410 also applies, see section 4.1.6 of this document.

4.1.3.4.5 Example E: "Safety net" classification category Chronic 4

DATA ELEMENTS	Value	Test method ((EC) No. 440/2008) or OECD guideline / remarks
Physico-chemical properties		
Water solubility:	0.009 mg/l	A.6. / pH:7.0, non-GLP
Log octanol/water partition coefficient (log K_{ow}):	5.4	A.8. / pH:7.5, GLP
Acute aquatic toxicity		
Fish:	No data	
Crustacea *Daphnia magna*:	> 1 mg/l (48 h EC_{50})	C.2. / static, nominal concentration, non-GLP
Algae/aquatic plants:	No data	
Chronic aquatic toxicity		
Fish:	No data	
Crustacea:	No data	
Algae/aquatic plants:	No data	
Degradation (evidence of rapid degradation)		
Biotic degradation: Abiotic degradation, hydrolysis (half-life (d)):	No data No data	
Bioaccumulation		
Bioconcentration factor in fish (BCF):	No data	

Aquatic hazard assessment, conclusions and comments:

Physico-chemical properties:

- The substance is poorly soluble. Log K_{ow} > 4, indicating high potential for bioaccumulation, which can be used in absence of BCF data.

Acute aquatic toxicity:

- Data poor substance. No acute toxicity recorded at levels up to the limit of water solubility.

Long-term aquatic toxicity:

- No adequate chronic toxicity data available for all three trophic levels.

Degradation (evidence of rapid degradation):

- The substance is considered not rapidly degradable by default in absence of measured data.

Bioaccumulation:

- Log K_{ow} 5.4, indicating high potential for bioaccumulation, which can be used in absence of BCF data.

Aquatic hazard classification and, where applicable, established M-factor(s):

Acute hazard: Not classified.

Long-term hazard: 'Safety net' classification category Chronic 4.

Reasoning:

Acute hazard: No acute aquatic toxicity recorded at levels up to the limit of water solubility;

Long-term hazard: No adequate chronic toxicity data available for all three trophic levels. Substance nevertheless of concern based on the following findings:

- Poorly soluble substance;
- No acute aquatic toxicity recorded at levels up to the limit of water solubility;
- Not rapidly degradable (by default in absence of measured data);
- High potential for bioaccumulation (in absence of BCF data, log K_{ow} > 4).
- No evidence on NOEC being > water solubility for all three trophic levels.
- No other evidence of rapid degradation in the environment

Labelling elements based on the classification:

Element	Code
GHS Pictogram	-
Signal Word	-
Hazard Statement	H413
Precautionary statement(s)	P273, P501

4.1.3.4.6 Example F: Substance difficult to test, toxicity above level of water solubility

DATA ELEMENTS		Value	Test method ((EC) No. 440/2008) or OECD guideline / remarks
Physico-chemical properties			
Water solubility:		< 0.2 mg/l	A.6. / pH: 7.0, non-GLP
Log octanol/water partition coefficient (log K_{ow}):		No data	Not determined due to instability of the substance in water
Acute aquatic toxicity			
Fish:	*Oncorhynchus mykiss*:	12 mg/l (96 h LC_{50})	C.1. / static, nominal concentration, non-GLP
Crustacea	*Daphnia magna*:	18 mg/l (48 h EC_{50})	C.2. / static, nominal concentration, non-GLP
Algae/aquatic plants	*Pseudokirchneriella subcapitata*	3.56 mg/l (96 h ErC_{50})	C.3. / static, nominal concentration, non-GLP
Chronic aquatic toxicity			
Fish:		No data	
Crustacea:		No data	
Algae/aquatic plants:		No data	
Degradation (evidence of rapid degradation)			
Biotic degradation:		No data	
Abiotic degradation, hydrolysis: (half-life (d)):		< 0.5 days (longest half-life within pH 4-9)	C.7. / pH: 7.0, non-GLP
Bioaccumulation			
Bioconcentration factor in fish (BCF):		No data	

Aquatic hazard assessment, conclusions and comments:

Physico-chemical properties:

- The water solubility test is not considered to be valid (Klimisch 3) as the substance is known to rapidly hydrolyse and this was not considered in this study. Log K_{ow} not determined.

Acute aquatic toxicity:

- This data is based on initial measured concentrations in the suspension and the reported EC_{50} values are far above the water solubility (Klimisch score 3). Tests undertaken in a static regime which is inappropriate for a substance which rapidly hydrolyses (see also IR/CSA R.7b for guidance on how to test difficult substances)
- It is not clear whether the reported effects in the acute toxicity studies are due to physical effects of the undissolved substance particles in the test media on the test species or inherent toxicity of the substance.

Long-term aquatic toxicity:

- No adequate long-term toxicity data available for all three trophic levels.

Degradation (evidence of rapid degradation):

- In the assessment of rapid degradability hydrolysis can be considered if the hydrolysis products do not fulfil the criteria for classification as hazardous to the aquatic environment. In this example hydrolysis is sufficient to show a rapid degradability of the parent substance in the environment but no information is available about the breakdown product(s). More data on degradation of this/these compound(s) would be necessary;
- In absence of data to show a rapid degradation of the breakdown product(s) the parent substance is considered not rapidly degradable.

Bioaccumulation:

- Log K_{ow} could not be determined experimentally. The parent substance has a low potential for bioaccumulation due to hydrolytical instability.

Aquatic hazard classification and, where applicable, established M-factor(s):

Acute aquatic hazard: Not classified in absence of adequate data (data of poor quality).

Long-term aquatic hazard: category Chronic 4.

Reasoning:

Acute hazard (Table 4.1.0 (a)): No acute aquatic toxicity as no adequate acute data available;

Long-term hazard: No adequate long-term toxicity data available for all three trophic levels. Substance nevertheless of concern based on the following findings:

- Poorly soluble substance (< 0.2 mg/l);
- No acute aquatic toxicity recorded at levels up to the limit of water solubility;

- Not rapidly degradable (see section 4.1.3.2.3.2 of this guidance (CLP legal text: point 4.1.2.9.3);
- No evidence of NOEC being > water solubility for all three trophic levels.
- No information available on the hydrolysis products and hence dataset not decisive whether these fulfil the criteria for classification as hazardous to the aquatic environment based upon:
    - Toxicity
    - Rapid degradability
    - Bioaccumulation
- In this case the safety net classification should be applied because of the large uncertainty on the fate and effects of the hydrolysis products.

Labelling elements based on the classification:

Element	Code
GHS Pictogram	-
Signal Word	-
Hazard Statement	H413
Precautionary statement(s)	P273, P501

4.1.4 Classification of mixtures hazardous to the aquatic environment

4.1.4.1 General considerations for classification of mixtures hazardous to the aquatic environment

Note that general principles for classification of mixtures under CLP are given in section 1.1.6.2 and section 1.6 of part 1 of this guidance document.

The basic principle of mixture classification under CLP is shown in the green box below and in Figure 4.1.2, which is also explained in the text below the box.

Annex I: 4.1.3.2 The approach for classification of aquatic environmental hazards is tiered, and is dependent upon the type of information available for the mixture itself and for its components. Figure 4.1.2 outlines the process to be followed.

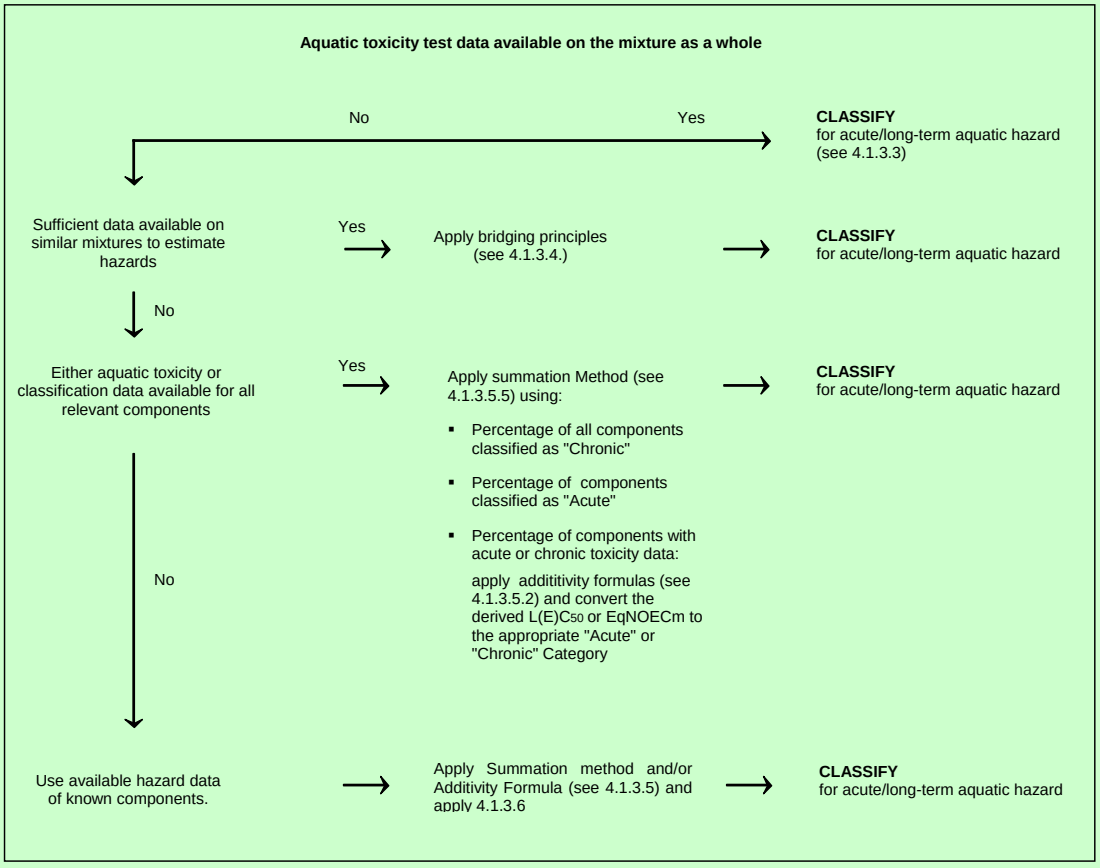
Elements of the tiered approach include:

– classification based on tested mixtures;

– classification based on bridging principles;

– the use of "summation of classified components" and/or an "additivity formula".

Figure 4. 1.2
Tiered approach to classification of mixtures for acute and long-term aquatic environmental hazards



Explanation of Figure 4.1.2:

- Horizontal arrow in first row: In some cases, particularly where specific and valid test data are already available on the mixture, there is a general obligation to use these data on the mixture itself for classification purposes. Valid data must normally then be available on each of fish, crustacea and algae or other aquatic plants, unless a decision to classify in the most stringent category(ies) (Acute 1 and/or Chronic 1) can be made without a full dataset (see section 4.1.4.3 of this document).

- Horizontal arrows in second row: In other cases, sufficient data may be available on similar tested mixtures to estimate hazards using the bridging principles (see section 4.1.4.4 of this document).

- Horizontal arrows in third row: In general, however, where either aquatic toxicity or classification data are available for all relevant components of a mixture the aquatic hazard classification shall be made through the identification of the hazards of the respective components in a first step, and then in a second step through the summation of the quantities of these hazardous components, applying the summation method (see section 4.1.4.5. of this document).When doing so:

    - The percentage of all components classified as Acute 1 and/or Chronic 1, 2, 3 & 4 is fed straight into the summation method (for relevant components see point 4.1.3.1 of Annex I to CLP);

    - For the percentage of the other components with acute or long-term toxicity data, the addititivity formulas (see point 4.1.3.5.2 of Annex I to CLP) may be applied. The derived $L(E)C_{50}$ or EqNOECm is converted to the appropriate "Acute" or "Chronic" Category and then, in a second step, fed into the summation method.[53]

- Horizontal arrows in fourth (last) row: Use available hazard data of known components.

    - This applies to mixtures containing unknown components and/or known components, for which neither toxicity data nor classifications are known. In these cases, apply the additional statement on the label and in the safety data sheet: *"Contains x % of components with unknown hazards to the aquatic environment"* (see the green box below). For classification based on the known part of the mixture, use the Summation Method and/or the Additivity Formula (see section 4.1.4.5 of this document).

Annex I: 4.1.3.6.1 In the event that no useable information on acute and/or long-term aquatic hazard is available for one or more relevant components, it is concluded that the mixture cannot be attributed to one or more definitive hazard category(ies). In this situation the mixture shall be classified based on the known components only, with the additional statement on the label and in the SDS that: "Contains x % of components with unknown hazards to the aquatic environment".

[53] As manufacturers and importers are obliged to classify all substances placed on the market within the EU, the summation method can usually be directly applied and the addititivity formula will be of limited application.

4.1.4.2 Information requirements

Before a classification can be made, available information on toxicity of the mixture as a whole as well as all the available information on the composition of the mixture and the hazard category of relevant components (substances) should be gathered. Note that manufacturers, importers or downstream users are not requested by the CLP Regulation to generate new data for determining the aquatic hazard classification of the mixture. Rather the supplier should be contacted if it is considered that the information on the substance or mixture supplied is not sufficient for classification purposes.

Generally, therefore, the constituent substance classifications should be used as the basis for to derivation of the correct hazard classification for the final mixture (see also section 1.6.4 of this guidance document).

Article 11 of the CLP-Regulation refers to cut-off values. These values are the minimum concentrations for a substance to be taken into account for classification purposes. The substances meeting these criteria are relevant ingredients or relevant components. When a classified substance is present in a concentration above the generic cut-off value it contributes to the mixture classification even if it may not trigger classification of the mixture directly.

> **Annex I: 4.1.3.1.** The classification system for mixtures covers all classification categories which are used for substances, i.e. categories Acute 1 and Chronic 1 to 4. In order to make use of all available data for purposes of classifying the aquatic environmental hazards of the mixture, the following is applied where appropriate:
>
> The "relevant components" of a mixture are those which are classified "Acute 1"or "Chronic 1" and present in a concentration of 0.1 % (w/w) or greater, and those which are classified "Chronic 2", "Chronic 3" or "Chronic 4" and present in a concentration of 1 % (w/w) or greater, unless there is a presumption (such as in the case of highly toxic components (see 4.1.3.5.5.5)) that a component present in a lower concentration can still be relevant for classifying the mixture for aquatic environmental hazards. Generally, for substances classified as "Acute 1" or "Chronic 1" the concentration to be taken into account is (0.1/M) %. (For explanation M-factor see 4.1.3.5.5.5).

For aquatic hazards the cut-off values are further addressed under point 1.1.2.2.2 (b) of Annex I to CLP. The calculation referred to in point (b)(i) of that point, is found in point 4.1.3.1 of Annex I to CLP (see the green box above).

This signals that highly toxic components will need to be considered at lower levels than the generic cut-off values, and this applies to any substance to which an M-factor greater than 1 has been assigned (see section 4.1.4.5 of this document).

Note that generic concentration limits (GCLs) should be given in weight percentages except for gaseous mixtures where they may be best described in volume percentage, (see CLP, Annex I, Note to Table 1.1).

When the information on the mixture has been gathered and validated, the following guidance should be followed depending on the type and level of information available.

4.1.4.3 Classification criteria for mixtures hazardous to the aquatic environment based on test data on the mixture as a whole

The testing of a mixture for aquatic toxicity is highly complex, both in terms of the conduct of the test, and in the interpretation of data from such testing. The different physico-chemical properties, such as water solubility, vapour pressure, and adsorption, make it almost impossible to prepare an exposure concentration that is characteristic of the mixture, while the multi-component analysis needed to verify such an exposure concentration is both complex and expensive.

Therefore, before any such new testing is conducted, alternative approaches such as the summation method, should be considered, particularly where testing would involve the use of vertebrate animals such as fish (see also section 1.1.6.2 of this document). Nevertheless, there are circumstances where test data may already be available, and should then be examined to assess its relevance for the purposes of classification. Data which has been prepared for Regulatory use in compliance with standard guidelines, such as test data on plant protection or biocidal products, may be considered as acceptable for classification. Where such valid test data, both acute and chronic, are available, they may be used in accordance with the general guidance below.

Annex I: 4.1.3.3.1 When the mixture as a whole has been tested to determine its aquatic toxicity, this information can be used for classifying the mixture according to the criteria that have been agreed for substances. The classification is normally based on the data for fish, crustacea and algae/plants (see sections 4.1.2.7.1 and 4.1.2.7.2). When adequate acute or chronic toxicity data for the mixture as a whole are lacking, "bridging principles" or "summation method" should be applied (see sections 4.1.3.4 and 4.1.3.5).

4.1.3.3.2 The long-term hazard classification of mixtures requires additional information on degradability and in certain cases bioaccumulation. Degradability and bioaccumulation tests for mixtures are not used as they are usually difficult to interpret, and such tests may be meaningful only for single substances.

4.1.3.3.3 Classification for category Acute 1

(a) When there are adequate acute toxicity test data (LC_{50} or EC_{50}) available for the mixture as a whole showing $L(E)C_{50} \leq 1$ mg/l:

Classify mixture as Acute 1 in accordance with point (a) of Table 4.1.0.

(b) When there are acute toxicity test data ($LC_{50}(s)$ or $EC_{50}(s)$) available for the mixture as a whole showing $L(E)C_{50}(s) > 1$ mg/l for normally all trophic levels:

No need to classify for acute hazard.

4.1.3.3.4 Classification for categories Chronic 1, 2 and 3

(a) When there are adequate chronic toxicity data (EC_x or NOEC) available for the mixture as a whole showing EC_x or NOEC of the tested mixture ≤ 1mg/l:

(i) Classify the mixture as Chronic 1, 2 or 3 in accordance with point (b)(ii) of Table 4.1.0. as rapidly degradable if the available information allows the conclusion that all relevant component of the mixture are rapidly degradable;

(ii) Classify the mixture as Chronic 1 or 2 in all other cases in accordance with point (b)(i) of Table 4.1.0.as non-rapidly degradable;

(b) When there are adequate chronic toxicity data (EC_x or NOEC) available for the mixture as a whole showing EC_x(s) or NOEC(s) of the tested mixture > 1 mg/l for normally all trophic levels:

No need to classify for long-term hazard in categories Chronic 1, 2 or 3.

4.1.3.3.5 Classification for category Chronic 4

If there are nevertheless reasons for concern:

Classify the mixture as Chronic 4 (safety net classification) in accordance with Table 4.1.0.

Where a classification is made based on test data, valid data should normally be available on each of fish, crustacea and algae or other aquatic plants, unless a decision to classify in the most stringent category(ies) (Acute 1 and/or Chronic 1) can be made without a full dataset. To be valid, it would normally be necessary to show that the tested organism has been exposed to the toxic components of the mixture in proportion to the composition of the mixture, and that this exposure has been maintained for the duration of the test. If this cannot be accomplished the classification should be based on information on the individual components. It is insufficient to simply prepare a water-accommodated fraction (WAF) for testing.

When there is adequate toxicity test data available for the mixture as a whole, this may be simplified to two basic rules for each of acute and long-term hazard classification:

Classification for acute (short-term) aquatic hazard:

i) If the lowest valid acute/short-term $L(E)C_{50}$ is ≤ 1 mg/l, classify as Acute 1.

ii) If valid acute/short-term test data are available on fish, crustacea and algae/aquatic plants (i.e. all three trophic levels), and all showing $L(E)C_{50}$ > 1 mg/l, there is no need to classify for acute aquatic hazard.

Classification for long-term aquatic hazard

i) If the lowest valid chronic toxicity test data (NOEC or EC_x) is ≤ 1 mg/l, classify as Chronic 1, 2 or 3, depending on the information on components degradability, e.g. if all components are known to be rapidly degradable.

ii) If valid chronic toxicity test data are available on fish, crustacea and algae/aquatic plants (i.e. all three trophic levels), and all showing NOEC or EC_x >1 mg/l, there is no need to classify for long-term aquatic hazard in Chronic 1, 2 or 3.

4.1.4.4 When experimental aquatic toxicity data are not available for the complete mixture: bridging principles

Annex I: 4.1.3.4.1 Where the mixture itself has not been tested to determine its aquatic environmental hazard, but there are sufficient data on the individual components and similar tested mixtures to adequately characterise the hazards of the mixture, this data shall be used in accordance with the bridging rules set out in Section 1.1.3. However, in relation to application of the bridging rule for dilution, sections 4.1.3.4.2 and 4.1.3.4.3 shall be used.

4.1.3.4.2 Dilution: if a mixture is formed by diluting another tested mixture or a substance

classified for its aquatic environmental hazard with a diluent which has an equivalent or lower aquatic hazard classification than the least toxic original component and which is not expected to affect the aquatic hazards of other components, then the resulting mixture may be classified as equivalent to the original tested mixture or substance. Alternatively, the method explained in section 4.1.3.5 may be applied.

4.1.3.4.3 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 be calculated from the original mixture or substance.

For circumstances where no or inadequate test data are available on the mixture itself, the classification of a mixture may be determined based on sufficient data for individual components of the mixture and on another similar tested mixture by an appropriate application of any of the specified "bridging principles". The identified relevant information needs to be evaluated for the purpose of classification, by comparing it with the criteria in point 1.1.3 of Annex I to CLP. Those rules allow characterisation of the hazards of the mixture without performing tests on it, but rather by building on the available information on similar tested mixtures (see also Part 1, section 1.6.3.2 of this guidance document).

4.1.4.5 When hazard data (information on toxicity or classification) are available for all the components of the mixture

Annex I: 4.1.3.5.1 The classification of a mixture is based on summation of the classification of its components. The percentage of components classified as "Acute" or "Chronic" is fed straight in to the summation method. Details of the summation method are described in 4.1.3.5.5.

Where no or inadequate test data on the mixture itself is available and the bridging principles are not applicable, the classification of the mixture is based on information on the components. The information that will most usually be available to aid classification of a mixture will be the classification applied to the individual components (substances). These data and any associated M-factor(s) are included in the Safety Data Sheets (SDS) and also in the Classification and Labelling Inventory (C&L Inventory) established and maintained by the Agency in the form of a database [link to be added once the public Inventory is available]. In cases the aquatic hazard classification of a mixture will be made based on data on the components, it is therefore generally the summation of the quantities of the hazardous components that should be used to determine a specific hazard classification of the mixture.

Provided the classification data, in part or in total, and the % of these components in the mixture are known, a classification of the mixture can be made according to the summation method. The following text from CLP describes the application of this method.

Annex I: 4.1.3.5.5 Summation method

4.1.3.5.5.1 Rationale

4.1.3.5.5.1.1 In case of the substance classification categories Chronic 1 to Chronic 3, the underlying toxicity criteria differ by a factor of 10 in moving from one category to another. Substances with a classification in a high toxicity band therefore contribute to the classification of a mixture in a lower band. The calculation of these classification categories therefore needs to consider the contribution of any substance classified as Chronic 1, 2 or 3.

4.1.3.5.5.2. Classification procedure

4.1.3.5.5.2.1 In general a more severe classification for mixtures overrides a less severe classification, e.g. a classification with Chronic 1 overrides a classification with Chronic 2. As a consequence, in this example, the classification procedure is already completed if the result of the classification is Chronic 1. A more severe classification than Chronic 1 is not possible. Therefore it is not necessary to undergo the further classification procedure.

4.1.3.5.5.3 Classification for category Acute 1

4.1.3.5.5.3.1 First all components classified as Acute 1 are considered. If the sum of the concentrations (in %) of these components multiplied by their corresponding M-factors is greater than 25 % the whole mixture is classified as Acute 1.

4.1.3.5.5.3.2 The classification of mixtures for acute hazards based on this summation of classified components is summarised in Table 4.1.1.

Table 4.1.1
Classification of a mixture for acute hazards, based on summation of classified components

Sum of components classified as:	Mixture is classified as:
Acute 1 × M[a] ≥ 25 %	Acute 1

a For explanation of the M-factor see 4.1.3.5.5.5

4.1.3.5.5.4 Classification for the categories Chronic 1, 2, 3 and 4

4.1.3.5.5.4.1 First all components classified as Chronic 1 are considered. If the sum of the concentrations (in %) of these components multiplied by their corresponding M-factors is equal to or greater than 25 %, the mixture is classified as Chronic 1. If the result of the calculation is a classification of the mixture as Chronic 1, the classification procedure is completed.

4.1.3.5.5.4.2 In cases where the mixture is not classified as Chronic 1, classification of the mixture as Chronic 2 is considered. A mixture is classified as Chronic 2 if 10 times the sum of the concentrations (in %) of all components classified as Chronic 1 multiplied by their corresponding M-factors plus the sum of the concentrations (in %) of all components classified as Chronic 2 is equal to or greater than 25 %. If the result of the calculation is classification of the mixture as Chronic 2, the classification process is completed.

4.1.3.5.5.4.3 In cases where the mixture is not classified either as Chronic 1 or Chronic 2, classification of the mixture as Chronic 3 is considered. A mixture is classified as Chronic 3 if 100 times the sum of the concentrations (in %) of all components classified as Chronic 1 multiplied by their corresponding M-factors plus 10 times the sum of the concentrations (in %) of all components classified with Chronic 2 plus the sum of the concentrations (in %) of all components classified as Chronic 3 is ≥ 25 %.

4.1.3.5.5.4.4 If the mixture is still not classified in Chronic 1, 2 or 3, classification of the mixture as Chronic 4 shall be considered. A mixture is classified as Chronic 4 if the sum of the concentrations (in %) of components classified as Chronic 1, 2, 3 and 4 is equal to or greater than 25 %.

4.1.3.5.5.4.5 The classification of mixtures for long-term hazards, based on this summation of the concentrations of classified components, is summarised in Table 4.1.2.

Table 4.1.2
Classification of a mixture for long-term hazards, based on summation of the concentrations of classified components

Sum of components classified as:	Mixture is classified as:
Chronic 1 × M[a] ≥ 25 %	Chronic 1
(M × 10 × Chronic 1) + Chronic 2 ≥ 25 %	Chronic 2
(M × 100 × Chronic 1) + (10 × Chronic 2) + Chronic 3 ≥ 25 %	Chronic 3
Chronic 1 + Chronic 2 + Chronic 3 + Chronic 4 ≥ 25 %	Chronic 4

a For explanation of the M-factor, see 4.1.3.5.5.5

4.1.3.5.5.1.2 When a mixture contains components classified as Acute 1 or Chronic 1, attention must be paid to the fact that such components, when their acute toxicity is below 1 mg/l and/or chronic toxicity is below 0,1 mg/l (if non-rapidly degradable) and 0.01 mg/l (if rapidly degradable) contribute to the toxicity of the mixture even at a low concentration. Active ingredients in pesticides often possess such high aquatic toxicity but also some other substances like organometallic compounds. Under these circumstances the application of the normal generic concentration limits leads to an "under-classification" of the mixture. Therefore, multiplying factors shall be applied to account for highly toxic components, as described in section 4.1.3.5.5.5.

For those components for which only toxicity data are available the additivity formulas offer a way for estimating what the toxicity of a mixture would be if the individual substance toxicities could be ‘added’ to each other in a straightforward way. Thus it assumes a similar ‘mode of action’ for each component.

To make full use of this approach access to the whole aquatic toxicity dataset and the necessary knowledge to select the best and most appropriate data is required. Clearly, the best use would be to add up separately each of the fish toxicity data, the crustacean toxicity data and the algae/aquatic plants toxicity data to derive a specific toxicity value for each trophic level. The lowest of the toxicity values would normally be used to define the appropriate hazard category for the mixture. Indeed, if it is only possible to characterise part of the mixture in this way, that part can be assigned a hazard category (and an M-factor for categories Acute 1 and/or Chronic 1) and then, in a second step, be used in the summation method.

The use of the additivity formulae is limited to those circumstances where the substance hazard category is not known. The following text from CLP describes the application of the additivity formulae.

Annex I: 4.1.3.5.2 Mixtures can be made of a combination of both components that are classified (as Acute 1 and/or Chronic 1, 2, 3, 4) and others for which adequate toxicity test data is 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) or (b), depending on the nature of the toxicity data:

(a) Based on acute aquatic toxicity:

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

where:

C_i = concentration of component i (weight percentage);

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

η = number of components, and i is running from 1 to n;

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

The calculated toxicity may be used to assign to that portion of the mixture an acute hazard category which is then subsequently used in applying the summation method;

(b) Based on chronic aquatic toxicity:

$$\frac{\sum Ci + \sum Cj}{EqNOEC_{\,m}} = \sum_{n} \frac{Ci}{NOECi} + \sum_{n} \frac{Cj}{0{,}1 \times NOECj}$$

where:

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

Cj = concentration of component j (weight percentage) covering the non-rapidly degradable components;

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

NOECj = NOEC (or other recognized measures for chronic toxicity) for component j 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;

The equivalent toxicity thus reflects the fact that non-rapidly degrading substances are classified one hazard category level more “severe” than rapidly degrading substances.

The calculated equivalent toxicity may be used to assign that portion of the mixture a long-term hazard category, in accordance with the criteria for rapidly degradable substances (point (b)(ii) of Table 4.1.0.), which is then subsequently used in applying the summation method.

4.1.3.5.3. When applying the additivity formula for part of the mixture, it is preferable to calculate the toxicity of this part of the mixture using for each substance toxicity values that relate to the same taxonomic group (i.e. fish, crustacean, algae or equivalent) and then to use the highest toxicity (lowest value) obtained (i.e. use the most sensitive of the three taxonomic groups).

However, when toxicity data for each component are not available in the same taxonomic group, the toxicity value of each component is selected in the same manner that toxicity values are selected for the classification of substances, i.e. the higher toxicity (from the most sensitive test organism) is used. The calculated acute and chronic toxicity is then used to assess whether this part of the mixture shall be classified as Acute 1 and/or Chronic 1, 2 or 3 using the same criteria described for substances.

Note that concentrations should be given in weight percentages except for certain gaseous mixtures where they may be best described in volume percentage, e.g. a single hazardous component in an inert diluent, e.g. nitrogen or helium.

NOTICE: 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.

4.1.4.6 When hazard data (information on toxicity or classification) are available for only some components of the mixture

This section is related to Figure 4.1.1. where one can decide to apply the summation method and/or the additivity formulae (see point 4.1.3.5 of Annex I to CLP) and apply point 4.1.3.6 of Annex I to CLP.

- Use available hazard data of known components.
    - This applies to mixtures containing unknown components and/or known components, for which neither toxicity data nor classifications are known. In these cases, for labelling purposes consider the provisions of point 4.1.3.6 in Annex I to CLP. For classification based on the known part of the mixture, use the summation method and/or the additivity formula (see point 4.1.3.5 of Annex I to CLP).
    - NOTE: If a mixture is classified in more than one way, the method yielding the most stringent result should be used.

4.1.4.7 Decision on classification: examples for mixtures

If the evaluation shows that the criteria are fulfilled, one category for acute aquatic hazard and/or one category for long-term aquatic hazards should be assigned. For the labelling elements, such as: hazard pictograms, signal words, hazard statements and precautionary statements, see Section 4.1.6.

List of the examples on mixtures classification included in this section:

The classification system for mixtures is complex as different methods are available. Which method to use is dependent upon the type of information available.

● Example A: When classification data are available for some or all components of a mixture: straightforward application of the summation method

● Example B1: When toxicity test data on the mixture as a whole are available for all three trophic levels: classification based on test data on the mixture

● Example B2: When information on the classification of the components and test data on the mixture as a whole are available for some, but not all three trophic levels: classification based on the summation method

● Example C: When no data are available on the mixture as a whole and its components, but test data are available on a similar tested mixture: use of the bridging principles – dilution with water

● Example D: When only test data are available for some, but not all components of the mixture: use of the additivity formulae and of the summation method

4.1.4.7.1 Example A: When classification data are available for some or all components of a mixture: straightforward application of the summation method

Information on ingredients classification and concentration					
	Acute aquatic hazard	M	Long-term aquatic hazard	M	C (%)
Astralamid	Acute 1	10	Chronic 1	10	1
Bastralamid	Acute 1	1	Chronic 2	-	3
Castralamid	Not classified	-	Chronic 2	-	10
Dastralamid		-	Chronic 3	-	10
Estralamid	Not classified	-	Not classified	-	10
Festralamid	Not classified	-	Not classified	-	66
	Not classified				

M = M-factor; C = Concentration

Aquatic hazard classification:

Acute aquatic hazard :
Not classified.

Long-term aquatic hazard:
Category Chronic 2

Reasoning:

- Valid test data on the mixture as a whole (for all three trophic levels) are not available.
- Valid test data on similar tested mixtures are not available, either, meaning that any bridging principle cannot be used.

Therefore, classification should be considered based on individual components using the summation method.

Acute aquatic hazard: Information on classification including associated M-factors and the % of the components in the mixture are available.
Classify for acute hazard if: $\sum$ (Acute 1 × M) ≥ 25%

Using the classification of the components of the mixture: (1 × 10) + (3 × 1) = 13 (which is < 25%). Hence, no classification for acute aquatic hazard.

Long-term aquatic hazard:

Step 1: Classify as Chronic 1 if: ∑ (Chronic 1 × M) ≥ 25% (if not, then go to Step 2).

Step 2: Classify as Chronic 2 if: ∑ (10 × Chronic 1 × M) + ∑ (Chronic 2) ≥ 25% (if not, then go to Step 3).

Step 3: Classify as Chronic 3 if: ∑ (100 × Chronic 1 × M) + ∑ (10 × Chronic 2) + ∑ (Chronic 3) ≥ 25% (if not, then go to Step 4).

Step 4: Classify as Chronic 4 if: ∑ (Chronic 1) + ∑ (Chronic 2) + ∑ (Chronic 3) + ∑ (Chronic 4) ≥ 25%

Using the classification of the components of the mixture:

Step 1: (1 × 10) = 10 (which is < 25% → Step 2).

Step 2: (10 × 1 × 10) + 3+10 = 113 (which is > 25%). Hence, classify as Category Chronic 2.

Labelling elements based on the classification:

Element	**Aquatic hazard information that could appear on the label**
GHS Pictogram	GHS09
Signal Word	-
Hazard Statement	H411
Precautionary statement(s)	P273, P391, P501

4.1.4.7.2 Example B1: When toxicity data on the mixture as a whole are available for all three trophic levels: classification based on test data on the mixture

Information on components classification and concentration					
	Acute aquatic hazard	M	Long-term aquatic hazard	M	C (%)
Frusthrin	Acute 1	1	Chronic 1	1	40
Gladobrin	Acute 1	1	Chronic 3	-	60

M = M-factor; C = Concentration

Acute (short-term) aquatic toxicity	Value	Test method ((EC) No. 440/2008) or OECD guideline / remarks
Fish: Mixture (*Cyprinus carpio*)	19 mg/l (96 hr LC_{50})	C.1 / static, GLP
Crustacea: Mixture (*Daphnia magna*)	3.5 mg/l (48 hr EC_{50})	C.2 / static, GLP
Algae/aquatic plants: Mixture (*Scenedesmus subspicatus*)	15 mg/l (72 or 96 hr ErC_{50})	C.3 / static, GLP
Chronic (long-term) aquatic toxicity		
Fish: Mixture (*Cyprinus carpio*)	0.09 mg/l (12 d NOEC)	OECD 210 / Early Life Stage, flow through, GLP
Crustacea: Mixture (*Daphnia magna*)	0.05 mg/l (21 d NOEC)	C.20 / semi-static, GLP
Algae/aquatic plants: Mixture (*Scenedesmus subspicatus*)	1.5 mg/l (96 h NOEC)	C.3 / static, GLP

Aquatic hazard classification:

Acute aquatic hazard: Not classified.

Long-term aquatic hazard: Chronic 1.

Reasoning:

Acute aquatic hazard:

Valid test data for all the three trophic levels are available for the mixture as a whole, therefore no need to consider bridging principles or classification of individual components for acute hazard classification of the mixture. Test data showed that $L(E)C_{50}$ > 1 mg/L. Consequently - no classification for acute aquatic hazard.

Long-term aquatic hazard:

Valid test data for all the three trophic levels are available for the mixture as a whole, therefore no need to consider classification of individual components for long-term hazard classification of the mixture. Test data showed that NOEC < 0.1 mg/l. No information on rapid degradation. Hence, the mixture is considered being not rapidly degradable. The mixture is classified as category Chronic 1.

Labelling elements based on the classification:

Element	Aquatic hazard information that could appear on the label
GHS Pictogram	GHS09
Signal Word	WARNING
Hazard Statement	H410
Precautionary statement(s)	P273, P391, P501

4.1.4.7.3 Example B2: When information on the classification of the components and toxicity data on the mixture as a whole are available for some, but not all three trophic levels: classification based on test data on the mixture

Information on components classification and concentration					
	Acute aquatic hazard	M	Long-term aquatic hazard	M	C (%)
Frusthrin	Acute 1	1	Chronic 1	1	40
Gladobrin	Acute 1	1	Chronic 3	-	60

M = M-factor; C = Concentration

Acute (short-term) aquatic toxicity	**Value**	**Test method ((EC) No. 440/2008) or OECD guideline / remarks**
Algae/aquatic plants: Mixture (*Scenedesmus subspicatus*)	15 mg/l (72 or 96 hr ErC_{50})	C.3 / static, GLP
Chronic (long-term) aquatic toxicity		
Algae/aquatic plants: Mixture (*Scenedesmus subspicatus*)	1.5 mg/l (96 h NOEC)	C.3 / static, GLP

Aquatic hazard classification:

Acute aquatic hazard: Acute 1.

Long-term aquatic hazard: Chronic 1.

Reasoning:

- Valid test data on the mixture as a whole are available for one, but not for all the three trophic levels and we don't know if algae is clearly the most sensitve trophic level for the mixture.
- Neither is valid test data on similar tested mixtures available, meaning that the bridging principles could not be used.

Therefore, classification should for both acute hazard and long-term hazard be considered based on individual components using the summation method. Testing should not be conducted for the mixture for the remaining trophic levels.

Acute aquatic hazard:
Information on classification including associated M-factors and the % of the components in the mixture are available.
Classify for acute hazard if: $\sum$ (Acute 1 × M) ≥ 25%

Using the classification of the components of the mixture: (40 × 1) + (60 × 1) = 100 (which is 25%). Hence - category Acute 1.

Long-term aquatic hazard:
Information on classification including associated M-factors and the % of the components in the mixture are available.

Step 1: Classify as Chronic 1 if: ∑ (Chronic 1 × M) ≥ 25% (if not, then go to Step 2).

Using the classification of the components of the mixture:

Step 1: (40 × 1) = 40 (which is ≥ 25%). Hence - Category Chronic 1.

Labelling elements based on the classification:

Element	**Aquatic hazard information that could appear on the label**
GHS Pictogram	GHS09
Signal Word	WARNING
Hazard Statement	H410[54]
Precautionary statement(s)	P273, P391, P501

[54] Note that in accordance with article 27 hazard statement H400 may be considered redundant and therefore not included on the label because hazard statement H410 also applies, see section 4.1.6.

4.1.4.7.4 Example C: When no data are available on the mixture as a whole and its components, but test data are available on a similar tested mixture: use of the bridging principles – dilution with water

Test Species	Information / Data
Fish	No data available
Crustacea	No data available
Algae	No data available

A reference mixture has shown a LC_{50} of 0.5 mg/l and adequate NOECs in the range 0.07 to < 0.1 mg/L. Based on this data it has been classified as Category Acute 1 and Category Chronic 1.

Subsequently, this mixture has been diluted in water by factor of 10 and the newly diluted mixture shall now be classified.

Aquatic hazard classification:

Acute aquatic hazard:
Not classified.

Long-term aquatic hazard:
Category Chronic 2.

Reasoning:

The mixture is formed by diluting another classified mixture with water, the toxicity of the mixture can therefore be calculated from the original mixture. (see section 4.1.4.4 of this document and CLP Annex I, point 4.1.3.4.3.)

Acute aquatic hazard:
LC_{50} = 5 mg/l (0.5x10). Hence - not classified.

Long-term aquatic hazard:
Adequate NOECs in the range 0.7 to < 1 mg/l (0.07x10 and 0.1x10). Hence - category Chronic 2.

Labelling elements based on the classification:

Element	**Aquatic hazard information that could appear on the label**
GHS Pictogram	GHS09
Signal Word	-
Hazard Statement	H411
Precautionary statement(s)	P273, P391, P501

1

4.1.4.7.5 Example D: When test data are available for some, but not all components of the mixture: use of the additivity formula and of the summation method

Information on components classification and concentration					
	Acute aquatic hazard	M	Long-term aquatic hazard	M	C (%)
Component 1	-	-	-	-	50
Component 2	-	-	-	-	10
Component 3	-	-	-	-	10
Component 4	Not classified	-	Chronic 1	-	30

Component toxicity data:

Data elements	**Component 1 (50% of the mixture)**	**Component 2 (10% of the mixture)**	**Test method ((EC) No. 440/2008) or OECD guideline / remarks**
Physico-chemical properties			
Water solubility (S_w):	200 mg/l	1000 mg/l	A.6 / pH: 7.0, non-GLP
Log octanol/water partition coefficient (log K_{ow}):	No data	No data	
Acute (short-term) aquatic toxicity			
Fish: *Oncorhynchus mykiss*	No data	0.3 mg/l (96 hr LC_{50})	C.1 / static, GLP
Crustacea: *Daphnia magna*	0.55 mg/l (48 hr EC_{50})	No data	C.2 / static, non-GLP

Algae/aquatic plants: *Scenedesmus subspicatus*	0.37 mg/l (72 hr E_rC_{50})	1.37 mg/l (72 hr E_rC_{50})	C.3 / static, GLP
Long-term aquatic toxicity			
Fish: *Oncorhynchus mykiss*	0.07 mg/l (28 d NOEC)	1.3 mg/l (28 d NOEC)	OECD 210 / semi-static
Crustacea: *Daphnia magna*	0.09 mg/l (21 d NOEC)	1.4 mg/l (21 d NOEC)	C.20 / semi-static, GLP
Algae/aquatic plants: *Scenedesmus subspicatus*	0.13 mg/L (72 hr NOEC)	0.53 mg/L (72 hr NOEC)	C.3 / static, GLP
Degradation (evidence of rapid degradation)			
Biotic degradation (% degradation in 28 days (or, if absent, half-life in water (d)): Abiotic degradation (Hydrolysis) (half-life (d)):	No data No data	No data No data	
Bioaccumulation			
Bioconcentration factor in fish (BCF):	No data	No data	

Chronic classification is known for 30% of the mixture.

Test data is available for 60% of the mixture.

For 10% of the mixture no information is available.

Aquatic hazard classification:

Acute aquatic hazard: Category Acute 1.

Long-term aquatic hazard: Category Chronic 1.

Reasoning:

- Valid test data on the mixture as a whole (for all three trophic levels) are not available.
- Valid test data on similar tested mixtures are not available, either, meaning that any bridging principle cannot be used.

Therefore, classification should be considered based on individual components using the summation method.

NOTICE! In the case of the downstream user or importer not having the classification of all the components, further dialogue with the supplier may be necessary to obtain additional information. The suppliers in a supply chain shall cooperate to meet the requirements for classification, labelling and packaging (see CLP Article 4(9)). This particular example, however, shows what could be done if the classification of some components in any case is not available (which, for example, could be the case when importing certain mixtures).

Acute aquatic hazard:

For component 1 the most sensitive species showed a $L(E)C_{50}$ 0.37mg/l. Thus, component 1, comprising 50% of the mixture, is classified as Acute 1; M factor 1.
Subsequently used in the summation method, more than 25% of the mixture is classified as category Acute 1. Hence, the mixture is classified as Acute 1.

Alternatively: You can calculate the combined toxicity for components 1 and 2 applying the *Additivity Formula*[55]:
$L(E)C_{50m}$ = 60 / (50/0.37 mg/L + 10/0.3mg/L) = 0.36 mg/L
Assign category Acute 1. This means that 60% of this mixture is classified as category Acute 1 and hence, subsequently used in the summation method, the whole mixture is classified as Acute 1.

Long-term aquatic hazard:

Assign hazard categories for each component for which there are adequate chronic toxicity data available:

	Relevant information	**Category**	**C (%)**
Component 1	0.07 mg/L (28 d NOEC Fish); No information on degradation. Hence, the substance is considered not rapidly degradable.	Assign Chronic 1, M factor 10	50 %
Component 2	0.53 mg/L (72 hr NOEC Algae); No information on degradation	Assign Chronic 2	10%

[55] In many cases it is possible to use the summation method straight away by assigning hazard categories to single components of a mixture when data is available.

Component 3	No data	-	10%
Component 4	Not classified	Chronic 1	10 %

More than 25% of the mixture is classified as category Chronic 1 and thus, the mixture is classified as category Chronic 1.

Alternatively: You can apply the *Additivity Formula*[56] to calculate the combined toxicity for components 1 and 2 (60% of the mixture)
$EqNOEC_m = 60 / (50/(0.1 \times 0.07) + 10/(0.1 \times 1.3)) = 0.008$ mg/l for fish
$EqNOEC_m = 60 / (50/(0.1 \times 0.09)) + 10/(0.1 \times 1.4)) = 0.011$ mg/l for crustaceans
$EqNOEC_m = 60 / (50/(0.1 \times 0.13) + 10/(0.1 \times 0.53)) = 0.015$ mg/l for algae

The lowest calculated $EqNOEC_m$ is 0.008 mg/l.
Apply table 4.1.0 b (i). Assign category Chronic 1, M factor 10 to that part of the mixture.
In addition component 4 of the mixture is classified as category Chronic 1 and comprises 10% of the mixture.
The long-term hazard category assigned to that part of the mixture the mixture is then subsequently used in applying the summation method:

Classify as Chronic 1 if: $\sum (\text{Chronic 1} \times \text{M}) \geq 25\%$

$\sum (60 \times 10) + 10 = 610$

Thus, the mixture is classified as category Chronic 1.

Labelling elements based on the classification:

Element	Aquatic hazard information that could appear on the label
GHS Pictogram	GHS09
Signal Word	WARNING
Hazard Statement	H410[57]
Precautionary statement(s)	P273, P391, P501

In the SDS and on the label it has to be stated: "Contains 10% of components with unknown hazards to the aquatic environment".

[56] See also section 4.1.4.6 of this guidance.
[57] Note that in accordance with CLP Article 27, the hazard statement H400 may be considered redundant and therefore not included on the label because hazard statement H410 also applies, see section 4.1.6 of tis document.

4.1.5 Metal and metal compounds

4.1.2.10. *Inorganic compounds and metals*

4.1.2.10.1. For inorganic compounds and metals, the concept of degradability as applied to organic compounds has limited or no meaning. Rather, such substances may be transformed by normal environmental processes to either increase or decrease the bioavailability of the toxic species. Equally the use of bioaccumulation data shall be treated with care*.

4.1.2.10.1. Poorly soluble inorganic compounds and metals may be acutely or chronically toxic in the aquatic environment depending on the intrinsic toxicity of the bioavailable inorganic species and the rate and amount of this species which enter solution. All evidence must be weighed in a classification decision. This would be especially true for metals showing borderline results in the Transformation/Dissolution Protocol.

_____

(*) Specific guidance has been issued by the European Chemicals Agency on how these data for such substances may be used in meeting the requirements of the classification criteria."

Annex IV provides the detailed guidance on the classification of metals and metal compounds.

The guidance on classification of alloys and complex metal containing materials is limited so far. More guidance is needed (see also Annex IV 5.5.1).

4.1.6 Hazard communication for hazards to the aquatic environment

A substance or mixture classified as hazardous and contained in packaging shall bear a label in accordance with the rules in Title III of CLP. The elements to be included in labels should be specified in accordance with the hazard pictograms, signal words, hazard statements and precautionary statements which form the core information of the CLP system. For general guidance on labelling see the *Introductory Guidance on the CLP Regulation (ECHA, 2009)* and also the *Guidance on Labelling and Packaging in accordance with Regulation (EC) No 1272/2008 (ECHA, 2011).*

Label elements shall be used for substances or mixtures meeting the criteria for classification in the hazard class *Hazardous to the Aquatic Environment* in accordance with Table 4.1.4 of Annex I to CLP.

Pictogram

The hazard pictogram shall satisfy the provisions of Annex V and Annex I, part 1.2 to the Regulation.

Symbol: *Environment*; Pictogram Code: *GHS09*

The pictogram GHS09 is required only for substances or mixtures classified as:

- Acute hazard category 1 and/or
- Long-term hazard categories 1 or 2

Signal word

The label shall include the relevant signal word in accordance with the classification of the hazardous substance or mixture. The signal word relevant for the hazard class *Hazardous to the Aquatic Environment* is:

WARNING

Signal Word Code: *Wng*

The signal word 'Warning' is required only for substances or mixtures classified as:

- Acute 1 and/or
- Chronic 1

Where the signal word 'Danger' is used on the label due to classification into another hazard class(es), the signal word 'Warning' shall not appear on the label.

Hazard statements

The label shall include the relevant hazard statements in accordance with the classification of the hazardous substance or mixture and shall be worded in accordance with Annex III to CLP.

The hazard statements (and the Hazard statement Codes) relevant for the hazard class *Hazardous to the Aquatic Environment* are:

- Very toxic to aquatic life (H400)
- Very toxic to aquatic life with long lasting effects (H410)
- Toxic to aquatic life with long lasting effects (H411)
- Harmful to aquatic life with long lasting effects (H412)
- May cause long lasting harmful effects to aquatic life (H413)

The hazard statement H400 is required only for substances or mixtures classified as:

- Acute 1

The hazard statements H410 to H413 are respectively required for substances or mixtures classified as:

- Chronic 1, 2, 3 or 4

Article 27 of CLP states that if a substance or mixture is classified within several hazard classes or differentiations of a hazard class, all hazard statements resulting from the classification shall appear on the label, unless there is evident duplication or redundancy.

This means that where the hazard statement H410 is used on the label due to classification into long-term hazard category Chronic 1, the hazard statement H400 shall not appear on the label. Furthermore, where a substance or a mixture is classified both in acute and long-term hazard categories, the hazard statement required to appear on the label shall for this hazard classification be H410 (see Table 4.1.6).

Table 4.1.6

Aquatic hazard classification	Associated hazard statement	Associated hazard statement that could appear on the label
Acute 1	H400	H400
Acute 1 and Chronic 1	H400; H410	H410
Acute 1 and Chronic 2	H400; H411	H410
Acute 1 and Chronic 3	H400; H412	H410
Acute 1 and Chronic 4[58]	H400; H413	H410
Chronic 1	H410	H410
Chronic 2	H411	H411
Chronic 3	H412	H412
Chronic 4	H413	H413

Precautionary statements

In accordance with CLP Articles 17 and 22 the label shall include the relevant precautionary statements. The precautionary statements that can in principle be used for the hazard class *Hazardous to the Aquatic Environment* are:

- Avoid release to the environment (P273)
- Collect spillage (P391)
- Dispose of contents/container to … (P501)

4.1.7 Re-classification of substances and mixtures classified as hazardous to the aquatic environment according to DSD/DPD

For the re-classification of substances and mixtures with regard to their hazards to the aquatic environment, a supplier has to apply the classification criteria specified in Annex I, part 4 of CLP. For this reason, all available information shall be re-evaluated in order to apply the criteria, as stated in CLP, accordingly. It is not suggested that new testing should be performed, but instead, available information should be evaluated for its relevance and reliability.

Besides the fact that M-factors need to be established for Acute 1 and Chronic 1 classifications, a direct translation of classification from the DSD/DPD to CLP can only be done in absence of chronic toxicity data. But also then, the translation for substances is not straightforward in all cases, for example:

[58] Please note that this combined classification only applies for mixtures.

– Differences between the CLP classification and the DSD classification of substances to which R53 - alone or in combination with R50, R51 or R52 - is applied. This is based on the slightly different criteria for classification, in particular higher cut-off values for logKow (i.e. 4 in CLP compared to 3 in DSD) and BCF (i.e. 500 in CLP compared to 100 in DSD). That means that only for those substances for which adequate chronic toxicity data is not available, for which the long-term aquatic hazard classification is based on a combination of acute toxicity data and bioaccumulation data (without data on rapid biodegradability affecting classification) and to which the currently applied R53 is based exclusively on a BCF between 100 and 500 or a $\log K_{ow}$ between 3 and 4 the classification would be subject to re-consideration.

4.1.8 References

European Communities, 2003: Technical guidance Document on Risk Assessment. Part II. European Commission, Joint Research Centre, http://ecb.jrc.ec.europa.eu/tgd/

OECD 2000: Series on Testing and Assessment Number 23, Guidance Document on aquatic toxicity Testing of difficult substances and mixtures. ENV/JM/MONO(2000)6

OECD 2006: Series on Testing and Assessment Number 54, Current approaches in the statistical analysis of ecotoxicity data: a guidance to application. ENV/JM/MONO(2006)18

PART 5: ADDITIONAL HAZARDS

5.1 HAZARDOUS TO THE OZONE LAYER

The criteria chapter for classification and labelling of substances and mixtures hazardous to the ozone layer are short and the need for guidance is limited to the actual ODP-value that would trigger classification for a substance.

Annex I:

5.1.2 Classification criteria for substances

5.1.2.1. A substance shall be classified as Hazardous to the Ozone Layer (Category 1) if the available evidence concerning its properties and its predicted or observed environmental fate and behaviour indicate that it may present a danger to the structure and/or the functioning of the stratospheric ozone layer.

5.1.3 Classification criteria for mixtures

5.1.3.1. Mixtures shall be classified as Hazardous to the Ozone Layer (Category 1) on the basis of the individual concentration of the substance(s) contained therein that are also classified as Hazardous to the Ozone Layer (Category 1), in accordance with Table 5.1.

Any substances having an Ozone Depleting Potential (ODP) greater or equal to the lowest ODP (i.e. 0.005) of the substances currently listed in Annex I to Regulation (EC) No 1005/2009[59] should be classified as hazardous to the ozone layer (category 1).

[59] Regulation (EC) No 1005/2009 of the European Parliament and of the Council of 16 September 2009 on substances that deplete the ozone layer

ANNEXES

I ANNEX I: AQUATIC TOXICITY

I.1 Introduction

The basis for the identification of a hazard to the aquatic environment for a substance is the aquatic toxicity of that substance. Classification is predicated on having toxicity data for fish, crustacea, and algae/aquatic plant available. These taxa are generally accepted as representative of aquatic fauna and flora for hazard identification. Data on these particular taxa are more likely to be found because of this general acceptance by regulatory authorities and the chemical industry. Other information on the degradation and bioaccumulation behaviour is used to better delineate the aquatic hazard. This section describes the appropriate tests for ecotoxicity, provides some basic concepts in evaluating the data and using combinations of testing results for classification. Further detailed guidance is given in the Integrated Testing Strategy (ITS) for aquatic toxicity for the substance (IR/CSA (R.7A) Chapters 7.8.3 – 7.8.5).

I.2 Description of tests

For classifying substances in the harmonised system, freshwater and marine species toxicity data can be considered as equivalent data. It should be noted that some types of substances, e.g. ionisable organic chemicals or organometallic substances may express different toxicities in freshwater and marine environments. Since the purpose of classification is to characterise hazard in the aquatic environment, the result showing the highest toxicity should normally be chosen. However, there are circumstances where a weight of evidence approach is appropriate.

The criteria for determining aquatic hazards should be test method neutral, allowing different approaches as long as they are scientifically sound and validated according to international procedures and criteria already referred to in existing systems for the hazard of concern and produce mutually acceptable data. Where valid data are available from non-standard testing and from non-testing methods, these shall be considered in classification provided they fulfil the requirements specified in Section 1 of Annex XI to the REACH Regulation (EC) No 1907/2006.

According to the proposed system (OECD 1998):

"Acute toxicity would normally be determined using a fish 96 hour LC_{50} (OECD Test Guideline 203 or equivalent), a crustacea species 48 hour EC_{50} (OECD Test Guideline 202 or equivalent) and/or an algal species 72 or 96 hour EC_{50} (OECD Test Guideline 201 or equivalent). These species are considered as surrogate for all aquatic organisms and data on other species such as the duckweed Lemna may also be considered if the test methodology is suitable."

Chronic testing involves an exposure that covers a significant period of time when compared to the organism´s life cycle. The term can signify periods from days to a year, or more depending on the reproductive cycle of the aquatic organism. Chronic tests can be done to assess certain information relating to growth, survival, reproduction and development.

"Chronic toxicity data are less available than acute data and the range of testing procedures less standardised. Data generated according to the OECD Test Guidelines 210 (Fish Early Life Stage), 202 Part 2 or 211 (Daphnia Reproduction) and 201 (Algal Growth Inhibition) or equivalent can be accepted. Other validated and internationally accepted tests could also be used. The NOECs or other equivalent EC_x should be used."

It should be noted that several of the test guidelines cited as examples for classification are being revised or are being planned for updating. Such revisions may lead to minor modifications of test conditions. Therefore, the expert group that developed the harmonised criteria for classification intended some flexibility in test duration and/or species and number of animals used.

Guidelines for conducting acceptable tests with fish, crustacea, and algae can be found in many sources (Test Methods Regulation 440/2008; OECD e.g. the OECD monograph No.11, Detailed Review Paper on Aquatic Toxicity Testing for Industrial Chemicals and Pesticides, 1999; EPA, 1996; ASTM, 1999; ISO EU).

I.2.1 Fish tests

I.2.1.1 Acute testing

Acute tests are generally performed with young juveniles 0.1 – 5 g in size for a period of 96 hours. The observational endpoint in these tests is mortality. Fish larger than this range and/or durations shorter than 96 hours are generally less sensitive. However, for classification, they could be used if no acceptable data with the smaller fish for 96 hours are available or the results of these tests with different size fish or test durations would influence classification in a more hazardous category. Tests consistent with OECD Test Guideline 203 (Fish 96 hour LC_{50}) or equivalent should be used for classification.

I.2.1.2 Chronic testing

Chronic or long-term tests with fish can be initiated with fertilized eggs, embryos, juveniles, or reproductively active adults. Tests consistent with OECD Test Guideline 210 (Fish Early Life Stage), the fish life-cycle test (US EPA 850.1500), or equivalent can be used in the classification scheme. Durations can vary widely depending on the test purpose (anywhere from 7 days to over 200 days). Observational endpoints can include hatching success, growth (length and weight changes), spawning success, and survival. Technically, the OECD 210 Guideline (Fish Early Life Stage) is not a "chronic" test, but a sub-chronic test on sensitive life stages. It is widely accepted as a predictor of chronic toxicity and is used as such for purposes of classification in the harmonised system. Fish early life stage toxicity data are much more available than fish life cycle or reproduction studies.

I.2.2 Tests with Crustaceae

I.2.2.1 Acute testing

Acute tests with crustacea generally begin with first instar juveniles. For daphnids, test duration of 48 hours is used. For other crustacea, such as mysids or others, duration of 96 hours is typical. The observational endpoint is mortality or immobilisation as a surrogate to mortality. Immobilisation is defined as unresponsive to gentle prodding. Tests consistent with OECD Test Guideline 202 Part 1 (Daphnia acute) or USA-EPA OPPTS 850.1035 (Mysid acute toxicity) or their equivalents should be used for classification.

I.2.2.2 Chronic testing

Chronic tests with crustacea also generally begin with first instar juveniles and continue through maturation and reproduction. For daphnids, in particular *Daphnia magna*, 21 days is sufficient for maturation and the production of 3 broods. For mysids, 28 days is necessary. Observational endpoints include time to first brood, number of offspring produced per female, growth, and survival. It is recommended that tests consistent with OECD test guidelines 211 and/or 202 Part 2 (Daphnia reproduction) or US-EPA 850.1350 (Mysid chronic) or their equivalents be used in the classification scheme.

I.2.3 Algae / other aquatic plant tests

I.2.3.1 Tests with algae

Algae are cultured and exposed to the test substance in a nutrient-enriched medium. Tests consistent with OECD Test Guideline 201 (Algal growth inhibition) should be used. Standard test methods employ a cell density in the inoculum in order to ensure exponential growth through the test, usually 3 to 4 days duration.

The algal growth inhibition test is a short-term test that provides both acute and chronic endpoints. However, the EC_{50} is treated as an acute value for classification purposes. Classification shall be based on both, the algal growth rate reduction endpoint, ErC_{50} [= EC_{50} (growth rate)] and NOErC [= NOEC (growth rate)] provided that the control growth is exponential (greater than a factor of 16). This endpoint is preferred because it is not dependent on the test design, whereas the endpoint, biomass (growth) inhibition (EbC_{50}) depends on both, growth rate of the test species as well as test duration and other elements of test design. Thus in circumstances where the basis of the EC_{50} is not specified and no ErC_{50} is recorded, classification shall be based on the lowest EC_{50} available. Where the algal toxicity ErC_{50} [= EC_{50} (growth rate)] falls more than 100 times below the next most sensitive species and results in a classification based solely on this effect, consideration should be given to whether this toxicity is representative of the toxicity to aquatic plants. Where it can be shown that this is not the case, professional judgment should be used in deciding if classification should be applied.

I.2.3.2 Tests with aquatic macrophytes

The most commonly used vascular plants for aquatic toxicity tests are duckweeds (*Lemna gibba* and *L. minor*). The Lemna test is a short-term test and, although it provides both acute and sub-chronic hazards, only the acute EC_{50} is used for classification in the harmonised system. The tests last for up to 14 days and are performed in nutrient enriched media similar to that used for algae, but may be increased in strength. The observational endpoint is based on change in the number of fronds produced. Tests consistent with OECD Test Guideline on Lemna (2006) and US-EPA 850.4400 (aquatic plant toxicity, Lemna) should be used.

Under the REACH Regulation growth inhibition study on aquatic plants, algae are the preferred species.

I.3 Aquatic toxicity concepts

This section addresses the use of acute and chronic toxicity data in classification, and special considerations for exposure regimes, algal toxicity testing, and use of QSARs.

I.3.1 Acute toxicity

Acute toxicity for purposes of classification refers to the intrinsic property of a substance to be injurious to an organism in a short-term exposure to that substance. Acute toxicity is

generally expressed in terms of a concentration which is lethal to 50% of the test organisms (lethal concentration, LC_{50}), causes a measurable adverse effect to 50% of the test organisms (e.g. immobilisation of daphnids, EC_{50}), or leads to a 50% reduction in test (treated) organism responses from control (untreated) organism responses (e.g. growth rate in algae, ErC_{50}).

Acute aquatic toxicity is normally determined using a fish 96 hour LC_{50}, a crustacea species 48 hour EC_{50}, an algal species 72 or 96 hour EC_{50} and/or aquatic plants 7 to 14 days EC50. These species cover a range of trophic levels and taxa and are considered as surrogate for all aquatic organisms. Data on other species (e.g. *Lemna* spp.) shall also be considered if the test methodology is suitable. The aquatic plant growth inhibition tests are short-term tests and, although they provide both acute and chronic hazards, only the EC_{50}s are treated as acute values for classification purposes. Since the purpose of classification is to characterise hazard in the aquatic environment, the result showing the highest toxicity should be chosen. However, there are circumstances, when a weight of evidence approach is appropriate.

Substances with an acute toxicity determined to be less than one part per million (1 mg/l) are generally recognised as being very toxic. The handling, use, or discharge into the environment of these substances poses a high degree of hazard and they are classified in category Acute 1. When classifying substances as Acute 1, it is necessary at the same time to indicate an appropriate Multiplying factor, M-factor. The multiplying factors are defined using a toxicity value (see Section 4.1.3.3.2).

I.3.2 Chronic toxicity

Chronic toxicity, for purposes of classification, refers to the intrinsic property of a substance to cause adverse effects to aquatic organisms during exposures which are determined in relation to the life-cycle of the organism. Such chronic effects usually include a range of sublethal endpoints and are generally expressed in terms of a No Observed Effect Concentration (NOEC), or an equivalent EC_x. Observable endpoints typically include survival, growth and/or reproduction. Chronic toxicity exposure durations can vary widely depending on the test endpoint measured and test species used.

For the classification based on chronic toxicity a differentiation is made between rapidly degradable and non-rapidly degradable substances. Substances that do rapidly degrade are classified in category Chronic 1 when the chronic toxicity NOEC or EC_x is determined to be $\leq$ 0.01 mg/l. Decimal bands are accepted for categorising chronic toxicity above this category. Substances with a chronic toxicity NOEC or EC_x between 0.01 and 0.1 mg/l are classified in category Chronic 2 for chronic toxicity. Substances with a chronic toxicity NOEC or EC_x between 0.1 and 1.0 mg/l are classified in category Chronic 3 for chronic toxicity. Finally, those substances with chronic toxicity NOECs or EC_xs over 1.0 mg/l are not classifiable for long-term hazard in any of the categories Chronic 1, 2 or 3. For substances that do not rapidly degrade or for which such has to be assumed by worst case (i.e. this applies in case where no information on rapid degradation is available) two chronic categories are used: category Chronic 1 if the chronic toxicity NOEC or EC_x is determined to be $\leq$ 0.1 mg/l and category Chronic 2 if the chronic toxicity NOEC or EC_x is determined to be between 0.1 and 1.0 mg/l.

When classifying substances as Chronic 1, it is necessary at the same time to indicate an appropriate M-factor. The multiplying factors are defined using a toxicity value (see Section 4.1.3.3.2).

Since chronic toxicity data are less common in certain sectors than acute data, for classification schemes, the potential for long-term hazard is in absence of chronic toxicity data, is identified by appropriate combinations of acute toxicity, lack of degradability, and/or the potential or actual bioaccumulation. However, where adequate chronic toxicity data exist, this shall be used in preference over the classification based on the combination of acute toxicity with degradability and/or bioaccumulation. In this context, the following general approach should be used.

(a) If adequate chronic toxicity data are available for all three trophic levels this can be used directly to determine an appropriate long-term hazard category;

(b) If adequate chronic toxicity data are available for one or two trophic levels, it should be examined if acute toxicity data are available for the other trophic level(s). A potential classification is made for the trophic level(s) with chronic data and compared with that made using the acute toxicity data for the other trophic level(s). In cases where the chronic data do not represent the species that is considerd the most sensitive in available short-term tests, the final classification shall be made according to the most stringent outcome.

I.3.3 Exposure regimes

Four types of exposure conditions are employed in both acute and chronic tests and in both freshwater and saltwater media: static, static-renewal (semi-static), recirculation, and flow-through. The choice for which test type to use usually depends on test substance characteristics, test duration, test species, and regulatory requirements.

I.3.4 Test media for algae and Lemna

Algal and Lemna tests are performed in nutrient-enriched media and use of one common constituent, EDTA, or other chelators, should be considered carefully. When testing the toxicity of organic chemicals, trace amounts of a chelator like EDTA are needed to complex micronutrients in the culture medium; if omitted, growth can be significantly reduced and compromise test utility. However, chelators can reduce the observed toxicity of metal test substances. Therefore, for metal compounds, it is desirable that data from tests with high concentration of chelators and/or tests with stoichiometrical excess of chelator relative to iron be critically evaluated. Free chelator may mask heavy metal toxicity considerably, in particular with strong chelators like EDTA (see Annex IV to this guidance on Metals and inorganic metal compounds). However, in the absence of available iron in the medium the growth of algae and Lemna can become iron limited, and consequently data from tests with no or with reduced iron and EDTA should be treated with caution.

I.3.5 Use of substance categorisation (read across and grouping) and (Q)SARs for classification and labelling

See Section 1.4 of this guidance.

I.4 Substances which are difficult to test

For classification of organic compounds, it is desirable to have stabilised and analytically measured test concentrations. Although measured concentrations are preferred, classification may, under certain circumstances, be based on studies where nominal concentrations are the

only valid data available. If the material is likely to substantially degrade or otherwise be lost from the water column, care must be taken in data interpretation and classification should be done taking into account the loss of the toxicant during the test, if relevant and possible. Additionally, metals present their own set of difficulties and are discussed separately (see Annex IV on metals).

In most cases where test conditions are hard to define, the actual test concentration is likely to be less than the nominal or expected test concentration. Where acute toxicities ($L(E)C_{50}$) are estimated to be less than 1 mg/l for a difficult to test substance, one can be fairly confident the classification as Acute 1 (and Chronic 1, if appropriate) is warranted. However, if the estimated toxicity is greater than 1 mg/l, the estimated toxicity is likely to under-represent the toxicity. In these circumstances, expert judgement is needed to determine the acceptability of a test with a difficult substance for use in classification. Where the nature of the testing difficulty is believed to have a significant influence on the actual test concentration when toxicity is estimated to be greater than 1 mg/l and the test concentration is not measured, then the test should be used with due caution in classification.

The following paragraphs provide some detailed guidance on some of these problems of interpretation. In doing so it should be remembered that this is guidance and hard and fast rules cannot be applied. The nature of many of the difficulties mean that expert judgement must always be applied both in determining whether there is sufficient information in a test for a judgement to be made on its validity, and also whether a toxicity level can be determined suitable for use in applying the classification criteria.

I.4.1 Unstable substances

While testing procedures should ideally have been adopted which minimise the impacts of instability in the test media, in practice, in certain tests, it can be almost impossible to maintain a concentration throughout the test. Common causes of lack of constant exposure concentration during the test are oxidation, hydrolysis, photodegradation and biodegradation. While the latter forms of degradation can more readily be controlled, such controls are frequently absent in much existing testing. Nevertheless, for some testing, particularly acute and chronic fish toxicity testing, a choice of exposure regimes is available to help minimise losses due to instability, and this should be taken into account in deciding on the test data validity.

Where instability is a factor in determining the level of exposure during the test, an essential prerequisite for data interpretation is the existence of measured exposure concentrations at suitable time points throughout the test. In the absence of analytically measured concentrations at least at the start and end of test, no valid interpretation can be made and the test should be considered as invalid for classification purposes. Where measured data are available, a number of practical rules can be considered by way of guidance in interpretation:

(a) where measured data are available for the start and end of test (as is normal for the acute Daphnia and algal tests), the $L(E)C_{50}$, for classification purposes, may be calculated based on the geometric mean concentration of the start and end of test. Where concentrations at the end of test are below the analytical detection limit, such concentrations shall be considered to be half that detection limit:

(b) where measured data are available at the start and end of media renewal periods (as may be available for the semi-static tests), the geometric mean for each renewal period should be calculated, and the mean exposure over the whole exposure period calculated from these data:

(c) where the toxicity can be attributed to a degradation breakdown product, and the concentrations of this are known, the $L(E)C_{50}$ for classification purposes may be calculated based on the geometric mean of the degradation product concentration, back calculated to the parent substance;

(d) similar principles may be applied to measured data in chronic toxicity testing.

I.4.2 Poorly soluble substances

These substances, usually taken to be those with a solubility in water of < 1 mg/l, are frequently difficult to dissolve in the test media, and the dissolved concentrations will often prove difficult to measure at the low concentrations anticipated. For many substances, the true solubility in the test media will be unknown, and will often be recorded as < detection limit in purified water. Nevertheless such substances can show toxicity, and where no toxicity is found, judgement must be applied to whether the result can be considered valid for classification. Judgement should err on the side of caution and should not underestimate the hazard.

Ideally, tests using appropriate dissolution techniques and with accurately measured concentrations within the range of water solubility should be used. Where such test data are available, they should be used in preference to other data. It is normal, however, particularly when considering older data, to find such substances with toxicity levels recorded in excess of the water solubility, or where the dissolved levels are below the detection limit of the analytical method. Thus, in both circumstances, it is not possible to verify the actual exposure concentrations using measured data. Where these are the only data available on which to classify, some practical rules can be considered by way of general guidance:

(a) where the acute toxicity is recorded at levels in excess of the water solubility, the $L(E)C_{50}$ for classification purposes may be considered to be equal to or below the measured water solubility. In such circumstances it is likely that category Chronic 1 and/or category Acute 1 should be applied. In making this decision, due attention should be paid to the possibility that the excess undissolved substance may have given rise to physical effects on the test organisms. Where this is considered the likely cause of the effects observed, the test should be considered as invalid for classification purposes;

(b) where no acute toxicity is recorded at levels in excess of the water solubility, the $L(E)C_{50}$ for classification purposes may be considered to be greater than the measured water solubility. In such circumstances, consideration should be given to whether the category Chronic 4 should apply. In making a decision that the substance shows no acute toxicity, due account should be taken of the techniques used to achieve the maximum dissolved concentrations. Where these are not considered as adequate, the test should be considered as invalid for classification purposes;

(c) where the water solubility is below the detection limit of the analytical method for a substance, and acute toxicity is recorded, the $L(E)C_{50}$ for classification purposes may be considered to be less than the analytical detection limit. Where no toxicity is observed, the $L(E)C_{50}$ for classification purposes, may be considered to be greater than the water solubility. Due consideration should also be given to the quality criteria mentioned above;

(d) where chronic toxicity data are available, the same general rules should apply. In principle, only data showing no observed effect concentrations at levels above the water solubility limit, or greater than 1 mg/l need be considered. Again, where these

data cannot be validated by consideration of measured concentrations, the techniques used to achieve the maximum dissolved concentrations must be considered as appropriate.

I.4.3 Other factors contributing to concentration loss

A number of other factors can also contribute to losses of test material from solution and, while some can be avoided by correct study design, interpretation of data where these factors have contributed may, from time to time, be necessary.

(a) sedimentation: this can occur during a test for a number of reasons. A common explanation is that the substance has not truly dissolved despite the apparent absence of particulates, and agglomeration occurs during the test leading to precipitation. In these circumstances, the $L(E)C_{50}$ for classification purposes, may be considered to be based on the end of test concentrations. Equally, precipitation can occur through reaction with the media. This is considered under instability above;

(b) adsorption: this can occur for substances of high adsorption characteristics such as high log Kow substances. Where this occurs, the loss of concentration is usually rapid and exposure may best be characterised by the end of test concentrations.

(c) bioaccumulation: losses may occur through the bioaccumulation of a substance into the test organisms. This may be particularly important where the water solubility is low and log K_{ow} correspondingly high. The $L(E)C_{50}$ for classification purposes, may be calculated based on the geometric mean of the start and end of test concentrations.

I.4.4 Perturbation of the test media

Strong acids and bases may exert their toxicity through extreme pH. Generally however changes of the pH in aquatic systems are normally prevented by buffer systems in the test medium. If no data are available on a salt, the salt should generally be classified in the same way as the anion or cation, i.e. as the ion that receives the most stringent classification. If the effect concentration is related to only one of the ions, the classification of the salt should take the molecular weight difference into consideration by correcting the effect concentration by multiplying with the ratio: $MW_{salt}/MW_{ion.}$

Polymers are typically not available in aquatic systems. Dispersible polymers and other high molecular mass materials can perturb the test system and interfere with uptake of oxygen, and give rise to mechanical or secondary effects. These factors need to be taken into account when considering data from these substances. Many polymers behave like complex substances, however, having a significant low molecular mass fraction which can leach from the bulk polymer. This is considered further below.

I.4.5 Complex substances

Complex substances are characterised by a range of chemical structures, frequently in a homologous series, but covering a wide range of water solubilities and other physico-chemical characteristics. On addition to water, equilibrium will be reached between the dissolved and undissolved fractions which will be characteristic of the loading of the substance. For this reason, such complex substances are usually tested as a WSF or WAF, and the $L(E)C_{50}$ recorded based on the loading or nominal concentrations. Analytical support data are not normally available since the dissolved fraction will itself be a complex mixture of components. The toxicity parameter is sometimes referred to as LL_{50}, related to the lethal

loading level. This loading level from the WSF or WAF may be used directly in the classification criteria.

Polymers represent a special kind of complex substance, requiring consideration of the polymer type and their dissolution/dispersal behaviour. Polymers may dissolve as such without change, (true solubility related to particle size), be dispersible, or portions consisting of low molecular weight fractions may go into solution. In the latter case, in effect, the testing of a polymer is a test of the ability of low molecular mass material to leach from the bulk polymer, and whether this leachate is toxic. It can thus be considered in the same way as a complex mixture in that a loading of polymer can best characterise the resultant leachate, and hence the toxicity can be related to this loading.

I.5 References

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II ANNEX II: RAPID DEGRADATION

II.1 Introduction

Degradability is one of the important properties of substances that have impact on the potential for substances to exert an aquatic hazard. Non-degradable substances will persist in the environment and may consequently have a potential for causing long-term adverse effects on biota. In contrast, degradable substances may be removed in the sewers, in sewage treatment plants or in the environment. It should be noted that data from degradability tests on mixtures are difficult or impossible to interpret, and are therefore not used in classification and labelling.

Classification of substances is primarily based on their intrinsic properties. However, the degree of degradation depends not only on the intrinsic degradability or recalcitrance of the molecule, but also on the actual conditions in the receiving environmental compartment such as redox potential, pH, temperature, presence of suitable micro-organisms, concentration of the substance and occurrence and concentration of other substrates. The interpretation of the degradation properties in an aquatic hazard classification context therefore requires detailed criteria that balance the intrinsic properties of the substance and the prevailing environmental conditions into a concluding statement on the potential for long-term adverse effects.

The term degradation is defined in Section 4.1 of Annex I to CLP as "the decomposition of organic molecules to smaller molecules and eventually to carbon dioxide, water and salts". For inorganic compounds and metals, the concept of degradability has no meaning. Rather the substance may be transformed by normal environmental processes to either increase or decrease the bioavailability of the toxic species. Therefore, the present section applies only to organic and organo-metal compounds. A separate section on the classification & labelling (C&L) of metals is provided in Part 4, section 4.1.5 and Annex IV to the CLP guidance.

Data on degradation properties of a substance may be available from standardised tests, or from other types of investigations, or they may be estimated from the structure of the molecules i.e. via SAR or QSAR approaches. The interpretation of such degradation data for classification purposes often requires detailed evaluation of the (test) data. The use of biodegradation data for classification purposes is only applicable to substances. Biodegradation data on mixtures cannot be used as it does not provide a reliable indication of environmental fate (CLP Annex I, point 4.1.3.3.1).

II.2 Interpretation of degradability data

Often a diverse range of test data is available that does not necessarily fit directly with the classification criteria. Consequently, guidance is needed on interpretation of existing test data in the context of the aquatic hazard classification. Based on the harmonised criteria, guidance for interpretation of degradation data is prepared below for several types of data comprised by the expression "rapid degradation" in the aquatic environment.

II.2.1 Ready biodegradability

Ready biodegradability is defined in the OECD Test Guidelines No. 301 methods A-F (OECD 1992), OECD 306 (marine water) and OECD 310 (OECD 2006). All organic substances that degrade to a level higher than the pass level in a standard OECD ready biodegradability test or in a similar test should be considered readily biodegradable, and consequently also rapidly degradable. Many test data found in the open literature, however, do not specify all of the conditions that should be evaluated to demonstrate whether or not the test fulfils the requirements of a ready biodegradability test. Expert judgement is therefore needed as regards the validity of the data before use for classification purposes. Before concluding on the ready biodegradability of a test substance, however, at least the following parameters should be considered.

II.2.1.1 Concentration of test substance

Relatively high concentrations of test substance are used in the OECD ready biodegradability tests (2-100 mg/l). Many substances may however be toxic to the inocula at such high concentrations, resulting in a low degradation of the substances in these tests, although the substances might be rapidly degradable at lower non-toxic concentrations. A toxicity test with micro-organisms, or inhibition of the inoculum observed with a positive control substance may demonstrate the toxicity of the test substance. Guidance on the selection of suitable microbial inhibition test methods is provided in IR/CSA Parts R7.8.14. When it is likely that inhibition is the reason for a substance being not readily degradable, results from a test employing lower non-toxic concentrations of the test substance should be used when available.

II.2.1.2 Time window

The harmonised criteria include a general requirement for all of the ready biodegradability tests on achievement of the pass level within ten days. This is not in line with the OECD Test Guideline 301 in which the ten-day time window applies to the OECD ready biodegradability tests except to the MITI I test (OECD Test Guideline 301C). In the Closed Bottle test (OECD Test Guideline 301D), a 14-days window may be used instead when measurements have not been made after ten days. Moreover, often only limited information is available in references of biodegradation tests. Thus, as a pragmatic approach the percentage of degradation reached after 28 days may be used directly for assessment of ready biodegradability when no information on the ten days time window is available. This should, however, only be accepted for existing test data and data from tests where the ten-day window does not apply.

Where there is sufficient justification, the ten-day window condition may be waived for certain complex substances and the pass level is applied at 28 days. This applies to multi-constituent and certain UVCB substances (such as oils and surfactants) consisting of structural similar constituents with different chain-lengths, degree and/or site of branching or stereo-isomers, even in their most purified commercial forms. Testing of each individual constituent may be costly and impractical. If a test on such a complex substance is performed and it is anticipated that a sequential biodegradation of the individual constituents is taking place, then the ten-day window should not be applied to interpret the results of the test. A case by case evaluation should however take place on whether a biodegradability test on such a substance would give valuable information regarding its biodegradability as such i.e. regarding the degradability of all the constituents, or whether instead an investigation of the degradability of carefully selected individual constituents of the complex substance is required (OECD 2006).

II.2.2 BOD_5/COD

Information on the 5-day biochemical oxygen demand (BOD_5) will be used for classification purposes only when no other measured degradability data are available. Thus, priority is given to data from ready biodegradability tests and from simulation studies regarding degradability in the aquatic environment. Therefore, this test should not be performed anymore for assessment of the ready biodegradability of substances. Older test data may however be used when no other degradability data are available. For substances where the chemical structure is known, the theoretical oxygen demand (ThOD) can be calculated and this value should be used instead of the chemical oxygen demand (COD).

II.2.3 Other convincing scientific evidence

Rapid degradation in the aquatic environment may be demonstrated by other data than a ready biodegradability test, or a BOD_5/COD ratio. These may be data on biotic and/or abiotic degradation. Data on primary degradation can only be used where it is demonstrated that the degradation products shall not be classified as hazardous to the aquatic environment, i.e. that they do not fulfil the classification criteria.

The fulfilment of criterion (c) of paragraph 4.1.2.9.5 of CLP requires that the substance is degraded in the aquatic environment to a level of > 70 % within a 28-day period. If first-order kinetics are assumed, which is reasonable at the low substance concentrations prevailing in most aquatic environments, the degradation rate will be relatively constant for the 28-day period. Thus, the degradation requirement will be fulfilled with an average degradation rate constant, $k > -(\ln 0.3 - \ln 1)/28 = 0.043$ day^{-1}. This corresponds to a degradation half-life, $t_{½} < \ln 2/0.043 = 16$ days.

Moreover, as degradation processes are temperature dependent, this parameter should also be taken into account when assessing degradation in the environment. Data from studies employing environmentally realistic temperatures e.g. 5 – 25°C should be used for the evaluation. When data from studies performed at different temperatures need to be compared, the traditional Q10 approach could be used, i.e. that the degradation rate is halved when the temperature decreases by 10°C.

The evaluation of data on fulfilment of this criterion should be conducted on a case-by-case basis by expert judgement. However, guidance on the interpretation of various types of data that may be used for demonstrating a rapid degradation in the aquatic environment is given below. In general, only data from aquatic biodegradation simulation tests are considered directly applicable. However simulation test data from other environmental compartments could be considered as well, but such data require in general more scientific judgement before use.

II.2.3.1 Aquatic simulation tests

Aquatic simulation tests (e.g. OECD 309, 2004) are tests conducted in the laboratory, but simulating environmental conditions and employing natural samples as inoculum. Results of aquatic simulation tests may be used directly for classification purposes, when realistic environmental conditions in surface waters are simulated, i.e.:

(a) substance concentration that is realistic for the general aquatic environment (often in the low µg/l range);

(b) inoculum from a relevant aquatic environment;

(c) realistic concentration of inoculum (10^3-10^6 cells/ml);

(d) realistic temperature e.g. 5 °C to 25 °C; and

(e) ultimate degradation is determined i.e. determination of the mineralisation rate or the individual degradation rates of the total biodegradation pathway.

II.2.3.2 Field investigations

Parallel to laboratory simulation tests are field investigations or mesocosm experiments. In such studies, fate and/or effects of chemicals in the environment or in environmental enclosures may be investigated. Fate data from such experiments can in principle be used for assessing the potential for a rapid degradation. This may, however, often be difficult, as it requires that ultimate degradation can be demonstrated. This may be documented by preparing mass balances showing that no non-degradable intermediates are formed, and which take the fractions into account that are removed from the aqueous system due to other processes such as sorption to sediment or volatilisation from the aquatic environment.

II.2.3.3 Monitoring data

Monitoring data may demonstrate the removal of contaminants from the aquatic environment. Such data are, however, very difficult to use for classification purposes. The following aspects should be considered before use:

(a) Is the removal a result of degradation, or is it a result of other processes such as dilution or distribution between compartments (sorption, volatilisation)?

(b) Is formation of non-degradable intermediates excluded?

Only when it can be demonstrated that removal as a result of ultimate degradation fulfils the criteria for rapid degradability, can such data be considered for use for classification purposes. In general, monitoring data should only be used as supporting evidence for demonstration of either persistence in the aquatic environment, or of rapid degradation.

II.2.3.4 Inherent and Enhanced Ready Biodegradability tests

Substances that are degraded more than 70% in tests for inherent biodegradability (OECD Test Guidelines 302) have the potential for ultimate biodegradation. However, because of the optimised conditions in these tests, the rapid biodegradability of inherently biodegradable substances in the environment cannot be assumed. The optimised conditions in inherent biodegradability tests stimulate adaptation of the micro-organisms thus increasing the biodegradation potential, compared to natural environments. Therefore, positive results in general should not be interpreted as evidence for rapid degradation in the environment.

IR/CSA Chapters R.7B and R.11 refer in the context of persistence testing to a new category of tests, i.e. the ‘enhanced ready (screening) biodegradability tests’. These are in essence ready biodegradability tests to which more flexibility is given to demonstrate the occurrence of degradation e.g. via prolonged testing times, larger test volumes, adaptation, etc. These methods are not yet validated and/or standardised for C&L.

II.2.3.5 Sewage treatment plant simulation tests

Results from tests simulating the conditions in a sewage treatment plant (STP) e.g. the OECD Test Guideline 303 cannot be used for assessing the degradation in the aquatic environment. The main reasons for this are that the microbial biomass in a STP is significantly different

from the biomass in the environment, that there is a considerably different composition of substrates, and that the presence of rapidly mineralised organic matter in waste water may facilitate degradation of the test substance by co-metabolism.

II.2.3.6 Soil and sediment degradation data

It has been argued that for many non-sorptive substances more or less the same degradation rates are found in soil and in surface water. For sorptive substances, a lower degradation rate may generally be expected in soil than in water due to a lower bioavailability caused by sorption. Thus, when a substance has been shown to be degraded rapidly in a soil simulation study, it is most likely also rapidly degradable in the aquatic environment. It is therefore proposed that an experimentally determined rapid degradation in soil is sufficient documentation for a rapid degradation in surface waters when:

(a) no pre-exposure (pre-adaptation) of the soil micro-organisms has taken place, and

(b) an environmentally realistic concentration of substance is tested, and

(c) the substance is ultimately degraded within 28 days with a half-life < 16 days corresponding to a degradation rate > 0.043 day^{-1} .

The same argumentation is considered valid for data on degradation in sediment under aerobic conditions.

II.2.3.7 Anaerobic degradation data

Data regarding anaerobic degradation cannot be used in relation to deciding whether a substance should be regarded as rapidly degradable, because the aquatic environment is generally regarded as the aerobic compartment where the aquatic organisms, such as those employed for aquatic hazard classification, live.

II.2.3.8 Hydrolysis

Data on hydrolysis e.g. OECD Test Guideline 111 might be considered for classification purposes only when the longest half-life $t_{½}$ determined within the pH range 4-9 is shorter than 16 days. However, hydrolysis is not an ultimate degradation and various intermediate degradation products may be formed, some of which may be only slowly degradable. Only when it can be satisfactorily demonstrated that the hydrolysis products formed do not fulfil the criteria for classification as hazardous for the aquatic environment, data from hydrolysis studies could be considered.

When a substance is quickly hydrolysed e.g. with $t_{½}$ < a few days, this process is a part of the degradation determined in biodegradation tests. Hydrolysis may be the initial transformation process in biodegradation.

II.2.3.9 Photochemical degradation

Information on photochemical degradation e.g. OECD 1997 is difficult to use for classification purposes. The actual degree of photochemical degradation in the aquatic environment depends on local conditions e.g. water depth, suspended solids, turbidity as well as seasonal influences, and the hazard of the degradation products is usually not known. Probably only seldom will enough information be available for a thorough evaluation based on photochemical degradation.

II.2.3.10 Estimation of degradation

Hydrolysis: Certain QSARs have been developed for prediction of an approximate hydrolysis half-life, which should only be considered when no experimental data are available, or in a Weight of Evidence approach. However, a hydrolysis half-life can only be used with great care in relation to classification, because hydrolysis does not concern ultimate degradability (see "Hydrolysis" of this Section). Furthermore the QSARs developed until now have a rather limited applicability and are only able to predict the potential for hydrolysis on a limited number of chemical classes (see also IR/CSA Chapter R.7.9.3.1).

Biodegradation: In general, no quantitative estimation method (QSAR) for estimating the degree of biodegradability of organic substances is yet sufficiently accurate to unequivocally predict rapid degradation. However, results from such methods may be used to predict that a substance is not rapidly degradable, or be used in a Weight of Evidence approach. For example, when in the Biodegradation Probability Program e.g. BIOWIN version 3.67, Syracuse Research Corporation the probability is < 0.5 estimated by the linear or non-linear methods, the substances should be regarded as not rapidly degradable (OECD, 1994; Pedersen *et al.*, 1995 & Langenberg *et al.*, 1996). Also other (Q)SAR methods may be used as well as expert judgement, for example, when degradation data for structurally analogue compounds are available, but such judgement should be conducted with great care. See also IR/CSA Chapter R.7.9.3.1.

In general, a QSAR prediction that the substance is not rapidly degradable is considered a better documentation for classification than application of a default classification, when no useful degradation data are available.

Degradation data from structurally related substances may provide evidence that a given substance displays very similar degradation properties. Such information may be employed in a read-across or weight of evidence approach for C&L.

II.2.3.11 Volatilisation

Chemicals may be removed from some aquatic environments by volatilisation. The intrinsic potential for volatilisation is determined by the Henry's Law constant (H) of the substance. Volatilisation from the aquatic environment is highly dependent on the environmental conditions of the specific water body in question, such as the water depth, the gas exchange coefficients (depending on wind speed and water flow) and stratification of the water body. Because volatilisation only represents removal of a chemical from the water phase, and not degradation, the Henry's Law constant cannot be used for assessment of degradation in relation to aquatic hazard classification of substances (see also Pedersen *et al.*, 1995).

II.2.4 No degradation data available

When no useful data on degradability are available - either experimentally determined or estimated data - the substance should be regarded by default as not rapidly degradable.

II.3 General interpretation problems

II.3.1 Complex substances

The harmonised criteria for classification of chemicals as hazardous for the aquatic environment focus on single substances. Some intrinsically complex substances are multi-constituent substances. They are typically of natural origin and need occasionally to be considered. This may be the case for chemicals that are produced or extracted from mineral

oil or plant material. Such complex chemicals are normally considered as single substances in a regulatory context. In most cases they are defined as a homologous series of substances within a certain range of carbon chain length and/or degree of substitution. When this is the case, no major difference in degradability is foreseen and the degree of degradability can be established from tests of the complex chemical. One exception would be when a borderline degradation is found because in this case some of the individual substances may be rapidly degradable and others may not be rapidly degradable. This requires a more detailed assessment of the degradability of the individual constituents in the complex substance. When the constituents that are not-rapidly-degradable constitute a significant part of the complex substance e.g. more than 20 %, or for a hazardous constituent, an even lower content, the substance should be regarded as not rapidly degradable.

II.3.2 Availability of the substance

The present standard methods for investigating degradability of substances are developed for readily soluble test compounds. However, many organic substances are only slightly soluble in water. As the standard tests require 2-100 mg/l of the test substance, sufficient availability may not be reached for substances with low water solubility. In general, the DOC Die-Away test (OECD Test Guideline 301A) and the Modified OECD Screening test (OECD Test Guideline 301E) are less suitable for testing the biodegradability of poorly soluble substances since adsorption may be confused with degradation. In such cases, test adaptations may be considered with e.g. continuous mixing and/or an increased exposure time. Also tests with a special design, where concentrations of the test substance lower than the water solubility have been employed e.g. with radiolabelled test chemicals, could be relevant.

II.3.3 Test duration less than 28 days

Sometimes degradation is reported for tests terminated before the 28 day period specified in the standards e.g. the MITI, 1992. These data are of course directly applicable when a degradation greater than or equal to the pass level is obtained. When a lower degradation level is reached, the results need to be interpreted with caution. One possibility is that the duration of the test was too short and that the chemical structure would probably have been degraded in a 28-day biodegradability test. If substantial degradation occurs within a short time period, the situation may be compared with the criterion $BOD_5/COD \geq 0.5$ or with the requirements on degradation within the 10-days time window. In these cases, a substance may be considered readily degradable (and hence rapidly degradable), if:

(a) the ultimate biodegradability exceeds 50% within 5 days; or

(b) the ultimate degradation rate constant in this period is greater than 0.1 day^{-1} corresponding to a half-life of 7 days.

These criteria are proposed in order to ensure that rapid mineralisation did occur, although the test was ended before 28 days and before the pass level was attained. Interpretation of test data that do not comply with the prescribed pass levels must be made with great caution. It is mandatory to consider whether a biodegradability result below the pass level was due to a partial degradation of the substance and not a complete mineralisation. If partial degradation is the probable explanation for the observed biodegradability, the substance should be considered not readily biodegradable.

II.3.4 Primary biodegradation

In some tests, only the disappearance of the parent compound i.e. primary degradation is determined for example by following the degradation by specific or group specific chemical analyses of the test substance. Data on primary biodegradability may be used for demonstrating rapid degradability only when it can be satisfactorily demonstrated that the degradation products formed do not fulfil the criteria for classification as hazardous to the aquatic environment.

II.3.5 Conflicting results from screening tests

The situation where more degradation data are available for the same substance introduces the possibility of conflicting results. In general, conflicting results for a substance which has been tested several times with an appropriate biodegradability test could be interpreted by a "weight of evidence approach". This implies that if both positive i.e. higher degradation than the pass level and negative results have been obtained for a substance in ready biodegradability tests, then the data of the highest quality and the best documentation should be used for determining the ready biodegradability of the substance. However, positive results in ready biodegradability tests could be considered valid, irrespective of negative results, when the scientific quality is good and the test conditions are well documented, i.e. guideline criteria are fulfilled, including the use of non-pre-exposed (non-adapted) inoculum.

The suitability of the inoculum for degrading the test substance depends on the presence and amount of competent degraders. When the inoculum is obtained from an environment that has previously been exposed to the test substance, the inoculum may be adapted as demonstrated by a degradation capacity greater than that of an inoculum from a non-exposed environment. As far as possible the inoculum must be sampled from an unexposed environment, but for substances that are used ubiquitously in high volumes and released widespread or more or less continuously, this may be difficult or impossible. When conflicting results are obtained, the origin and density of the inoculum should be checked in order to clarify whether or not differences in the adaptation of the microbial community may be the reason.

As mentioned above, many substances may be toxic or inhibitory to the inoculum at the relatively high concentrations tested in ready biodegradability tests. Especially in the Modified MITI (I) test (OECD Test Guideline 301C) and the Manometric Respirometry test (OECD Test Guideline 301F) high concentrations (100 mg/l) are prescribed. The lowest test substance concentrations are prescribed in the Closed Bottle test (OECD Test Guideline 301D) where 2-10 mg/l is used. The possibility of toxic effects may be evaluated by including a toxicity control in the ready biodegradability test or by comparing the test concentration with toxicity test data on micro-organisms (for test methods see IR/CSA Chapter R.7.8.14).

Volatile substances should only be tested in closed systems as the Closed Bottle test (OECD Test Guideline 301D), the MITI I test (OECD Test Guideline 301C) the Manometric Respirometry test (OECD Test Guideline 301F), or OECD 310 (CO2 in sealed vessels – Headspace Test). Results from other tests should be evaluated carefully and only considered if it can be demonstrated, e.g. by mass balance estimates, that the removal of the test substance is not a result of volatilisation.

II.3.6 Variation in simulation test data

A number of simulation test data may be available for certain high priority chemicals. Often such data provide a range of half-lives in environmental media such as soil, sediment and/or surface water. The observed differences in half-lives from simulation tests performed on the

same substance may reflect differences in test conditions, all of which may be environmentally relevant. A suitable half-life in the higher end i.e. a realistic worst case of the observed range of half-lives from such investigations should be selected for classification by employing a weight of evidence approach and taking the realism and relevance of the employed tests into account in relation to environmental conditions. In general, simulation test data of surface water are preferred relative to aquatic sediment or soil simulation test data in relation to the evaluation of rapid degradability in the aquatic environment.

II.4 Decision scheme

The following decision scheme may be used as a general guidance to facilitate decisions in relation to rapid degradability in the aquatic environment and classification of chemicals hazardous to the aquatic environment.

A substance is considered to be **not** rapidly degradable **unless** at least one of the following is fulfilled:

(g) The substance is demonstrated to be readily biodegradable in a 28-day test for ready biodegradability. The pass level of the test (70% DOC removal or 60% theoretical oxygen demand) must be achieved within 10 days from the onset of biodegradation, if it is possible to evaluate this according to the available test data (the ten-day window condition may be waived for complex multi-component substances and the pass level applied at 28 days, as discussed in II.2.3). If this is not possible, then the pass level should be evaluated within a 14 days time window if possible, or after the end of the test; or

(h) The substance is demonstrated to be ultimately degraded in a surface water simulation test 3 with a half-life of < 16 days (corresponding to a degradation of >70% within 28 days); or

(i) The substance is demonstrated to be primarily degraded biotically or abiotically e.g. via hydroysis, in the aquatic environment with a half-life <16 days (corresponding to a degradation of > 70 % within 28 days), and it can be demonstrated that the degradation products do not fulfill the criteria for classification as hazardous to the aquatic environment.

When these preferred data types are not available rapid degradation may be demonstrated if one of the following criteria is justified:

(j) The substance is demonstrated to be ultimately degraded in an aquatic sediment or soil simulation test 3 with a half-life of < 16 days (corresponding to a degradation of > 70 % within 28 days); or

(k) In those cases where only BOD_5 and COD data are available, the ratio of BOD_5/COD is greater than or equal to 0.5. The same criterion applies to ready biodegradability tests of a shorter duration than 28 days, if the half-life furthermore is < 7 days; or

(l) A weight of evidence approach based on read-across provides convincing evidence that a given substance is rapidly degradable.

If none of the above types of data are available then the substance is considered as **not** rapidly degradable. This decision may be supported by fulfilment of at least one of the following criteria:

(i) the substance is not inherently degradable in an inherent biodegradability test; or

(ii) the substance is predicted to be slowly biodegradable by scientifically valid QSARs, e.g. for the Biodegradation Probability Program, the score for rapid degradation (linear or non-linear model) < 0.5; or

(iii) the substance is considered to be not rapidly degradable based on indirect evidence, such as knowledge from structurally similar substances; or

(iv) no other data regarding degradability are available.

II.5 References

OECD (2006). Revised introduction to the OECD guidelines for testing of chemicals, section 3. OECD, 23 March 2006.

III ANNEX III: BIOACCUMULATION

III.1 Introduction

Bioaccumulation of a substance by an organism is not in itself a hazard. However, the bioaccumulation of a substance should be considered in relation to the potential for that substance to exert long-term effects. Chemical concentration and accumulation may result in internal concentrations of a substance in an organism (body burden), which may or may not lead to toxic effects over long-term exposures. For most organic chemicals uptake from water (bioconcentration) is believed to be the predominant route of uptake. Only for very hydrophobic substances does uptake from food become important. The classification criteria use the bioconcentration factor (BCF) or in the absence of it the octanol/water partition coefficient (log K_{ow}) as the measure of the potential for bioaccumulation. For these reasons, the present guidance document mainly considers bioconcentration and does not discuss in detail uptake via food or other routes. However, the possibility to use information on the biomagnification factor (BMF) as supportive evidence for bioaccumulation of highly lipophilic substances may be taken into account on a case by case basis.

Classification of a substance is primarily based on its intrinsic properties. However, the degree of bioconcentration also depends on factors such as the degree of bioavailability, the physiology of test organism, maintenance of constant exposure concentration, exposure duration, metabolism inside the body of the target organism and excretion from the body. The interpretation of the bioconcentration potential in a chemical classification context therefore requires an evaluation of the intrinsic properties of the substance, as well as of the experimental conditions under which bioconcentration factor (BCF) has been determined. IR/CSA (R.7C) Chapter 7.10.5.1 discusses the suitability of bioconcentration data, log K_{ow} data and other information (e.g. evidence for limited bioaccumulation potential) for classification purposes. Use of measured biomagnification data is discussed in relation to the screening approach in IR/CSA (R.7C) Chapter 7.10.4.5. Bioaccumulation of metals is discussed in Annex IV.

Information on the bioaccumulation potential of a substance may be available from standardised tests or may be estimated from the structure of the molecule. The interpretation of such bioconcentration data for classification purposes often requires detailed evaluation of test data. Guidance has been developed in IR/CSA in order to facilitate this evaluation. Chapter 7.1.8 (R.7A) gives guidance on n-octanol/water partition coefficient and Chapter 7.10.4 (R.7C) gives guidance on how to evaluate laboratory data on aquatic bioaccumulation. The use of bioaccumulation data for classification purposes is only applicable to substances. Bioaccumulation data on mixtures cannot be used as it does not provide a reliable indication of environmental fate (CLP Annex I, point 4.1.3.3.1).

III.2 Interpretation of bioconcentration data

Aquatic hazard classification of a substance is normally based on existing data on its environmental properties. Test data will only seldom be produced with the main purpose of facilitating a classification. Often a diverse range of test data is available which does not necessarily match the classification criteria. Further guidance on how to use this data is given in Chapter 7.10.5 of IR/CSA (R.7C).

Bioconcentration of an organic substance can be experimentally determined in bioconcentration experiments, during which BCF is measured as the concentration in the

organism relative to the concentration in water under steady-state conditions and/or estimated from the uptake rate constant and the elimination rate constant. In general, the potential of an organic substance to bioconcentrate is primarily related to the lipophilicity of the substance. A measure of lipophilicity is the n-octanol/water partition coefficient (K_{ow}) which, for lipophilic non-ionised organic substances, undergoing minimal metabolism or biotransformation within the organism, is correlated with the bioconcentration factor. Therefore, K_{ow} is often used for estimating the bioconcentration of non-ionised organic substances, based on the empirical relationship between log BCF and log K_{ow}. For those organic substances, estimation methods are available for calculating the K_{ow}. Data on the bioconcentration properties of non-ionised organic substances may thus be (i) experimentally determined, (ii) estimated from experimentally determined K_{ow}, or (iii) estimated from K_{ow} values derived by use of Quantitative Structure Activity Relationships (QSARs). Guidance for interpretation of such data is given in Chapters 7.10.4 and 7.10.5 of IR/CSA (R.7C). Guidance is also given on ionised chemicals and other classes that need special attention (see section III.3.1).

III.2.1 Bioconcentration factor (BCF)

The bioconcentration factor is defined as the ratio on a weight basis between the concentration of the chemical in biota and the concentration in the surrounding medium, here water, at steady state. BCF can thus be experimentally derived under steady-state conditions, on the basis of measured concentrations. In addition BCF can also be calculated as the ratio between the first-order uptake and elimination rate constants; a method which does not require steady state (equilibrium conditions).

Different test guidelines for the experimental determination of bioconcentration in fish have been documented and adopted, the most generally applied being the OECD test guideline 305 [60] (OECD, 1996; C.13 in Test Methods Regulation 440/2008 is a corresponding test).

Experimentally derived BCF values of high quality studies are ultimately preferred for classification purposes as such data override surrogate data, e.g. K_{ow}.

High quality data are defined as data where the validity criteria for the test method applied are fulfilled and described. Further guidance is provided in Chapter 7.10.4 of IR/CSA (R.7C).

BCF results from poor or questionable quality may give an erroneous BCF value. Therefore, such data should be carefully evaluated before use and consideration should be given to using K_{ow} instead.

If there is no BCF value for fish species, high-quality data on the BCF value for invertebrate species may be used. An invertebrate (mussel, oyster of scallop) BCF can be used as a worst case (conservative) value for fish. BCF for algae should not be used.

Experimental BCF data on highly lipophilic substances (e.g. with log K_{ow} above 6) will have a higher level of uncertainty than BCF values determined for less lipophilic substances. For highly lipophilic substances, e.g. with log K_{ow} above 6, experimentally derived BCF values tend to decrease with increasing log K_{ow}. Conceptual explanations of this non-linearity mainly refer to either reduced membrane permeation kinetics or reduced biotic lipid solubility for large molecules. A low bioavailability and uptake of these substances in the organism will thus occur. Other factors comprise experimental artifacts, such as equilibrium not being reached, reduced bioavailability due to sorption to organic matter in the aqueous phase, and

[60] Note that OECD 305 is currently under revision. All adopted OECD guidelines can be freely accessed via the OECD iLibrary.

analytical errors. Special care should thus be taken when evaluating experimental data on BCF for highly lipophilic substances as these data will have a much higher level of uncertainty than BCF values determined for less lipophilic substances.

III.2.1.1 BCF in different test species

BCF values used for classification are based on whole body measurements. As stated previously, the optimal data for classification are BCF values derived using the OECD test guideline 305 or corresponding EU test guideline C.13 or internationally equivalent methods, which uses small fish. Due to the higher gill surface-to-weight ratio in smaller organisms than in larger ones, steady-state conditions will be reached sooner in smaller organisms than in larger ones. The size of the organisms (fish) used in bioconcentration studies is thus of considerable importance in relation to the time used in the uptake phase, when the reported BCF value is based solely on measured concentrations in fish and water at steady-state. Thus, if large fish, e.g. adult salmon, have been used in bioconcentration studies, it should be evaluated whether the uptake period was sufficiently long for steady state to be reached or to allow for a kinetic uptake rate constant to be determined precisely. Also possible growth dilution should be taken into account when calculating the BCF values for smaller fish that grow during the bioconcentration studies.

Furthermore, when using existing data for classification, it is possible that the BCF values could be derived from several different fish or other aquatic species (e.g. clams) and for different organs in the fish. Thus, to compare diverse measured BCF data from different species to each other and to the criteria, normalisation to common basis lipid content will be required to reduce variability. Detailed guidance can be found in IR/CSA (R.7C) Chapter 7.10.4.1 for 'correction factors'.

Generally, the highest valid BCF value expressed on this common lipid basis is used to determine the wet weight based BCF-value in relation to the cut off value for BCF of 500 of the classification criteria.

III.2.1.2 Use of radio-labelled substances

The use of radio-labelled test substances can facilitate the analytical measurents in water and fish samples. However, unless combined with a specific analytical method, the total radioactivity measurements potentially reflect the presence of the parent substance as well as possible metabolite(s) and possible metabolised carbon, which have been incorporated in the fish tissue in organic molecules. BCF values determined by use of radio-labelled test substances are therefore normally overestimated.

When using radio-labelled substances, the labelling is most often placed in the stable part of the molecule, for which reason the measured BCF value includes the BCF of the metabolites as well as the BCF from the parent substance. For some substances it is the metabolite which is the most toxic or which has the highest bioconcentration potential. Selective measurements of the parent substance as well as the metabolites may thus be important for the interpretation of the aquatic hazard (including the bioconcentration potential) of such substances.

In experiments where radio-labelled substances have been used, high radio-label concentrations are often found in the gall bladder of fish. This is interpreted to be caused by biotransformation in the liver and subsequently by excretion of metabolites in the gall bladder (Comotto *et al.*, 1979; Wakabayashi *et al.*, 1987; Goodrich *et al.*, 1991; Toshima *et al.*, 1992).

The BCF from radio-labelled studies should, preferentially, be based on the parent compound. If these are unavailable, for classification purposes, the BCF based on total radio-labelled residues can be used. If the BCF, in terms of radio-labelled residues, is ≥ 1000, the identification and quantification of degradation products documented to be ≥ 10 % of total residues in fish tissues at steady state, are strongly recommended.

When fish do not eat, the content of the gall bladder is not emptied into the gut, and high concentrations of metabolites may build up in the gall bladder. The feeding regime may thus have a pronounced effect on the measured BCF. In the literature many studies are found where radio-labelled compounds are used, and where the fish are not fed. In these studies the bioconcentration may in most cases have been overestimated.

III.2.2 Octanol-water-partitioning coefficient (K_{ow})

For organic substances experimentally derived high-quality K_{ow} values are preferred over other determinations of K_{ow}. When no experimental data of high quality are available, validated Quantitative Structure Activity Relationships (QSARs) for log K_{ow} may be used in the classification process. Such validated QSARs may be used without modification to the agreed criteria if they are restricted to chemicals for which their applicability domain is well characterised. For substances like strong acids and bases, substances which react with the eluent, or surface-active substances, a QSAR estimated value of K_{ow} or an estimate based on individual *n*-octanol and water solubilities should be provided instead of an analytical determination of K_{ow}. Measurements should be taken on ionisable substances in their non-ionised form (free acid or free base) only by using an appropriate buffer with pH below pK for free acid or above the pK for free base. If multiple log K_{ow} data are available for the same substance, the reasons for any differences should be assessed before selecting a value. Generally, the highest valid value should take precedence. Further details are provided in IR/CSA (R.7A) Chapter 7.1. Guidance on pH correction for ionisable substances is given in chapter 7.1.20.

III.2.2.1 Experimental determination of K_{ow}

For experimental determination of K_{ow} values, several different methods are described in standard guidelines. Chapter 7.1.8.3 in IR/CSA (R.7A) gives guidance on direct measurement methods (Shake Flask Method, Generator Column Method, and Slow Stirring Method), and on one indirect measurement method (Reverse Phase HPLC Method).

III.2.2.2 Use of QSARs for determination of log K_{ow}

When an estimated K_{ow} value is found, the estimation method has to be taken into account. Numerous QSARs have been and continue to be developed for the estimation of K_{ow}. The performances of top six programs, as evaluated in 2007, are given in Table III.2.2.2 below. It is recommended that at least one of the below software programs be used for the prediction of log K_{ow}. If possible, the average of several predictions should be taken. More guidance is provided is Chapter 7.1.8.3 in IR/CSA (R.7A).

Table II.2.2.2 Examples of *software programs for the estimation of log K_{ow} (from IR/CSA (R.7A), Chapter 7.1.8.3)*

Software	Website	Availability	Batch Operation	% Predicted within 0.5 Log unit	Standard Error
ADMET	www.simulationsplus.com	Purchase	Yes	94.2	0.27
ACDLabs	www.acdlabs.com	Purchase	Yes	93.5	0.27
ChemSilico	www.logp.com	Free on line	No	93.5	0.30
KOWWIN	www.epa.gov/oppt/exposure/pubs/episuitedl.htm	Free to download	Yes	89.1	0.34
SPARC	ibmlc2.chem.uga.edu/sparc	Free on line	No	88.5	0.33
ClogP	www.daylight.com	Purchase	Yes	88.4	0.29

III.3 Chemical classes that need special attention with respect to BCF and K_{ow} values

There are certain physico-chemical properties of substances, which can make the determination of BCF or its measurement difficult. These may be substances, which do not bioconcentrate in a manner consistent with their other physico-chemical properties, e.g. steric hindrance or substances which make the use of descriptors inappropriate, e.g. surface activity, which makes both the measurement and use of log K_{ow} inappropriate.

III.3.1 Substances difficult to test

The methods presented above are generally designed for non-ionised organic substances. They are therefore of limited usefulness for a large number of other substances, collectively termed difficult substances, which include complex mixtures and chemicals that are charged at environmental pH (such as inorganic compounds). Substances difficult to test may be poorly soluble substances, complex mixtures, high molecular weight substances, surface active substances, inorganic substances, ionisable substances, or organic substances that do not partition to lipid. Some guidance is given in this Chapter. More detailed guidance is provided in IR/CSA (R.7C), mainly in Chapter 7.10.7.

In order to bioconcentrate in aquatic organisms, an organic substance needs to be present in the water, available for transfer across the fish gills and soluble in lipids. Factors that may alter this availability will thus change the actual bioconcentration of a substance, when compared with the prediction. For example, readily biodegradable substances may only be present in the aquatic compartment for short periods of time. Similarly, volatility, and hydrolysis will reduce the concentration and the time during which a substance is available for bioconcentration. A further important parameter, which may reduce the actual exposure concentration of a substance, is adsorption, either to particulate matter or to surfaces in general. There are a number of substances, which have shown to be rapidly transformed in the organism, thus leading to a lower BCF value than expected. Substances that form micelles or aggregates may bioconcentrate to a lower extent than would be predicted from simple physico-chemical properties. This is also the case for hydrophobic substances that are contained in micelles formed as a consequence of the use of dispersants. Therefore, the use of

dispersants in bioaccumulation tests is discouraged. Further guidance is given in IR/CSA (R.7C) Chapter 7.10.3.4 on how to consider the factors that affect the bioaccumulation potential of many substances and that are important especially in the absence of a fully valid BCF test result.

In general, for substances difficult to test, measured BCF and K_{ow} values – based on the parent substance – are a prerequisite for the determination of the bioconcentration potential. Furthermore, proper documentation of the test concentration is a prerequisite for the validation of the given BCF value.

III.3.2 Poorly soluble and complex substances

Special attention should be paid to poorly soluble substances. Frequently the solubility of these substances is recorded as less than the detection limit, which creates problems in interpreting the bioconcentration potential. Where the test data indicate that the concentrations in the study are below the limit of detection, then the test is invalid and cannot be used. For such substances the bioconcentration potential should be based on experimental determination of log K_{ow} or QSAR estimations of log K_{ow} (see Section III. 2.2). Complex substances contain a range of individual substances which can have a great variation in their physico-chemical and toxicological properties. It is generally not recommended to estimate an average or weighted BCF value. It is preferable to identify one or more representative constituents for further consideration. Further guidance is given in Chapter 7.10.7.2 in IR/CSA (R.7C) 2008.

III.3.3 High molecular weight substances

A number of regulatory systems use molecular weight as an indicator for reduced or minimal bioconcentration. It is, however, concluded in IR/CSA (R.7C) 2008, Chapter 7.10.3.4 that molecular mass and size should not be used in isolation as confirmatory evidence of lack of bioaccumulation (ECETOC 2005). However, supported by other data and by employing expert judgement, it may be concluded by a weight of evidence argument that such substances are unlikely to have a high bioconcentration factor (regardless of the log K_{ow} value). More details can be found in PBT assessment guidance (IR/CSA (R.11) 2008).

III.3.4 Surface-active substances (surfactants)

Surfactants consist of an apolar, lipophilic part (most often an alkyl chain) (the hydrophobic tail) and a polar part (the hydrophilic headgroup). According to the charge of the headgroup, surfactants are subdivided into classes of anionic, cationic, non-ionic, or amphoteric surfactants. Due to the variety of different headgroups, surfactants are a structurally diverse class of compounds, which is defined by surface activity rather than by chemical structure. The bioaccumulation potential of surfactants should thus be considered in relation to the different subclasses (anionic, cationic, non-ionic, or amphoteric) instead of to the group as a whole. Surface-active substances may form emulsions, in which the bioavailability is difficult to ascertain. Micelle formation can result in a change of the bioavailable fraction even when the solutions are apparently formed, thus giving problems in interpretation of the bioaccumulation potential**.** See Chapter 7.10.7.4 in IR/CSA (R.7C) 2008 for further guidance.

Measured (experimentally derived) BCF values on surfactants show that BCF tends to increase with increasing alkyl chain length and be dependent of the site of attachment of the head group, other structural features and whether the alkyl part is subject to biotransformation.

III.3.4.1 Octanol-water-partition coefficient (K_{ow})

The octanol-water partition coefficient for surfactants cannot be determined using the shakeflask or slow stirring method because of the formation of emulsions. In addition, the surfactant molecules will exist in the water phase almost exclusively as ions, whereas they will have to pair with a counter-ion in order to be dissolved in octanol. Therefore, experimental determination of K_{ow} does not characterise the partition of ionic surfactants (Tolls, 1998). On the other hand, it has been shown that the bioconcentration of anionic and non-ionic surfactants increases with increasing lipophilicity (Tolls, 1998). Tolls (1998) showed that for some surfactants, an estimated log K_{ow} value using LOGKOW could represent the bioaccumulation potential; however, for other surfactants some 'correction' to the estimated log K_{ow} value using the method of Roberts (1989) was required. These results illustrate that the quality of the relationship between log K_{ow} estimates and bioconcentration depends on the class and specific type of surfactants involved. Therefore, the classification of the bioconcentration potential based on log K_{ow} values should be used with caution. Further guidance is provided in Chapter 7.10.7.4 in IR/CSA (R.7C) 2008.

III.4 Conflicting data and lack of data

III.4.1 Conflicting BCF data

When multiple BCF data are available for the same substance, the possibility of conflicting results may arise. In general, conflicting results for a substance, which has been tested several times with an appropriate bioconcentration test, should be interpreted by a "weight of evidence approach". This implies that if experimentally determined BCF data, both $\geq$ and $<$ 500, have been obtained for a substance the data of the highest quality and with the best documentation should be used for determining the bioconcentration potential of the substance. If differences still remain, if for example high-quality BCF values for different fish species are available, generally the highest valid value should be used as the basis for classification. When larger data sets (4 or more values) are available for the same species and life stage, the geometric mean of the BCF values may be used as the representative BCF value for that species.

III.4.2 Conflicting log K_{ow} data

When multiple log K_{ow} data are available for the same substance, the possibility of conflicting results might arise. If log K_{ow} data both $\geq$ and $<$ 4 have been obtained for a substance, then the data of the highest quality and the best documentation should be used for determining the bioconcentration potential of the substance. If differences still exist, generally the highest valid value should take precedence. In such situation, QSAR estimated log K_{ow} could be used as guidance.

III.4.3 Expert judgement

If no experimental BCF or log K_{ow} data or no predicted log K_{ow} data are available, the potential for bioconcentration in the aquatic environment may be assessed by expert judgement. This may be based on a comparison of the structure of the molecule with the structure of other substances for which experimental bioconcentration or log K_{ow} data or predicted K_{ow} are available. IR/CSA (R.7C) 2008 gives guidance on read-across and categories in Chapter 7.10.3.2.

III.5 Decision scheme

Based on the above discussions and conclusions, a decision scheme has been elaborated which may facilitate decisions as to whether or not a substance has the potential for bioconcentration in aquatic species.

Experimentally derived BCF values of high quality are ultimately preferred for classification purposes. BCF results from poor or questionable quality studies should not be used for classification purposes. If no BCF is available for fish species, high quality data on the BCF for some invertebrates (e.g. blue mussel, oyster and/or scallop) may be used as a worst case surrogate.

For non-ionised organic substances, experimentally derived high quality K_{ow} values, or values which are evaluated in reviews and assigned as the "recommended values", are preferred. If no experimentally data of high quality are available validated Quantitative Structure Activity Relationships (QSARs) for log K_{ow} may be used in the classification process. Such validated QSARs may be used without modification in relation to the classification criteria, if restricted to chemicals for which their applicability is well characterised. For difficult substances like strong acids and bases, metal complexes, and surface-active substances a QSAR estimated value of K_{ow} or an estimate based on individual *n*-octanol and water solubilities should be provided instead of an analytical determination of K_{ow}.

If data are available but not validated, expert judgement should be used.

Whether or not a substance has a potential for bioconcentration in aquatic organisms could thus be decided in accordance with the following scheme:

Valid/high quality experimentally determined BCF value → YES:

→BCF ≥ 500: *The substance meets the criterion*

→BCF < 500: *The substance does not meet the criterion*

Valid/high quality experimentally determined BCF value → NO:

→Valid/high quality experimentally determined log K_{ow} value → YES:

→log K_{ow} ≥ 4: *The substance meets the criterion*

→log K_{ow} < 4: *The substance does not meet the criterion*

Valid/high quality experimentally determined BCF value → NO:

Valid/high quality experimentally determined log K_{ow} value → NO:

Use of validated QSAR for estimating a log K_{ow} value → YES:

→log K_{ow} ≥ 4: *The substance meets the criterion*

→log K_{ow} < 4: *The substance does not meet the criterion*

III.6 References

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IV ANNEX IV: METALS AND INORGANIC METAL COMPOUNDS

IV.1 Introduction

The harmonised system for classifying chemical substances is a hazard-based system, and the basis of the identification of hazard is the aquatic toxicity of the substances, and information on the degradation and bioaccumulation behaviour (OECD 2001). Since this document deals only with the hazards associated with a given substance when the substance is dissolved in the water column, exposure from this source is limited by the solubility of the substance in water and bioavailability of the substance to organisms in the aquatic environment. Thus, the hazard classification schemes for metals and metal compounds are limited to the acute and long-term hazards posed by metals and metal compounds when they are available (i.e. exist as dissolved metal ions, for example, as M+ when present as M-NO_3), and do not take into account exposures to metals and metal compounds that are not dissolved in the water column but may still be bioavailable, such as metals in foods. This section does not take into account the non-metallic ion (e.g. CN^-) of metal compounds which may be toxic. For such metal compounds the hazards of the non-metallic ions must also be considered.

Also organometal compounds may be of concern given they may pose bioaccumulation or persistence hazards. Organometals do not dissociate or dissolve in water as the metal ion, as metals and inorganic metal compounds do. Organometals (e.g. methyl mercury or tributyltin) that do not release metal ions are thereby excluded from the guidance of this section and should be classified according to the general guidance provided in section 4. Metal compounds that contain an organic component but that dissociate easily in water or dissolve as the metal ion should be treated in the same way as metal compounds and classified according to this annex (e.g. zinc acetate).

The level of the metal ion which may be present in solution following the addition of the metal and/or its compounds, will largely be determined by two processes: the extent to which it can be dissolved, i.e. its water solubility, and the extent to which it can react with the media to transform to water soluble forms. The rate and extent at which this latter process, known as "transformation" for the purposes of this guidance, takes place can vary extensively between different compounds and the metal itself, and is an important factor in determining the appropriate hazard class. Where data on transformation are available, they should be taken into account in determining the classification. The Protocol for determining this rate is available as Annex 10 to the UN GHS.

Generally speaking, the rate at which a substance dissolves is not considered relevant to the determination of its intrinsic toxicity. However, for metals and many poorly soluble inorganic metal compounds, the difficulties in achieving dissolution through normal solubilisation techniques are so severe that the two processes of solubilisation and transformation become indistinguishable. Thus, where the compound is sufficiently poorly soluble that the levels dissolved following normal attempts at solubilisation do not exceed the available L(E)C_{50}, it is the rate and extent of transformation, which must be considered. The transformation will be affected by a number of factors, not least of which will be the properties of the media with respect to pH, water hardness, alkalinity, temperature etc. In addition to these properties, other factors such as the size and, in particular, the specific surface area of the particles which have been tested, the length of time over which exposure to the media takes place and, of course the mass or surface area loading of the substance in the media will all play a part in determining the level of dissolved metal ions in the water. Transformation data can generally, therefore, only be considered as reliable for the purposes of classification if conducted

according to the standard protocol in Annex 10 to UN GHS. This protocol aims at standardising the principal variables such that the level of dissolved ion can be directly related to the loading of the substance added. It is this loading level which yields the level of metal ion equivalent to the available $L(E)C_{50}$ or $NOEC/EC_{10}$ that can then be used to determine the acute or long-term hazard category appropriate for classification. The testing methodology is detailed in Annex 10 to the UN GHS. The strategy to be adopted in using the data from the testing protocol, and the data requirements needed to make that strategy work, are described in Annex IV.2, IV.3 and in more detail in Annex IV.5 of this document.

In considering the classification of metals and metal compounds, both readily and poorly soluble, recognition has to be paid to a number of factors. As defined in Annex II, section II.1, the term "degradation" refers to the decomposition of organic molecules. For inorganic compounds and metals, clearly the concept of degradability, as it has been considered and used for organic substances, has limited or no meaning. Rather, the substance may be transformed by normal environmental processes to either increase or decrease the bioavailability of the toxic species. Equally, the log K_{ow} cannot be considered as a measure of the potential to accumulate. Nevertheless, the concept that a substance, or a toxic metabolite/reaction product may not be rapidly lost from the environment and/or may bioaccumulate, are as applicable to metals and metal compounds as they are to organic substances.

Speciation of the soluble form can be affected by pH, water hardness and other variables, and may yield particular forms of the metal ion which are more or less toxic. In addition, metal ions could be made non-available from the water column by a number of processes (e.g. mineralisation and partitioning). Sometimes these processes can be sufficiently rapid to be analogous to degradation in assessing chronic (long-term) aquatic hazard. However, partitioning of the metal ion from the water column to other environmental media does not necessarily mean that it is no longer bioavailable, nor does it necessarily mean that the metal has been made permanently unavailable.

Information pertaining to the extent of the partitioning of a metal ion from the water column, or the extent to which a metal has been or can be converted to a form that is less toxic or non-toxic is frequently not available over a sufficiently wide range of environmentally relevant conditions, and thus, a number of assumptions will need to be made as an aid in classification. These assumptions may be modified if available data show otherwise. In the first instance it should be assumed that the metal ions, once in the water, are "not rapidly partitioned" from the water column. Underlying this is the assumption that, although speciation can occur, the species will remain available under environmentally relevant conditions. This may not always be the case, as described above, and any evidence available that would suggest changes to the bioavailability over the course of 28 days, should be carefully examined.

The term "Rapid removal" is a more accurate description for metals in this respect, because partitioning (e.g. by precipitation and especially speciation processes) can lead to the non available form and the elimination of metals from the water column.

The bioaccumulation of metals and inorganic metal compounds is a complex process and bioaccumulation data should be used with care. The application of bioaccumulation criteria will need to be considered on a case-by-case basis taking due account of all the available data.

A further assumption that can be made, which represents a cautious approach, is that, in the absence of any solubility data for a particular metal compound, either measured or calculated,

the metal compound will be assumed to be sufficiently soluble to cause toxicity at the level of the ecotoxicity reference value (ERV), being the acute ERV (expressed as $L(E)C_{50}$), and/or the chronic ERV (expressed as the NOEC/ECx or an HC5 for extensive data sets) and thus may be classified in the same way as other soluble salts of the metal. Again, this is clearly not always the case, and it may be wise to generate appropriate solubility data. Absence of solubility data on the metallic form for a metal for which the soluble salts are classified for the environment, will therefore lead to a default classification due to potential hazard concerns.

This Annex IV deals with metals and inorganic metal compounds. Within the context of this guidance document, metals and metal compounds are characterised as follows:

(a) metals ($M^{0)}$ in their elemental state are not soluble in water but may transform to yield the available form (eg Fe^0 will not dissolve as such but the Fe^0 molecules present at the surface of a massive/powder will be first transformed into Fe^{2+} or Fe^{3+} compounds prior to their solubilisation). This means that a metal in the elemental state may react with water or a dilute aqueous electrolyte to form soluble cationic or anionic products, and in the process the metal will oxidise, or transform, from the neutral or zero oxidation state to a higher one;

(b) in a simple metal compound, such as an oxide or sulphide, the metal already exists in the oxidised state, so that further metal oxidation is unlikely to occur when the compound is introduced into an aqueous medium.

Organo-metals are outside the scope of this section.

While oxidisation may not change, interaction with the media may yield more soluble forms. A sparingly soluble metal compound can be considered as one for which a solubility product can be calculated, and which will yield a small amount of the available form by dissolution. However, it should be recognised that the final solution concentration may be influenced by a number of factors, including the solubility product of some metal compounds precipitated during the transformation/dissolution test, e.g. aluminium hydroxide.

IV.2 Application of aquatic toxicity data and solubility data for classification

IV.2.1 Interpretation of aquatic toxicity data

Ecotoxicity data of soluble inorganic compounds are used and combined to define the toxicity of the metal ion under consideration. The ecotoxicity of soluble inorganic metal compounds is dependent on the physico-chemistry of the medium, irrespective of the original metal species released in the environment. Reading across metal compounds can therefore be conducted by comparing the soluble metal ion concentration (µg Me/L) causing the ecotoxicity effect and translating this towards the compound under investigation. A molecular weight correction of the ecotoxicity reference value may be required to classify soluble metal compounds (MW soluble substance/MW metal ion[61]). Poorly soluble metal compounds and metals do not require Molecular weight correction given the amount used for Transformation Dissolution already recognises this into the loading calculation. The comparison is therefore directly done by comparing the soluble fraction measured after Transformation Dissolution with the ecotoxicity reference values of the soluble metal ion (based on the UN GHS, 2009).

[61] Note that this calculation needs to be adjusted to reflect the stoichiometry of the compound, for example for $Zn_3(PO_4)_2$ the MW metal would be multiplied by three.

When evaluating ecotoxicity data, the general guidance on the weight of evidence (see section 4.1.3.6 of this document) is also applicable to metals.

The term adequacy covers here both the *reliability (*inherent quality of a test relating to test methodology and the way that the performance and results of a test are described) and the *relevance (*extent to which a test is appropriate to be used for the derivation of an ecotoxicity reference value) of the available ecotoxicity data:

Under the reliability criteria, metal specific considerations include the description of some abiotic parameters in the test conditions for enabling the consideration of the bioavailable metal concentration and free metal ion concentration:

- *Description of the physical test conditions:* further to the general parameters (O_2, T°, pH, …) abiotic parameters such as dissolved organic carbon (DOC), hardness, alkalinity of the water that govern the speciation and hence the metal bioavailability is required. A proper description of culture conditions related to the level of essential metals is required to avoid artefacts due to acclimatisation/adaptation (see also below)
- *Description of test materials and methods*: to calculate the free metal ion concentration with speciation models the concentrations of dissolved major ions and cations like Al, Fe, Mg, Ca… are required
- *Concentration-effect relationship; hormesis*: sometimes an increased performance in growth or reproduction is seen at low metal doses that exceed the control values, referred to as hormesis. Such effects can be important especially for major trace nutrients such as Fe, Zn and Cu but can also occur with a wide variety of non-essential substances. In such cases, positive effects should not be considered in the derivation of acute ERV's and especially chronic ERV's, likely other models than the conventional log-logistic dose-response model should be used to fit the dose-response curve and consideration should be given to the adequacy of the control diet/exposure. Due to the essential nutritional needs, caution is needed with regards to extrapolation of the dose-response curve (eg to derive an acute ERV) below the lowest tested concentration.

Under the relevancy criteria, certain considerations need to be made, related to the relevancy of the test substance and to acclimatisation/adaptation:

- *Relevance of the test substance:* soluble metal salts should be used for the purpose of classification of inorganic metals/metal compounds. The ecotoxicity adapted from organic metal compounds exposure should not be used.
- *Acclimatisation/adaptation:* For essential metals, the culture medium should contain a minimal concentration not causing deficiency for the test species used. This is especially relevant for organisms used for long-term toxicity tests where the margin between essentiality and toxicity may become small. As an example, for algae, deletion of the strong complexing agent EDTA from the medium may result in iron deficiency.

Aquatic toxicity studies carried out according to a recognised protocol should normally be acceptable as valid for the purposes of classification. Annex I should also be consulted for generic issues that are common to assessing any aquatic toxicity data point for the purposes of classification.

IV.2.1.1 Metal complexation and speciation

The toxicity of a particular metal in solution, appears to depend primarily on (but is not strictly limited to) the level of dissolved free metal ions and the physico-chemistry of the environment. Abiotic factors including alkalinity, ionic strength and pH can influence the toxicity of metals in two ways: (i) by influencing the chemical speciation of the metal in water (and hence affecting the availability) and (ii) by influencing the uptake and binding of available metal by biological tissues. For the classification of metals, Transformation/Dissolution is carried out over a pH range. Ideally both T/D and ecotoxicity data are compared at a similar pH since both parameters will vary with pH. However, the majority of ecotoxicity tests are performed at the higher pH range (i.e. > pH 7.5) and ecotoxicity data obtained at lower pH are often scarce. Bioavailability and speciation models (e.g. respectively Biotic Ligand Models and WHAM (Tipping, 1994), as discussed below) may allow to normalise ecotoxicity data obtained at a given pH to other pH values, relevant to the T/D data. The applicability of the bioavailability models to the biological species for which data are available must be evaluated. Guidance on the Bioavailability correction for metals can be found in IR/CSA Annex R.7.13.2).

Where chemical speciation is important, it may be possible to model the concentrations of the different chemical forms of the metal, including those that are likely to cause toxicity. Analysis methods for quantifying exposure concentrations, which are capable of distinguishing between the complexed and uncomplexed fractions of a test substance, may not always be available or economic.

Complexation of metals to organic and inorganic ligands in test media and natural environments can be estimated from metal speciation models. Speciation models for metals, including pH, hardness, DOC, and inorganic substances such as MINTEQ (Brown and Allison, 1987), WHAM (Tipping, 1994) and CHESS (Santore and Driscoll, 1995) can be used to calculate the uncomplexed and complexed fractions of the metal ions.

Alternatively, and when available for the metal, the Biotic Ligand Model (BLM), allows, for the calculation of the acute and/or chronic ERV's of the metal ion, for different pH values, through integration of metal speciation and its interaction with the organism. The BLM model has at present been validated for a number of metals, organisms, and end-points (Santore and Di Toro, 1999). The models and formula used for the characterisation of metal complexation in the media should always be clearly reported, allowing for their translation back to natural environments (OECD, 2000). In case a metal-specific BLM is available covering an appropriate pH range, a normalised comparison of aquatic toxicity data can be made using the entire effects database for different reference pH values.

IV.2.2 Interpretation of solubility data

When considering the available data on solubility, their validity and applicability to the identification of the hazard of metal compounds should be assessed. In particular, the pH and the medium in which the data were generated should be known.

IV.2.2.1 Assessment of existing data

Existing data will be in one of the three forms: *for soluble, insoluble metal compounds and the metallic form*. For some well-studied metals, there will be solubility products and/or solubility data for the various inorganic metal compounds. It is also possible that the pH

relationship of the solubility will be known. However, for many metals or metal compounds, it is probable that the available information will be descriptive only, e.g. poorly soluble or resulting from the water solubility test form the OECD 105 physico-chemical water dissolution test. Unfortunately there appears to be very little (consistent) guidance about the solubility ranges for such descriptive terms. Where these are the only information available it is most probable that solubility data will need to be generated using the Transformation/Dissolution Protocol (Annex 10 to the UN GHS).

IV.2.2.2 Screening T/D test for assessing solubility of metal compounds

In the absence of solubility data, a simple "Screening Test" for assessing solubility, based on the high rate of loading (100 mg/l) for 24 h and rigid stirring conditions, should be used for metal compounds as described in the Transformation/Dissolution Protocol (Annex 10 to the UN GHS). The function of the screening test is to identify those metal compounds which undergo either dissolution or rapid transformation such that they are indistinguishable from soluble forms and hence may be classified based on the dissolved ion concentration and those who dissolves slowly and can be assessed in the same way as the metallic form. Where data are available from the screening test detailed in the Transformation/Dissolution Protocol, the maximum solubility obtained over the tested pH range should be used. Where data are not available over the full pH range, a check should be made that this maximum solubility has been achieved by reference to suitable thermodynamic speciation models or other suitable methods (see section IV.2.1.1 of this document). It should be noted that this test is only intended to be used for inorganic metal compounds. Metals should immediately be assessed at the level of the full T/D test.

IV.2.2.3 Full T/D test for assessing solubility of metals and metal compounds

The Full Transformation Dissolution test should be carried out at the pH[62] that maximises the concentration of dissolved metal ions in solution and that expresses the highest toxicity.

Based on the data from the Full Test, it is possible to generate a concentration of the metal ions in solution after 7 days (short-term test) for each of the three loadings (i.e. 1 mg/l as "low", 10 mg/l as "medium" and 100 mg/l as "high loading") used in the test. If the purpose of the test is to assess the long-term hazard of the substance, then the loadings[63] should be 0.01 mg/l, 0.1 mg/l or 1 mg/l depending on the removal rate and the duration of the test being extended to 28 days (long-term test).

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[62] The UN-GHS transformation/dissolution protocol specifies a pH range of 6-8.5 for the 7days test and 5.5 to 8 .5 for the 28 days test. Considering the difficulty in carrying out transformation/dissolution tests at pH 5.5, the OECD only validated the test in the pH range of 6-to 8.5.

[63] The standard protocol in Annex 10 to UN GHS presently only foresees a long-term loading rate of 1 mg/l and lower loading rates may not even be practically feasible for each case**.** While TDp testing at lower loading rates is in principle the best way forward it is technically often not feasible for the lower chronic loading rates. Extensive experience with the T/D protocol demonstrated that reliable predictions can be made for other loading rates. In order to make maximal use of existing Transformation Dissolution data, the 28 days results for the lower chronic loading rates (0,1 and 0,01 mg/l) can therefore be derived by extrapolation from TDp evidence from other loading rates. Such read across should be justified on a case by case basis and supported by reliable information on the T/D at different loading rates, e.g. over 7 and/or 28 days. It should be noted that the relationship between loading rate and dissolved metal concentration may well not be linear. Therefore extrapolation of T/D data to lower loadings should preferably be made by using the equations of section A10.6.1 of the UN-Annex 10 transformation dissolution protocol or alternatively by extrapolating in a precautionary way.

The UN announced to change/update Annex 10 in the near future to bring it better in line with the chronic classification strategy an aim that is already anticipated in this guidance note for the CLP.

IV.2.3 Comparison of aquatic toxicity data and solubility data

A decision on whether or not the substance is classified will be made by comparing aquatic toxicity data and solubility data. Depending on the available data two approaches can be followed.

1) When only a *limited dataset* is available existing data should be taken together irrespective of whether the toxicity and dissolution data are at the same pH and the lowest data point should give the basis for classification (this should be used as the default approach). This default approach may lead to the lowest toxicity data point compared with the highest Transformation Dissolution result each derived at different pH levels used for the purpose of classification.

2) When a more *extensive toxicity/dissolution dataset* is available, a split of the acute and chronic ecotoxicity reference values can be performed according to their pH used during T/D test. The worst case classification entry across pHs should be used based on comparing TDp data with relevant ecotox data across the pH range. Meaning that toxicity data and transformation data are in this case always compared at the same pH.

This split of the effects data into pH classes would apply in an equal way to the acute and the long-term effects data sets.

IV.3 Assessment of environmental transformation

Environmental transformation of one species of a metal to another species of the same metal does not constitute "degradation" as applied to organic compounds and may increase or decrease the availability and bioavailability of the toxic species. In addition naturally occurring geochemical processes can partition metal ions from the water column while also other processes may remove metal ions from the water column (e.g. by precipitation and speciation). Data on water column residence time, the processes involved at the water – sediment interface (i.e. deposition and re-mobilisation) are fairly extensive for some metals. Using the principles and assumptions discussed above in section IV.1 of this document, it may therefore be possible to incorporate this approach into the classification.

Such assessments are difficult to give guidance for and will normally be addressed on a case-by-case approach. However, the following may be taken into account:

(a) Changes in speciation if they are to non-available forms, however, the potential for the reverse change to occur must also be considered;

(b) Changes to a metal compound which is considerably less soluble than that of the metal compound being considered.

Some caution is recommended; see section IV.1 of this document, the 5th and 6th paragraph.

Comment by ECHA: Please note that in the light of a lack of scientific consensus on the interpretation of rapid removal from the water column in the context with classification, it has been decided to remove this part from the draft update guidance for the time being until further discussions have taken place.

IV.4 Bioaccumulation

While log Kow is a good predictor of BCF for certain types of organic compounds e.g. nonpolar organic substances, it is irrelevant for inorganic substances such as inorganic metal compounds because metals, in contrast to organic substances, are not lipophilic and are not

passively transported through cellular membranes. Uptake of metal ions occurs through active processes.

The mechanisms for uptake and depuration rates of metals are very complex and variable and there is at present no general model to describe this. Instead the bioaccumulation of metals according to the classification criteria should be evaluated on a case-by-case basis using expert judgement.

While BCFs are indicative of the potential for bioaccumulation there may be a number of complications in interpreting measured BCF values for metals and inorganic metal compounds. For most metals and inorganic metal compounds the relationship between water concentration and BCF in aquatic organisms is inverse, and bioconcentration data should therefore be used with care. This is particularly relevant for metals that are biologically essential. Metals that are biologically essential are actively regulated in organisms in which the metal is essential (homeostasis). Removal and sequestration processes that minimise toxicity are complemented by an ability to up-regulate concentrations for essentiality. Since nutritional requirement of the organisms can be higher than the environmental concentration, this active regulation can result in high BCFs and an inverse relationship between BCFs and the concentration of the metal in water. When environmental concentrations are low, high BCFs may be expected as a natural consequence of metal uptake to meet nutritional requirements and can in these instances be viewed as a normal phenomenon. Also, while a metal may be essential in a particular organism, it may not be essential in other organisms. Therefore, where the metal is not essential or when the bioconcentration of an essential metal is above nutritional levels, special consideration should be given to the potential for bioconcentration and environmental concern.

Non- essential metals are also actively regulated to some extent and therefore also for non-essential metals, an inverse relationship between the metal concentration and the external concentration may be observed (McGeer et al., 2003).

Consequently for both essential and non-essential elements, measured BCFs decline as external concentration increases. When external concentrations are so high that they exceed a threshold level, or overwhelm the regulatory mechanism, this can cause harm to the organism

BCF and BAF may be used to estimate metal accumulation by:

a) Considering information on essentiality and homeostasis of metals/ metal compounds. As a result, of such regulation, the “bioaccumulative” criterion is not applicable to these metals.

b). Assessing bioconcentration factors for non-essential metals, should preferably be done from BCF studies using environmentally relevant concentrations in the test media.

IV.5 Classification strategies for metals and metal compounds

IV.5.1 Introduction

Notice! *Acute and long-term hazard assessment* are assessed individually.

For determination of long-term hazards preference should be given in applying the approach based on chronic toxicity data. Such evidence is often frequently available for the bioavailable forms of metals.

The schemes for the determination of acute and long-term aquatic hazards of metals and metal compounds are described below and summarised diagrammatically in the figures:

IV.5.2.1 (acute hazard classification of metals),

IV.5.2.2 (a and b) (long-term hazard of metals);

IV.5.3.1 (acute hazard classification of metal compounds);

IV.5.3.2 (a and b) (long-term hazard of metal compounds).

There are several stages in these schemes where data are used for decision purposes. It is not the intention of the classification schemes to generate new ecotoxicity data. In the absence of valid data, it will be necessary to use all available data and expert judgement.

In the following sections, the reference to the acute and chronic ERV's refer to the data point(s) that will be used to select the hazard category(ies) for the metal or metal compound.

When considering acute and chronic ERV's data for metal compounds, it is important to ensure that the data point to be used as the justification for the classification is expressed in the weight of the molecule of the metal compound to be classified. This is known as correcting for molecular weight. Thus while most metal data is expressed in, for example, mg/l of the metal (ion), this value will need to be adjusted to the corresponding weight of the metal compound. Thus:

Acute $ERV_{\mathbf{compound}}$ = acute ERV of the metal compound = acute ERV of metal ion x (Molecular weight of metal compound /atomic weight of the metal).

Chronic $ERV_{\mathbf{compound}}$ = chronic ERV of the metal compound = chronic ERV of metal ion x (Molecular weight of metal compound /atomic weight of the metal).

IV.5.2 Classification strategies for metals

Notice! Acute and long-term hazard assessment is assessed individually for metals.

IV.5.2.1 Classification strategy for determining *acute* aquatic hazard for metals

The scheme for the determination of *acute* aquatic hazard for metals are described in this section and summarised diagrammatically in Figure IV.5.2.1.

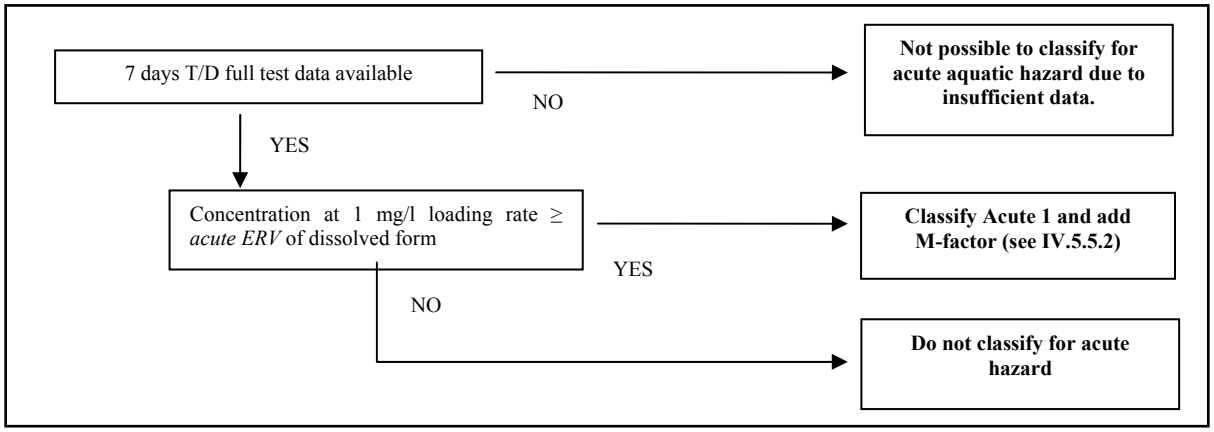
Where *the acute ERV* for the metal ions of concern is greater than 1 mg/l the metals need not be considered further in the classification scheme for acute hazard.

Where the acute ERV for the metal ions of concern is less than or equal to 1 mg/l consideration must be given to the data available on the rate and extent to which these ions can be generated from the metal. Such rate and extend data, to be valid and useable should have been generated using the Transformation/Dissolution Protocol (Annex 10 to UN GHS) for a 7d period.

Where 7d data from the Transformation/Dissolution protocol are available, then the results should be used to classify, according to the following rule:

Classify the metal as ***Category Acute 1*** if the dissolved metal ion concentration after a period of 7 days (or earlier for a significant time period) at a loading rate of 1 mg/l exceeds that of the acute ERV, an M-factor must also be established as part of this classification (see IV 5.5.2).

Figure IV.5.2.1 Classification strategy for determining *acute* aquatic hazard for metals.



IV.5.2.2 Classification strategy for determining long-term aquatic hazard for metals

The scheme for the determination of *long-term* aquatic hazard for metals are described in this section and summarised diagrammatically in Figures IV.5.2.2 (a and b).

Metals can be classified for long-term aquatic hazards:

1) using chronic reference data when available; or
2) using the surrogate approach in absence of appropriate chronic toxicity reference data.

In case relevant chronic ecotoxicity data (chronic ERV) are available the approach comparing chronic ERV with 28 days transformation/dissolution reference should be applied as described under IV.5.2.2.1 while otherwise the surrogate approach (see IV.5.2.2.2) should be followed.

IV.5.2.2.1 Approach based on available chronic toxicity reference data

Where *the chronic ERV* for the metal ions of concern is greater than 1 mg/l, the metals need not be considered further in the classification scheme.

Where the chronic ERV for the metal ions of concern is less than or equal to 1 mg/l consideration must be given to the data available on the rate and extent to which these ions can be generated from the metal. Such rate and extend data, to be valid and useable should have been generated using the Transformation/Dissolution Protocol (Annex 10 to UN GHS) for a 28 d period.

Where such T/Dp data are unavailable the surrogate approach should be applied (see section 5.2.2.2). Where 28d data from the Transformation/Dissolution protocol are available, then, the results should be used to aid classification according to the following rules:

a) **Classify** the metal as ***Category Chronic 1*** if the dissolved metal ion concentration obtained at a loading rate of 0.1 mg/l is greater than or equal to the chronic ERV, an M-factor must also be established as part of this classification (see IV.5.5.2); or

b) **Classify** the metal as ***Category Chronic 2*** if the dissolved metal ion concentration obtained at a loading rate of 1 mg/l is greater than or equal to the chronic ERV.

If there is evidence of rapid removal from the water column:

c) **Classify** the metal as ***Category Chronic 1*** if the dissolved metal ion concentration obtained at a loading rate of 0.01 mg/l is greater than or equal to the chronic ERV, an M-factor must also be established as part of this classification (see IV 5.5.2). ; or

d) **Classify** the metal as ***Category Chronic 2*** if the dissolved metal ion concentration obtained at a loading rate of 0.1 mg/l is greater than or equal to the chronic ERV; or

e) **Classify** the metal as ***Category Chronic 3*** if the dissolved metal ion concentration obtained at a loading rate of 1 mg/l is greater than or equal to the chronic ERV.

Do not classify for long-term hazard if the dissolved metal ion concentration obtained from the 28 day Transformation/Dissolution test at ***a loading rate of 1 mg/l*** is less than the chronic ERV of the metal ion.

IV.5.2.2.2 The surrogate approach

Where the acute ERV for the metal ions of concern is less than or equal to 100 mg/l consideration must be given to the data available on the rate and extent to which these ions can be generated from the metal. Such rate and extend data, to be valid and useable should have been generated using the Transformation/Dissolution Protocol (Annex 10 to UN GHS) for a 7d period.

Where such T/Dp data are unavailable, i.e. there is no clear data of sufficient validity to show that the transformation to metal ions will not occur; the safety net classification (Category Chronic 4) should be applied since the known classifiable toxicity of these soluble forms is considered to give rise to sufficient concern.

Where T/Dp data are available classification should be according to the following rules:

(a) **Classify** the metal as ***Category Chronic 1*** if the dissolved metal ion concentration obtained from the 7 day transformation test at the low loading rate (1 mg/l) is greater than or equal to the acute ERV, an M-factor must also be established as part of this classification (see IV.5.5.2).;

(b) **Classify** the metal as ***Category Chronic 2*** if the dissolved metal ion concentration obtained from the 7 day transformation test at the medium loading rate (10 mg/l) is greater than or equal to the acute ERV;

(c) **Classify** the metal as ***Category Chronic 3*** if the dissolved metal ion concentration obtained from the 7 day transformation test at the high loading rate (100 mg/l) is greater than or equal to the acute ERV.

(d) **Classify** the metal as ***Category Chronic 4*** if the dissolved metal ion concentration obtained from the 7 day transformation test at the high loading rate (100 mg/l) is lower than the acute ERV.

Figure IV.5.2.2a Classification strategy for determining long-term aquatic hazard for metals.

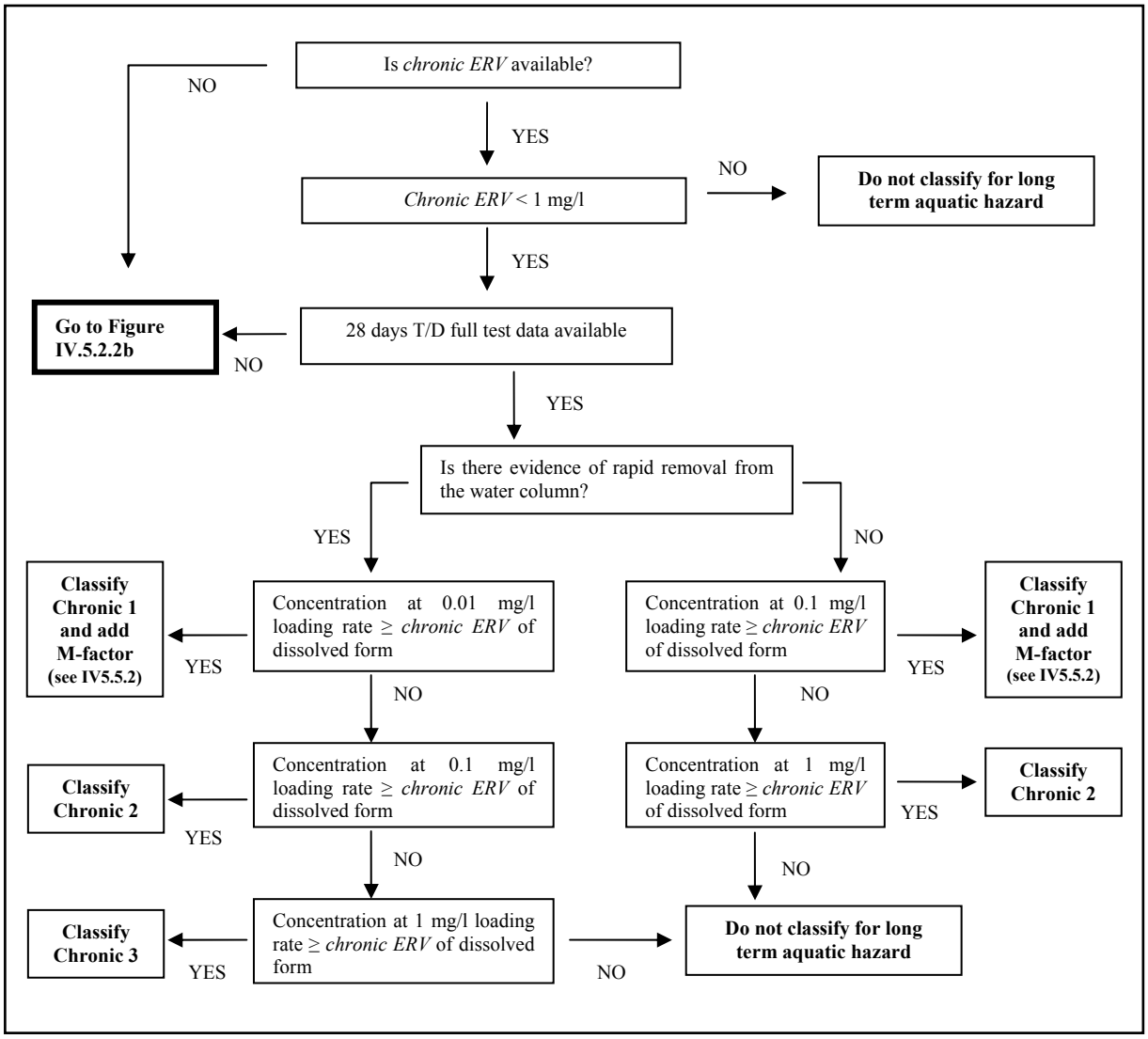
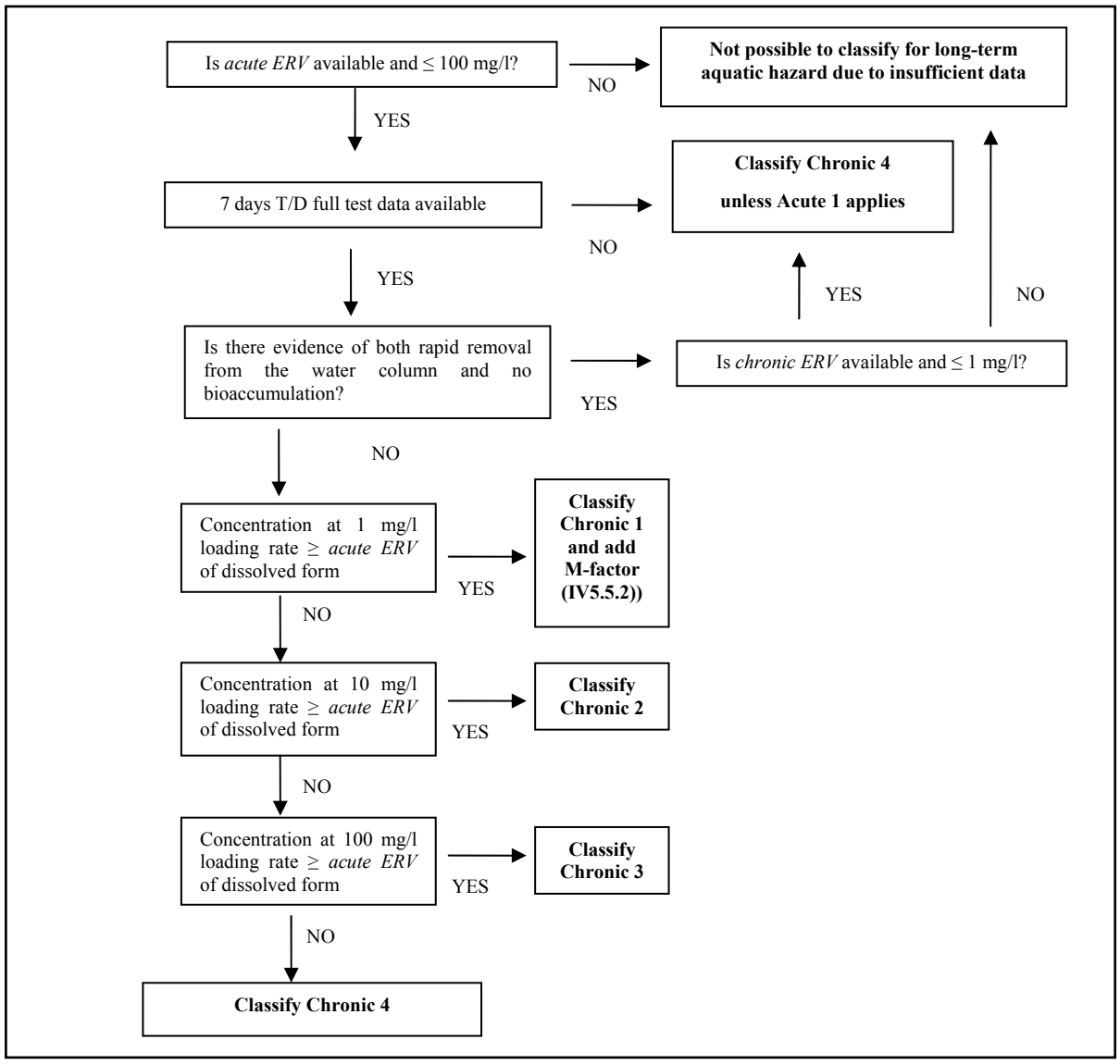


Figure IV.5.2.2b Classification strategy for determining long-term aquatic hazard for metals in absence of appropriate chronic toxicity reference and/or T/Dp data.



IV.5.3 Classification strategies for metal compounds

Notice! Acute and long-term hazard assessment is assessed individually for metal compounds.

A metal compound will be considered as ***readily soluble*** if:

- the water solubility (measured through a 24-hour Dissolution Screening test or estimated e.g. from the solubility product) is greater or equal to the acute ERV of the dissolved metal ion concentration; or
- If such data are unavailable, i.e. there are no clear data of sufficient validity to show that the transformation to metal ions will not occur;

Care should be exercised for metal compounds whose solubility is close to the acute toxicity reference value as the conditions under which solubility is measured could differ significantly from those of the acute toxicity test. In these cases the results of the Dissolution Screening Test are preferred.

Metal compounds that have lower water solubility than the acute ERV through a 24-hour Dissolution Screening test or estimated from the solubility product, are considered as ***poorly soluble metal compound.***

IV.5.3.1 Classification strategies for determining acute aquatic hazard for metal compounds

The scheme for the determination of *acute* aquatic hazard for metal compounds are described in this section and summarised diagrammatically in Figure IV.5.3.1.

Where the acute ERV for the metal ions of concern corrected for the molecular weight of the compound (further called as *acute* $ERV_{compound}$) is greater than 1 mg/l, the metal compounds need not to be considered further in the classification scheme for acute hazard.

Where the acute $ERV_{compound}$ is less than or equal to 1 mg/l, consideration must be given to the data available on the rate and extent to which these ions can be generated from the metal compound. Such data, to be valid and useable should have been generated using the T/D (Annex 10 to UN GHS).

Readily soluble metal compounds

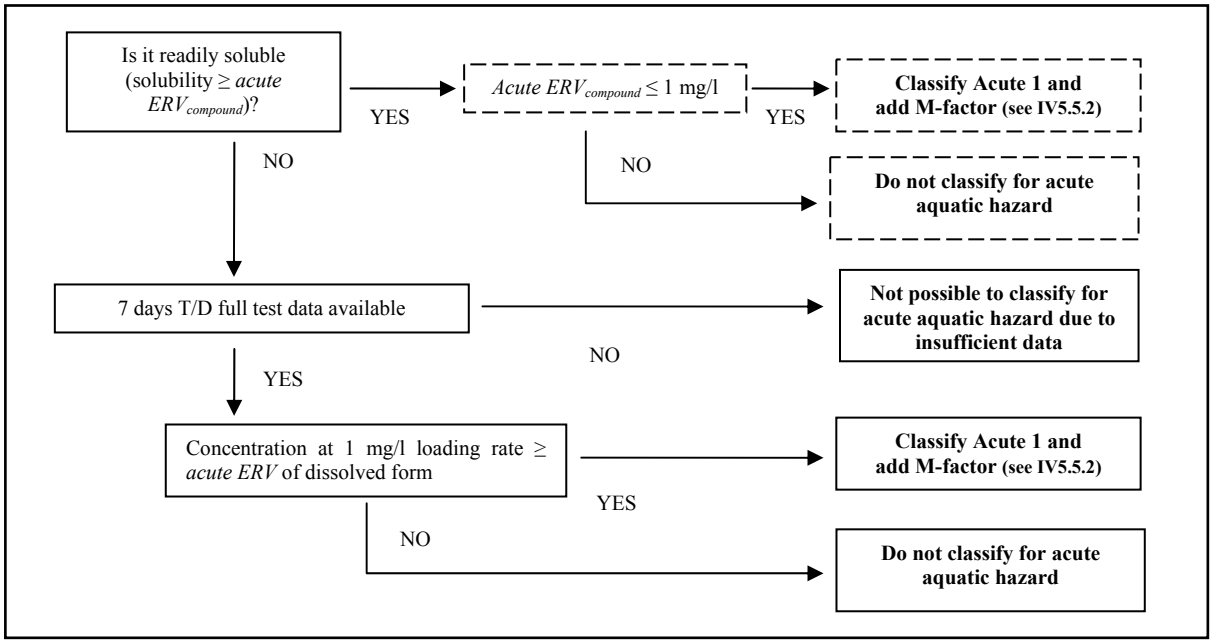
Classify the metal compound as ***Category Acute 1*** if the acute $ERV_{compound} \leq 1$ mg/l, an M-factor must also be established as part of this classification (see IV.5.5.2).

Poorly soluble metal compounds

Where 7d data from the Transformation/Dissolution protocol are available, then the results should be used to classify sparingly soluble metal compounds, according to the following rule:

> Classify the metal compound as *Category Acute 1* if the dissolved metal ion concentration after a period of 7 days (or earlier for a significant time period) at a loading rate of 1 mg/l exceeds that of the acute ERV, an M-factor must also be established as part of this classification(see IV.5.5.2).

Figure IV.5.3.1 Classification strategy for determining acute aquatic hazard for metal compounds.


Is it readily soluble (solubility ≥ *acute ERV*$_{compound}$)?
YES
Acute ERV$_{compound}$ ≤ 1 mg/l
YES
Classify Acute 1 and add M-factor (see IV5.5.2)
NO
NO
Do not classify for acute aquatic hazard
7 days T/D full test data available
NO
Not possible to classify for acute aquatic hazard due to insufficient data
YES
Concentration at 1 mg/l loading rate ≥ *acute ERV* of dissolved form
YES
Classify Acute 1 and add M-factor (see IV5.5.2)
NO
Do not classify for acute aquatic hazard

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2

IV.5.3.2 Classification strategy for determining long-term aquatic hazard for metal compounds

The scheme for the determination of *long-term* aquatic hazard for metal compounds are described in this section and summarised diagrammatically in Figures IV.5.3.2 (a and b).

Metal compounds can be classified for long-term aquatic hazards:

1) using chronic reference data when available; or
2) using the surrogate approach in absence of appropriate chronic toxicity reference data.

In case relevant chronic ecotoxicity data (chronic ERV) are available the approach comparing chronic ERV of the dissolved metal ion with release data of 28 days transformation/dissolution , should be applied as described under IV.5.3.2.1 while otherwise the surrogate approach (see IV.5.3.2.2) should be followed.

IV.5.3.2.1 Approach based on available chronic toxicity reference data

Where the chronic ERV for the metal ions of concern corrected for the molecular weight of the compound (further called as *chronic* $ERV_{compound}$) is greater than 1 mg/l, the metal compounds need not to be considered further in the classification scheme for long-term hazard.

Readily soluble metal compounds

Readily soluble metal compounds are classified on the basis of chronic ERV of the dissolved metal ion, corrected for the molecular weight of the compound (further called as chronic $ERV_{compound}$) .

If there is *no evidence* of rapid removal from the water column

a) Classify the metal compound as Category Chronic 1 if the chronic $ERV_{compound} \leq 0.1$ mg/l, an M-factor must also be established as part of this classification (see IV.5.5.2); or
b) Classify the metal compound as Category Chronic 2 if the chronic $ERV_{compound} >$ 0.1mg/l and ≤ 1 mg/l.

If there is *evidence* of rapid removal from the water column

c) **Classify** the metal compound as ***Category Chronic 1*** if the chronic ERVcompound $\leq$ 0.01 mg/l,an M-factor must also be established as part of this classification (see IV.5.5.2); or
d) **Classify** the metal compound as ***Category Chronic 2*** if the chronic $ERV_{compound} >$ 0.01mg/l and ≤ 0.1 mg/l; or
e) **Classify** the metal compound as ***Category Chronic 3*** if the chronic $ERV_{compound} >$ 0.1mg/l and ≤ 1 mg/l.

Poorly soluble metal compounds

Where *the chronic ERV* for the metal ions of concern is greater than 1 mg/l, the metals need not be considered further in the classification scheme.

Where the chronic $ERV_{compound}$ is less than or equal to 1 mg/l consideration must be given to the data available on the rate and extent to which these ions can be generated from the metal compound. Such rate and extend data, to be valid and useable should have been generated using the Transformation/Dissolution Protocol (Annex 10 to UN GHS) for a 28d period.

Where 28d T/Dp data are unavailable, the surrogate approach should be applied (see section 5.3.2.2).

Where 28d data from the Transformation/Dissolution protocol are available, then classify according to the following rules:

a) **Classify** the metal compound as ***Category Chronic 1*** if the dissolved metal ion concentration obtained from the 28 day transformation test at a loading rate of 0.1 mg/l is greater than or equal to the chronic ERV, an M-factor must also be established as part of this classification (see IV.5.5.2); or

b) **Classify** the metal compound as ***Category Chronic 2*** if the dissolved metal ion concentration obtained from the 28 day transformation test at a loading rate of 1 mg/l is greater than or equal to the chronic ERV.

If there is evidence of rapid removal from the water column:

c) **Classify** the metal compound as ***Category Chronic 1*** if the dissolved metal ion concentration obtained from the 28 day transformation test at a loading rate of 0.01 mg/l is greater than or equal to the chronic ERV, an M-factor must also be established as part of this classification (see IV.5.5.2); or

d) **Classify** the metal compound as ***Category Chronic 2*** if the dissolved metal ion concentration obtained from the 28 day transformation test at a loading rate of 0.1 mg/l is greater than or equal to the chronic ERV; or

e) **Classify** the metal compound as ***Category Chronic 3*** if the dissolved metal ion concentration obtained from the 28 day transformation test at a loading rate of 1 mg/l is greater than or equal to the chronic ERV.

Do not classify for long-term hazard if the dissolved metal ion concentration obtained from the 28 day Transformation/Dissolution test at a loading rate of 1 mg/l is less than the chronic ERV of the dissolved metal ion.

IV.5.3.2.2 The surrogate approach

Readily soluble metal compounds

In absence of relevant chronic toxicity data, and unless there is evidence of both rapid removal from the water column and evidence of no bioaccumulation (see sections IV.3 and IV.4), ***Readily soluble metal compounds*** are classified as:

a) **Category Chronic 1** if the acute ERVcompound ≤ 1 mg/l, an M-factor must also be established as part of this classification (see IV.5.5.2); or

b) **Category Chronic 2** if the acute ERVcompound > 1mg/l and ≤ 10 mg/l; or

c) **Category Chronic 3** if the acute ERVcompound > 10mg/l and ≤ 100 mg/l.

Poorly soluble metal compounds

Where the acute $ERV_{compound}$ is less than or equal to 100 mg/l consideration must be given to the data available on the rate and extent to which these ions can be generated from the metal. Such rate and extend data, to be valid and useable should have been generated using the Transformation/Dissolution Protocol (Annex 10 to UN GHS) for a 7d period.

Where such 7d T/Dp data are unavailable, i.e. there is no clear data of sufficient validity to show that the transformation to metal ions will not occur; the safety net classification (Category Chronic 4) has to be applied.

Where T/Dp data are available but relevant chronic ERVs are absent, the results should be used to aid classification according to the following rules:

a) **Classify** the metal compound as ***Category Chronic 1*** if the dissolved metal ion concentration obtained from the 7 day transformation test at the low loading rate (1 mg/l) is greater than or equal to the acute ERV and there is no evidence of rapid removal from the water column and no bioaccumulation, an M-factor must also be established as part of this classification(see IV.5.5.2);

b) **Classify** the metal compound as ***Category Chronic 2*** if the dissolved metal ion concentration obtained from the 7 day transformation test at the medium loading rate (10 mg/l) is greater than or equal to the acute ERV and there is no evidence of rapid removal from the water column and no bioaccumulation;

c) **Classify** the metal compound as ***Category Chronic 3*** if the dissolved metal ion concentration obtained from the 7 day transformation test at the high loading rate (100 mg/l) is greater than or equal to the acute ERV and there is no evidence of rapid removal from the water column and no bioaccumulation;

d) **Classify** the metal compound as ***Category Chronic 4*** if the dissolved metal ion concentration obtained from the 7 day transformation test at the high loading rate (100 mg/l) is lower than the acute ERV and there is no evidence of rapid removal from the water column and no bioaccumulation.

Figure IV.5.3.2a Classification strategy for determining long-term aquatic hazard for metal compounds.

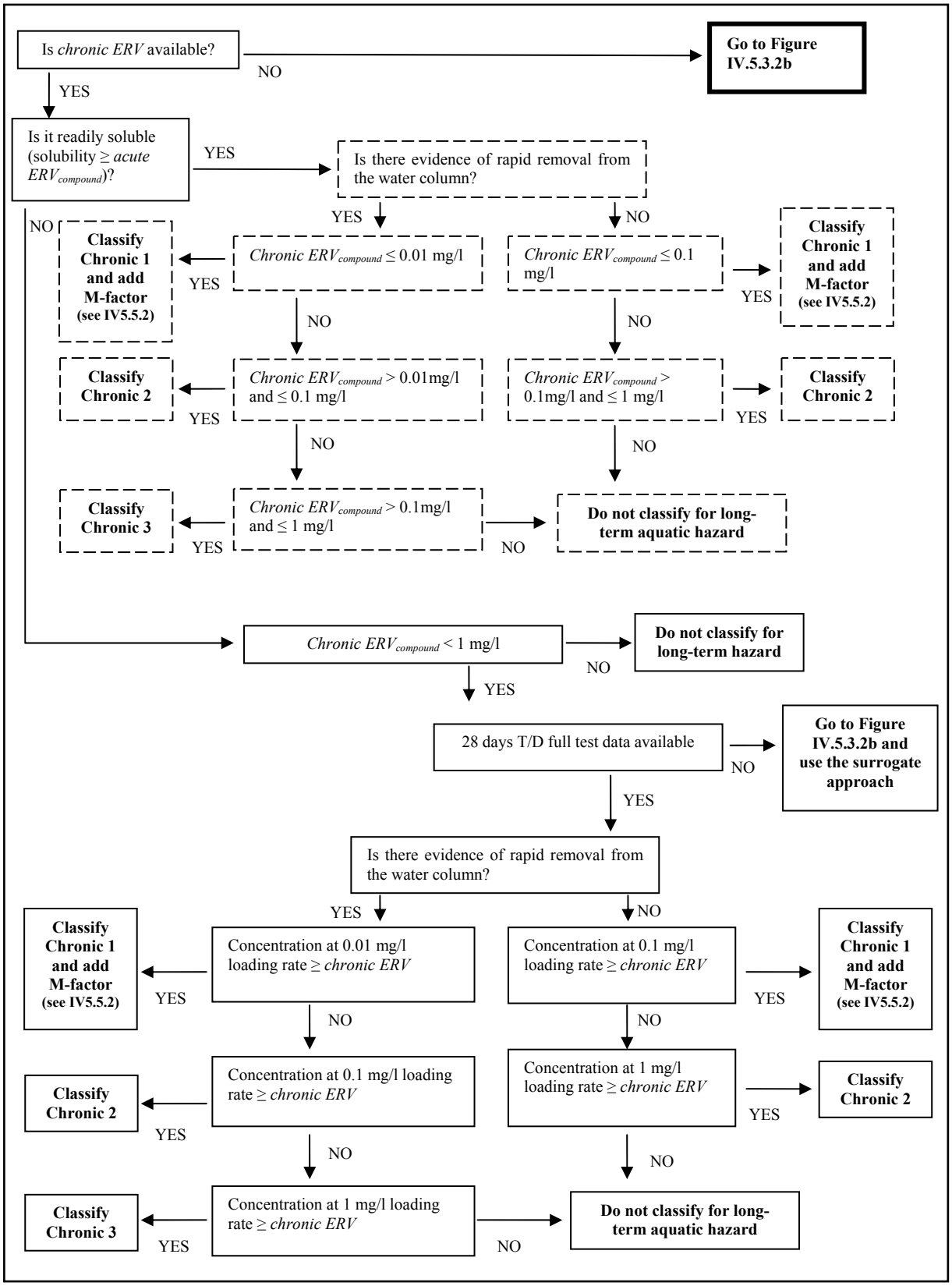
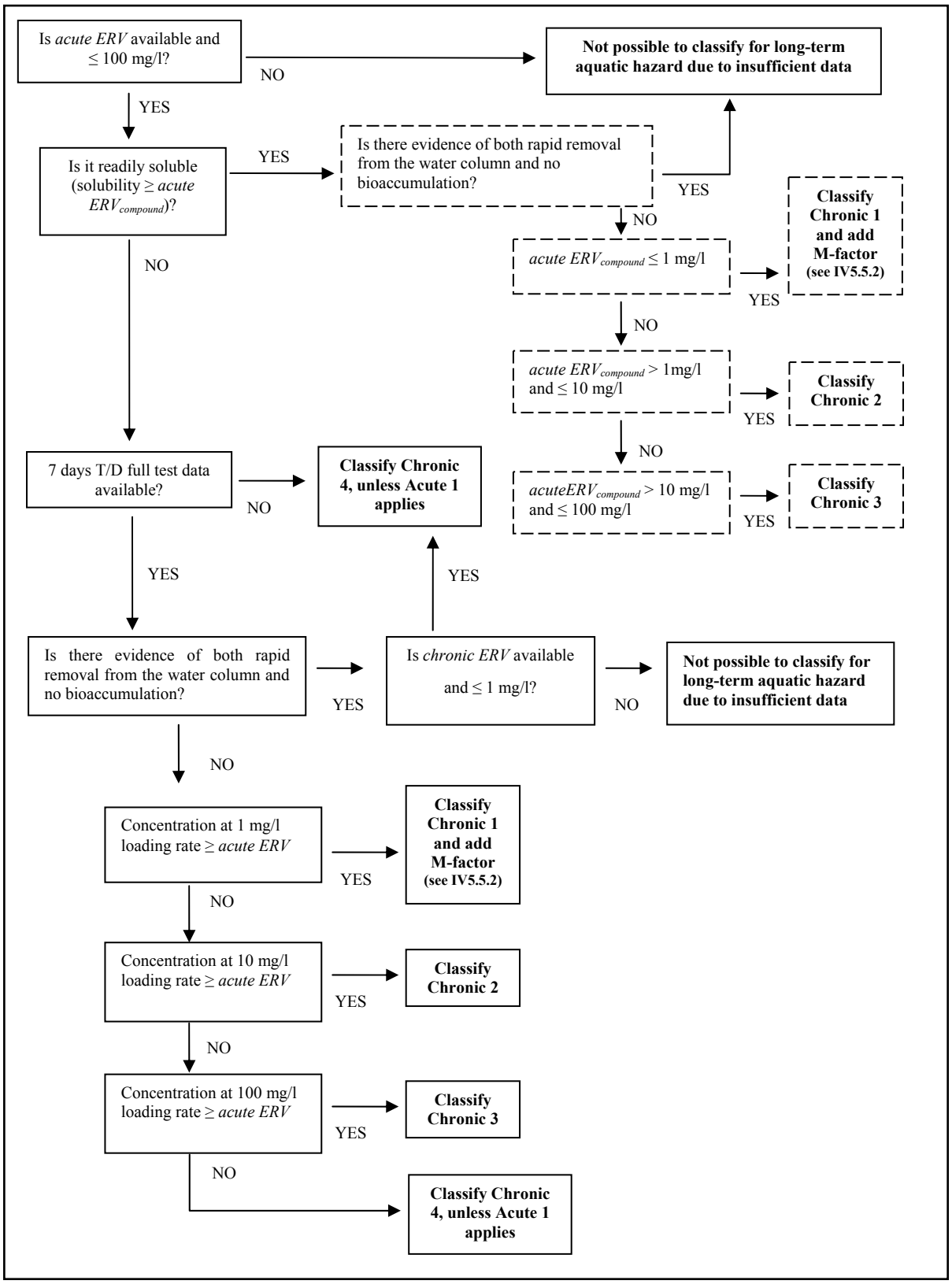


Figure IV.5.3.2b Classification strategy for determining long-term aquatic hazard for metal compounds in absence of appropriate chronic toxicity reference and/or T/Dp data.



IV.5.4 Particle size and surface area

Surface area is a crucial parameter in that any variation in surface area tested may cause a significant change in the levels of metals ions released in a given time-window. Thus, particle size or surface area is fixed for the purposes of the transformation test, allowing the comparative classifications to be based solely on the loading level. Normally, the classification data generated would have used the smallest particle size marketed to determine the extent of transformation. There may be cases where data generated for a particular metal powder are not considered as suitable for classification of the massive forms. For example, where it can be shown that the tested powder is structurally a different material (e.g. different crystallographic structure) and/or it has been produced by a special process and is not generally generated from the massive metal, classification of the massive can be based on testing of a more representative particle size or surface area, if such data are available. The powder may be classified separately based on the data generated on the powder. However, in normal circumstances it is not anticipated that more than two classification proposals would be made for the same metal.

Metals with a particle size smaller than the default diameter value of 1 mm can be tested on a case-by-case basis. One example of this is where metal powders are produced by a different production technique or where the powders give rise to a higher dissolution (or reaction) rate than the massive form leading to a more stringent classification.

The particle sizes tested and/or used for classification and labelling depend on the substance being assessed and are shown in the table below:

Type	Particle size	Comments
Metal compounds	Smallest representative size sold	Never larger than 1 mm
Metals – powders	Smallest representative size sold	May need to consider different sources if yielding different crystallographic/ morphologic properties
Metals – massive	1 mm	Default value may be altered if sufficient justification

Massives will usually be tested as 1 mm particles. Alternatively, the T/D testing of materials with different surface area's may result in highly reliable dissolution kinetic equations that allows to define the "Critical Particle Diameter" (CPD) for appropriate loadings for the acute and long-term hazard assessment .

For most metals and some metal compounds, it is possible, using the Transformation/Dissolution Protocol (Annex 10 to UN GHS), to obtain a correlation between the concentration of the metal ion after a specified time interval as a function of the surface area loadings of the forms tested. Such correlations should be established for the relevant pH ranges as specified in the protocol. In such cases, it could then be possible to estimate the level of dissolved metal ion concentration at a given pH of the metal with different particles, using the critical surface area approach [Skeaff *et. al.* (2000)]. From this correlation and a linkage to the appropriate toxicity data at corresponding pH level, it is possible to determine a "Critical Surface Area" (CSA) of the substance that delivers the $L(E)C_{50}$ to the dissolution medium and then to convert the CSA to a Critical Particle Diameter (CPD) (see example). This CPD at appropriate mass loadings for acute and long-term hazard assessment can then be used to:

- determine the classification category of powders based on the finest representative powder on the market and
- determine an accurate classification of the massive metal by applying a 1 mm (default) diameter

Within the CSA Approach an equation is developed to predict metal ion release (based on previously measured metal ion release from different loadings of the metal), which is correlated to measured surface area, and a corresponding calculated equivalent particle diameter. The basis of the CSA Approach is that ***the release of metal ions is dependent on the surface area of the substance***, with this release being predictable once the relationship has been established. The CSA is the surface area loading (mm^2/l) to a medium that delivers a selected ecotoxicity reference value to that medium. The term *SA* is the measured specific surface area (m^2/g) of the metal sample. The measured specific critical surface area (SA_{crit}) (m^2/g) is the measured specific surface areas for the corresponding low, medium and high loadings which are associated with the respective acute and long-term aquatic toxicity classification categoriess in the classification scheme for metals and metal compounds. A typical equation for this relationship for a given substance, aquatic medium, pH and retention time is:

$$\log (C_{Me(aq)}, mg/l) = a + b \log(A_{meas})$$

$C_{Me(aq)}$ = total dissolved concentration of metal ion (mg/l) at a particular length of test time (*i.e.* 168 hours for acute toxicity transformation testing) under certain conditions (*i.e.* pH, specified medium, etc.), as determined by transformation/dissolution testing of different surface area loadings

a, *b* = regression coefficients

A_{meas} = initial surface area loading (mm^2/l) [equals (measured specific surface area, *SA*, in m^2/g) X (substance mass loading in g/l) X 10^6], where *SA* was measured with the BET nitrogen adsorption-desorption technique.

IV.5.5 Classification of mixtures of metals and metal compounds

Simple composed metal or metal compound mixtures should be handled as mixtures and classified according to the mixtures rules described in Section 4.1.4 given they normally express toxicity as a function of their composing ingredients. Ores and concentrates and UVCB inorganics are considered as substances in respect to CLP, but follow in general the mixture ruling. to determine their classification unless specific ecotoxicity data are available for the mineral(s) under consideration.

Ores and concentrates and inorganic UVCBs are considered substances under CLP. In the absence of substance specific ecotoxicity data, their classification can be assessed by applying the mixtures rule. The metals industry has developed classification tools that allow for the hazard ID and environmental classification of these complex materials, by integrating all aspects of this guidance with a knowledge of their mineralogical and other typical metal properties.

Metal alloys are defined by the CLP as “special preparations” because their (eco)toxicity profile differs from that of their constituents. Further information on how to assess the environmental hazard classification of alloys and other complex metal containing materials is provided hereunder.

IV.5.5.1 Classification of alloys and complex metal containing materials

Metal alloys, or alloy manufacturing products are not simple mixtures of metals or metal compounds, since the alloy has clearly distinctive properties compared to a classical mixture of its metal components. Justified by their intrinsic properties, the solubility properties can differ substantially from what is observed for each individual constituent in that alloy (eg the rate and extend of metals release from pure metals are different from the ones from alloys). The rate and extend to which the ingredient of the alloy react with the media to transform to water soluble forms can be measured in the same way as with metals (by using the OECD Transformation/Dissolution test (Annex 10 to UN GHS)). However, alloys often react slowly and to a very limited extent, making the application of the T/D protocol more complex. Special care should be taken in this respect to the detection limit and the accurate determination of the measured surface. Initial testing of alloys, using the T/D protocol, shows that this can be useful but **further additional guidance on this aspect is recommended**.

More complex metals or metal compounds containing inorganic substances like e.g. ores and concentrates are not simple mixtures of metals or metal compounds. Justified by their intrinsic properties, the solubility properties can differ substantially from what is observed for each individual constituent of that complex substance (e.g. the rate and extent of metals release from e.g. ores/concentrates are different from the ones from simple metals). All these materials are typically not readily soluble in any aqueous medium. In addition, these materials are often heterogeneous in size and composition on a microscopic/macroscopic scale. Therefore, adequate amounts of the material could be used to evaluate the extent to which the substances can be dissolved, i.e. its water solubility and/or the extent to which the metals can react with the media to transform to water soluble forms e.g. through Transformation/Dissolution tests. Additional guidance on this aspect is needed for complex metal mixtures.

An **ecotoxicity validation step** may be important for alloys and complex metal containing materials (e.g. ores, concentrates, slags), where binding of the metal to abiotic and biological binding sites will in many cases be competitive. Therefore the “additivity mode” is not necessarily valid and additional information may be relevant.

Therefore, information from ecotoxicity validation steps could be useful in cases where a significant uncertainty is associated with the existing toxicity data. This ecotoxicity validation should have been derived from tests using most sensitive species at dissolved ion concentrations equivalent to those measured in the T/D medium. However, information from ecotoxicity testing directly in the T/D medium is not recommended because the composition of this medium is unlikely to meet the requirements for standard test media to ensure proper survival and/or reproduction. Therefore, ecotoxicity tests should have been conducted in standard media dosed at metal concentration equivalent to the concentration level actually measured in the T/D medium.

IV.5.5.2 M-factor application for metal mixtures and alloys

For appropriate classification of metal mixtures, Ecotoxicity Reference Values (ERVs) for the metal ion(s) or metal compounds contained in the mixture are used to derive cut-off values for mixtures. If these ERVs is/are below the lowest dose level (e.g. 1mg/L for acute toxicity or 0,1 mg/L or 0,01 mg/l for respectively Chronic toxicity without and with

demonstration of removal), an appropriate acute or Chronic M-factor is needed. This M-factor derived for the metal or metal compound is then used to ensure the mixture containing the metal compound is appropriately classified.

For *soluble metal compounds* M-factors are applied as for organic substances (see table IV.5.5.2).

For poorly soluble metal compounds and metals M-factors can be estimated from the ratio of the soluble metal ions concentrations obtained from Transformation Dissolution (at respectively 7 d or 28 d's for a loading of 1 mg/l) and the ERV of the dissolved metal ion taking the considerations mentioned in I.V.2.3 into account. If this ratio is:

- below 10 then an M-factor of 1 should be applied
- $\geq$ 10 and < 100 then the M-factor would be 10,
- $\geq$ 100 and < 1000 then the M-factor would be 100,

Continue in factor 10 intervals

Table IV.5.5.2: M-factors for inorganic substances.

Acute ERV (mg/L)	**Multiplying factors (M)**
0,1 < Acute ERV < 1	1
0,01 < Acute ERV < 0,1	10
0,001 < Acute ERV < 0,01	100
0,0001 < Acute ERV < 0,001	1000
Continue in factor 10 intervals	10000

Chronic ERV (mg/L)	**Multiplying factors (M)**	
	No rapid removal	Rapid removal
0,01 < Chronic ERV < 0,1	1	1
0,001 < Chronic ERV < 0,01	10	1
0,0001 < Chronic ERV < 0,001	100	10
0,00001 < Chronic ERV < 0,0001	1000	100
Continue in factor 10 intervals		

IV.6 References

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IV.7 Decision on classification: examples for metals and metal compounds

List of examples:

- Example A: Soluble metal compound with acute and chronic toxicity data and evidence of rapid removal from the water column (Me_2 $(SO4)_2$).
- Example B: Poorly soluble metal compound with acute and chronic toxicity data, Transformation Dissolution data at 7 days (low loading rate) and 28 days (low, medium and high loading rates) and evidence of rapid removal from the water column.
- Example C: Poorly soluble metal compound with acute and chronic toxicity data equal to example B, Transformation/Dissolution data at 7 days (low loading rate) and at 28 days (only low and medium loading rates) and no evidence of Rapid removal from the water column.

- Example D: Metal in powder and massive form with acute and chronic toxicity data and Transformation/Dissolution data at 7 days (low, medium and high loading rates) and at 28 days (only the high loading rate) and evidence of rapid removal from the water column.
    - *Explanatory note to Example D* - Critical Surface Area (CSA) Approach.
- Example E: Hazard classification of a soluble metal salt: the case of removal through speciation in the water column.

Example A: Soluble metal compound with acute and chronic toxicity data and evidence of rapid removal from the water column ($Me_2 (SO4)_2$).

DATA ELEMENTS	Value	Test method ((EC) No. 440/2008) or OECD guideline / remarks
Transformation dissolution protocol evidence		
Screening test (24 h) at 100 mg/l loading	pH 6 : 6240 µg/l pH 8 : 840 µg/l	Metals TDp, non-GLP
7 d TDp test	Not applicable	
28 d TDp test	Not applicable	
MWT of the metal ion versus compound	60 / 312	
Acute aquatic toxicity of metal ion[64]		
Fish: *Oncorhynchus mykiss*:	120 µg/l (96 h LC_{50}) at pH 7,8 106 µg/l (96 h LC_{50}) at pH 7,8 104 µg/l (96 h LC_{50}) at pH 7,8 78 µg/l (96 h LC_{50}) at pH7,8 *(species mean: 102 µg/l at pH 7,8)*	C.1. / static, GLP C.1. / static, non-GLP C.1. / static, GLP C.1. / static, non-GLP
Crustacea *Daphnia magna*:	180 µg/l (48 h EC_{50}) at pH 8	C.2. / static, non-GLP
Algae/aquatic plants *Scenedesmus subspicatus*: *Lemna gibba*:	154 µg/l (72 h ErC_{50}) at pH 8 670 µg/l (7 d ErC_{50}) at pH 8	C.3. / static, GLP C.26. / semi-static, GLP
Chronic aquatic toxicity[65]		
Fish: *Danio rerio*: Marine Fish	24 µg/l (28 d NOEC) at pH 6 87 µg/l (28 d NOEC) at pH 8 1414 µg/l (28 d EC10)	OECD 210 / 28 d flow-through, non-GLP OECD 210 /28 d flow through, GLP) OECD 210 /28 d flow through, GLP)
Crustacea: *Daphnia magna*: Marine decapoda	37 µg/l (21 d EC_{10}) at pH 7.8 8.6 µg/l (21 d NOEC) at pH 6.4 1612 µg/l (21 d NOEC)	C.20. / semi-static, GLP C.20./semi-static non-GLP Non standard test

[64] Tests performed with readily soluble salts such as metal sulphates and metal chlorides.
[65] Tests performed with readily soluble salts such as metal sulphates and metal chlorides.

Algae/aquatic plants: *Scenedesmus subspicatus*:	21.6 µg/l (72 h NOEC) at pH 8 8.7 µg/l (72 h NOEC) at pH 6.2	C.3. / static, GLP C.3. / static, non-GLP
Degradation (evidence of rapid degradation)		
Rapid removal	The speciation of the metal compound in water to form insoluble and non classifiable[66] forms for aquatic hazard, is low (12% within 28 days).	Based on literature data and empirical reaction kinetics
Bioaccumulation		
Bioconcentration factor in fish	+/- 200 at NOEC level	

Aquatic hazard assessment, conclusions and comments:

Transformation Dissolution :

- The substance passes the 24 h screening TDp test at pH 6 given the dissolution at a loading of 100 mg/l is 6240 µg/l > acute ERV of the soluble ion being 102 µg/l at pH 7.8.

Acute aquatic toxicity:

- The acute ecotoxicity reference value is driven by the Fish data. No data are available for the low pH end.
- The acute ERV for the metal compound is 102 * (312/(2*60)) = **265 µg/l**.

Degradation (evidence of rapid removal from the water column):

Since the speciation of the metal compound in water to form insoluble and non classifiable forms[67] (for aquatic hazard is low (12% removal of the soluble species within 28 days corresponding), this cannot be considered as rapid removal from the water column. The substance can consequently **not** be considered for classification purposes as rapidly degradable.

Chronic aquatic toxicity:

- The chronic aquatic ecotoxicity reference toxicity value based on the lowest of the available toxicity values is slightly below 10 µg/l for Daphnia magna at pH 6,4 for the metal ion.
- The chronic ERV for the metal compound is 8.6 * (312/(2*60)) = **22.4 µg/l**.

Aquatic hazard classification and, where applicable, established M-factor(s):

- Acute (short-term) aquatic hazard: category Acute 1, M-factor: 1

[66] To speciate to non-bioavailable and non-classifiable form(s) for aquatic hazard as to fulfil the requirements for rapid removal means that the potential for the reverse change to occur has been considered, and assessed as negligible.

[67] To speciate to non-bioavailable and non-classifiable form(s) for aquatic hazard as to fulfil the requirements for rapid removal means that the potential for the reverse change to occur has been considered, and assessed as negligible.

- Long-term aquatic hazard: category Chronic 1, M-factor: 1

Reasoning:

Acute aquatic hazard

- The acute ecotoxicity reference value is driven by the Fish data. A species mean of 102 µg/l for the metal ion, is calculated for *Oncorhynchus mykiss* given 4 or more toxicity data for the same species under comparable conditions are available.
- Acute aquatic hazard expressed as the ERV for the metal compound after molecular weight correction ≤ 1 mg/l. M-factor is 1 given the acute ERV is between 1 and 0.1 mg/l.
- The molecular weight correction recognises that 2 metal ions are included.
- The substance passes the 24 h screening dissolution test by comparing acute toxicity data at pH 7.8 with TDp data at pH6 given an acute toxicity data set at pH 6 is lacking and the chronic data indicate more toxic behaviour of the metal at the lower pH end.

Long-term aquatic hazard:

- Adequate information on chronic toxicity (all 3 trophic levels) is available allowing long-term hazard classification (no use of the surrogate approach). [68]
- Marine toxicity data are not included in the chronic ERV assessment given far less sensitive as fresh water toxicity references and data for 3 trophic levels for the freshwater are available
- The Daphnia magna reference at pH6 is the lowest and determines the chronic ERV.
- A molecular weight correction is applied to the substance recognising that 2 metal ions are included.
- Rapid removal cannot be demonstrated given the lack of sufficient speciation to the non-bioavailable form in 28 d.
- The M-factor of 1 is based on the chronic ERV of 22 µg/l (so between 0.01 and 0.1 mg/l.) without rapid removal.

Labelling elements based on the classification:

[68] In absence of adequate chronic toxicity data for all trophic levels, the subsequent step is to combine two types of information, i.e. chronic info for the trophic level with such data and acute aquatic toxicity data and environmental fate information for lacking info on trophic levels. For details see section 4.1.3.3 and Table 4.1.0.

Element	Code
GHS Pictogram	GHS09
Signal Word	WARNING
Hazard Statement	H400, H410 → H410[69]
Precautionary statement(s)	P273, P391, P501

1

[69] In accordance with CLP Article 27, the hazard statement H400 may be considered redundant on the label and therefore not included on the label because hazard statement H410 also applies, see section 4.1.6 of this document.

Example B: Poorly soluble metal compound with acute and chronic toxicity data, Transformation Dissolution data at 7 days (low loading rate) and 28 days (low, medium and high loading rates) and evidence of rapid removal from the water column.

DATA ELEMENTS		Value	Test method ((EC) No. 440/2008) or OECD guideline / remarks
Transformation dissolution protocol evidence			
Screening test (24 h) at 100 mg/l loading		pH 6 : 74 µg/l pH 8 : 34 µg/l	Metals TDp, non-GLP
7 d TDp test	at 1 mg/l loading	pH 6 : 50 µg/l pH 8 : 16 µg/l	Metals TDp, non-GLP Metals TDp, non-GLP
28 d TDp test	at 1 mg/l loading at 0,1 mg/l loading at 0,01 mg/l loading	pH 6: 182 µg/l pH 8: 71 µg/l pH 6: 18 µg/l pH 8: 7 µg/l pH 6: 2 µg/l pH 8: < 1 (DL)	Metals TDp, non-GLP Metals TDp, non-GLP Metals TDp, non-GLP Metals TDp, non-GLP
MWT of the metal ion versus compound		**60 / 91**	
Acute aquatic toxicity of metal ion[70]			
Fish:	*Oncorhynchus mykiss*:	186µg/l (48 h LC_{50}) at pH 7 120 µg/l (96 h LC_{50}) at pH 7.8 106 µg/l (96 h LC_{50}) at pH 7.8 104 µg/l (96 h LC_{50}) at pH 7.8 78 µg/l (96 h LC_{50}) at pH 7.8 *(species mean for 4values : 102 µg/l at pH 7.8)* *78 µg/l* (96 h LC_{50}) at pH 6.4	C.1. / static, non-GLP C.1. / static, GLP C.1. / static, non-GLP C.1. / static, GLP C.1. / static, non-GLP
Crustacea	*Daphnia magna*:	180 µg/l (48 h EC_{50}) at pH 8	C.2. / static, non-GLP

[70] Tests performed with readily soluble salts such as metal sulphates and metal chlorides.

	106 µg/l (48 h EC_{50}) at pH 8	
Algae/aquatic plants *Scenedesmus subspicatus*:	154 µg/l (72 h ErC_{50}) at pH 8	C.3. / static, GLP
	78 µg/l (72 h ErC_{50}) at pH 6	
Lemna gibba:	670 µg/l (7 d ErC_{50}) at pH 8	C.26. / semi-static, GLP
Chronic aquatic toxicity[71]		
Fish: *Danio rerio*:	24 µg/l (28 d NOEC) at pH 6	OECD 210 / 28 d flow-through, non-GLP
	87 µg/l (28 d NOEC) at pH 8	OECD 210 /28 d flow through, GLP)
Crustacea: *Daphnia magna*	37 µg/l (21 d EC_{10}) at pH 7.8	C.20. / semi-static, GLP
	8.6 µgl (21 d NOEC) at pH 6.4	C.20. / semi-static, non-GLP
Algae/aquatic plants: *Scenedesmus subspicatus*:	21.6 µg/l (96 h NOEC) at pH 8	C.3. / static, GLP
	8.7 µg/l (72 h EC_{10}) at pH 6.2	C.3. / static, non-GLP
Degradation (evidence of rapid degradation)		
Rapid removal	The speciation of the metal compound in water to form insoluble and non classifiable[72] forms for aquatic hazard is high (>90% removal of the soluble species within 28 days)	Based on literature data and empirical reaction kinetics.
Bioaccumulation		
Bioconcentration factor in fish	+/- 200 at NOEC level	

[71] Tests performed with readily soluble salts such as metal sulphates and metal chlorides.
[72] To speciate to non-bioavailable and non-classifiable form(s) for aquatic hazard as to fulfil the requirements for rapid removal means that the potential for the reverse change to occur has been considered, and assessed as negligible.

Aquatic hazard assessment, conclusions and comments:

Transformation/Dissolution screening outcome:

- The substance fail the 24 h screening Transformation Dissolution test given the dissolution at a loading of 100 mg/l :
  - at pH 6 is 74 µg/l < acute ERV of the soluble ion being 78 µg/l (borderline case)
  - at pH 8 is 34 µg/l < acute ERV of the soluble ion being 102 µg/l

Acute aquatic toxicity: for more details see example A

- Adequate data on pH 6 and 8 are available allowing to derive an acute ERV for the (soluble) metal ion :
  - at the lower pH end (around pH 6) : ***78 µg/l***
  - at the higher pH end (around pH 8) : ***102 µg/l***

7 days Transformation/Dissolution outcome :

- The acute release after 7 d is the highest at pH 6 (50 µg/l) being lower than the acute toxicity level (78 µg/l) at this corresponding pH
- The acute release is lower at or around pH 8 (16 µg/l), which is significantly lower than the acute toxicity level (102 µg/l) at this corresponding pH

Degradation/Transformation (evidence of rapid removal from the water column):

- More than 90 % removal from the water column through speciation to an insoluble and non classifiable form for aquatic hazard[73] (so non bioavailable) is demonstrated, thereby fulfilling the conditions for rapid removal from the water column.

Chronic aquatic toxicity for a substance rapidly removing from the water column

- The chronic ERV for the (soluble) metal ion is ***8.6 µg/l*** around pH 6 and ***21.6 µg/l*** around pH 8

28 days transformation/dissolution outcome for a substance rapidly removing from the water column:

- The release after 28 d at a loading of 0.01 mg/l is the highest at ***pH 6*** (2 µg/l) being lower than the acute toxicity level 8.6 µg/l at this corresponding pH. The measured release rate at 0.1 mg/l loading (18 µg/l) which is already twice as high as the chronic ERV of the soluble metal ion and the release rate at 1 mg/l loading (182 µg/l) almost 9 times as high.
- The release after 28 d at a loading of 0.01 mg/l is lower at ***pH 8*** being <1 µg/l, which is significantly lower than the chronic toxicity level of the soluble metal ion (21.6 µg/l) at this pH level. The measured release rates at 0,1 mg/l loading and at 1 mg/l respectively are 7 and 71 µg/l which would be respectively smaller and larger than the chronic ERC at pH 8 (21.6 µg/l)

Aquatic hazard classification and, where applicable, established M-factor(s):

Acute (short-term) aquatic hazard: no acute hazard classification

Long-term aquatic hazard: category Chronic 2

Reasoning:

The metal compound can be considered as poorly soluble since failing the OECD transformation dissolution screening test at a 100 mg/l loading. The screening test further confirmed pH 6 as the pH of the highest release rate.

Acute aquatic hazard

- The acute ecotoxicity reference value is driven by the Fish data for the high pH and by algae data for the low pH level. For the high pH end (around pH 8) a species mean of 102 µg/l for the metal ion is calculated for *Oncorhynchus mykiss* and a single reference of 78 µg/l for *Scenedesmus subspicatus* at around pH 6.
- A poorly soluble substance is evaluated for classification by comparing the dissolved metal ion level resulting from the TDp at 7d, at a loading rate of 1 mg/l with the acute ERV as determined for the (soluble) metal ion. A molecular weight correction for the poorly metal compound is consequently not required given this factor has already been included for the loading rate of the TDp test.

[73] To speciate to non-bioavailable and non-classifiable form(s) for aquatic hazard as to fulfil the requirements for rapid removal means that the potential for the reverse change to occur has been considered, and assessed as negligible.

- The dissolution level of the poorly soluble metal compound from the 7d TDp at 1 mg loading is lower than the acute ERVs of the soluble metal ion for both pH levels, thereby not resulting in an acute classification.

Long-term aquatic hazard:

- Adequate information on chronic toxicity (all 3 trophic levels) for the higher and lower pH levels are available allowing direct long-term hazard classification (no use of the surrogate approach).
- The speciation of the metal compound in water to form insoluble and non classifiable[74] forms for aquatic hazard is high (>90% removal of the soluble species within 28 days).
- As indicated for the acute assessment level no Molecular Weight Correction is applied to the poorly soluble metal compound given the classification scheme is based on the comparison of the dissolved fraction of the poorly metal compound with the chronic ERV of the soluble metal ion at both pH 6 and pH8.
- The dissolution level from the 28 d TDp at 0.01mg/l for the poorly soluble metal compound (2 µg/l at pH 6 and < 1 µg/l at pH 8) is lower than the chronic ERVs of the soluble metal ion for both pH levels (8.6 µg/l at pH 6 and 21.6 µg/l at pH 8) thereby not warranting a chronic 1 classification. The measured dissolved concentration at the 0.1 mg/l loading rate at pH 6 (18 µg/l) is > than the chronic ERV at pH 6 (8.6 µg/l) warranting a chronic 2 classification. The classification is somewhat less at pH 8 given a less sensitive toxicity response and a lower dissolution rate.
- No M-factor is required given a classification as Chronic 2.

Labelling elements based on the classification:

Element	Code
GHS Pictogram	GHS09
Signal Word	none
Hazard Statement	H411
Precautionary statement(s)	P273, P391, P501

[74] To speciate to non-bioavailable and non-classifiable form(s) for aquatic hazard as to fulfil the requirements for rapid removal means that the potential for the reverse change to has been considered, and assessed as negligible.

Example C: Poorly soluble metal compound with acute and chronic toxicity data equal to example B, transformation/dissolution data at 7 days (low loading rate) and at 28 days (only low and medium loading rates) and no evidence of rapid removal from the water column

DATA ELEMENTS	Value	Test method ((EC) No. 440/2008) or OECD guideline / remarks
Transformation dissolution protocol evidence	**See example B**	
Screening test (24 h) at 100 mg/l loading	pH 6: 74 µg/l pH 8: 34 µg/l	Metals TDp, non-GLP
7 d TDp test at 1 mg/l loading	pH 6: 50 µg/l pH 8: 16 µg/l	Metals TDp, non-GLP Metals TDp, non-GLP
28 d TDp test at 0.1 mg/l loading at 0.01 mg/l loading	pH 6: no data available pH 8: no data available pH 6: 9 µg/l pH 8: <1 (DL)	Metals TDp, non-GLP Metals TDp, non-GLP Metals TDp, non-GLP Metals TDp, non-GLP
MWT of the metal ion versus compound	60 / 91	
Acute aquatic toxicity of metal ion[75]	See example B	
Chronic aquatic toxicity[76]	See example B	
Degradation (evidence of rapid degradation)		
Rapid removal	No data available therefore considered as not rapidly removing from the water column	
Bioaccumulation		
Bioconcentration factor in fish	+/- 200 at NOEC level	

[75] Tests performed with readily soluble salts such as metal sulphates and metal chlorides.
[76] Tests performed with readily soluble salts such as metal sulphates and metal chlorides.

Aquatic hazard assessment, conclusions and comments:

Transformation Dissolution screening outcome: see example B

- The substance fail the 24 h screening Transformation Dissolution test at both pH levels

Acute aquatic toxicity: see example B

7 days Transformation/Dissolution outcome : see example B

Degradation/Transformation (evidence of rapid removal from the water column):

- No information, so substance considered as failing the Rapid Removal criterion.

Chronic aquatic toxicity for a substance not rapidly removing from the water column :

- The chronic ERV for the (soluble) metal ion is ***8.6 µg/l*** around pH 6 and ***21.6 µg/l*** around pH 8 (see example B)

28 days Transformation dissolution outcome for a substance not rapidly removing from the water column:

- The release after 28 d at pH 6 at a loading of 0.1 mg/l isn't available and needs to be extrapolated from the 0.01 loading rate assuming a 10 times higher dissolution level (10x9=90 µg/l), which is significantly larger than the chronic ERV at pH 6 (8.6 µg/l).
- The release for the 0.1 mg/l loading is also extrapolated in the same way and is much lower at pH 8. The calculated release rate of < 10 µg/l is still lower than the chronic toxicity level 21.6 µg/l at this pH level. The calculated release rates at 1 mg/l loading would be < 100 µg/l which is significantly larger than the chronic ERV at pH 8.

Aquatic hazard classification and, where applicable, established M-factor(s):

Acute (short-term) aquatic hazard: no acute classification

Long-term aquatic hazard: category Chronic 1, M-factor 10

Reasoning:

The metal compound is considered as poorly soluble since it fails the OECD transformation dissolution screening test at a 100 mg/l loading. The test confirmed pH 6 as the pH of the highest release rate.

Acute aquatic hazards: see example B

Long-term aquatic hazard:

- Adequate information on chronic toxicity (all 3 trophic levels) for the higher and lower pH levels are available allowing direct long-term hazard classification (no use of the surrogate approach).
- No valid info is available on the removal rate so the poorly soluble metal compound is considered to be not rapidly removing from the water column.
- No Molecular Weight Correction is applied for the poorly soluble metal compound given the classification scheme is based on the comparison of the dissolved fraction of the poorly metal compound with the chronic ERV of the soluble metal ion at both pH 6 and pH 8.
- No TDp data are available for the 0.1 mg/l and 1 mg/l loading. The calculated dissolution level from the 28d TDp at pH 6 at 0.1mg/l loading (+/- 90 µg/l) for the poorly soluble metal compound is much higher than the chronic ERV's of the soluble metal ion for pH 6 (8.6 µg/l) warranting a chronic 1 classification. The classification is much less sensitive at pH 8 given a less toxic and a lower dissolution rate.
- The M-factor associated with the long-term hazard classification is derived by using the solubility level derived from the 28d TDp test at the 0,1 mg/l loading (90 µg/l at pH 6) divided by the ERV of the dissolved metal ion (8.6 µg/l at pH 6): 90/8.6=10.45. Accordingly to section IV.5.5.2 the substance will get an M-factor 10, given this factor was between 10 and 100.

Labelling elements based on the classification:

Element	Code
GHS Pictogram	GHS09
Signal Word	WARNING
Hazard Statement	H410
Precautionary statement(s)	P273, P391, P501

Example D: Metal in powder and massive form with acute and chronic toxicity data and Transformation/Dissolution data at 7 days (low, medium and high loading rates) and at 28 days (only the high loading rate) and evidence of rapid removal from the water column.

DATA ELEMENTS	Value	Test method ((EC) No. 440/2008) or OECD guideline / remarks
Transformation dissolution protocol evidence For metal in POWDER form		
Screening test (24 h) at 100 mg/l loading	Not applicable for metals	Metals TDp, non-GLP
7 d TDp test at 1 mg/l loading	pH 6 : 1.7 µg/l (.) pH 8 : 3 µg/l	Metals TDp, non-GLP
at 10 mg/l loading	pH 6 : 24 µg/l pH 8 : 29 µg/l	
at 100 mg/l loading	pH 6 : 340 µg/l pH 8 : 280 µg/l	
28 d TDp test at 1 mg/l loading	pH 6: 2.3 µg/l pH 8: 3.5 µg/l	Metals TDp, non-GLP
at 0.1 mg/l loading	no measured data available	
at 0.01 mg/l loading	no measured data available	
MWT of the metal	**59**	
Acute aquatic toxicity of metal ion[77]		
Fish:	Large data sets available for the 2 pH ends but less sensitive than crustacean at high pH end and Algae at low pH end	C.1. / static, non-GLP C.1. / static, GLP
Crustacea *Ceriodaphnia dubia*	Most sensitive species at high ph end (pH 8.3-8.7) : Geometric mean for 6 values under comparable test conditions (EC_{50} 48h): 68 µg metal ion/l	C.2. / static, non-GLP
Algae/aquatic plants	Data sets available for the 2 pH ends but less sensitive than crustacean at high pH end and most sensitive endpoint at low end.	C.3. / static, GLP And non-GLP
Pseudokirchneriella subcapitata	Most sensitive value (96 h EC_{10}) at the low pH range: 120 µg metal ion/l	C.26. / static, non GLP

[77] Tests performed with readily soluble salts such as metal sulphates and metal chlorides.

Chronic aquatic toxicity[78]		
Fish:	Large data sets available for different pHs but less sensitive than crustacean at high and low pH	
Crustacea: *Ceriodaphnia dubia*	Most sensitive species at high and low pH end: - At low pH (NOEC 7d): 20 µg/l - At high pH: (EC10 7d): 2.4 µg /l	C.20. / semi-static, non-GLP
Algae/aquatic plants:	Large data sets available for different pH's but less sensitive than crustacean at high and low pH	C.3. / static, GLP C.3. / static, non-GLP
Degradation (evidence of rapid degradation)		
Rapid removal	The speciation of the metal compound in water to form insoluble and non classifiable[79] forms for aquatic hazard is in this case high (>70% removal of the soluble species within 28 days).	Based on literature data and empirical reaction kinetics.
Bioaccumulation		
Bioconcentration factor in fish	<< 500 at NOEC or EC50 level	

Transformation Dissolution screening outcome: not applicable for metals

Acute aquatic toxicity:

- Adequate data at high and low pH are available allowing deriving an acute ERV for the (soluble) metal ion
  - at the lower pH end (around pH 6) : **120 *µg/l***
  - at the higher pH end (above pH 8) : ***68 µg/l***

7 days Transformation/Dissolution outcome for the powder form:

- The release after 7 d's is the highest at pH 8 while lower at pH 8. The table below compares the TDp results with the acute ERV values at the corresponding pH ranges

Loading (mg metal ion/l)	**pH***	**Highest dissolution (mg metal/l)**	**Reference toxicity value (mg metal/l)**	**Dissolution > toxicity reference value?**
1	low	0.0017	0.12	No

[78] Tests performed with readily soluble salts such as metal sulphates and metal chlorides.
[79] To speciate to non-bioavailable and non-classifiable form(s) as to fulfil the requirements for rapid removal means that the potential for the reverse change to occur has been considered, and assessed as negligible.

10	low	0.024	0.12	No
100	low	0.35	0.12	**Yes**
1	high	0.003	0.068	No
10	high	0.029	0.068	No
100	high	0.28	0.068	**Yes**

* pH value at which dissolution testing was conducted and similar to the pH for the acute toxicity reference value

- The release from the metal powder[80] at a loading of 100 mg/l is for both pH ranges higher than the acute ERV.

7 days Transformation/Dissolution outcome for the massive form :

The CSA Approach can be used to calculate a Critical Particle Diameter (CPD) for the dissolution rates from the metal powder. The metal in massive form will be classified as hazardous to the aquatic environment if the CPD is above or equal to 1 mm. The measured critical surface area (SA_{crit}) that releases sufficient ions at to reach the acute ERV for the most critical pH (6) is $\boldsymbol{SA_{crit}}$ **0.101 m²/g** corresponding to an equivalent critical spherical particle diameter (CD_{spec}) of 6.67 µm at a 100 mg/l loading rate. This is far less than 1 mm.

Degradation/Transformation (evidence of rapid removal from the water column):

- A 70 % removal rate from the water column through speciation to the non bioavailable form is demonstrated within 28 days, thereby fulfilling the conditions of rapid removal from the water column.

Chronic aquatic toxicity:

- The chronic ERV for the (soluble) metal ion is ***2.4 µg/l*** at around pH 8 and ***20 µg/l*** around pH 6 which is an inverse relationship with pH as for the acute level.

28 days Transformation/Dissolution outcome for a substance rapidly removing from the water column:

- The release after 28 d at a loading of 1 mg/l is slightly higher at ***pH 8*** (3.5 µg/l) than at pH 6 (2.3 µg/l).
- TDp data for lower loadings are not available and were calculated given that the rate of metal ion release from the metal in the OECD 203 medium at high pH at the 28 days can be predicted by the equation: $\log (C_{Me(aq)}) = -5.144 + 1.0229\log(A_{meas})$, whereby

  $C_{me(aq)}$ = total dissolved concentration of metal (mg/l)

[80] The finest representative metal powder should be used for TDp testing.

A_{meas} = initial surface area loading (mm^2/l) [equals (measured specific surface area, *SA*, in m^2/g) × (substance mass loading in g/l) X 10^{81}], where *SA* was measured with the BET nitrogen adsorption-desorption technique.

An equal approach can be followed for the lower pH level.

- Measured and estimated transformation dissolution data for the *metal powder* are listed in the table below

Loading (mg metal ion/l)	**Measured or *calculated***	**pH***	**Highest dissolution (mg metal/l)**	**Reference toxicity value (mg metal/l)**	**Dissolution > toxicity reference value?**
1	Measured	low	0.0023	0.020	No
1	Measured	high	0.0035	0.0024	**Yes**
0.1	Estimated	Low	0.00023	0.020	No
0.1	Estimated	High	0.00035	0.0024	No

* pH value at which dissolution testing was conducted and similar to the pH for the acute toxicity reference value

- The release after 28 days at the 1 mg/l loading for the higher pH level slightly exceeds the chronic ERV, while no such effect is noted at pH 6 mainly due to the lower sensitivity of the species.

Aquatic hazard classification and, where applicable, established M-factor(s):

Acute (short-term) aquatic hazard:

- for the powder form: no acute hazard classification
- for the massive form: no acute hazard classification

Long-term aquatic hazard:

- for the powder form: category Chronic 3
- for the massive form: no long-term hazard classification

Reasoning :

The single environmental classification for all ***metal powders*** (spherical diameter ≤ 1 mm) of the considered metal can be derived by comparing the transformation/dissolution data for the smallest commercially representative metal powder with the acute and chronic toxicity reference values (for the soluble metal compounds).

Acute hazard classification:

- The ***dissolution rate for the finest powder*** on the market does not reach the concentration corresponding with the ERV, within 7 days at a loading of 1 mg/l. This is only reached at a loading of 100 mg/l. Therefore, **no acute hazard classification is required**.
- The ***dissolution rate for the massive forms*** (spherical diameter > 1 mm) is lower than those for powders given the lower available surface area. The Critical surface area approach confirms that above a diameter of 6.7 µm the acute ERV cannot be reached within 7 days at a loading of 1 mg/l.

[81] To speciate to non-bioavailable and non-classifiable form(s) for aquatic hazard as to fulfil the requirements for rapid removal means that the potential for the reverse change to occur has been considered, and assessed as negligible.

(Not even at a 100 mg/l loading.) Thereby confirming no need for an acute hazard classification. More explanation on the CSA assessment of the powder form for this metal is included in the explanatory note to example D (see below).

Long-term hazard classification:

- The metal fulfils the criterion for rapid removal from the water column given that > 70 % of the substance is transformed through speciation in a non-bioavailable form within 28 days.
- T/D data are only available for 1 mg/l loading rate. The medium loading rate of 0,1 mg/l required for the long-term hazard assessment could be safely extrapolated from existing evidence given clear relationships between concentration and dissolution were established for both pH levels.
- The comparison of chronic ERV's with the 28 days TDp results concludes that the chronic ERV for the metal ion is only reached at a loading rate of 1 mg/l at pH 8. Given the metal is rapidly removing from the water column, this results in a ***chronic 3 hazard classification for the metal in the powder form***[82].
- Given the surface of the particle reference ***for massive metal*** is > 100 larger than for the smallest commercially representative form this corresponds to a Critical Particle Diameter > 1 mm at the high loading rate. Therefore there is no need to classify the massive form for long-term hazard.

Labelling elements based on the classification for the <u>powder form</u>:

Element	Code
GHS Pictogram	none
Signal Word	none
Hazard Statement	H412
Precautionary statement(s)	P273, P501

Labelling elements based on the classification for the <u>massive form</u>: none

Element	Code
GHS Pictogram	none
Signal Word	none
Hazard Statement	none
Precautionary statement(s)	none

[82] The metal in the powder form would have been classified as chronic 2 in case evidence on rapid removal from the water column would not have been available or negative.

Explanatory note to Example D - Critical Surface Area (CSA) approach

Acute hazard:

For the metal powder in this example, the data showed that the concentration of metal released in the OECD 203 medium at pH 8 at the 168 hr can be predicted by the equation:

$$\log (C_{Me(aq)}) = -5.122 + 0.9875 \log (A_{meas})$$

$C_{Mel(aq)}$ = total dissolved concentration of Metal ion (mg/l) at 168 hr and pH 8;

A_{meas} = initial surface area loading (mm^2/l) [equals (measured specific surface area, *SA*, in m^2/g) × (substance mass loading in g/l) × 10^6], where *SA* was measured with the BET nitrogen adsorption-desorption technique.

The CSA approach can subsequently determine what surface areas and particle diameters would result in different levels of aquatic toxicity classification using the regression coefficients from the above equation, *a* (-5.122) and *b* (0.9875), and the proposed acute toxicity reference value (0.068 mg Me/l) as the $C_{Me(aq)}$. The critical surface area (*CSA*) would be the A_{meas} at which the metal ion is released at the concentration of the acute toxicity reference value. The following equations can be used to derive these values for this case:

$$\log L(E)C_{50} = -5.122 + 0.9875 \log CSA$$

$L(E)C_{50}$ = acute ecotoxicity reference value for classification (mg/l)

CSA = critical surface area (mm^2/l) that releases metal ion in the concentration of the acute ecotoxicity reference value to the aquatic medium

The *CSA* can be derived as follows:

$$\log CSA = \left(\frac{\log L(E)C_{50} + 5.122}{0.9875} \right)$$

For an acute toxicity reference value of 0.068 mg Me/l, the *CSA* is thus 10,100 mm^2/l. This is the surface area loading of metal that will deliver the reference value amount of metal ion to the OECD 203 medium at pH 8 and at a time of 168 hr.

The critical specific surface areas, SA_{crit}s for a loading of 1 mg/l will deliver the acute toxicity reference value to the OECD 203 medium at pH 8 and a time of 168 hr can be calculated by:

SA_{crit} = critical specific surface area (m^2/g) corresponding to the acute ecotoxicity reference value

CP = classification cut-off loading of 1 mg/l that yield a classification as acute 1)

Thus, for the metal powder under consideration a ***CSA* of 10.100 mm^2/l and the *CP* of 1 mg/l, the SA_{crit} is 10,1 m^2/g**.

The equivalent critical spherical particle diameter (CD_{spec}) associated with the acute ecotoxicity reference value is determined by:

$$CDspec = \left(\frac{6}{SA_{crit} \times \rho Me} \right)$$

ρ_{Me} = density of the metal (g/cm^3)

CD_{spec} = critical diameter of the sphere (μm) corresponding to the acute ecotoxicity reference value

For the above SA_{crit} of 10,1 m^2/g, corresponding to the 1 mg/l loading, the critical diameter would be 0,067 μm. The EU-CLP system defines that the finest representative metal powder should be used for TDp testing and classification of the metal powder form.

An acute toxicity classification can therefore be assigned to all metal powders (diameter ≤ 1 mm) by **measuring the real surface area** using the BET nitrogen adsorption-desorption technique and comparing it to SA_{crit}. If the surface area of the reference material is greater than the SA_{crit} for the associated acute toxicity classification then the representative metal sample would classify for that acute hazard category ***and classify all powder types of that metal in the same way***. If the measured surface area is less than the SA_{crit}s of all of the classification categories then all powders of this metal would not classify for aquatic toxicity.

The CSA Approach can consequently be used to assign an acute hazard classification to the metal powders based on measured surface area using the **measured surface area of0.43 m^2/g** for the smallest representative size powder on the EU market. Since this surface area is greater than 0.1 m^2/g but less than 1 m^2/g, there is according to this approach no need for an ***acute hazard classification of the metal powders in this example***.

The CSA Approach can also be used to calculate a Critical Particle Diameter (CPD) to be used to determine an accurate classification of the **metal massive** (diameter > 1 mm), where the measured surface area of the tested granules is 0.086 m^2/g. This surface area is far less than all of the SA_{crit} so there is ***no need for an acute classification for the metal massive***.

Long-term hazard: For this example it has been shown that rate of metal ion release from the metal in the OECD 203 medium at high pH at the 672 hr can be predicted by the equation:

$$\log (C_{Me(aq)}) = -5.144 + 1.0229\log(A_{meas})$$

$C_{me(aq)}$ = total dissolved concentration of metal (mg/l)

A_{meas} = initial surface area loading (mm^2/l) [equals (measured specific surface area, *SA*, in m^2/g) × (substance mass loading in g/l) X 10^6], where *SA* was measured with the BET nitrogen adsorption-desorption technique.

The CSA Approach can determine what surface areas and particle diameter would result in chronic (long-term) hazard classification by using the regression coefficients from the above equation, *a* (-5.144) and *b* (1.0229), and the proposed chronic toxicity reference value (0.0024 mg Me/l) as the $C_{Me(aq)}$. The critical surface area (*CSA*) would be the A_{meas} at which metal ion is released at the concentration of the chronic toxicity reference value. The following equations can be used to derive these values.

$$\log \textit{chronic toxicity} = -5.144 + 1.0229\log \textit{CSA}$$

chronic toxicity = chronic ecotoxicity reference value for classification (mg/l), using calculated EC_{10}s or measured NOECs (if the EC_{10} is less than the NOEC)

CSA = critical surface area (mm^2/l) that releases metal in the concentration of the chronic toxicity reference value to the aquatic medium

The *CSA* can be derived as follows:

$$\log CSA = \left(\frac{\log chronictoxicity + 5.144}{1.0229} \right)$$

For the chronic hazard classification derivation exactly the same approach as for the acute hazard assessment can be followed to define SA_{crit} and CD_{spec}. For this metal powder example this results in a CSA of 3,420 mm^2/l and the CP of 1 mg/l, the SA_{crit} is 0.342 m2/g.

For a SA_{crit} of 0.342 m^2/g, corresponding to the 1 mg/l loading, the critical diameter would be 2 μm.

Equivalent as for the assessment of the acute hazard the CSA Approach can be used to assign a long-term hazard classification to all powders based on measured surface area of the reference powder, using the measured surface area at 100 mg/l loading (0.43 m^2/g) for the smallest representative size powder on the EU market. Since this surface area is greater than 0.342 m^2/g, ***all metal powders would be classified as Chronic 3***.

The CSA Approach can also be used to **classify the massive metal (diameter > 1 mm)**, where the measured surface area of the massive at 100 mg/l loading) is 0.086 m^2/g. This surface area is less than the chronic SA_{crit} so the massive metal form would ***not be classified for long-term environmental hazard***.

Example E: Hazard classification of a soluble metal salt: the case of removal through speciation in the water column

General approach

The example was selected because

(i) it illustrates the use of information on the metal oxidation and the removal of metal ions from the water column for classification decisions.

(ii) It provides further information related to testing of sparingly soluble metal salts

The metal ion selected for this example, Me(II), is unstable when its solutions are exposed to air, and it oxidises to the Me(III), which then forms the familiar insoluble, hydrated, amorphous, gelatinous precipitate, $Me(OH)_3$ (metal hydroxide). The question then arises as to whether the metal hydroxide precipitate forms rapidly enough to decrease the concentration of Me(II) and Me(III) ions to levels below which there is no cause for concern over the aquatic environment. Consideration of the rates at which Me(II) oxidises to Me(III) is relevant to this question to proof rapid removal from the water column.

Additionally, the classification of substances of concern for the aquatic environment requires evaluation of aquatic toxicity. Results for this case were evaluated against standard acceptability criteria for use in this classification assessment.

Results

"Metal" fate and assessment of the removal from the water column:

A review of the scientific literature on the oxidation of metal sulphate reveals the following: *Metal sulphate reacts with oxygen in water to form metal hydroxide ($MeOH_2$), moderately insoluble, Ksp = 1.6×10^{-14}) this in turn undergoes further oxidation to form metal hydroxide ($MeOH_3$) which is highly insoluble (Ksp = 1×10^{-36}). Formation of metal hydroxide at pH levels above 5.0 limits the presence of metal ions in aqueous systems. In sediments the metal hydroxide is expected to result in enriched concentrations of insoluble metal sulphide.*

The rates at which dissolved metal sulphate (Me^{++}) oxidises to (Me^{+++}) and forms the metal hydroxide [$Me(OH)_3$] precipitate:

- Is highly dependent on pH (100 fold from pH 6 to 8);
- decreases with increase in ionic strength of the aqueous medium (pristine waters contain less metal ions);
- dependent to some extent on the anions present in solution such as sulphate and chloride;
- increases 10-fold for a 15 °C increase in temperature;
- exhibits a linear dependence on the partial pressure of oxygen; and
- dependent on the initial concentration of metal sulphate and exhibits linear reaction kinetics at Me(II) loadings less than ~50 micromolar (~3 mg/l). At concentrations greater than 50 micromolar, rates of reaction increase with increasing concentration of metal sulfate (about 4× for each order of magnitude).

Based on literature data and empirical reaction kinetics, it can be calculated that, at low pH (reasonable worst case scenario) in the OECD 203 medium (diluted by 10 as per the Transformation/Dissolution Protocol), the half-times for the oxidation of Me(II) are 11, 9 and 3.6 hr, for 1, 10 and 100 mg/l loadings of $MeSO_4$, respectively. At high pH, the reaction is estimated to be as short as 8 seconds. The rapid precipitation of metal ions from aqueous

systems accounts for low "metal" concentrations found in most natural aquatic systems (all except natural waters at very low pH values (i.e. < pH 5.5)). Under the reasonable worst case scenario of low pH and a low initial concentration of 1 mg/l $MeSO_4$, the 70% removal from solution is calculated to be achieved in 19hr and 90% removal would be achieved by 36hr. Since the removal of the metal sulphate are due to reaction with oxygen in water to form highly insoluble and non classifiable metal hydroxide and the half life for the removal of the soluble specie are less than 16 days this can be considered as rapid removal from the water column and the substance considered for classification purposes as rapidly degradable.

To support this, evidence of rapid loss of "Metal ions" (and other metals) from the water column has been reported in mesocosm lake experiments (Perch Lake). The data are presented as half lives as a function of time, partition coefficient and first stability constant. Half lives for metal ions in the mesocosms are calculated to be approximately 11 days under the given conditions. The data support that half lives are short and loss from the water column can be related to both formation of the metal hydroxide but also to sorption to suspended particles that are settling.

Aquatic Toxicity:

Acute ERV values lie in the range of 1-37 mg/l (see Table). Two values for *Daphnia magna* were less than 10 mg/l. Four *Daphnia magna* studies were performed and the geometric mean value for this species is 5.77 mg/l. The values for fish were all greater than 10 mg/l. No algal studies were deemed reliable. All these values are expressed as mg/l Me. If the classification relates specifically to metal sulphate of which the most common form is the heptahydrate $MeSO_4.7H_2O$. The numerical ERV values detailed should be adjusted according to the table below and the species under consideration to calculate the toxicity on a metal sulfate basis.

Chemical Species	**Molecular Weight**	**Ratio**
$MeSO_4 7H_2O$	278.0	4.978
$MeSO_4 H_2O$	169.91	3.043
$MeSO_4$	151.90	2.720
Me	55.84	1.0

The data cover all the reliable results available for aquatic toxicity of binary "metal" and any observed toxicity effects could relate to the Me ion which could be in Me(II) or metal Me(III) oxidation states.

Conversion of the acute ERV values for the metal ion to those appropriate for $MeSO_4.7H_2O$ implies an acute toxicity range of 6.4 to 199 mg/l.

Table IV.7.1 *Acute toxicity data deemed reliable for "Metal" are presented as mg/l Me.*

Test substance	**Test organism**	**Duration**	**Endpoints**	**L(E)C_{50} (mg Me L^{-1})**
$MeCl_3.6H_2O$	*Pimephales promelas*	96h	Survival	21.8
	Lepomis macrochirus	96h	Survival	20.3
$MeSO_4.7H_2O$	*Oncorhynchus mykiss*	96h	Survival	16.6
$Me_2(SO_4)_3$	*Oncorhynchus mykiss*	96h	Survival	>27.9
$MeSO_4$	*Daphnia pulex*	24h	Immobility	36.9
$MeSO_4$	*Daphnia magna*	24h	Immobility	17

Test substance	Test organism	Duration	Endpoints	L(E)C_{50} (mg Me L^{-1})
$MeCl_3.6H_2O$	*Daphnia pulex*	48h	Immobility	12.9
$Me_2(SO_4)_3$	*Daphnia longispina*	48h	Immobility	11.5
$MeCl_3.6H_2O$	*Daphnia magna*	48 h	Immobility	9.6
$MeSO_4$	*Daphnia magna*	24h	Immobility	5.25
$MeSO_4.7H_2O$	*Daphnia magna*	48h	Immobility	1.29

Table IV.7.2 *Chronic toxicity data deemed reliable for "Metal" are presented as mg/l Me.*

Test substance	Test organism	Duration	Endpoints	NOEC/LOEC (mg Me L^{-1})
$Fe(OH)_3$	*Salvelinus fontinalis*	30 days	Hatching Growth Survival	 >10.3
$Fe(OH)_3$	*Oncorhynchus kisuth*	30 days	Hatching Growth Survival	>10.3 2.81/>10.3 >10.3
$FeCl_3.6H_2O$	*Pimephales promelas*	33 days	Survival Length Weight	 1.0/1.6 1.61/2.81
$FeCl_3.6H_2O$	*Daphnia pulex*	21 days	Immobility Total offspring Brood size	2.51/5.01 0.63/1.26 1.26/2.51
$FeCl_3.6H_2O$	*Daphnia magna*	21 days	Immobility Reproduction	5.9 EC50 4.4 EC16

Aquatic hazard classification*:*

Acute hazard: Not classified.

Long-term hazard: Not classified.

Reasoning:

Acute aquatic toxicity > 1 mg/l.

Chronic aquatic toxicity values are all greater than 1 mg/l. Rapid and permanent removal from the water column. Metal precipitates form large polymers that remain insoluble and become buried in the sediments.

Labelling elements based on the classification:

Element	Code
GHS Pictogram	none
Signal Word	none
Hazard Statement	none
Precautionary statement(s)	none

V Annex V: Collection of internet links for the users of the guidance

Reference/Site name	Host	URL
ECHA website	ECHA	http://echa.europa.eu/
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://guidance.echa.europa.eu
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/findDocument/0,3354,en_2649_34377_1_1_1_1_1,00.html
Public C&L Inventory	ECHA	**To be inserted here before publication of the guidance**