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EUROPEAN CHEMICALS AGENCY

GUIDANCE

Guidance on the application of the CLP criteria

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

Version 3.0 November 2012

LEGAL NOTICE

This document contains guidance to Regulation (EC) No 1272/2008 (CLP Regulation). However, users are reminded that the text of the CLP Regulation is the only authentic legal reference and that the information in this document does not constitute legal advice. The European Chemicals Agency does not accept any liability with regard to the contents of this document.

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DOCUMENT HISTORY

Version	Comment	Date
n.a.	First edition	August 2009
n.a.	Please note that change between the version published in August 2009 and that of April 2011 are not recorded in this document history.	April 2011
Version 2	Revision of the Guidance addressing content in relation to the environmental criteria chapters and Annexes following the 2nd Adaptation to Technical Progress to the CLP Regulation (Commission Regulation (EU) No 286/2011). The ECHA Secretariat revised the Guidance *Part 4 - Environmental hazards* and *Annexes* of the guidance document referring to the revised criteria for the long-term aquatic hazard for substances and mixtures and added new *Part 5 – Additional hazards* referring to the hazard class "hazardous to the ozone layer". As well, a number of examples have been included in the respective Parts and Annexes to illustrate the revisions performed. Further to this, a range of editorial corrections were proposed for *Part 1- General principles for classification and labelling*. The update includes the following: - Revision of Part 1, by eliminating and amending out of date information and restructuring the text in order to reflect the Guidance update. - All green boxes in Part 4 that are impacted by the 2nd ATP were updated. As the CLP legal text uses commas instead of dots to define numbers smaller than 1, the green boxes now show commas as well. - Revision of Part 4, by providing guidance on the application of the new long-term aquatic hazard criteria for substances and mixtures. - Section 4.1.3 Classification of substances hazardous to the aquatic environment and section 4.1.4 Classification of mixtures hazardous to the aquatic environment were substantially revised, for example by addition of new references, as well as the new/ revised examples to illustrate relevant topics in the Part 4. - New *Part 5 - Additional hazards* was added (please note that Part 5: Labelling was deleted from the Guidance in previous non recorded versions and covered via a new *Guidance on Labelling and Packaging in accordance with Regulation (EC) No 1272/2008* published in April 2011). - Most of the I.3 sub-sections in *Annex I – Aquatic toxicity* were revised. - In *Annex II – Rapid degradation* the terminology was modified. - Most of the *Annex IV – Metals and Inorganic Metal Compounds* was substantially modified and revised, as well as in sub-section IV.7 new examples were added.	April 2012

Version 3	Revision of Guidance Part 3 Health Hazards, relating to specific concentration limits (SCLs) for 4 hazard classes and the inclusion of a new Annex The update includes the following: - Revision of Part 3, by providing guidance on the setting of lower and higher SCLs for 4 health hazard classes in section 3.2.2.5 Skin Corrosion/Irritation; section 3.3.2.5 Serious Eye Damage/Eye Irritation; section 3.7.2.5 Reproductive Toxicity and section 3.8.2.6 STOT-SE, in accordance with CLP Article 10(7); - Inclusion of a new Annex (Annex VI) providing guidance on setting SCLs for the reproductive toxicity hazard class based on potency considerations.	November 2012

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 (for example on setting of specific concentration limits (SCLs)), on the long-term aquatic hazard and in relation to labelling and packaging. In addition 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]). 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, on the aspiration hazard and other human health related points, as well as on the physico- chemical points that were revised following the 2nd ATP to the CLP Regulation are not part of this update and are planned for a future update of this document in 2013. .

[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.

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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]
DSD	Directive 67/548/EEC on the classification and labelling of Dangerous Substances[7]

[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]

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
ERV	Ecotoxicity Reference Value
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)
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 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

[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]

	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
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

[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

T95	Inhalation chamber equilibrium (attained at the time t95)
T/D	Transformation/Dissolution
T/Dp	Transformation/Dissolution Protocol
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

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 AND LABELLING

1.1 INTRODUCTION

1.1.1 The objective of the guidance document

This document is a comprehensive technical and scientific guidance on the application of Regulation (EC) No 1272/2008 on the classification, labelling and packaging of substances and 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://echa.europa.eu/documents/10162/13562/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.

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[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:

[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://echa.europa.eu/web/guest/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment).

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 in accordance with both DSD Directive and CLP Regulation 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). Labelling and packaging shall be in accordance with CLP Regulation.

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

[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 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.

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.

1.1.7 Data evaluation and reaching a decision on classification

1.1.7.1 Classification of substances

[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]

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, table 3.2, 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.

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 classification and labelling of substances shall be normally partial and cover only hazard classes of particular concern listed in Article 36(1) CLP (i.e. respiratory sensitisation, germ cell mutagenicity, carcinogenicity and reproductive

[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]

toxicity). A substance that is used as an active substance in the meaning of Directives 91/414/EEC and 98/8/EC shall normally be subjected to harmonised classification and labelling (Article 36(2) CLP). Where a substance fulfils the criteria for hazard classes other than those referred in Article 36(1) CLP and does not fall under Directives 91/414/EEC and 98/8/EC, a harmonised classification and labelling may be added to Annex VI to CLP on a case-by-case basis, if justification is provided demonstrating the need for action at EU level (Article 36(3) CLP). 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/web/guest/regulations/clp/cl-inventory/notification-to-the-cl-inventory .

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.

Guidance on setting of SCLs is supplied in the respective chapters of the different health hazard classes. A general overview on the applicability of SCLs and guidance availability for setting SCLs for health hazards is given in this chapter.

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
	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.

[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.

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

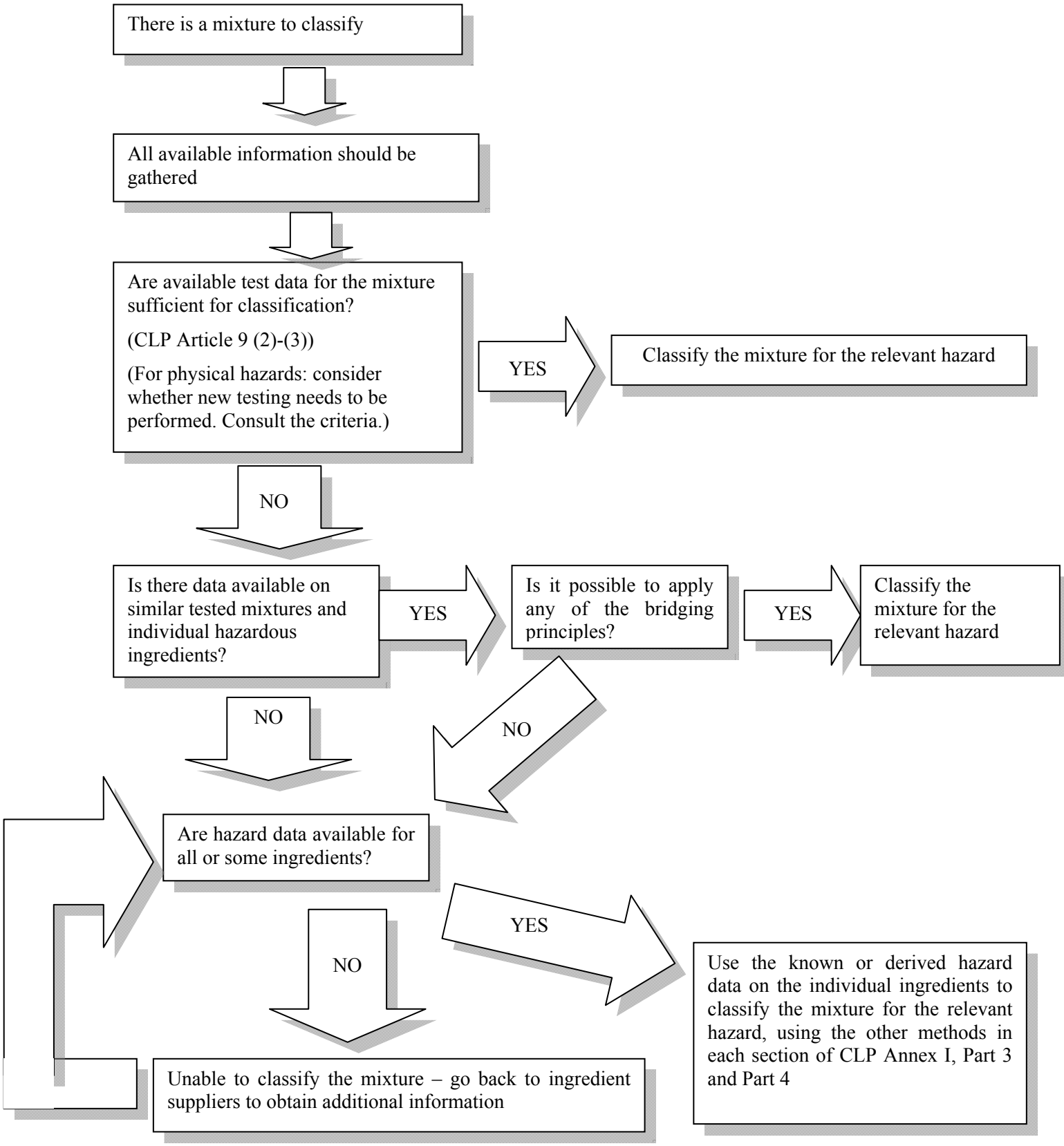
(b) in an individual concentration of ≥ 0,1 % by weight for non-gaseous mixtures at least one substance that is carcinogenic category 2 or toxic to reproduction category 1A, 1B and 2, skin sensitiser category 1, respiratory sensitiser category 1, or has effects on or via lactation or is persistent, bioaccumulative 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/danger/publi/manual/manual_e.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.

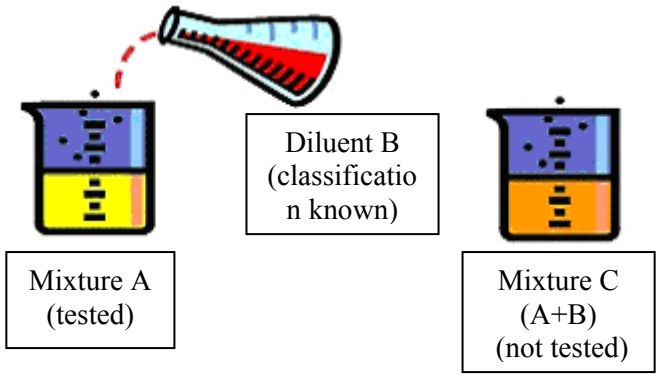
Not all of the bridging principles as described in sections 1.6.3.2.1-1.6.3.2.5 of this document need to be applied when assessing a particular health or environmental hazard. It is necessary to consult Annex I of CLP, Part 3 for health hazards and Part 4 for environmental hazards, before undertaking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

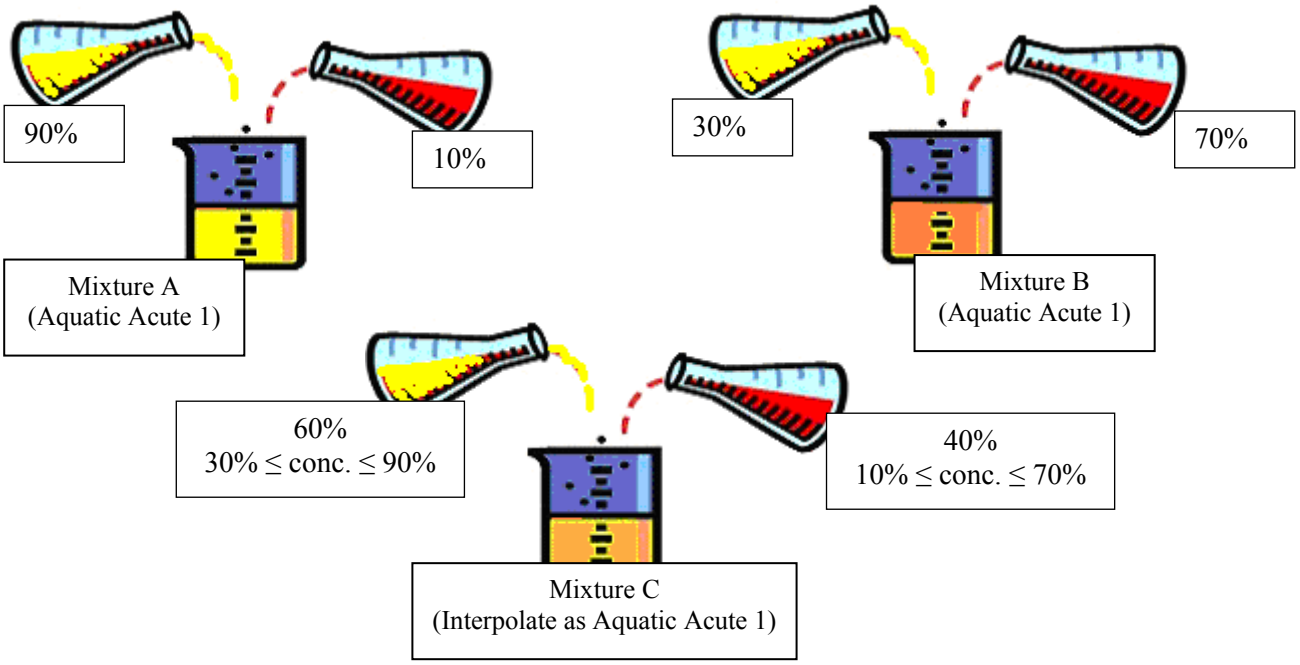
1.6.3.2.3 Concentration of highly hazardous mixtures

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).

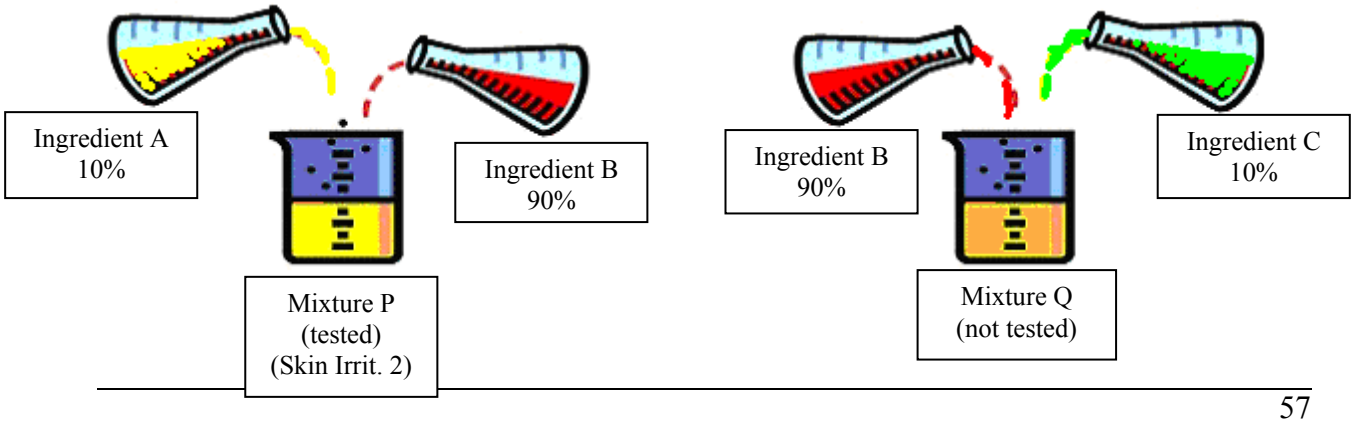
Figure 1.6.3.2.4 *Application of the bridging principle: interpolation for determining the aquatic acute hazard classification of a mixture*



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:

$$\frac{\sum C_i + \sum C_j}{Eq\ NOEC_m} = \sum_{n} \frac{C_i}{NOEC_i} + \sum_{n} \frac{C_j}{0{,}1 \times NOEC_j}$$

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 concerning aquatic hazard, for a substance with an established M-factor, the cut-off

[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

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:

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

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

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

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 (see list of ingredients below)	20.00	not tested	Eye Dam.1 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	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.

2 PART 2: PHYSICAL HAZARDS[42]

2.1 INTRODUCTION

2.1.1 General remarks about the prerequisites of classification and testing

The purpose of this chapter is to give some general guidance with respect to the generation of test data for physical hazards and their interpretation. The intention of CLP is to identify hazards of chemical substances and mixtures and to provide a systematic approach – using classification - to communicate them based on harmonized criteria. The classification process involves three steps:

1. Gathering of relevant information regarding the hazards of a substance or mixture (articles 5 – 8);

2. Evaluation of hazard information to ascertain the hazards associated with the substance or mixture (articles 9 ff); and

3. A decision on whether the substance or mixture will be classified as a hazardous substance or mixture and the degree of hazard, where appropriate, by comparison of the data with agreed hazard classification criteria (article 13).

Generally for both, substances and mixtures, testing is required to determine physical hazards including the physico-chemical properties necessary for the respective classification unless alternative methods are specifically permitted. Before undertaking testing of substances, enquiries should be made to ascertain the availability of data, e.g. flash points, on the substance.

2.1.2 Safety

In most cases, the classification is based on test data which are determined in a laboratory. Special care is required when new or unknown substances or mixtures are tested. If possible, preliminary tests should be carried out before larger quantities are handled. Appendix 6 of the UN Manual of Tests and Criteria (UN-MTC) ('Screening procedures') allows gathering valuable information about physico-chemical properties based on small-scale tests. Further aspects of safety are given in the general introduction, Section 1.4 of the UN-MTC or within the individual test procedures.

2.1.3 General conditions for testing

Samples offered for testing must in all aspects be representative of the substance or mixture to be classified. Therefore, it is helpful to characterise or specify the sample for the purposes of documentation (i.e. batch number, production code etc.). Further characterisation (i.e. analysis) is highly recommended in cases where the presence of diluents, activators, stabilisers or moisture may influence the outcome of the test.

[42] The guidance provided in this chapter is based on the classification criteria from the original version of the CLP Regulation (EC) No 1272/2008. This chapter is currently being updated based on the 2nd ATP to the CLP Regulation and planned for a future update of this document in 2013.

In some cases, additional parameters (physical condition, particle size, density, crystal structure) may influence the test result. Where relevant, the test should be performed on the substance or mixture in the appropriate physical form where changes in that form may influence the outcome of the test (see also Articles 5 and 6 of CLP and Section 1.2 on form and physical state).

2.1.4 Physical state

The physical state determines which hazard classes should be considered for testing. The definitions for gases, liquids and solids are given in Annex I, Part 1 of CLP:

Annex I: Part 1, 1.0. *Definitions*

Gas means a substance which:

(i) at 50 °C has a vapour pressure greater than 300 kPa (absolute); or

(ii) is completely gaseous at 20 °C at a standard pressure of 101.3 kPa;

Liquid means a substance or mixture which:

(i) at 50 °C has a vapour pressure of not more than 300 kPa (3 bar);

(ii) is not completely gaseous at 20 °C and at a standard pressure of 101,3 kPa; and

(iii) which has a melting point or initial melting point of 20 °C or less at a standard pressure of 101,3 kPa;

Solid means a substance or mixture which does not meet the definitions of liquid or gas.

In some cases (i.e. viscous substances or mixtures), a specific melting point cannot be determined. Such substance or mixture shall be regarded as a liquid if either the result of the ASTM D 4359-90 test (standard test method for determining whether a material is a liquid or a solid) indicates 'liquid' or the result of the test for determining fluidity (penetrometer test) prescribed in Section 2.3.4 of Annex A of ADR indicates 'not pasty'.

2.1.5 Quality

The determination of data should be based on the methods named in Annex I, Part 2 of CLP. For most hazard classes (except gases and liquids) in Annex I, Part 2 there is reference made to the UN-MTC which gives very detailed descriptions of the test methods. For gases and liquids there are references to international standards. Whenever possible, the methods used should be validated. Any deviation from the test procedure or standard should be documented and, if necessary, justified.

The reliability of all test results used for the classification of dangerous substances is important and therefore their transparency and comparability must be ensured.

For these purposes, CLP requires in Article 8 the following:

Article 8 (5)

Where new tests for physical hazards are carried out for the purposes of this Regulation, they shall be carried out, at the latest from 1 January 2014, in compliance with a relevant recognised quality system or by laboratories complying with a relevant recognised standard.

Even though the quality requirement does not become immediately effective, it is highly recommended to do so if reasonably possibly. In general, the following alternative strategies can be pursued:

1. compliance with the principles of good laboratory practice (GLP) (as formerly required by the DSD)
2. application of EN ISO/IEC 17025 "General requirements for the competence of testing and calibration laboratories" as a relevant recognised standard.
3. other internationally recognised standards of comparable scope.

Any testing organisation that carries out physical hazard tests for classification purposes can therefore choose how to fulfill the quality requirements of CLP.

2.2 EXPLOSIVES

2.2.1 Introduction

The classification of substances, mixtures and articles in the class of explosives and further allocation to a division is a very complex procedure. Reference to Part I of the UN RTDG Manual of Testing and Criteria (MTC) and related expertise are necessary.

The GHS classification system is almost entirely adopted of the UN Recommendations on the Transport of Dangerous Goods, which is very appropriate for transport and also storage of packaged explosives.

The explosive properties of substances and mixtures regarding their stability and sensitivity are only investigated within test series 1, 2 and 3 during the acceptance procedure. Subsequent tests for the assignment to the divisions 1.1, 1.2, 1.3 and 1.4 (test series 6) are carried out with the packaged substance / mixture or articles. The type of packaging may significantly influence the test outcome.

For unpacked or repacked explosive substances and mixtures there are some deficiencies in the hazard communication of the GHS, especially for substances and mixtures, which are provisionally accepted in the class of explosives but later are rejected from this class due to their packaging in the assignment procedure. These substances and mixtures have explosive properties but there might be no hazard communication about these properties due to the subsequent classification in a hazard class other than the class of explosives. The example for musk xylene (see Section 2.2.6.2) clarifies this issue. The results of test series 6 for musk xylene in the specified packaging lead to the exclusion of this substance from the hazard class of explosives. But musk xylene on its own (unpacked) shows explosive properties due to heating under confinement (Koenen test). Also repacking of the substance in a packaging other than tested can result in a completely different outcome of test series 6.

This issue is not sufficiently clarified under GHS, but should be kept in mind by everyone applying CLP.

Some R-phrases which are not yet covered by hazard classes in the GHS are added as supplemental hazard statements in Annex II part 1 of CLP. The following EU hazard statements are important in connection with explosive properties:

EUH001 “Explosive when dry”

EUH044 “Risk of explosion if heated under confinement”

For more information on additional labelling provisions, see Section 2.2.4.

2.2.2 Definitions and general considerations for the classification of explosives

The following definition is given in CLP for the class of explosives.

Annex I: 2.1.1.1. The class of explosives comprises

(a) Explosive substances and mixtures;

(b) Explosive articles, except devices containing explosive substances or mixtures in such quantity or of such a character that their inadvertent or accidental ignition or initiation shall not cause any effect external to the device either by projection, fire, smoke, heat or loud noise; and

(c) Substance, mixtures and articles not mentioned under (a) and (b) which are manufactured with the view to producing a practical, explosive or pyrotechnic effect.

Additional remark related to 2.1.1.1 (a) (reference to *UN RTDG, Model Regulations, Volume 1)*:

A substance or mixture which is not itself an explosive but which can form an explosive atmosphere of gas, vapour or dust is not included in this class.

A substance or mixture with explosive properties, but where the predominant hazard is covered by another class (e.g. organic peroxides, self-reactive substances and mixtures), is not included in the class of explosives.

In addition the following definitions apply for explosives:

Annex I: 2.1.1.2. An explosive substance or mixture is a solid or liquid substance or mixture of substances which is in itself capable by chemical reaction of producing gas at such a temperature and pressure and at such a speed as to cause damage to the surroundings.

Pyrotechnic substances are included even when they do not evolve gases.

A pyrotechnic substance or mixture is a substance or mixture of substances designed to produce an effect by heat, light, sound, gas or smoke or a combination of these as the result of non-detonative self-sustaining exothermic chemical reactions.

An unstable explosive is an explosive which is thermally unstable and/or too sensitive for normal handling, transport and use.

An explosive article is an article containing one or more explosive substances or mixtures.

A pyrotechnic article is an article containing one or more pyrotechnic substances or mixtures.

An intentional explosive is a substance, mixture or article which is manufactured with a view to produce a practical explosive or pyrotechnic effect.

2.2.3 Classification of substances, mixtures or articles as explosives

2.2.3.1 Identification of hazard information

Information on the following types of hazards is relevant for the evaluation of substances, mixtures and articles for the class of explosives:

- sensitivity to shock
- effects of heating and ignition under confinement
- thermal stability
- sensitiveness to impact and friction

- mass explosion hazard
- projection hazard
- fire and radiant heat hazard

2.2.3.2 Screening procedures and waiving of testing

The screening procedure is described in:

- CLP, Annex I, Part 2, paragraphs 2.1.4.2 and 2.1.4.3
- Appendix 6 of the UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria
- Technical Guidance Document on the Information Requirements for REACH, Part 2 EWG 1-7, REACH Implementation Project (RIP) 3.3 Phase 2, chapter 7.1.11.3

The screening procedure may be used for new substances which are suspected of having explosive properties. It should not be used for substances manufactured with the intention of producing a practical explosive or pyrotechnic effect.

Explosive properties are associated with the presence of certain chemical groups in a molecule which can react to produce very rapid increases in temperature or pressure. The screening procedure is aimed at identifying the presence of such reactive groups and the potential for rapid energy release.

If the screening procedure identifies the material to be a potential explosive or if the substance is a mixture containing any known explosives, the classification (acceptance) procedure for the class of explosives (see Section 2.2.3.5.1) should be applied. If the exothermic decomposition energy of organic materials is less than 800 J/g, neither a Series 1 type (a) propagation of detonation test nor a Series 2 type (a) test of sensitivity to detonative shock is required.

A substance or mixture shall not be classified as explosive:

(a) When there are no chemical groups associated with explosive properties present in the molecule. Examples of groups which may indicate explosive properties are:

- C-C unsaturation (e.g. acetylenes, acetylides, 1, 2-dienes),
- C-Metal, N-Metal (e.g. Grignard reagents, organo-lithium compounds),
- Contiguous nitrogen atoms (e.g. azides, aliphatic azo compounds, diazonium salts, hydrazines, sulphonylhydrazides)
- Contiguous oxygen atoms (e.g. peroxides, ozonides)
- N-O (e.g. hydroxyl amines, nitrates, nitro compounds, nitroso compounds, N-oxides, 1,2-oxazoles)
- N-halogen (e.g. chloramines, fluoroamines)
- O-halogen (e.g. chlorates, perchlorates, iodosyl compounds)

or

(b) When the substance or mixture contains chemical groups associated with explosive properties which include oxygen and the calculated oxygen balance is less than -200.

The oxygen balance is calculated for the chemical reaction:

$$C_xH_yO_z + \left[x + \left(\frac{y}{4}\right) - \left(\frac{z}{2}\right)\right]O_2 \leftrightarrows x\,CO_2 + \left(\frac{y}{2}\right)H_2O$$

using the formula:

$$-1600 \times \frac{[2x + (y/2) - z]}{\text{molecular weight}}$$

or

(c) When the organic substance or a homogenous mixture of organic substances contains chemical groups associated with explosive properties but the exothermic decomposition energy is less than 500 J/g and the onset of exothermic decomposition is below 500 ºC. (The temperature limit is to prevent the procedure being applied to a large number of organic materials which are not explosive but which will decompose slowly above 500 ºC to release more than 500 J/g.) The exothermic decomposition energy may be determined using a suitable calorimetric technique.

or

(d) For mixtures of inorganic oxidising substances with organic material(s), the concentration of the inorganic oxidising substance is:

- less than 15 % by mass, if the oxidising substance is assigned to Categories 1 or 2;
- less than 30 % by mass, if the oxidising substance is assigned to Category 3.

2.2.3.3 Classification criteria

The criteria for the classification of explosives are given in the following tables.

Annex I: 2.1.2.1. Substances, mixtures and articles of this class are classified as an unstable explosive on the basis of the flowchart in Figure 2.1.2. The test methods are described in Part I of the UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria

2.1.2.2. Substances, mixtures and articles of this class, which are not classified as an unstable explosive, shall be assigned to one of the following six divisions depending on the type of hazard they present:

(a) Division 1.1 Substances, mixtures and articles which have a mass explosion hazard (a mass explosion is one which affects almost the entire quantity present virtually instantaneously).

(b) Division 1.2 Substances, mixtures and articles which have a projection hazard but not a mass explosion hazard.

(c) Division 1.3 Substances, mixtures and articles which have a fire hazard and either a minor blast hazard or a minor projection hazard or both, but not a mass explosion hazard:

(i) combustion of which gives rise to considerable radiant heat; or

(ii) which burn one after another, producing minor blast or projection effects or both.

(d) Division 1.4 Substances, mixtures and articles which present no significant hazard:

- Substances, mixtures and articles which present only a small hazard in the event of ignition or initiation. The effects are largely confined to the package and no projection of fragments of appreciable size or range is to be expected. An external fire shall not cause virtually instantaneous explosion of almost the entire contents of the package.

(e) Division 1.5 Very insensitive substances or mixtures which have a mass explosion

hazard:

- Substances and mixtures which have a mass explosion hazard but are so insensitive that there is very little probability of initiation or of transition from burning to detonation under normal conditions.

(f) Division 1.6 Extremely insensitive articles which do not have a mass explosion hazard:

- Articles which contain only extremely insensitive detonating substances or mixtures and which demonstrate a negligible probability of accidental initiation or propagation.

2.1.2.3. Explosives, which are not classified as an unstable explosive, shall be classified in one of the six divisions referred to in section 2.1.2.2 based on Test Series 2 to 8 in Part I of the UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria according to the results of the tests laid down in Table 2.1.1:

Table 2.1.1

Criteria for explosives

Category	Criteria
Unstable explosives or explosives of Divisions 1.1 to 1.6	For explosives of Divisions 1.1 to 1.6, the following are the core set of tests that need to be performed: Explosibility: according to UN Test Series 2 (section 12 of the UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria). Intentional explosives[43] shall not be subject to UN Test Series 2. Sensitiveness: according to UN Test Series 3 (section 13 of the UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria). Thermal stability: according to UN Test 3(c) (sub-section 13.6.1 of the UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria). Further tests are necessary to allocate the correct Division.

Certain physical hazards (due to explosive properties) are altered by dilution, as is the case for desensitized explosives, by inclusion in a mixture or article, packaging or other factors.

Explosive substances and mixtures wetted with water or alcohols, or diluted with other substances to suppress their explosive properties, may be treated differently in terms of classification and other hazard classes may apply, according to their physical properties.

Where the test is conducted in the package form and the packaging is changed, a further test shall be conducted where it is considered that the change in packaging will affect the outcome of the test.

Classification tests should be performed on the substance or mixture as presented and used.

If the same chemical is to be presented in a physical form different from that which was tested and which is considered likely to materially alter its performance in a classification test, the substance or mixture must also be tested in the new form.

2.2.3.4 Testing and evaluation of hazard information

[43] This comprises substances, mixtures and articles which are manufactured with a view to producing a practical, explosive or pyrotechnic effect.

Where test data are available, these shall be evaluated against the set criteria for classification and labelling.

When the screening procedure indicates that a substance or mixture may possess explosive properties, a cautious approach when performing the tests is necessary to ensure safe handling.

For information on the test procedures see the following Section 2.2.3.5 where the individual test series are described in context with the respective decision logic.

The test procedures for the classification of explosives are described in detail in the Part I of the UN-MTC.

2.2.3.5 Classification procedure and decision logics

Any substance, mixture or article having or suspected of having explosives characteristics shall be considered for classification in the hazard class of explosives. Substances, mixtures and articles classified in this hazard class shall be assigned to the appropriate division or as unstable explosive.

The classification is divided into two stages, the acceptance procedure and the assignment procedure.

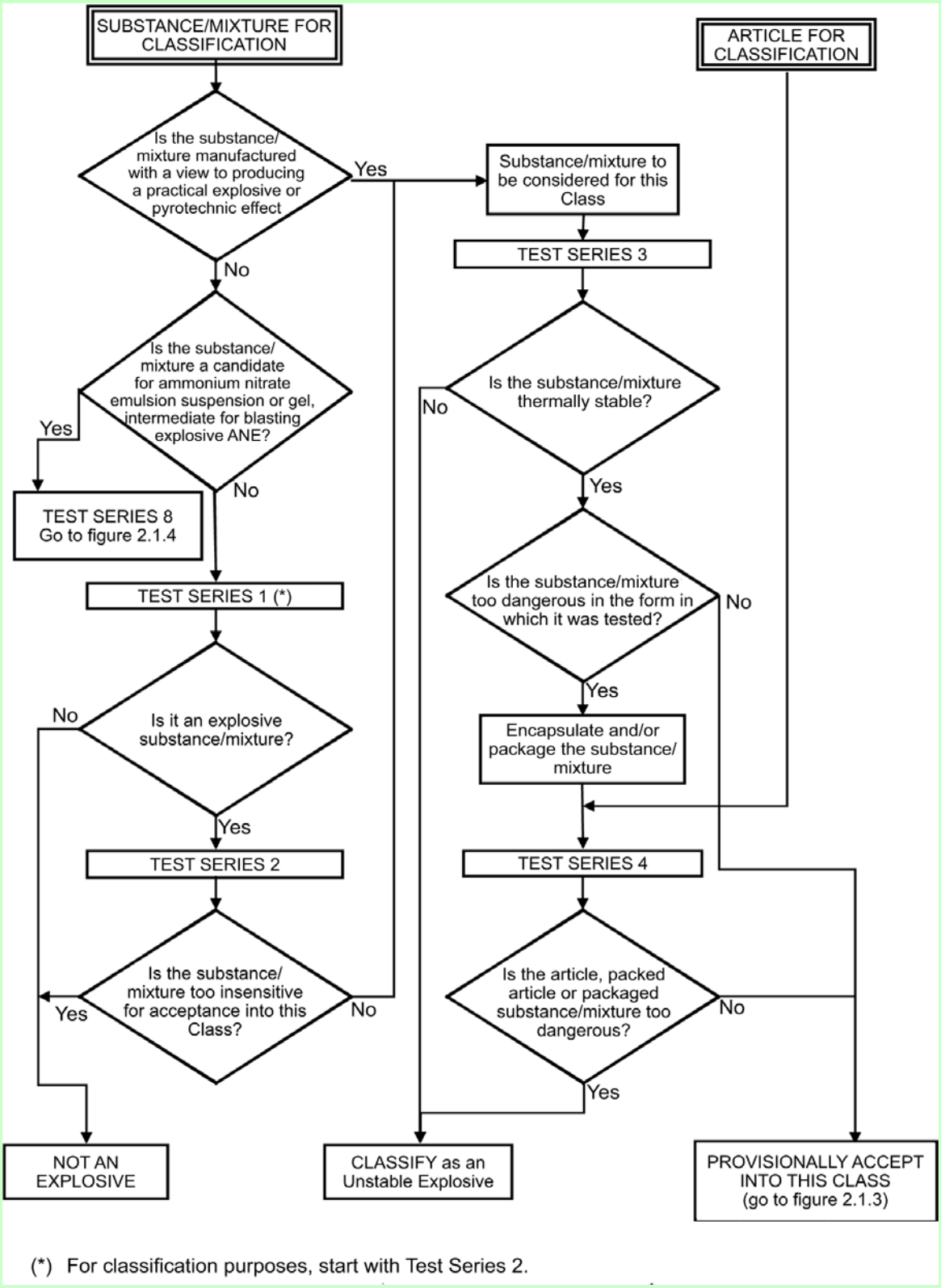
In the acceptance procedure, the potential of a substance, mixture or article to explode should be ascertained and its stability and sensitivity shown to be acceptable. If the substance, mixture or article is not characterised as unstable explosive and is provisionally accepted into the class of explosives, it is then necessary to ascertain the correct division by the assignment procedure. The further subdivision into compatibility groups A to S is described in detail in the UN-RTDG, section 2.1.1. The compatibility groups and their recommended combination identify types of explosives which are deemed to be compatible, e.g. for combined storage or transportation and can therefore be used to distinguish technical requirements (especially) in these sectors.

The tests for acceptance and the further tests to determine the correct division are grouped into eight test series. Classification procedures, test methods and criteria are described in detail in Part I of the UN-MTC.

NOTE: The person responsible for classification should study the criteria for classification before and during use of the decision logics.

Annex I: *Figure 2.1.2*

Procedure for provisional acceptance of a substance, mixture or article in the class of explosives (Class 1 for transport)



2.2.3.5.1 Acceptance procedure

The acceptance procedure is used to determine whether or not a substance, mixture or article is a candidate for the class of explosives or is an unstable explosive.

The test methods used for deciding on provisional acceptance into the class of explosives are grouped into four series, numbered 1 to 4 (see CLP Annex I, Figure 2.1.2).

The numbering of test series 1 to 4 relates to the sequence of assessing the results rather than the order in which the tests are conducted. **It may be important for the safety of experimenters that certain tests, using small amounts of material, be conducted first before proceeding to experiment with larger quantities.** To start the testing procedure with test series 3 is highly recommended, because these tests involve relatively small sample sizes, which reduces the risk to test personnel.

Test series 1

Within test series 1 the question "Is it an explosive substance / mixture?" is answered on the basis of international definitions of an explosive substance and the results of three types of series 1 test enable to assess possible explosive effects. The question is answered "yes" if a "+" is obtained in any of the three types of test. If the answer is “no”, the substance / mixture is rejected from this class; it is not an explosive.

The three types of test used are (recommended test is indicated within brackets):

Type 1 (a): a shock test with defined booster and confinement to determine the ability of the substance to propagate a detonation (UN Gap test):

Type 1 (b): a test to determine the effect of heating under confinement (Koenen test); and

Type 1 (c): a test to determine the effect of ignition under confinement (time/pressure test).

Test series 2

Series 2 tests are used to answer the question "Is the substance / mixture too insensitive for acceptance into this Class?". In general, the basic apparatus and method used is the same as that for Test Series 1 but with less stringent criteria, e.g. in the case of gap tests, the gap used is greater than zero. The question is answered "no" if a "+" is obtained in any of the three types of test. If the answer is “yes”, the substance / mixture is rejected from this class; it is not an explosive.

If the substance / mixture is excluded at this point without performing test series 3, no information about the thermal stability and the sensitivity to mechanical stimuli (impact, friction) of the substance or mixture will be available. Also for this reason a general performance of test series 3 is highly recommended.

The following three types of test are used (recommended test is indicated within brackets):

Type 2 (a): a shock test with defined initiation system and confinement to determine sensitivity to shock (UN Gap test);

Type 2 (b): a test to determine the effect of heating under confinement (Koenen test); and

Type 2 (c): a test to determine the effect of ignition under confinement (time/pressure test).

If the substance is manufactured with a view to producing a practical explosive or pyrotechnic effect, it is unnecessary to conduct Test Series 1 and 2.

Test series 3

Test series 3 is used to answer the questions "Is the substance / mixture thermally stable?" and "Is the substance / mixture too dangerous in the form in which it was tested?" This involves tests for determining the sensitiveness of the substance to mechanical stimuli (impact and friction), and to heat and flame.

The following four types of tests are used (recommended test is indicated within brackets):

Type 3 (a): a falling weight test to determine sensitiveness to impact (BAM Fallhammer);

Type 3 (b): a friction, or impacted friction, test to determine sensitiveness to friction (BAM friction apparatus);

Type 3 (c): an elevated temperature test to determine thermal stability (thermal stability test at 75 °C); and

Type 3 (d): an ignition test to determine the response of a substance to fire (small scale burning test)

The first question is answered "no" if a "+" is obtained in test type 3(c) and the substance / mixture is considered as thermally unstable and is classified as an unstable explosive.

The second question is answered "yes" if a "+" is obtained in any of the test types 3(a), 3(b) or 3(d). If a "+" is obtained, the substance / mixture may be encapsulated or otherwise desensitized or packaged to reduce its sensitiveness to external stimuli or is classified as an unstable explosive.

Test series 4

Series 4 tests are intended to answer the question "Is the article, packaged article or packaged substance too dangerous?". Conditions which may occur during supply and use include high /low temperature and high relative humidity, vibration, bumping and dropping.

The two types of test to be carried out are:

Type 4 (a): a test of thermal stability for articles; and

Type 4 (b): a test to determine the hazard from dropping.

The question is answered "Yes" if a "+" is obtained in either test type 4 (a) or 4 (b) and the article is classified as an unstable explosive.

It is important to note that a substance / mixture which fails test series 2 may still, if properly packaged, leave the class of explosives provided that the product is not designed to have an explosive effect and does not exhibit any explosive hazard in test series 6 of the assignment procedure (see example for musk xylene). Such an exclusion from the class of explosives is restricted to the specific type and size of package tested.

Especially for substances / mixtures, which have explosive properties according to test series 1 and 2 but can leave the class of explosives after test series 6 due to proper packaging, it is necessary to communicate these properties in the Safety Data Sheet (SDS). Furthermore, the

results from test types 3 (a) and 3 (b) should be documented in the SDS when they meet the criteria of the EU test method A 14 in Council Regulation (EC) No 440/2008.

2.2.3.5.2 Assignment procedure to a division

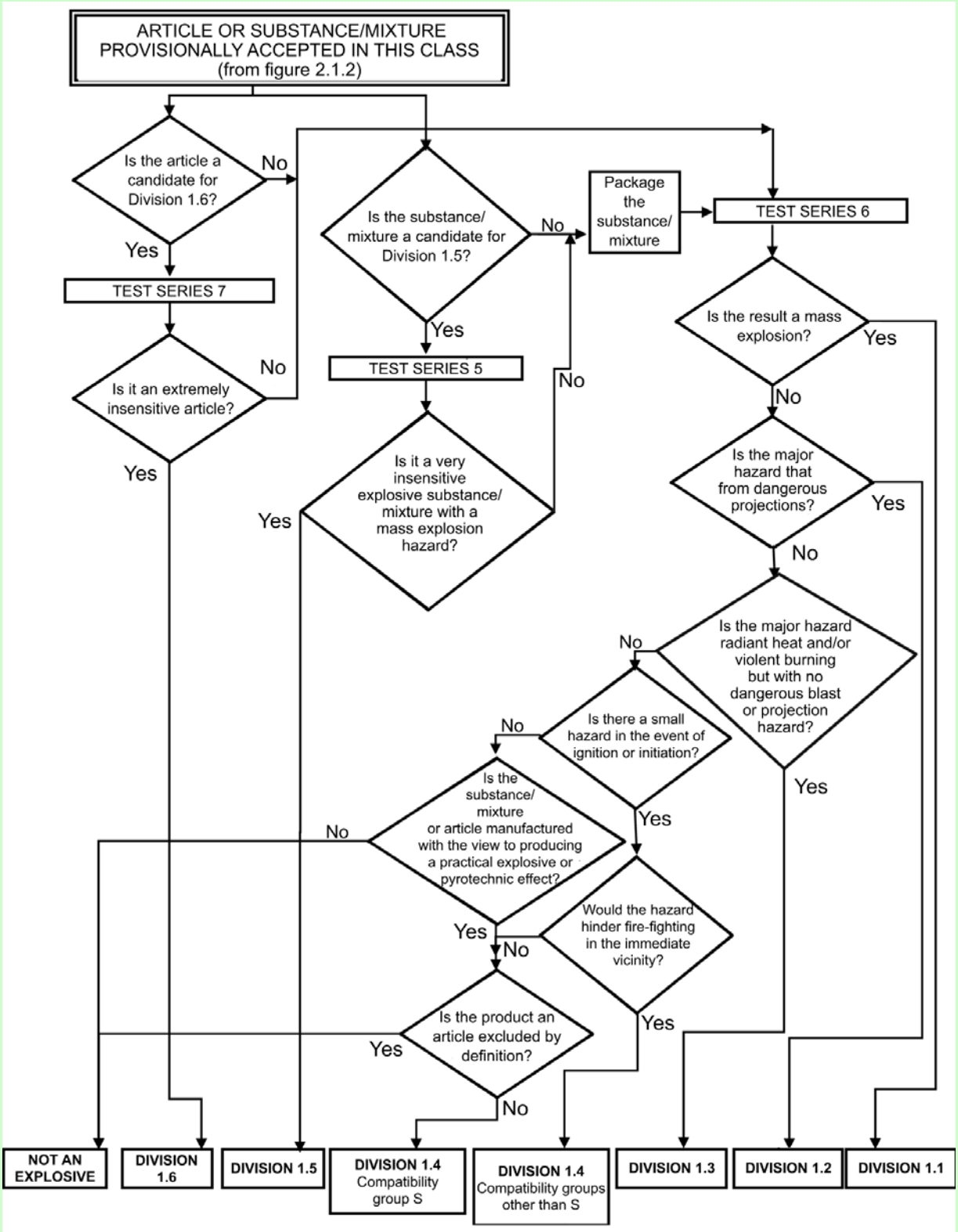
The assignment procedure to one of six divisions, depending on the type of hazard they present, applies to all substances, mixtures and/or articles that are candidates for class of explosives. A substance or article should be assigned to the division which corresponds to the results of the tests to which the substance, mixture or article, as offered for supply and use, has been subjected. Other test results, and data assembled from accidents which have occurred, may also be taken into account.

The test methods used for assignment to a division are grouped into three series - numbered 5 to 7 - designed to provide the information necessary to answer the questions in Figure 2.1.3 in CLP.

NOTE: The person responsible for classification should study the criteria for classification before and during use of the decision logics.

Annex I: *Figure 2.1.3*

Procedure for assignment to a division in the class of explosives (Class 1 for transport)



Test series 5

The results from three types of series 5 tests are used to answer the question "Is it a very insensitive explosive substance with a mass explosion hazard?"

The test types are (recommended test is indicated within brackets):

Type 5 (a): a shock test to determine the sensitivity to intense mechanical stimulus (cap sensitivity test[)];

Type 5 (b): thermal tests to determine the tendency for transition from deflagration to detonation (USA DDT test); and

Type 5 (c): a test to determine if a substance, when in large quantities, explodes when subjected to a large fire.

The question is answered "No" if a "+" is obtained in any of the three test types. A candidate for Division 1.5 should pass one test of each type.

Test series 6

The results from three types of series 6 tests are used to determine which division, amongst Divisions 1.1, 1.2, 1.3 and 1.4, corresponds most closely to the behaviour of a product if a load is involved in a fire resulting from internal or external sources or an explosion from internal sources. The results are also necessary to assess whether a product can be assigned to Compatibility Group S of Division 1.4 and whether or not it should be excluded from this class. Test series 6 should be applied to packages of explosive substances and articles in the condition and form in which they are offered for supply and use.

The three types of test are (recommended test is indicated within brackets):

Type 6 (a): a test on a single package to determine if there is mass explosion of the contents (single package test);

Type 6 (b): a test on packages of an explosive substance or explosive articles, or non-packaged explosive articles, to determine whether an explosion is propagated from one package to another or from a non-packaged article to another (stack test); and

Type 6 (c): a test on packages of an explosive substance or explosive articles, or non-packaged explosive articles, to determine whether there is a mass explosion or a hazard from dangerous projections, radiant heat and/or violent burning or any other dangerous effect when involved in a fire (bonfire test).

Test types 6 (a), 6 (b) and 6 (c) are performed in alphabetical order. However, it is not always necessary to conduct tests of all types. Test type 6 (a) may be waived if explosive articles are carried without packaging or when the package contains only one article. Test type 6 (b) may be waived if in each type 6 (a) test:

- The exterior of the package is undamaged by internal detonation and/or ignition; or
- The contents of the package fail to explode, or explode so feebly as would exclude propagation of the explosive effect from one package to another in test type 6(b).

Test type 6(c) may be waived if, in a type 6(b) test, there is practically instantaneous explosion of virtually the total contents of the stack. In such cases the product is assigned to Division 1.1.

If a substance gives a "—" result (no propagation of detonation) in the Series 1 type (a) test, the 6(a) test with a detonator may be waived.

If a substance gives a "—" result (no or slow deflagration) in a Series 2 type (c) test, the 6 (a) test with an igniter may be waived.

Test series 7

The question "Is it an extremely insensitive explosive article?" is answered by series 7 tests and any candidate for Division 1.6 should pass one of each of the ten types of test comprising the series. The first six types of test (7(a)-7(f)) are used to establish if a substance is an Extremely Insensitive Detonating Substance (EIDS) and the remaining four types of test (7(g), 7(h), 7(j) and 7 (k)) are used to determine if an article containing an EIDS may be assigned to Division 1.6.

Test series 7 aims at military explosives and is generally not relevant for explosives for civil use. Therefore the individual tests are not described here. If needed, they can be found in the UN Manual of Test and Criteria, Part I, Section 17.

Test series 8

The question "Is the substance a candidate for "ammonium nitrate emulsion or suspension or gel, intermediate for blasting explosives (ANE)?" (CLP Annex I, Figure 2.1.4) is answered by series 8 tests and any candidate should pass each of the three tests comprising the series. The three test types are (recommended test is indicated within brackets):

Type 8 (a): a test to determine the thermal stability (Thermal Stability Test for ANE);

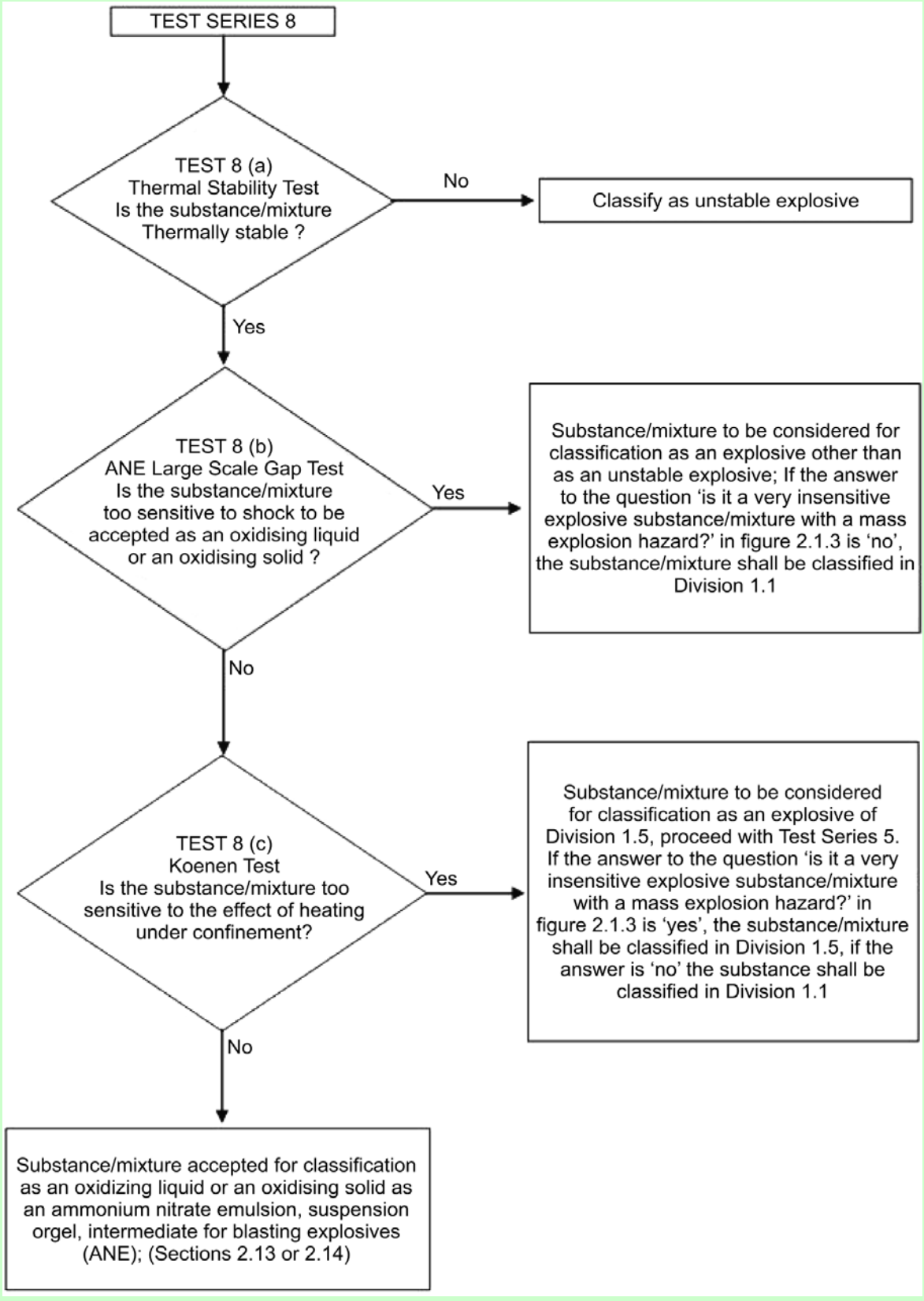
Type 8 (b): a shock test to determine sensitivity to intense shock (ANE gap test); and

Type 8 (c): a test to determine the effect of heating under confinement (Koenen test).

Test series 8 should be used to establish whether an ammonium nitrate emulsion or suspension or gel, intermediate for blasting explosives (ANE) shall be classified as an oxidising liquid or solid. Substances failing any of the tests shall be classified as explosives (Division 1.1. or 1.5) or as an unstable explosive in accordance with CLP Annex I, Figure 2.1.4.

Figure 2.1.4

Procedure for classification of ammonium nitrate emulsions, suspensions or gels



2.2.4 Hazard communication for explosives

2.2.4.1 Pictograms, signal words, hazard statements and precautionary statements

Annex I: *Table 2.1.2* **Label elements for explosives**							
Classification	**Unstable Explosive**	**Division 1.1**	**Division 1.2**	**Division 1.3**	**Division 1.4**	**Division 1.5**	**Division 1.6**
GHS Pictograms							
Signal Word	Danger	Danger	Danger	Danger	Warning	Danger	No signal word
Hazard Statement	H200: Unstable Explosive	H201: Explosive; mass explosion hazard	H202: Explosive; severe projection hazard	H203: Explosive; fire, blast or projection hazard	H204: Fire or projection hazard	H205: May mass explode in fire	No hazard statement
Precautionary Statement Prevention	P201 P202 P281	P210 P230 P240 P250 P280	P210 P230 P240 P250 P280	P210 P230 P240 P250 P280	P210 P240 P250 P280	P210 P230 P240 P250 P280	No precautionary statement
Precautionary Statement Response	P372 P373 P380	P370+P380 P372 P373	P370+P380 P372 P373	P370+P380 P372 P373	P370+P380 P372 P373	P370+P380 P372 P373	No precautionary statement
Precautionary Statement Storage	P401	P401	P401	P401	P401	P401	No pre-cautionary statement
Precautionary Statement Disposal	P501	P501	P501	P501	P501	P501	No precautionary statement

The wording of the Precautionary Statements is found in CLP Annex IV, Part 2.

2.2.4.2 Additional labelling provisions

According to CLP Annex I, 2.1.3, unpackaged explosives or explosives repacked in packaging other than the original or similar packaging shall have the following label elements:

Annex I: 2.1.3. *Hazard communication*
(a) the pictogram: exploding bomb;

(b) the signal word: “Danger”; and

(c) the hazard statement: 'explosive; mass explosion hazard'

unless the hazard is shown to correspond to one of the hazard categories in Table 2.1.2, in which case the corresponding symbol, signal word and/or the hazard statement shall be assigned.

Supplemental hazard statements shall be included in the section for supplemental information on the label and are defined in Annex II of CLP as follows:

Annex II: 1.1.1. EUH001 “Explosive when dry”

For explosive substances and mixtures as referred to in chapter 2.1 of part 2 of Annex I, placed on the market wetted with water or alcohols or diluted with other substances to suppress their explosives properties

Annex II: 1.1. 6 EUH044 “Risk of explosion if heated under confinement”

For substances and mixtures not in themselves classified as explosive in accordance with section 2.1 of part 2 of Annex I, but which may nevertheless display explosive properties in practice if heated under sufficient confinement. In particular, substances which decompose explosively if heated in a steel drum do not show this effect if heated in less-strong containers.

2.2.5 Re-classification of substances and mixtures classified as explosive according to DSD or already classified for transport

2.2.5.1 Re-classification of substances and mixtures classified in accordance with DSD

A direct “translation” from classification according to DSD or DPD to the GHS classification according to CLP is not possible.

A lot of substances and mixtures which are labelled with the symbol “E” and the risk phrases R2 or R3 in accordance with DSD will be classified as "explosive" under CLP and the respective division can be derived from the transport classification. However, there are also many substances and mixtures which will be classified in other hazard classes, such as organic peroxides, self-reactives, flammable solids (e.g. musk xylene) or oxidising solids (e.g. troclosone).

In DSD explosive properties are determined by the EU test method A.14 as described in Regulation (EC) No 440/ 2008 (former Annex V to DSD). The EU test method A.14 is based on the sensitivity of substances and mixtures to thermal and mechanical stimuli.

The EU test method A.14 comprises three parts:

- thermal sensitivity test to determine the effect of heating under confinement (Koenen test)
- mechanical sensitivity test to determine the sensitivity to impact
- mechanical sensitivity test to determine the sensitivity to friction

The criterion linked of the thermal sensitivity test to determine the effect of heating under confinement (Koenen test) is equal in EU test method A.14 and GHS test series 2.

At first glance, the tests for mechanical sensitivity to impact and friction also seem to be the same in EU test method A.14 and GHS test series 3. However, the questions to be answered by these tests and the criteria are different. The results of tests 3(a) and 3(b) in the GHS lead

to the decision whether a substance/mixture is too sensitive to mechanical stimuli. For this purpose, lower limits are stated. On the other hand, upper limits as defined in the A.14 test method result in the decision whether a substance/mixture has an explosive hazard.

Some additional remarks are necessary regarding differences between the above mentioned supplemental hazard statements EUH001 and EUH044 and their respective R-phrases R1 and R44. These differences originate from the different systematic approach of classifying explosives and explosive properties, respectively.

EUH001 can be assigned only to such explosive substances and mixtures of the hazard class of explosives which are properly desensitised to fulfil the criteria of the future hazard class "Desensitised Explosives" (and therefore do not meet the criteria of the hazard class of explosives).

Risk phrase R1 shall be assigned to all explosive substances and preparations (evaluated by test method A14 and which have E; R2 or R3 in the undiluted state) put on the market in solution or in a wetted form.

The criteria for the assignment of R44 according to DSD, Annex VI are defined as follows:

"For substances and preparations not in themselves classified as explosive in accordance with section 2.2.1 above but which may nevertheless display explosive properties in practice if heated under sufficient confinement. For example, certain substances which would decompose explosively if heated in a steel drum do not show this effect if heated in less-strong containers."

It has to be mentioned that there is a slight difference between the criteria for EUH044 in CLP and the criteria for R44 in DSD, Annex VI. According to the DSD, Annex VI labelling with R44 is possible for substances and mixtures which do not fulfil the criteria for R3 or R2 (evaluated by test method A.14). According to CLP labelling with EUH044 is possible for substances and mixtures which are not classified as explosive.

2.2.5.2 Relation to transport classification

Normally, the transport classification can be translated one-to-one into the CLP classification for explosives, which are packaged in authorised transport packaging.

For the use of other packaging's or for unpacked substances the additional labelling provisions (see Section 2.2.4.2) have to be observed or re-testing is necessary.

2.2.6 Examples of classification for explosives

Examples are given below for the classification of substances; however, these are also valid for the classification of mixtures.

2.2.6.1 Example of substances and mixtures fulfilling the classification criteria

A) RESULTS FROM APPLICATION OF THE ACCEPTANCE PROCEDURE

0. General data:			
0.1 Name of the substance / mixture	Hexanitrostilbene		
1. Is the substance a candidate for ammonium nitrate emulsion, suspension or gel, intermediate for blasting explosive ANE?	No		

2. Is the substance manufactured with the view to producing a practical explosive or pyrotechnic effect?	Yes		
3. Test Series 3			
3.1 Thermal stability:	75 °C/48 hour test (test 3(c))	Result: "—", thermally stable	
3.2 Impact sensitivity:	BAM Fallhammer test (test 3(a)(ii))	Result: Limiting impact energy 5 J	"—", not too dangerous in form tested
3.3 Friction sensitivity:	BAM friction test (test 3(b)(i))	Result:Limiting load > 240 N	"—", not too dangerous in form tested
4. Is the substance thermally stable?	Yes		
5. Is the substance too dangerous in the form in which it was tested?	No		
6. Conclusion:	**PROVISIONALLY ACCEPT INTO THIS CLASS**		
10.1 Exit:	Apply the assignment procedure		

B) RESULTS FROM APPLICATION OF THE ASSIGNMENT PROCEDURE

1. Is the substance a candidate for Division 1.5?	No	Result: Package the substance	
2. Test Series 6			
2.1 Effect of initiation in the package:	Test 6(a) with detonator	Result: detonation, crater	
2.2 Effect of propagation:	Type 6(b) with detonator	Result: detonation of the whole stack of packages, crater	
2.4 Effect of fire engulfment:	Test 6(c) may be waived because of the result of 6(b) test.		
3. Is the result a mass explosion?	Yes		
4. Conclusion:	**Assignment to Division 1.1**		

2.2.6.2 Example of substances and mixtures not fulfilling the classification criteria

This example is taken from the UN Manual of Tests and Criteria, Part I, Section 10.5.2, Figure 10.5.

A) RESULTS FROM APPLICATION OF THE ACCEPTANCE PROCEDURE

0. General data:			
0.1 Name of the substance	5-tert-butyl-2,4,6-trinitro-m-xylene (musk xylene)		
1. Is the substance a candidate for ammonium nitrate emulsion, suspension or gel, intermediate for blasting explosive ANE?	No		
2. Is the substance manufactured with the view to producing a practical explosive or pyrotechnic effect?	No		
3. Test Series 1			
3.1 Propagation of Detonation:	UN gap test (test 1(a))	Result:"+", propagation of detonation	
3.2 Effect of heating under confinement:	Koenen test (test 1(b))	Result: Limiting diameter 12.0 mm	Fragmentation type "F" "+", shows some explosive effects on heating under confinement
3.3 Effect of ignition under confinement:	Time/pressure test (test 1(c)(i))	Result: "—", no effect on ignition under confinement	
4. Is it an explosive substance?	Yes		
5. Test Series 2			
5.1 Sensitivity to shock:	UN gap test (test 2(a))	Result: "—", not sensitive to shock	
5.2 Effect of heating under confinement:	Koenen test (test 2(b))	Result:Limiting diameter 12.0 mm	Fragmentation type "F" "+", violent effect on heating under confinement.
5.3 Effect of ignition under confinement:	Time/pressure test (test 2(c)(i))	Result: "—", no effect on ignition under confinement	
6. Is the substance too insensitive for acceptance into this class?	No		
Conclusion:	Substance to be considered for this class		
7. Test Series 3			
7.1 Thermal stability:	75 °C/48 hour test (test 3(c))	Result: "—", thermally stable	
7.2 Impact sensitivity:	BAM Fallhammer test	Result: Limiting	

	(test 3(a)(ii))	impact energy 25 J", not too dangerous in form tested.	
7.3 Friction sensitivity:	BAM friction test (test 3(b)(i))	Result: Limiting load > 360 N	"—", not too dangerous in form tested
8. Is the substance thermally stable?	Yes		
9. Is the substance too dangerous in the form in which it was tested?	No		
10. Conclusion:	**PROVISIONALLY ACCEPT INTO THIS CLASS**		
10.1 Exit	Apply the assignment procedure		

B) RESULTS FROM APPLICATION OF THE ASSIGNMENT PROCEDURE

1. Is the substance a candidate for Division 1.5?	No	Result: Package the substance	
2. Test Series 6			
2.1 Effect of initiation in the package:	Test 6(a) with detonator	Result: Only localised decomposition around detonator	No significant reaction
2.2 Effect of ignition in the package:	Test 6(a) with igniter	Result: Only localised decomposition around igniter	No significant reaction
2.3 Effect of propagation:	Type 6(b) test not required as no effect outside package between packages in 6(a) test		
2.4 Effect of fire engulfment:	Test 6	Result: Only slow burning with black smoke occurred.	No effects which would hinder fire fighting
3. Is the result a mass explosion?	No		
4. Is the major hazard that from dangerous projections?	No		
5. Is the major hazard radiant heat and/or violent burning but with no dangerous blast or projection hazard?	No		
6. Is there nevertheless a small hazard in the event of ignition or initiation?	No		
7. Is the substance manufactured with the view to producing a practical explosive or pyrotechnic effect?	No		

8. Conclusion:	**NOT AN EXPLOSIVE**		
8.1 Exit	Consider for another class (e.g. flammable solid)		

2.3 FLAMMABLE GASES

2.3.1 Introduction

The requirements in Chapter 2.2 "Flammable Gases" of Annex I of CLP are identical to those in Chapter 2.2 of GHS.

In addition, the DSD identifies R6 flammable gases that are unstable under certain conditions.

2.3.2 Definitions and general considerations for the classification of flammable gases

Annex I: 2.2.1. *Definitions*

Flammable gas means a gas or gas mixture having a flammable range with air at 20°C and a standard pressure of 101.3 kPa

The flammability range of a flammable gas is defined between the "lower flammability limit" (LFL) in air and the "upper flammability limit" (UFL) in air. In technical literature, the terms "lower explosion limit" (LEL) and "upper explosion limit" (UEL) are often used instead of the LFL and UFL, respectively.

2.3.3 Relation to other physical hazards

For flammable gases that are packaged in aerosols dispensers, see Section 2.4 Flammable aerosols.

2.3.4 Classification of substances and mixtures as flammable gases

2.3.4.1 Identification of hazard information

Many gases are classified in Annex VI of CLP and more gases are classified in the RTDG.

For gases that are not classified in Annex VI nor in the RTDG, there is ample scientific literature giving the flammability range for most gases (e.g. IEC 79-20 "*Data for flammable gases and vapours, relating to the use of electrical apparatus*" – under revision or the databank Chemsafe at http://www.dechema.de/en/chemsafe.html).

In the case a gas or gas mixture needs to be tested for flammability, a recognised international standard shall be used such as EN 1839:2003, *Determination of explosion limits of gases and vapours* or ISO 10156: 1996 *Gases and gas mixtures – Determination of fire potential and oxidising ability for the selection of cylinder valves outlets* (under revision).

2.3.4.2 Screening procedures and waiving of testing for gas mixtures

There are thousands of gas mixtures on the market and there are a limited number of test reports for the flammability of gas mixtures in the scientific literature. Tests to determine the flammability range are time consuming and expensive for gas mixtures that are made on

demand. In most of the cases, the formulator of the gas mixture will use a calculation method as described in ISO 10156 (see Section 2.3.4.4) to determine if the mixture is flammable or not.

2.3.4.3 Classification criteria

Annex I, 2.2.2. *Table 2.2.1* **Criteria for flammable gases**	
Category	Criteria
1	Gases, which at 20°C and a standard pressure of 101.3 kPa: (a) are ignitable when in a mixture of 13% or less by volume in air; or (b) have a flammable range with air of at least 12 percentage points regardless of the lower flammable limit.
2	Gases, other than those of Category 1, which, at 20°C and a standard pressure of 101.3 kPa, have a flammable range while mixed in air.

2.3.4.4 Testing and evaluation of hazard information

The calculation method described in ISO 10156 uses the criterion that a gas mixture is considered non-flammable in air if:

$$\sum_{i=1}^{n} \frac{A'_i}{T_{ci}} \leq 1 \qquad \text{Equation 2.3.4.4 (a)}$$

where:

$$A'_i = \frac{A_i}{\sum_{i=1}^{n} A_i + \sum_{k=1}^{p} K_k B_k} \qquad \text{Equation 2.3.4.4 (b)}$$

and where:

A'_i is the equivalent content in mole% of the *i*:th flammable gas in the mixture

T_{ci} is the maximum content in mole% of the flammable gas *i* which, when mixed with nitrogen, is not flammable in air

A_i is the molar fraction in mole% of the *i*:th flammable gas in the mixture

B_k is the molar fraction in mole% of the *k*:th inert gas in the mixture

K_k is the coefficient of equivaleny of the inert gas *k* compared to nitrogen

n is the total number of flammable gases in the mixture

p is the total number of inert gases in the mixture

The principle of the calculation method is the following: Where a gas mixture contains an inert diluent other than nitrogen, the volume of this diluent is adjusted to the equivalent volume of nitrogen using the equivalency coefficient for the inert gas K_k. From this the equivalent contents A'_i are then derived through Equation 2.3.4.4(b), which should be viewed as the corresponding concentration of the flammable gases if nitrogen was the only inert gas

present in the mixture. In Equation 2.3.4.4(a) the equivalent contents are then compared to the constants T_{ci}, which have been experimentally found using nitrogen as the (only) inert gas.

It should be noted that ISO 10156 uses molar fractions in some of its equations. For most gases under normal (i.e. non-extreme) conditions, however, the volume fraction can be assumed to be equal to the molar fraction, which is the same as assuming ideal gas behaviour for all gases in the mixture. Furthermore, although normally a fraction is a number ranging from 0 to 1, in this case it is easier to express it as percentage, i.e. the fraction multiplied by 100.

The calculation method described in ISO 10156 determines only if the mixture is flammable or not. It does not determine a flammability range and therefore the calculation method cannot determine if the mixture is flammable Category 1 or Category 2. Therefore, to be on the safe side, mixtures determined to be flammable according the calculation method are classified "Flammable gas; Category 1". If, however, there is a need to distinguish between Category 1 and 2, the lower and the upper explosion limits have to be determined by using a suitable test method (e.g. EN 1839 or ISO 10156).

For mixtures containing both flammable and oxidising components, special calculation methods are described in ISO 10156.

2.3.5 Hazard communication for flammable gases

2.3.5.1 Pictograms, signal words, hazard statements and precautionary statements

Annex I: 2.2.3. *Table 2.2.2* **Label elements for flammable gases**		
Classification	Category 1	Category 2
GHS Pictogram		No pictogram
Signal word	Danger	Warning
Hazard statement	H220: Extremely flammable gas	H221: Flammable gas
Precautionary Statement Prevention	P210	P210
Precautionary Statement Response	P377 P381	P377 P381
Precautionary Statement Storage	P403	P403
Precautionary Statement Disposal		

The wording of the Precautionary Statements is found in CLP Annex IV, Part 2.

2.3.5.2 Additional labelling provisions

Some flammable gases are unstable under certain conditions. This is identified by the allocation of the phrase EUH006.

Annex II, 1.1.2. EUH006 — 'Explosive with or without contact with air'

For substances and mixtures which are unstable at ambient temperatures, such as acetylene.

So far, EUH006 has been allocated to two flammable gases (acetylene, ethylene oxide) in Annex VI to CLP. The test method and criteria to allocate this hazard statement are under development at the UN Sub-Committee of experts on the GHS.

2.3.6 Re-classification of substances and mixtures classified as flammable gases according to DSD or already classified for transport

2.3.6.1 Re-classification of substances and mixtures classified in accordance with DSD

Because DSD has no sub-categories for flammable gases, there is no direct translation possible between the classification for flammability of the gases according to DSD and the two categories for flammable gases according to CLP.

Flammable gases that are listed in Annex I of DSD with "F+; R12" have all been reclassified in accordance with the criteria above and identified with either "Flam.Gas1; H220" or "Flam.Gas 2; H221" in Annex VI of CLP.

Flammable gases that are not listed in Annex VI should be reclassified according to the new criteria.

2.3.6.2 Relation to transport classification

The criteria for Category 1 correspond to the criteria that have been in use for classifying "Flammable Gases" in the RTDG. Consequently all gases listed as flammable in the RTDG shall be classified as "Flam.Gas 1; H220".

2.3.7 Example of classification for flammable gases

Example of a classification using the calculation method of ISO 10156

Example mixture: 2 % (H_2) + 6 % (CH_4) + 27 % (Ar) + 65 % (He)

Calculation steps:

Step 1: Assign the gases and state their molar fractions, assuming the molar fractions are equal to the volume fractions (ideal gas behaviour for all gases).

H_2 is flammable gas 1, yielding $A_1 = 2$ mole %

CH_4 is flammable gas 2, yielding $A_2 = 6$ mole %

Ar is inert gas 1, yielding $B_1 = 27$ mole %

He is inert gas 2, yielding $B_2 = 65$ mole %

$n = 2$ since there are two flammable gases in the mixture

$p = 2$ since there are two inert gases in the mixture

Step 2: Look up the values of T_{ci} and K_i in ISO 10156.

T_{c1} = 5.7 mole %

T_{c2} =14.3 mole %

K_1 = 0.5

K_2 = 0.5

Step 3: Calculate the equivalent gas contents A'_i for the flammable gases according to Equation 2.3.4.4(b).

$$A'_1 = \frac{2}{(2+6)+(0.5\times 27+0.5\times 65)} = 3.7 \text{ mole \%}$$

$$A'_2 = \frac{6}{(2+6)+(0.5\times 27+0.5\times 65)} = 11.1 \text{ mole \%}$$

Step 4: Calculate the flammability of the gas mixture according to Equation 2.3.4.4(a).

$$\sum_{i=1}^{2} \frac{A'_i}{T_{ci}} = \frac{A'_1}{T_{c1}} + \frac{A'_2}{T_{c2}} = \frac{3.7}{5.7} + \frac{11.1}{14.3} = 1.43$$

Step 5: Compare the outcome to the criterion in Equation 2.3.4.4(a).

Since 1.43 > 1, this particular gas mixture is considered to be flammable.

2.4 FLAMMABLE AEROSOLS

2.4.1 Introduction

The criteria for flammable aerosols are found in Annex I, Section 2.3 of CLP and in the Aerosol Dispensers Directive 75/324/EEC.

2.4.2 Definitions and general considerations for the classification of flammable aerosols

Annex I: 2.3.1. Aerosols, this means aerosol dispensers, are any non-refillable receptacles made of metal, glass or plastics and containing a gas compressed, liquefied or dissolved under pressure, with or without a liquid, paste or powder, and fitted with a release device allowing the contents to be ejected as solid or liquid particles in suspension in a gas, as a foam, paste or powder or in a liquid state or in a gaseous state.

2.4.3 Classification of flammable aerosols

2.4.3.1 Classification criteria

Annex I, 2.3.2.1. Aerosols shall be considered for classification as flammable in accordance with 2.3.2.2 if they contain any component which is classified as flammable according to the criteria contained in this part i.e.:

– Liquids with a flash point ≤ 93°C, which includes flammable liquids according to section 2.6 of this Annex

– Flammable gases (see 2.2);

– Flammable solids (see 2.7)

Note

Flammable components do not cover pyrophoric, self-heating or water-reactive substances and mixtures because such components are never used as aerosol contents.

2.3.2.2. A flammable aerosol shall be classified in one of the two categories for this Class on the basis of its components, of its chemical heat of combustion and, if applicable, of the results of the foam test (for foam aerosols) and of the ignition distance test and enclosed space test (for spray aerosols) in accordance with Figure 2.3.1 and the UN Recommendations on the Transport of Dangerous Goods, the Manual of Tests and Criteria, part III, chapters 31.4, 31.5 and 31.6.

Note: Flammable aerosols do not fall additionally within the scope of sections 2.2 (flammable gases), 2.6 (flammable liquids) or 2.7 (flammable solids) of Annex I of CLP. Depending on their contents, aerosol dispensers may additionally fall within the scope of other hazard classes (e.g. health and environmental hazard classes).

The following definitions can be found in the Aerosol Dispensers Directive 75/324/EEC:

Non-flammable aerosol: The aerosol is not classified in the hazard class for flammable aerosols if it contains 1% or less flammable components **and** the chemical heat of combustion is less than 20 kJ/g.

Extremely flammable aerosol: The aerosol is classified as extremely flammable aerosol (Category 1) in the hazard class for flammable aerosols if it contains 85% or more flammable components **and** the chemical heat of combustion exceeds or is equal to 30 kJ/g.

Other aerosols: All other aerosols will be submitted to appropriate flammability classification procedures in order to select the appropriate Category 1 or 2 or to decide not to classify the aerosol.

If the aerosols are not submitted to the flammability classification procedures, then they shall be automatically classified as 'extremely flammable', as specified in Directive 75/324/EEC.

Under Directive 75/324/EEC, flammability classification for aerosols refers to 'extremely flammable' and 'flammable'. This corresponds to the terms 'Category 1' and 'Category 2' which are used in CLP.

The chemical heat of combustion will be determined in accordance with CLP Annex I, 2.3.4.1 or with point 1.10 of the Annex to Directive 75/324/EEC.

2.4.3.2 Testing and evaluation of hazard information

Results from the ignition distance test, the enclosed space test and the foam flammability test may be used for the classification for flammable aerosols. These test methods also described under point 6.3 of the Annex to Directive 75/324/EEC and are therefore available in all EU languages.

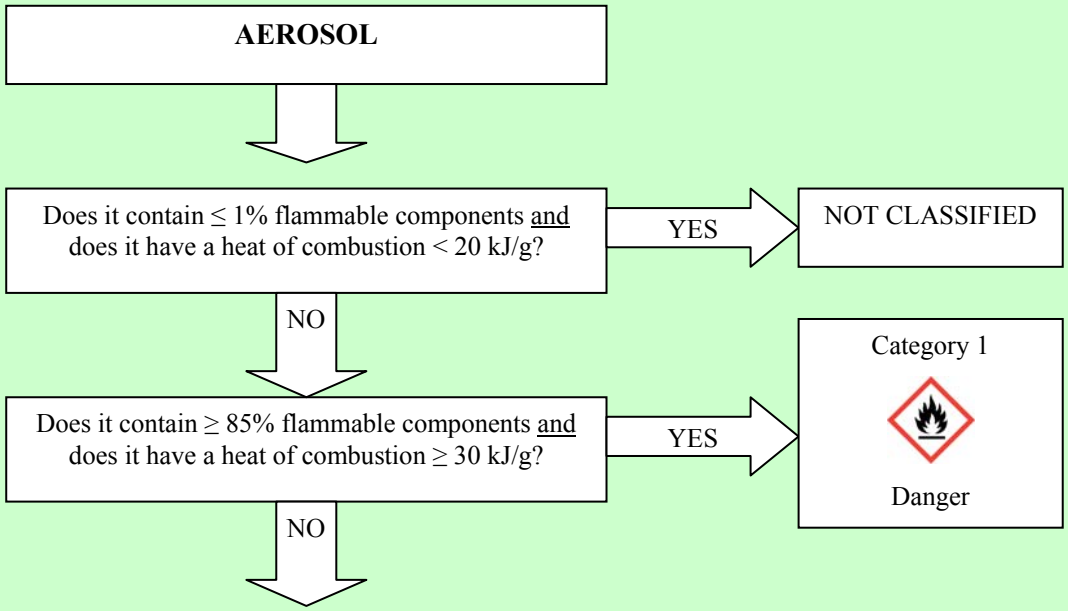
If the evaluation according to the appropriate criteria (see previous sections) shows that the classification criteria are fulfilled, the aerosol will be classified in one of the two categories.

2.4.3.3 Decision logic

NOTE: The person responsible for classification should study the criteria for classification before and during use of the decision logics.

Annex I: *Figure 2.3.1*

Figure 2.3.1 (a) for flammable aerosols



For spray aerosols, go to decision logic 2.3.1 (b);

For foam aerosols, got to decision logic 2.3.1 (c).

Figure 2.3.1 (b) for spray aerosols

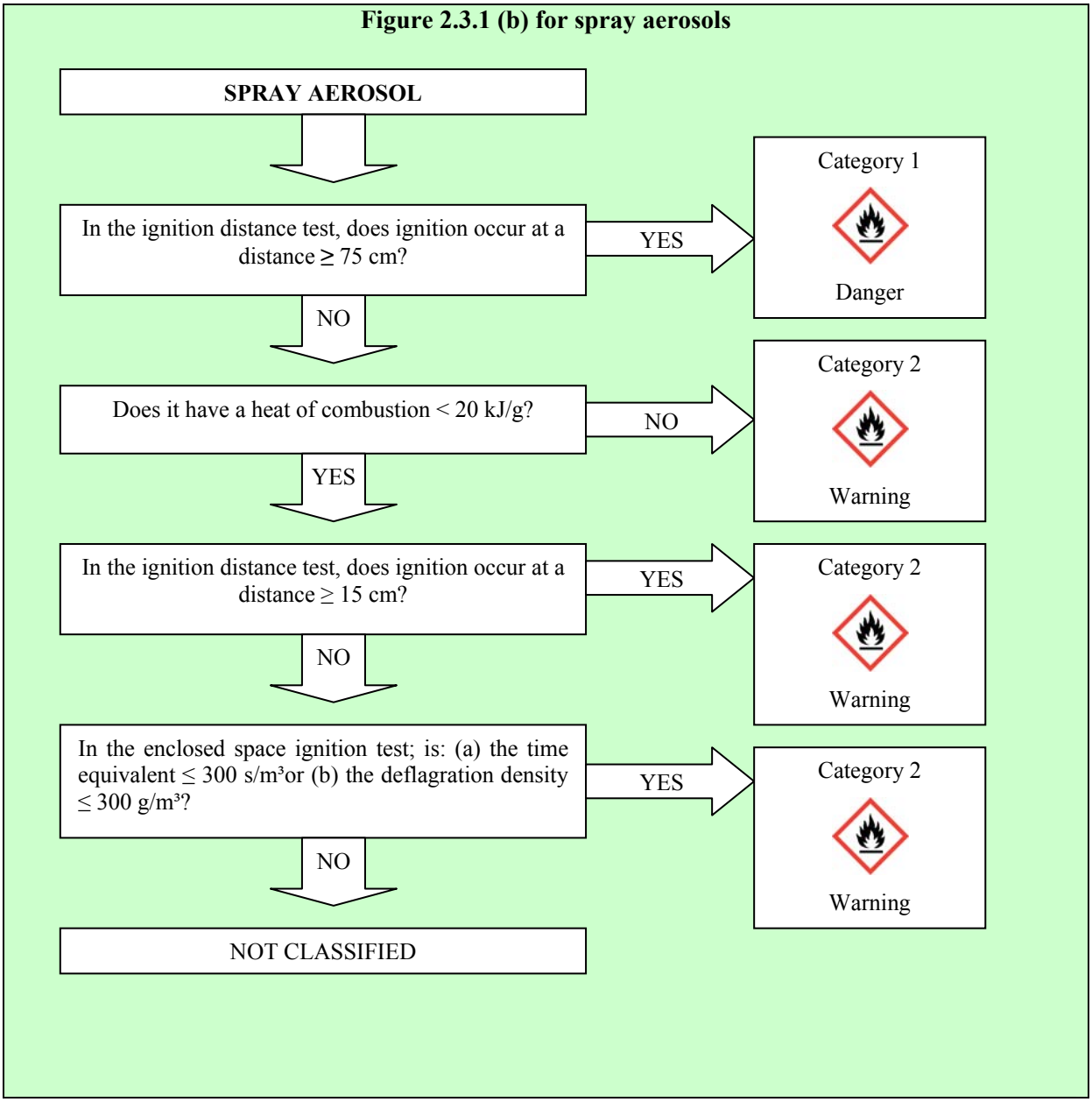
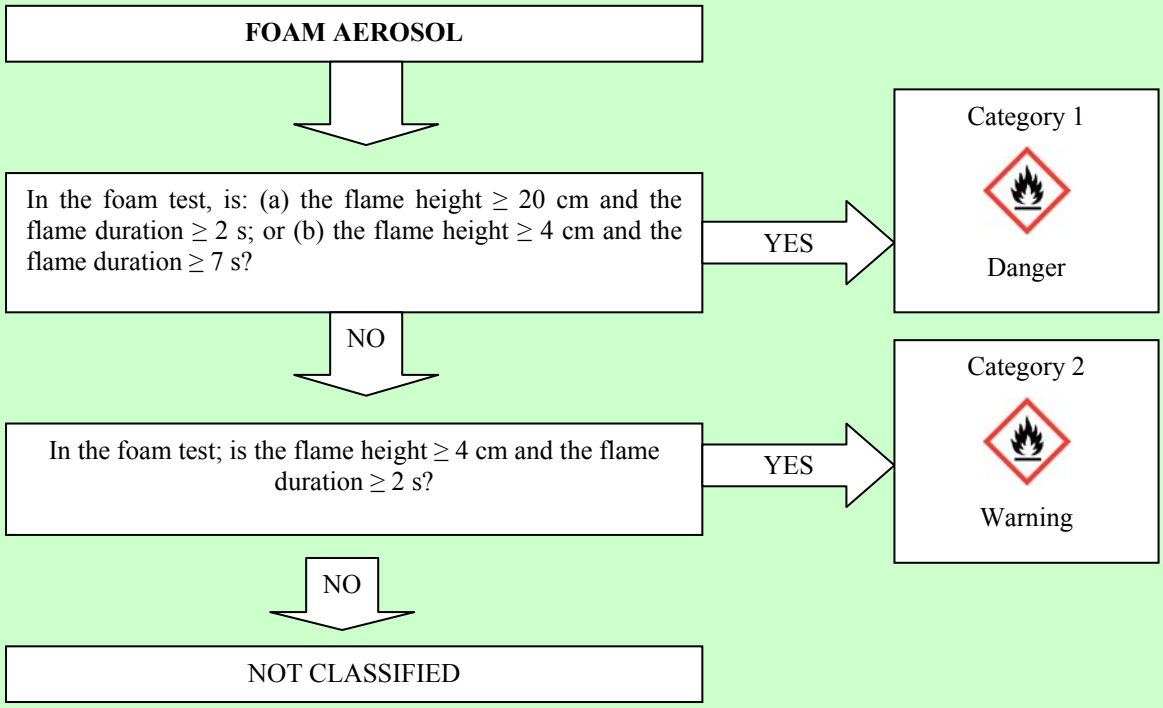


Figure 2.3.1 (c) for foam aerosols



2.4.4 Hazard communication for flammable aerosols

2.4.4.1 Pictograms, signal words, hazard statements and precautionary statements

Annex I: 2.3.3. *Table 2.3.2* **Label elements for flammable aerosols**		
CLASSIFICATION	Category 1	Category 2
GHS Pictograms		
Signal word	Danger	Warning
Hazard statement	H222: Extremely flammable aerosol	H223: Flammable aerosol
Precautionary Statement Prevention	P210 P211 P251	P210 P211 P251
Precautionary Statement		

Response		
Precautionary Statement Storage	P410 + P412	P410 + P412
Precautionary Statement Disposal		

The wording of the Precautionary Statements is found in CLP Annex IV, Part 2.

2.4.4.2 Additional labelling provisions

Directive 75/324/EEC imposes additional labelling requirements on all aerosols, flammable or not, including those which are not within the scope of CLP.

For example:

- Where an aerosol dispenser contains flammable components but is not classified as flammable, the quantity of flammable material contained in the aerosol dispenser must be stated clearly on the label, in the form of the following wording: "X% by mass of the contents are flammable".

2.4.5 Re-classification of flammable aerosols according to DSD

In DSD no hazard class 'flammable aerosols' is defined. In CLP flammable aerosols is a new distinct hazard class. DSD made, in its Annex VI, point 1.7, reference to the flammability criteria of the Aerosol Dispensers Directive 75/324/EEC. No previous classification is useful to complete classification under CLP.

Until 2008, the Aerosol Dispensers Directive 75/324/EEC followed a very conservative approach as in principle all aerosols with flammable contents (according to the criteria laid down for the categories "extremely flammable", "highly flammable" and "flammable" and listed in Annex VI to DSD) had to be considered as flammable in the strictest category concerned, regardless of the amount of flammable content.

Only where the person responsible for the marketing of aerosol dispensers was in possession of test results or other data showing that although those aerosol dispensers had flammable contents they did not present any risk of ignition under normal or reasonably foreseeable conditions of use, he could on his own responsibility decide not to apply the labelling provisions for flammable aerosols. Only very few aerosol products could benefit from that exemption. Flammability testing of aerosols was the exception, as it was easily foreseeable that the vast majority of aerosol products could not fulfil these strict conditions anyway. Due to the widespread use of propellants which are classified as 'extremely flammable', the vast majority of aerosols were labelled as 'extremely flammable'.

At UN level this conservative philosophy of the former Aerosol Dispensers Directive was acknowledged and a provision was introduced stating that *aerosols not submitted to the flammability classification procedures shall be classified (as 'extremely flammable') in Category 1*.

Following the CLP criteria for flammable aerosols, the vast majority of aerosols will therefore continue to be classified as 'extremely flammable' in Category 1, without the need to perform superfluous testing.

2.4.6 Examples of classification for flammable aerosols

For reasons of simplification the active materials chosen in the examples have been considered as non combustible materials (ΔH_c = 0 kJ/g). However this is not the case in practice.

2.4.6.1 Examples of aerosols fulfilling the classification criteria

Deodorant:

Composition:

Butane/propane: 70% (flammable components, ΔH_c = 43.5 kJ/g)

Ethanol: 25% (flammable components, ΔH_c = 24.7 kJ/g)

Others: 5% (non-flammable components, ΔH_c = 0 kJ/g)

This spray aerosol contains 95% of flammable components, and its chemical heat of combustion equals 36.6 kJ/g (= 0.70 * 43.5 + 0.25 * 24.7).

This aerosol is classified in Category 1.

Air freshener (wet):

Composition:

Butane/propane: 30% (flammable components, ΔH_c = 43.5 kJ/g)

Others: 70% (non-flammable components, ΔH_c = 0 kJ/g)

This spray aerosol contains 30% of flammable components and its chemical heat of combustion equals 13.1 kJ/g.

In the ignition distance test, the ignition occurs at less than 75 cm but more than 15 cm.

This aerosol is classified in Category 2.

2.4.6.2 Examples of aerosols not fulfilling the classification criteria

Shaving foam:

Composition:

Butane/propane: 4% (flammable components, ΔH_c = 43.5 kJ/g)

Others: 96% (non-flammable components, ΔH_c = 0 kJ/g)

This foam aerosol contains 4% of flammable components and its chemical heat of combustion equals 1.7 kJ/g.

In the foam test, the flame height is less than 4 cm and the flame duration less than 2 s.

This aerosol is not classified as flammable aerosol.

However the quantity of flammable components must be stated clearly on the label: “4% by mass of the contents are flammable”.

2.5 OXIDISING GASES

2.5.1 Introduction

The requirements in Chapter 2.4 "Oxidising Gases" of Annex I of CLP are identical to those in chapter 2.4 of the GHS.

2.5.2 Definitions and general considerations for the classification of oxidising gases

Annex I: 2.4.1. Oxidising gas means any gas or gas mixture which may, generally by providing oxygen, cause or contribute to the combustion of other material more than air does.

2.5.3 Classification of substances and mixtures as oxidising gases

2.5.3.1 Identification of hazard information

There are not many gases that are oxidising. Most oxidising gases are identified as such in the RTDG and in ISO 10156-2: 2005 *Gas cylinders - Gases and gas mixtures*: - *Part 2: Determination of oxidizing ability of toxic and corrosive gases and gas mixtures.*

2.5.3.2 Screening procedures and waiving of testing

There are thousands of gas mixtures containing oxidising gases on the market and there are very few test reports on oxidising potential of gas mixtures in the scientific literature. Tests according to ISO 10156-2 in order to determine the oxidising potential are time consuming and expensive for gas mixtures that are made on demand. In most of the cases, the formulator of the gas mixture will use a calculation method as described in ISO 10156: 1996 *Gases and gas mixtures – Determination of fire potential and oxidising ability for the selection of cylinder valves outlets* (under revision) or ISO 10156-2 to determine if the mixture is oxidising or not.

2.5.3.3 Classification criteria

Annex I: 2.4.2. *Table 2.4.1*

Criteria for oxidising gases

Category	Criteria
1	Any gas which may, generally by providing oxygen, cause or contribute to the combustion of other material more than air does.

The criteria "more than air does" is further defined in the Note as "having an oxidising power greater than 23.5% as determined by a method specified in the last revision of ISO 10156 and ISO 10156-2".

2.5.3.4 Testing and evaluation of hazard information

The classification method described in ISO 10156:1996 and ISO 10156-2:2005 uses the criterion that a gas mixture should be considered as more oxidising than air if the "Oxidising ¨Power (OP)" of the gas mixture is higher than 0.235 (23.5%).

The OP is calculated as follows:

$$OP = \frac{\sum_{i=1}^{n} x_i C_i}{\sum_{i=1}^{n} x_i + \sum_{k=1}^{p} K_k B_k}$$

Where:

x_i is the molar fraction in mole% of the *i*:th oxidising gas in the mixture

C_i is the coefficient of oxygen equivalency of the *i*:th oxidising gas in the mixture

K_k is the coefficient of equivalency of the inert gas *k* compared to nitrogen

B_k is the molar fraction in mole % of the *k*:th inert gas in the mixture

n is the total number of oxidising gases in the mixture

p is the total number of inert gases in the mixture

For mixtures containing both flammable and oxidising components, special calculation methods are described in ISO 10156.

2.5.4 Hazard communication for oxidising gases

2.5.4.1 Pictograms, signal words, hazard statements and precautionary statements

Annex I: 2.4.3. *Table 2.4.2* **Label elements for oxidising gases**	
Classification	**Category 1**
GHS Pictogram	
Signal word	Danger
Hazard statement	H270: May cause or intensify fire; oxidiser
Precautionary Statement Prevention	P220 P244
Precautionary Statement Response	P370 + P376
Precautionary Statement Storage	P403
Precautionary Statement Disposal	

The wording of the Precautionary Statements is found in CLP Annex IV, Part 2.

2.5.5 Re-classification of substances and mixtures classified as oxidising gases according to DSD or already classified for transport

2.5.5.1 Re-classification of substances and mixtures classified in accordance with DSD

Oxidising gases that were listed in Annex I of DSD with O; R8 have all been identified with "Ox. Gas 1; H270" in the Annex VI of CLP. Steps have been taken to align the classification of oxidising gases both in the transport regulations (e.g. for chlorine) and in CLP (e.g. nitrogen dioxide, chlorine).

2.5.5.2 Relation to transport classification

Most oxidising gases are classified as such with subsidiary risk 5.1 in the RTDG. Consequently all gases listed as oxidising in the RTDG shall be classified as "Ox. Gas 1".

2.5.6 Examples of classification for oxidising gases

Example of a classification using the calculation method of ISO 10156

Example Mixture: 9 % (O_2) + 16 % (N_2O) + 75 % (N_2)

Calculation steps

Step 1: Ascertain the coefficient of oxygen equivalency (Ci) for the oxidising gases in the mixture and the nitrogen equivalency factors (K_k) for the non-flammable, non-oxidising gases.

C_i (N_2O)	= 0.6 (nitrous oxide)
C_i (O)	= 1 (oxygen)
K_k (N_2)	= 1 (nitrogen)

Step 2: Calculate if the Oxidising Power (OP) of the gas mixture

$$OP = \frac{\sum_{i=1}^{n} x_i C_i}{\sum_{i=1}^{n} x_i + \sum_{k=1}^{p} K_k B_k} = \frac{0{,}09 \times 1 + 0{,}16 \times 0{,}6}{0{,}09 + 0{,}16 + 0{,}75 \times 1} = 0{,}186$$

18.6 < 23.5, therefore the mixture is not considered as an oxidising gas.

Important note:

The example is only given to illustrate the principles of the calculation method described in ISO 10156:1996 and ISO 10156-2:2005. For the actual classification of gas mixtures, the most recent version of the ISO standards shall be used where all C_i values for oxidising gases can be found.

2.6 GASES UNDER PRESSURE

2.6.1 Introduction

The requirements in Chapter 2.5 "Gases under pressure" of Annex I of CLP are identical to those in chapter 2.5 of GHS. The hazard Class "Gases under pressure" corresponds to the danger class 2 "Gases" in the RTDG.

2.6.2 Definitions and general considerations for the classification of gases under pressure

2.6.2.1 Definition of "gas"

Annex I: 1.0. Gas means a substance which (i) at 50 °C has a vapour pressure greater than 300 kPa (absolute); or (ii) is completely gaseous at 20 °C at a standard pressure of 101.3 kPa;

This definition means that pure substances are considered as gases when their boiling point (BP) is not higher than 20°C. Substances with a boiling point higher than 20°C are "liquids" except those few that develop a vapour pressure higher than 300 kPa at 50°C; these liquids are considered as "gases" because of the hazard of pressure when packaged.

Hydrogen fluoride (HF) with a BP of 19.4°C is a borderline line case that has always been classified as a liquid.

2.6.2.2 Definition of "gases under pressure"

Annex I: 2.5.1.1. Gases under pressure are gases or gas mixtures which are contained in a receptacle at a pressure of 200 kPa (gauge) or more, or which are liquefied or liquefied and refrigerated.

They comprise compressed gases, liquefied gases, dissolved gases and refrigerated liquefied gases.

This definition means in practice that compressed gases or dissolved gases that are packaged at a pressure less than 200 kPa are not classified for this hazard.

Dissolved gases packaged at a pressure less than 200 kPa (gauge) are liquids and should be classified as such if they have other hazardous properties, e.g. flammable liquids.

Also, liquids packaged under a layer of inert gas (e.g. nitrogen or helium) remain to be classified as liquids and not as "gases under pressure".

2.6.3 Relation to other physical hazards

Gases under pressure need also to be classified for the hazard classes 'flammable gases' and 'oxidising gases' where relevant.

2.6.4 Classification of substances and mixtures as gases under pressure

2.6.4.1 Identification of hazard information

Many gases are identified as such in the RTDG and many flammable gases and some oxidising gases are identified as gases in Annex VI of CLP. The RTDG identify further if the gas can be packaged as a "compressed gas", "liquefied gas", "refrigerated liquefied gas" and "dissolved gas". When the gas is not listed in the RTDG and in case of doubt, the following physical characteristics are necessary to classify a pure substance as a gas:

- The boiling point
- The vapour pressure at 50°C ;

For those pure substances that meet the definition of a gas (see Section 2.6.2), the critical temperature is also necessary.

The following references generally provide good quality data on boiling points, vapour pressure and the critical temperature of pure substances (see Section 2.7.8 for full references):

(a) CRC Handbook of Chemistry and Physics (CRC, 2005)

(b) The Merck Index (Merck, 2001)

(c) ChemFinder (ChemFinder, database)

(d) CHEMSAFE (contains evaluated/recommended data) (CHEMSAFE, database)

(e) Safety Characteristic Data (contains evaluated/recommended data) (Brandes, 2008)

2.6.4.2 Classification criteria

Annex I: 2.5.2. *Table 2.5.2*

Criteria for gases under pressure

Group	Criteria

Compressed gas	A gas which when packaged under pressure is entirely gaseous at -50°C; including all gases with a critical temperature ≤ -50°C.
Liquefied gas	A gas which when packaged under pressure, is partially liquid at temperatures above -50°C. A distinction is made between: i) High pressure liquefied gas: a gas with a critical temperature between -50°C and +65°C; and ii) Low pressure liquefied gas: a gas with a critical temperature above +65°C.
Refrigerated liquefied gas	A gas which when packaged is made partially liquid because of its low temperature.
Dissolved gas	A gas which when packaged under pressure is dissolved in a liquid phase solvent.

2.6.4.3 Testing and evaluation of hazard information

The critical temperature of pure gases is well defined and can be found in technical literature, e.g. EN 13096 "*Transportable gas cylinders — Conditions for filling gases into receptacles — Single component gases"*.

For gas mixtures, the classification is based on the "pseudo-critical temperature" which can be estimated as the mole weighted average of the components' critical temperatures.

$$\text{Pseudo Critical Temperature} = \sum_{i}^{n} x_i \times C_{Tk}$$

where x_i is the component in molar fraction and C_{Tk} is the Critical Temperature of the component in Kelvin.

2.6.5 Hazard communication for gases under pressure

2.6.5.1 Pictograms, signal words, hazard statements and precautionary statements

Annex I: 2.5.3. *Table 2.5.2* **Label elements for gases under pressure**	
Classification	Compressed gas
GHS Pictograms	
Signal word	Warning
Hazard statement	H280: Contains gas under pressure; may explode if heated
Precautionary Statement Prevention	
Precautionary Statement Response	
Precautionary Statement Storage	P410 + P403
Precautionary Statement	

Disposal	

The wording of the Precautionary Statements is found in CLP Annex IV, Part 2.

Packages of gases labelled for transport do not need to bear the relevant GHS Pictograms for classification for "gases under pressure" (Article 33 (3)).

2.6.6 Re-classification of substances and mixtures classified as gases under pressure according to DSD or already classified for transport

2.6.6.1 Re-classification of substances and mixtures classified in accordance with DSD

The hazard class "gases under pressure" is a new hazard class that was not considered in DSD.

Gases that are classified in Annex VI of CLP have been identified with the indication "Press.Gas" in the Classification column but without the indication of the group and the corresponding hazard statement (H280 or H281). The group depends on the physical state in which the gas is packaged and therefore has to be assigned case-by-case (see note U in Part 1 of Annex VI).

2.6.6.2 Relation to transport classification

More gases are classified in the RTDG (ADR/RID/ADN) with an indication of the physical state in the Classification Code that can be used to identify the group of "gases under pressure" according to CLP:

- 1 = compressed gas (e.g. Argon, compressed: Classification code: 1A)
- 2 = liquefied gas (e.g. Butane: Classification code: 2F)
- 3 = refrigerated liquefied gas (e.g Oxygen, refrigerated liquid: 3O)
- 4 = dissolved gas (e.g. Acetylene, dissolved: 4F)

2.6.7 Examples of classification for gases under pressure

Example mixture: 9%(O_2) + 16%(N_2O) + 75%(N_2)

Calculation steps:

Step 1: Ascertain the critical temperatures in Kelvin for the gases in the mixture:

Oxygen (O_2): Temp.Crit.= -118.4°C= 154.75 K

Nitrous Oxide (N_2O): Temp.Crit.= +36.4°C= 309.55 K

Nitrogen (N_2): Temp.Crit.= -147°C= 126.15 K

Step 2: Calculate the pseudo-critical temperature:

0.09×154.75 K + 0.16×309.55 K + 0.75×126.15 K= 158.7 Kelvin = - 115.08 °C

The pseudo-critical temperature is lower than -50°C, therefore the mixture is a "compressed gas"

2.7 FLAMMABLE LIQUIDS

2.7.1 Introduction

Flammable liquids with a flashpoint not more than 60°C are classified in accordance with CLP into one of three categories according to their boiling point and flashpoint.

The threshold limits for the categories differ from the respective threshold limits of DSD for flammable liquids (see Section 2.7.6.1).

They are however identical to the threshold limits of packing group 1, 2 and 3 when classifying "flammable liquids" according to the RTDG.

Substances or mixtures which do not show a flashpoint but do have an explosion range or may become flammable in use have to be marked with EUH018.

2.7.2 Definitions and general considerations for the classification of flammable liquids

Annex I: 2.6.1. Flammable liquid means a liquid having a flashpoint of not more than 60°C

The flashpoint is the lowest temperature of the liquid, corrected to a barometric pressure of 101.3 kPa, at which application of a test flame causes the vapour of the liquid to ignite momentarily and a flame to propagate across the surface of the liquid under the specified conditions of test. This means, the lower explosion limit is exceeded at the flashpoint.

2.7.3 Relation to other physical hazards

For flammable liquids that are packaged in aerosols dispensers, see Section 2.4.3 Flammable aerosols.

2.7.4 Classification of substances and mixtures as flammable liquids

2.7.4.1 Identification of hazard information

For the decision if a substance or mixture is a liquid see Section 2.1.4.

For the classification of a substance or mixture as a flammable liquid, data on the flash point and on the boiling point (or the initial boiling point) are needed. For experimental determination of the flash point information on the viscosity of the liquid is needed, in order to select a suitable method. Furthermore, in order to make use of the derogation for classification in Category 3 according to Annex I Section 2.6.4.5 of CLP (see Section 2.7.4.1.3), information on sustained combustibility is necessary.

Experimentally determined data or data taken from reliable data sources are to be preferred over calculated ones. See also IR/CSA, Section R7.1.3 (boiling point), R7.1.9 (flashpoint).

The following references generally provide good quality data on boiling points (a,b,c,d,e) and flashpoint (c,d,e) of pure substances may be found in:

(a) CRC Handbook of Chemistry and Physics (CRC, 2005)

(b) The Merck Index (Merck, 2001)

(c) ChemFinder (ChemFinder, database)

(d) CHEMSAFE (contains evaluated/recommended data) (CHEMSAFE, database)

(e) Safety Characteristic Data (contains evaluated/recommended data) (Brandes, 2008)

Special care is required when viscous substances or mixtures are tested or when halogenated compounds are present (see Section 2.7.4.4.1).

2.7.4.2 Screening procedures and waiving of testing

2.7.4.2.1 Boiling point

Normally calculation methods based on increments give satisfying results for pure substances and mixtures. With respect to the interesting figure for flammable liquids (35°C) only that method with a mean absolute error lower than 5 °C could be recommended for screening.

2.7.4.2.2 Flash point

Calculation should work for pure liquids, neglecting impurities, if the vapour pressure curve and lower explosion limit are accurately known. For mixtures, calculation of the flashpoint is sometimes not reliable and at this time, it is not possible to predict what reliance can be placed on a calculated value. Calculation can be used as a screening test for mixtures, and a flashpoint need not be determined experimentally if the calculated value using the method cited in CLP Annex I, 2.6.4.3 is 5 °C greater than the relevant classification criterion. However, the restrictions outlined in the CLP Annex I, 2.6.4.2 should be taken account of.

Calculation based on structural similarity or properties is often only applicable to a narrowly defined set of substances. For mixtures they are not yet applicable.

Therefore for both flashpoint and boiling point experimental determination is recommended.

2.7.4.3 Classification criteria

A flammable liquid has to be classified in one of the 3 categories of this class.

Annex I: 2.6.2. *Table 2.6.1*

Label elements for flammable liquids

Category	Criteria
1	Flash point < 23°C and initial boiling point ≤ 35°C
2	Flash point < 23°C and initial boiling point > 35°C
3	Flash point ≥ 23°C and ≤ 60°C[1]

[1] For the purpose of this Regulation gas oils, diesel and light heating oils having a flash point between > 55°C and ≤ 75°C may be regarded as Category 3

Furthermore,

Annex I: 2.6.4.5. Liquids with a flash point of more than 35 °C may be regarded as non-flammable liquids if negative results have been obtained in the sustained combustibility test L.2 of the UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria.

The sustained combustibility test L.2 can be found in the UN-MTC, Part III, section 32.5.2.

Gas oils, diesel and light heating oils in the flashpoint range of 55-75°C may be regarded as a whole as diesel and these hydrocarbon mixtures have varying flashpoints in that range due to seasonal requirements (EN 590). If they are regarded as a whole for CLP they have to be regarded as Category 3. This states however no preliminary decision with respect to downstream Regulations and legislation.

2.7.4.4 Testing and evaluation of hazard information

The assignment to the respective hazard category will determine the technical means to be taken to avoid dangerous events. In combination with other endpoints like explosion limits or auto ignition temperature this can lead to clear restrictions in the conditions of use. The relevant data are to be communicated via the CSR and SDS (see IR/CSA Parts F and G, respectively).

2.7.4.4.1 Testing

Suitable methods are listed in CLP Annex I, Table 2.6.3.

In case of substances with a high decomposition potential, a method using small amounts of liquid (e.g. EN ISO 3679: 2004 *Determination of flash point - Rapid equilibrium closed cup method*) is recommended to reduce the amount of substance under test.

The method to be used has to be chosen taking into account the properties of the liquid (viscosity, halogenated compounds present) and the scope of the standard.

For classification purposes it is recommended to use the mean of at least two test runs. One of these runs may be automated. In case of a deviation between manual and automated determination beyond the tolerance limits of the method, the lower value should be taken or at least the result the determination should be repeated with manual observation. If the experimentally determined flashpoint is found to be within ± 2 °C a threshold limit when using a non-equilibrium method, it is recommended to repeat the determination with an equilibrium method.

If in doubt, or if no flashpoint is found up to 60 °C and the conditions laid down in EUH018, EUH209 and EUH209A are met, (presence of (partly) halogenated compounds, possibility to a loss of volatile flammable or non-flammable components) determination of explosion limits according to EN 1839:2003, *Determination of explosion limits of gases and vapours* or ISO 10156: 1996 *Gases and gas mixtures – Determination of fire potential and oxidising ability for the selection of cylinder valves outlets* (under revision) or determination of explosion points according to DIN EN 15794: 2008, *Determination of explosion points of flammable liquids*, is recommended to decide on labelling with EUH018, EUH209 or EUH209A.

Substances

For pure non-halogenated substances, the flashpoint is usually found 80 °C to 130 °C below the boiling point. Special care has to be taken when a sample contains impurities with a lower boiling point than the main compound. Even if their concentration is below 0.5%, especially if their boiling point is substantially lower, they may have a strong effect on the test result. Impurities with a higher boiling point will normally have no effect on the flashpoint.

Within the respective scope, every standard is applicable.

Mixtures

The flashpoint may be lower than the lowest flashpoint of the components and non-volatile components may influence the flashpoint.

Equilibrium methods are advised if the boiling points of the components of the mixture cover a wide range of temperatures or their concentrations are very different. They are also advised in case of viscous mixtures (alternatively: test methods with low heating rates (1 °C per min) using a stirrer).

In case of viscous mixtures or if an inerting substance is present at low concentrations and this is a highly volatile compound, the ignitability of the mixture may depend on the temperature

at which the tests are started. When an inerting substance is present temperature ranges may exist where the vapour phase is inerted and other temperature ranges where it is not.

Halogenated compounds

The difference between boiling point and flashpoint may be lower than with non-halogenated compounds.

It is highly recommended to run the tests under careful control with manual observation.

Test results may be very difficult to reproduce. In such cases, classification should be based on the lowest value found (flash or burning inside or outside the cup) or on the value obtained during the screening run if in the main trial performed in accordance with the standard, no flash could be found.

2.7.4.4.2 Evaluation of hazard information

Experimentally derived boiling points are to be preferred over calculated ones because of the error of most of the QSAR methods.

Flashpoints determined by testing or from the mentioned internationally recognised qualified literature are to be preferred over those derived by calculation because of the error of most of the QSAR methods respectively their limited application range.

If in literature different flashpoints are found for the same substance the one found as evaluated/recommended has to be preferred.

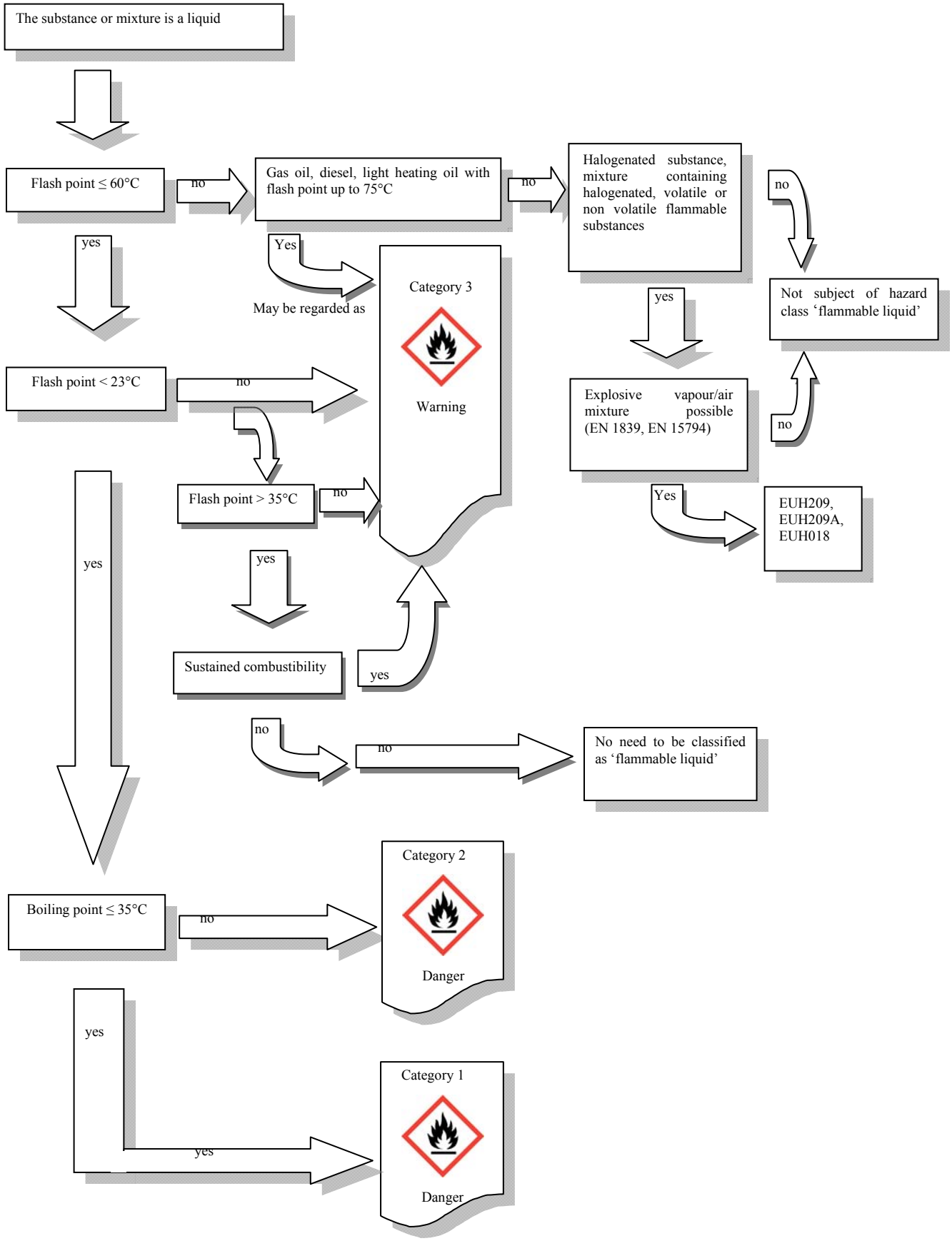
If in literature different flashpoints are found for the same substance where none is found as evaluated/recommended the lower one has to be preferred because of safety reasons or an experimental determination should be carried out.

According to the criteria either Category 1, 2 or 3, including the relevant hazard statement and signal word, have to be assigned (see Section 2.7.5). In case the criteria for EUH018, EUH209 or EUH209A are met, the liquid has to be labelled with either one of these supplemental hazard statements as well. In the majority of cases EUH018 covers EUH209 and EUH209A.

2.7.4.5 Decision logic

NOTE: The person responsible for classification should study the criteria for classification before and during use of the decision logics.

This decision logic is amended to include EUH phrases 018, 209 and 209A.



2.7.5 Hazard communication for flammable liquids

2.7.5.1 Pictograms, signal words, hazard statements and precautionary statements

Annex I: 2.6.3. *Table 2.6.2* **Label elements for flammable liquids**			
Classification	Category 1	Category 2	Category 3
GHS Pictograms			
Signal word	Danger	Danger	Warning
Hazard statement	H224: Extremely flammable liquid and vapour	H225: Highly flammable liquid and vapour	H226: Flammable liquid and vapour
Precautionary Statement Prevention	P210 P233 P240 P241 P242 P243 P280	P210 P233 P240 P241 P242 P243 P280	P210 P233 P240 P241 P242 P243 P280
Precautionary Statement Response	P303 + P361 + P353 P370 + P378	P303 + P361 + P353 P370 + P378	P303 + P361 + P353 P370 + P378
Precautionary Statement Disposal	P501	P501	P501

The wording of the Precautionary Statements is found in CLP Annex IV, Part 2.

2.7.5.2 Additional labelling provisions for flammable liquids

Annex II: 1.1.4. EUH018 - 'In use, may form flammable/explosive vapour-air mixture'

For substances and mixtures not classified as flammable themselves, which may form flammable/explosive vapour-air mixtures. For substances this might be the case for halogenated hydrocarbons and for mixtures this might be the case due to a volatile flammable component or due to the loss of a volatile non-flammable component.

Annex II: 2.9. Liquid mixtures containing halogenated hydrocarbons

For liquid mixtures which show no flashpoint or a flashpoint higher than 60 ˚C but not more than 93 ˚C and contain a halogenated hydrocarbon and more than 5 % highly flammable or flammable substances, the label on the packaging shall bear one of the following statements, depending on whether the substances referred to above are highly flammable or flammable:

EUH209 — 'Can become highly flammable in use' or

EUH209A — 'Can become flammable in use'

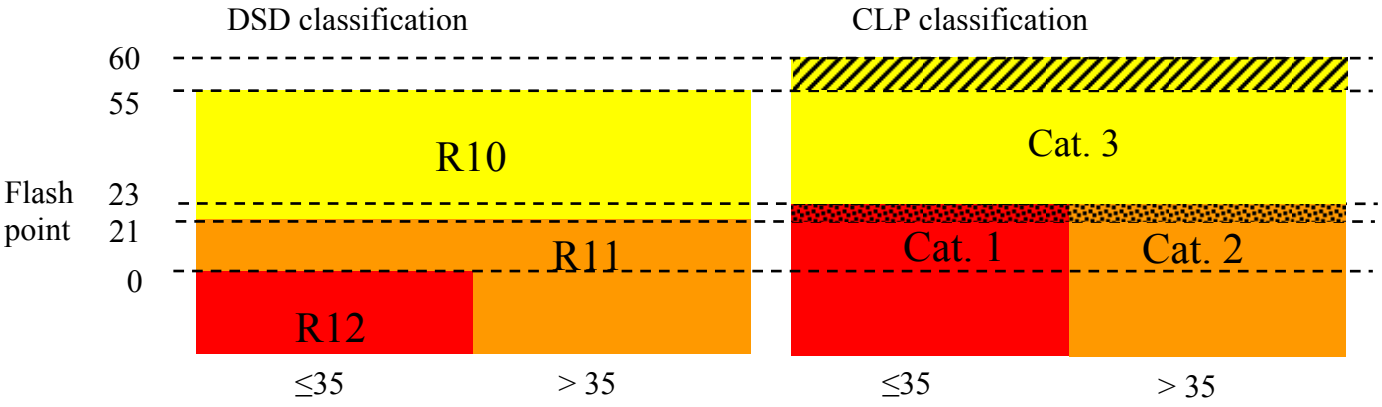
Note: EUH209 and EUH209A are limited to special types of mixtures whereas EUH018 covers a wider range of mixtures. In the majority of cases EUH018 covers EUH209 and EUH209A.

2.7.6 Re-classification of substances classified as flammable liquids according to DSD or already classified for transport

2.7.6.1 Re-classification according to DSD

Direct translation is only partly possible, see Figure 2.7.6.1. For substances and mixtures which are R11 or R10 according to DSD the flashpoint and boiling point as well as the sustained combustibility (R10) data have to be re-evaluated. Re-determination may be necessary if only the flashpoint range is available.

Figure 2.7.6.1: *Comparison of the DSD and the CLP classification*



2.7.6.2 Relation to transport classification

In transport class 3 corresponds to hazard class 'flammable liquid'. Except UN 1203 direct translation of the packing groups into categories is possible if class 3 is the main risk. If class 3 is a subsidiary risk no general one-to-one translation is possible.

2.7.7 Examples of classification for flammable liquids

2.7.7.1 Examples of substances and mixtures fulfilling the classification criteria

Example 1

Mixture of: Butylacetate + 1-Methoxy-2-propylacetate + Xylene + Methylisobutylketone

(24 mol% + 5 mol% + 69 mol% + 2 mol%)

Initial boiling point (calculated):	130 °C
Flash point (calculated):	22 °C
calculated flashpoint is within 5 °C to the limiting value of 23°C ⇨ flash point has to be measured.	
Dyn. Viscosity at 20 °C (DIN 53019):	8 mPas

Flash point (EN ISO 3679):	25.0 °C
⇨ According to boiling point and measured flashpoint result: **Category 3**	

Example 2

Mixture of: Hydrocarbons and dichloromethane

(70 vol % + 30 vol%)

Initial Boiling point (calculated):	52 °C
Flash point:	no flashpoint according to a standard
⇨ Because the hydrocarbon part of the mixture has a flashpoint by itself (-12 °C) the question "is an explosive vapour/air mixture possible (EN 1839, DIN EN 15794) or can it become highly flammable / flammable during use?" has to be answered. **Answer: Yes an explosion range exists, yes it can become highly flammable during use.**	
⇨ According to the answer, **the mixture has to be labelled with EUH018 or EUH209** Note: In that case EUH018 covers EUH209	

2.7.7.2 Examples of substances and mixtures not fulfilling the classification criteria

Example 3

Aqueous formulation of aliphatic polyurethane resin

Boiling point (EC 440/2008 A.2):	92 °C
Dyn. Viscosity at 20 °C (DIN 53019):	1938 mPas
Sample is highly viscous, use low heating rate for flashpoint determination (1 °C /min).	
Flash point (EN ISO 13736):	42.5 °C
Sustained combustibility test (UN L.2) at 60.5 °C:	combustion not sustained
Sustained combustibility test (UN L.2) at 75 °C:	combustion not sustained
⇨ According to the flashpoint result: Category 3 May however **not be regarded as Category 3** because it did not sustain combustion.	

2.7.8 References

Brandes, E. and Möller, W.: Safety Characteristic Data, Volume 1, Flammable gases and liquids, nw-Verlag, 2008

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HEMSAFE (database): http://www.dechema.de/en/chemsafe.html

CRC (2005) CRC Handbook of Chemistry and Physics 86th Edition. Editor in Chief, D. Lide. CRC Press, Taylor and Francis, Boca Raton, FL

Merck (2001) Merck Index 13th Edition. Edited by S Budavari *et al*. Merck & Co, Inc, USA

2.8 FLAMMABLE SOLIDS

2.8.1 Introduction

Solid substances and mixtures are classified as flammable according to their burning behaviour.

2.8.2 Definitions and general considerations for the classification of flammable solids

Annex I: 2.7.1.1. A flammable solid means a solid which is readily combustible**,** or may cause or contribute to fire through friction.

Readily combustible solids are powdered, granular, or pasty substances or mixtures which are dangerous if they can be easily ignited by brief contact with an ignition source, such as a burning match, and if the flame spreads rapidly.

2.8.3 Relation to other physical hazards

Explosives, organic peroxides, self-reactive substances and mixtures as well as pyrophoric or oxidising solids should not be considered for classification as flammable solids since flammability is an intrinsic hazard in these classes.

However, flammable solids can present other physical hazards at the same time, i.e. they might be self-heating or corrosive or emit flammable gases in contact with water.

For flammable solids that are packaged in aerosols dispensers, see Section 2.4, Flammable aerosols.

2.8.4 Classification of substances and mixtures as flammable solids

2.8.4.1 Identification of hazard information

In many cases, a simple screening test (see Section 2.8.4.4) can be used to determine whether a solid should be classified as flammable.

For the classification of a substance or mixture as a flammable solid data on the following properties are needed:

- Melting point
- Information on water reactivity
- Information on flash point if solids containing flammable liquids

Many organic solid substances or mixtures fulfil the criteria to be classified as flammable solids. For inorganic solids, the classification as flammable is rather rare.

2.8.4.2 Screening procedures and waiving of testing

In general, a possible classification as a flammable solid should be considered for any solid organic substance or mixture containing such material. For inorganic material, testing may be waived in cases where the substance is commonly known to be not flammable (i.e. stable salts or metal oxides) or where a flammability hazard can be excluded by any other scientific reasoning.

The test method as described in sub-section 33.2.1.4.3.1 in the UN-MTC should be applied for screening purposes. Alternatively, for determination of explosion characteristics, the

burning index as obtained from the Grewer Oven test (VDI guideline 2263, part 1, 1990, Test methods for the Determination of the Safety Characteristics of Dusts) may be used. If a burning index of 3 or less is found, the substance should not be classified as a flammable solid and no further testing is required. However, if smouldering or a flame is observed, the full test must be carried out.

2.8.4.3 Classification criteria

The classification criteria are fully in accordance with the GHS system.

Annex I: 2.7.2.1. Powdered, granular or pasty substances or mixtures (except powders of metals or metal alloys – see 2.7.2.2) shall be classified as readily combustible solids when the time of burning of one or more of the test runs, performed in accordance with the test method described in Part III, sub-section 33.2.1, of the UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria, is less than 45 seconds or the rate of burning is more than 2,2 mm/s.

2.7.2.2. Powders of metals or metal alloys shall be classified as flammable solids when they can be ignited and the reaction spreads over the whole length of the sample in 10 minutes or less.

2.7.2.3. A flammable solid shall be classified in one of the two categories for this class using Method N.1 as described in 33.2.1 of the UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria.

Table 2.7.1

Criteria for flammable solids

Category	Criteria
1	Burning rate test Substances and mixtures other than metal powders: (a) wetted zone does not stop fire and (b) burning time < 45 seconds or burning rate > 2.2 mm/s Metal powders: burning time ≤ 5 minutes
2	Burning rate test Substances and mixtures other than metal powders: (a) wetted zone stops the fire for at least 4 minutes and (b) burning time < 45 seconds or burning rate > 2.2 mm/s Metal powders: burning time > 5 minutes and ≤ 10 minutes

Note

The test shall be performed on the substance or mixture in its physical form as presented. If, for example, for the purposes of supply or transport, the same chemical is to be presented in a physical form different from that which was tested and which is considered likely to materially alter its performance in a classification test, the substance shall also be tested in the new form.

2.8.4.4 Testing and evaluation of hazard information

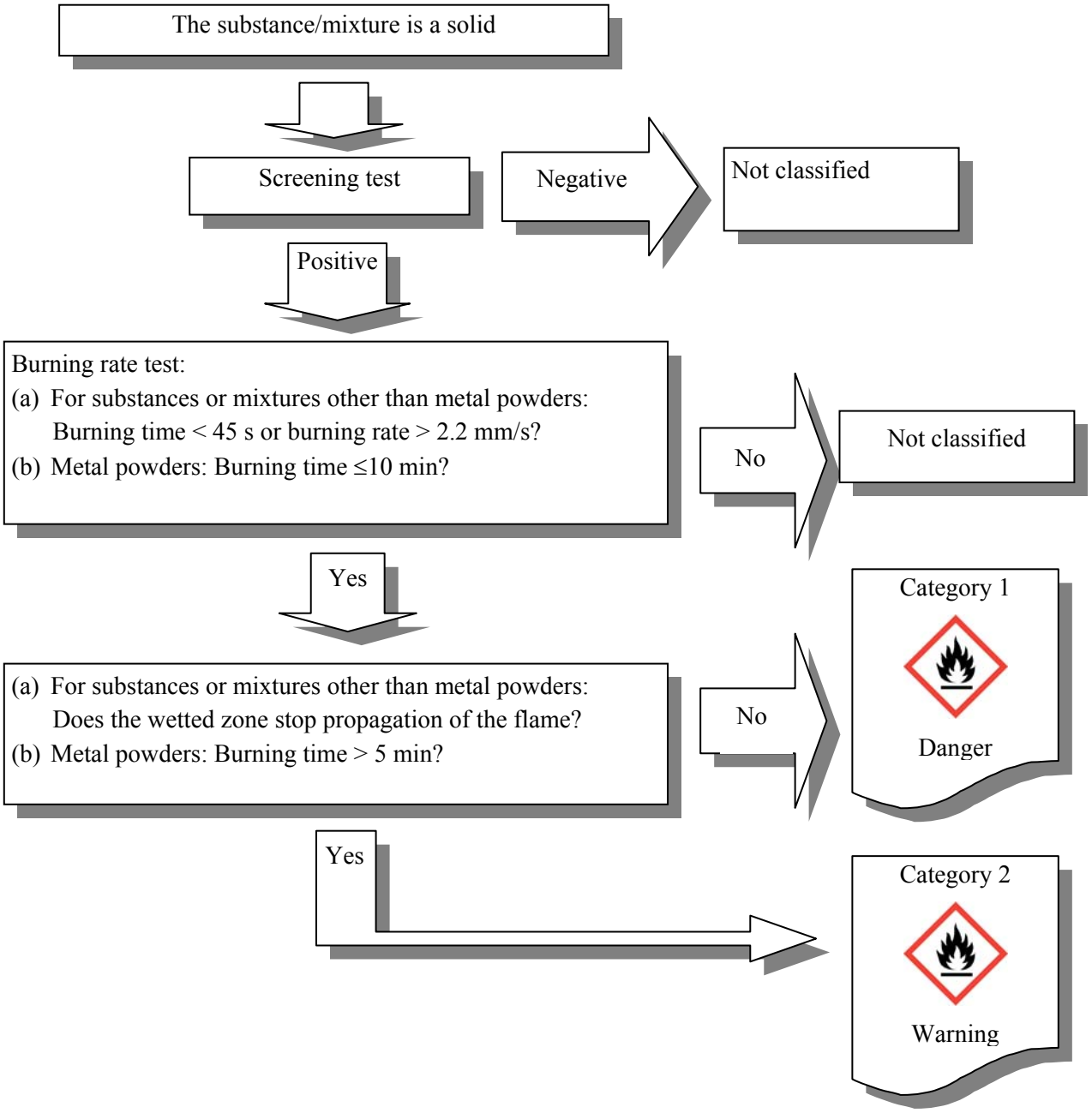
For safety reasons, it is advisable to test for explosive and self-reactive properties first and to rule out pyrophoric behaviour before performing this test. The classification test is described in sub-section 33.2.1.4.3.2 of the UN-MTC. The sample should be tested in its commercially relevant form. Special care has to be taken that the sample forms an unbroken strip or powder

train in the test mould. Large pieces that do not fit into the mould should be gently crushed. For pasty or sticking substances it may be helpful to line the mould with a thin plastic foil which is withdrawn after having formed the train. Classification is based upon the fastest burning rate / shortest burning time obtained in six test runs, unless a positive result is observed earlier. For substances and mixtures other than metal powders, the category is assigned depending on whether the wetted zone is able to stop the flame.

2.8.4.5 Decision logic

NOTE: The person responsible for classification should study the criteria for classification before and during use of the decision logics.

Decision logic for Flammable solids (Decision logic 2.7 of GHS Revision 2):



2.8.5 Hazard communication for flammable solids

2.8.5.1 Pictograms, signal words, hazard statements and precautionary statements

Annex I: 2.7.3. *Table 2.7.2* **Label elements for flammable solids**		
Classification	Category 1	Category 2
GHS Pictograms		
Signal Word	Danger	Warning
Hazard Statement	H228: Flammable Solid	H228: Flammable Solid
Precautionary Statement Prevention	P210 P240 P241 P280	P210 P240 P241 P280
Precautionary Statement Response	P370 + P378	P370 + P378
Precautionary Statement Storage		
Precautionary Statement Disposal		

The wording of the Precautionary Statements is found in CLP Annex IV, Part 2.

2.8.6 Re-classification of substances and mixtures classified as flammable solids according to DSD or already classified for transport

2.8.6.1 Re-classification of substances and mixtures classified in accordance with DSD

In most cases, solid substances and mixtures classified as "F; R11" according to DSD will translate into a flammable solid in CLP. However, such a translation is not unambiguous, and each case should be carefully checked. A substance or mixture classified as "F; R11" might be self-reactive or even – in rare cases – explosive according to CLP. Factors like chemical structure, energy content and decomposition onset as obtained from a Differential Scanning Calorimetry measurement should be taken into account where an unambiguous decision cannot be taken.

Once the classification as flammable solid is established, the assignment of the correct category remains difficult. In case of any doubt, a conservative approach should be taken, and Category 2 should be assigned only if the decision can be reasonably justified.

2.8.6.2 Relation to transport classification

If a transport classification is available, the following translation applies. It should be kept in mind that transport classification is based on prioritisation of hazards (see ADR, section 2.1.3.5.3) and that flammable solids have a relatively low rank in the precedence of hazards. Therefore, the translation from transport classification to CLP using the table below should be only done if a transport classification as shown is explicitly available. The conclusion that a substance or mixture not classified as flammable solid for transport should not be classified as a flammable solid according to CLP is, in general, not correct.

2.8.7 Examples of classification for flammable solids

2.8.7.1 Example of substances and mixtures fulfilling the classifiction criteria

The following example shows a classification based on test data:

Test substance: „Flammalene“ (organic material, solid):

Screening test (VDI 2263, part 1): Burning index: 5 (burning with an open flame or emission of sparks)

Conclusion: Substance is candidate for classification as a flammable solid, further testing required.

UN N.1 test (Test method for readily combustible solids):

Burning times for a distance of 100 mm (6 runs): 44 s; 40 s; 49 s; 45 s; 37 s; 41 s.

Shortest burning time is less than 45 s; substance is a flammable solid.

Wetted zone stops the fire, no reignition.

Conclusion: Classify as flammable solid, Category 2.

2.8.7.2 Examples of substances and mixtures not fulfilling the classification criteria

Many inorganic salts and oxides are not flammable such as NaCl, NaBr, KI, FeO, MnO etc.

Urea or phthalic acid anhydride are examples of organic substances that would not be classified as flammable solids.

2.9 SELF-REACTIVE SUBSTANCES

2.9.1 Introduction

In general, substances classified as self-reactive substances can decompose strongly exothermically when 50 kg are exposed to temperatures of 75 °C or lower depending on the Self-Accelerating Decomposition Temperature (SADT) of the substance or mixture.

Self-reactive substances and mixtures display a very wide range of properties. The most hazardous type is TYPE A of self-reactive substances and mixtures that are too dangerous to transport commercially though they can be stored safely with appropriate precautions. At the other end of the scale this classification includes substances that only decompose slowly at temperatures well above the normal storage and transport temperatures (e.g. 75 °C).

The decomposition of self-reactive substances can be initiated by heat, contact with catalytic impurities (e.g. acids, heavy-metal compounds, and bases), friction or impact. The rate of decomposition increases with temperature and varies with the substance. Decomposition, particularly if no ignition occurs, may result in the evolution of toxic gases or vapours. For certain self-reactive substances, the temperature shall be controlled during storage and handling. Some self-reactive substances may decompose explosively, particularly if confined. This characteristic may be modified by the addition of diluents or by the use of appropriate packaging. Some self-reactive substances burn vigorously. Self-reactive substances are, for example, some compounds of the types listed below:

(a) Aliphatic azo compounds (-C-N=N-C-);

(b) Organic azides (-C-N_3);

(c) Diazonium salts ($-CN_2^+Z^-$);

(d) N-nitroso compounds (-N-N=O); and

(e) Aromatic sulfohydrasides ($-SO_2-NH-NH_2$).

This list is not exhaustive and substances with other reactive groups, combination of groups and some mixtures of substances may have similar properties. Additional guidance on substances, which may have self-reactive properties, is given in Appendix 6, section 5.1 of the UN-MTC.

Additional hazardous properties, resulting in subsidiary labelling, are indicated in the list of already classified self-reactive substances incorporated included in the UN RTDG, Section 2.4.2.3.2.3.

Neither the burning properties nor the sensitivity to impact and friction form part of the classification procedure for self-reactive substances in CLP. These properties may be of importance in safe handling of self-reactive substances (see additional tests in Section 2.9.3.3.2).

Commercial self-reactive substances are commonly formulated by dilution with solid and liquid substances with which they are compatible.

2.9.2 Definitions and general considerations for the classification of self-reactives

In CLP the following definition is given for self-reactive substances:

Annex I: 2.8.1.1. Self-Reactive substances or mixtures are thermally unstable liquid or solid substances or mixtures liable to undergo a strongly exothermic decomposition even without participation of oxygen (air). This definition excludes substances and mixtures classified according to this Part as explosives, organic peroxides or as oxidising.

2.8.1.2. A self-reactive substance or mixture is regarded as possessing explosive properties when in laboratory testing the formulation is liable to detonate, to deflagrate rapidly or to show a violent effect when heated under confinement.

General considerations

Annex I, 2.8.3. *Hazard communication*

Type G has no hazard communication elements assigned but shall be considered for properties belonging to other hazard classes.

2.9.3 Classification of substances and mixtures as self-reactive

2.9.3.1 Identification of hazard information

The classification of a self-reactive substance in one of the seven categories “Types A to G” is dependent on its detonation, explosive thermal explosion and deflagrating properties, its response to heating, the concentration and the type of diluent added to desensitize the substance. Specifications of acceptable diluents that can be used safely are given in the UN RTDG, Section 2.4.2.3.5.

The classification of a self-reactive substance as Type A, B or C is also dependent on the type of packaging in which the substance is tested as it affects the degree of confinement to which the substance is subjected. This has to be considered in when handling of the substance; stronger packaging may result in more violent reactions when the substance decomposes. This is why it is important that storage and transport is done in packaging, allowed for the type of

self-reactive substance, that conforms the requirements of the UN-packaging or IBC instruction (P520/IBC520) or tank instruction (T23).

The traditional aspects of explosive properties, such as detonation, deflagration and thermal explosion, are incorporated in the decision logic Figure 2.8.1 of CLP (see Section 2.9.3.4). Consequently, the determination of explosive property properties determination as prescribed in the hazard class explosives needs not to be conducted for self-reactive substances.

2.9.3.2 Classification criteria

According CLP, substances and mixtures should be considered for classification in this hazard class, unless:

Annex I: 2.8.2.1.

(a) They are explosives, according to the criteria given in 2.1;

(b) They are oxidising liquids or solids, according to the criteria given in 2.13 or 2.14, except that mixtures of oxidising substances, which contain 5% or more of combustible organic substances shall be classified as self-reactive substances according to the procedure defined in 2.8.2.2;

(c) They are organic peroxides, according to the criteria given in 2.15;

(d) Their heat of decomposition is less than 300 J/g; or

(e) Their self-accelerating decomposition temperature (SADT) is greater than 75°C for a 50 kg package (See United Nations Manual of Tests and Criteria, sub-sections 28.1, 28.2, 28.3 and Table 28.3.)

2.8.2.2. Mixtures of oxidising substances, meeting the criteria for classification as oxidising substances, which contain 5% or more of combustible organic substances and which do not meet the criteria mentioned in (a), (c), (d) or (e) in 2.8.2.1, shall be subjected to the self-reactive substances classification procedure;

Such a mixture showing the properties of a self-reactive substance type B to F (see 2.8.2.3) shall be classified as a self-reactive substance.

In addition to the above, substances and mixtures should be considered for classification in this hazard class unless:

(f) There are no chemical groups present in the molecule associated with explosive or self-reactive properties; examples of such groups are given in Tables A6.1 and A6.2 in the UN RTDG, Manual of Tests and Criteria, Appendix 6.

In the CLP decision logic (see Section 2.9.3.4), classification of self-reactive substances is based on performance based testing in both small scale tests and, where necessary, some larger scale tests with the substance in its packaging. The concept of "intrinsic properties" is, therefore, not necessarily, applicable to this hazard class.

Self-reactive substances are classified in one of the seven categories of "Types A to G" according to the classification criteria given in Section 2.8.2.3 of Annex I, of CLP. The classification principles are given in the decision logic in Figure 2.8.1 of CLP (see Section 2.9.3.4) and the test series A to H, as described in the Part II of the UN-MTC, should be performed.

Annex I: 2.8.2.3. Self-reactive substances and mixtures shall be classified in one of the seven categories of 'types A to G' for this class, according to the following principles:

(a) any self-reactive substance or mixture which can detonate or deflagrate rapidly, as packaged, shall

be defined as self-reactive substance TYPE A;

(b) any self-reactive substance or mixture possessing explosive properties and which, as packaged, neither detonates nor deflagrates rapidly, but is liable to undergo a thermal explosion in that package shall be defined as self-reactive substance TYPE B;

(c) any self-reactive substance or mixture possessing explosive properties when the substance or mixture as packaged cannot detonate or deflagrate rapidly or undergo a thermal explosion shall be defined as self-reactive substance TYPE C;

(d) any self-reactive substance or mixture which in laboratory testing:

(i) detonates partially, does not deflagrate rapidly and shows no violent effect when heated under confinement; or

(ii) does not detonate at all, deflagrates slowly and shows no violent effect when heated under confinement; or

(iii) does not detonate or deflagrate at all and shows a medium effect when heated under confinement;

shall be defined as self-reactive substance TYPE D;

(e) any self-reactive substance or mixture which, in laboratory testing, neither detonates nor deflagrates at all and shows low or no effect when heated under confinement shall be defined as self-reactive substance TYPE E;

(f) any self-reactive substance or mixture which, in laboratory testing, neither detonates in the cavitated state nor deflagrates at all and shows only a low or no effect when heated under confinement as well as low or no explosive power shall be defined as self-reactive substance TYPE F;

(g) any self-reactive substance or mixture which, in laboratory testing, neither detonates in the cavitated state nor deflagrates at all and shows no effect when heated under confinement nor any explosive power, provided that it is thermally stable (SADT is 60 °C to 75 °C for a 50 kg package), and, for liquid mixtures, a diluent having a boiling point not less than 150 °C is used for desensitisation shall be defined as self-reactive substance TYPE G. If the mixture is not thermally stable or a diluent having a boiling point less than 150 °C is used for desensitisation, the mixture shall be defined as self-reactive substance TYPE F.

Where the test is conducted in the package form and the packaging is changed, a further test shall be conducted where it is considered that the change in packaging will affect the outcome of the test.

A list of currently classified self-reactive substances is included in the UN RTDG, Section 2.4.2.3.2.3.

2.9.3.3 Testing and evaluation of hazard information

2.9.3.3.1 Thermal stability tests and temperature control

In addition to the classification tests given in decision logic Figure 2.8.1 of CLP, the thermal stability of the self-reactive substances has to be assessed in order to determine the Self-Accelerating Decomposition Temperature (SADT).

The SADT is defined as the lowest temperature at which self-accelerating decomposition may occur with a substance in the packaging as used in transport, handling and storage. The SADT is a measure of the combined effect of the ambient temperature, decomposition kinetics, package size and the heat transfer properties of the substance and its packaging.

There is no relation between the SADT of a self-reactive substance and its classification in one of the seven categories “Types A to G”. The SADT is used to derive safe handling, storage and transport temperatures (control temperature) and alarm temperature (emergency temperature).

Depending on its SADT a self-reactive substance needs temperature control and the rules as given in CLP Annex I, 2.8.2.4, consist of the following two elements:

1) Criteria for temperature control

Self-reactive substances need to be subjected to temperature control when the SADT is ≤ 55° C.

2) Derivation of control and emergency temperatures:

Type of receptacle	**SADT[a)]**	**Control temperature**	**Emergency temperature**
Single packagings and IBC's	20 °C or less	20 °C below SADT	10 °C below SADT
	over 20 °C to 35 °C	15 °C below SADT	10 °C below SADT
	over 35 °C	10 °C below SADT	5 °C below SADT
Tanks	< 50 °C	10 °C below SADT	5 °C below SADT

a) i.e. the SADT of the substance as packaged for transport, handling and storage.

It should be emphasized that the SADT is dependent on the nature of the self-reactive substance itself, together with the volume and heat-loss characteristics of the packaging or vessel in which the substance is handled. The temperature at which self-accelerating decomposition occurs falls:

- as the size of the packaging or vessel increases; and
- with increasing efficiency of the insulation on the package or vessel.

The SADT is only valid for the substance as tested and when handled properly. Mixing the self-reactive substance with other chemicals, or contact with incompatible materials (including incompatible packaging or vessel material) may reduce the thermal stability due to catalytic decomposition, and lower the SADT. This may increase the risk of decomposition and has to be avoided.

2.9.3.3.2 Additional testing

The sensitivity of self-reactive substances to impact (solids and liquids) and friction (solids only) may be of importance for the safe handling of the substances, in the event that these substances have pronounced explosive properties (e.g. rapid deflagration and/or violent heating under confinement). Test methods to determine these properties are described in test series 3 of the UN-MTC. This information should be part of the hazard communication in safety data sheets.

The flashpoint for liquid self-reactive substances is only relevant in the temperature range where the product is thermally stable. Above the SADT of the product flashpoint determination is not relevant because decomposition products are evolved.

Note: In case a flashpoint determination seams reasonable (expected flashpoint below the SADT) a test method using small amount of sample is recommended. In case the self-reactive substance is diluted or dissolved, the diluent may determine the flashpoint.

Although there are currently no dedicated storage guidelines for self-reactive substances (although in some countries under development), often the regulations for organic peroxides are referred to. For storage classification the burning rate is commonly used, see Section 2.14 on organic peroxides.

The determination of the auto ignition temperature is not relevant for self-reactive substances, because the vapours decompose during the execution of the test. Available test methods are for non-decomposing vapour phases. Auto ignition of self-reactive substance vapours when

they decompose, can never be excluded. This information should be part of the hazard communication in safety data sheets.

Also self-ignition temperature determination (test applicable for solids) is not relevant. The thermal stability of self-reactive substances is quantitatively given by the SADT test.

2.9.3.3.3 Additional classification considerations

Determination of explosive property properties is incorporated in the classification decision logic. Flammability is not incorporated in the decision flow chart.

Currently, the following properties are not incorporated in CLP:

- mechanical sensitivity i.e. impact and friction sensitivity (for handling purposes);
- burning tests (for storage purposes); and
- flammability aspects.

In addition to the GHS criteria CLP mentions that:

Annex I: 2.8.2.2

Where the test is conducted in the package form and the packaging is changed, a further test shall be conducted where it is considered that the change in packaging will affect the outcome of the test.

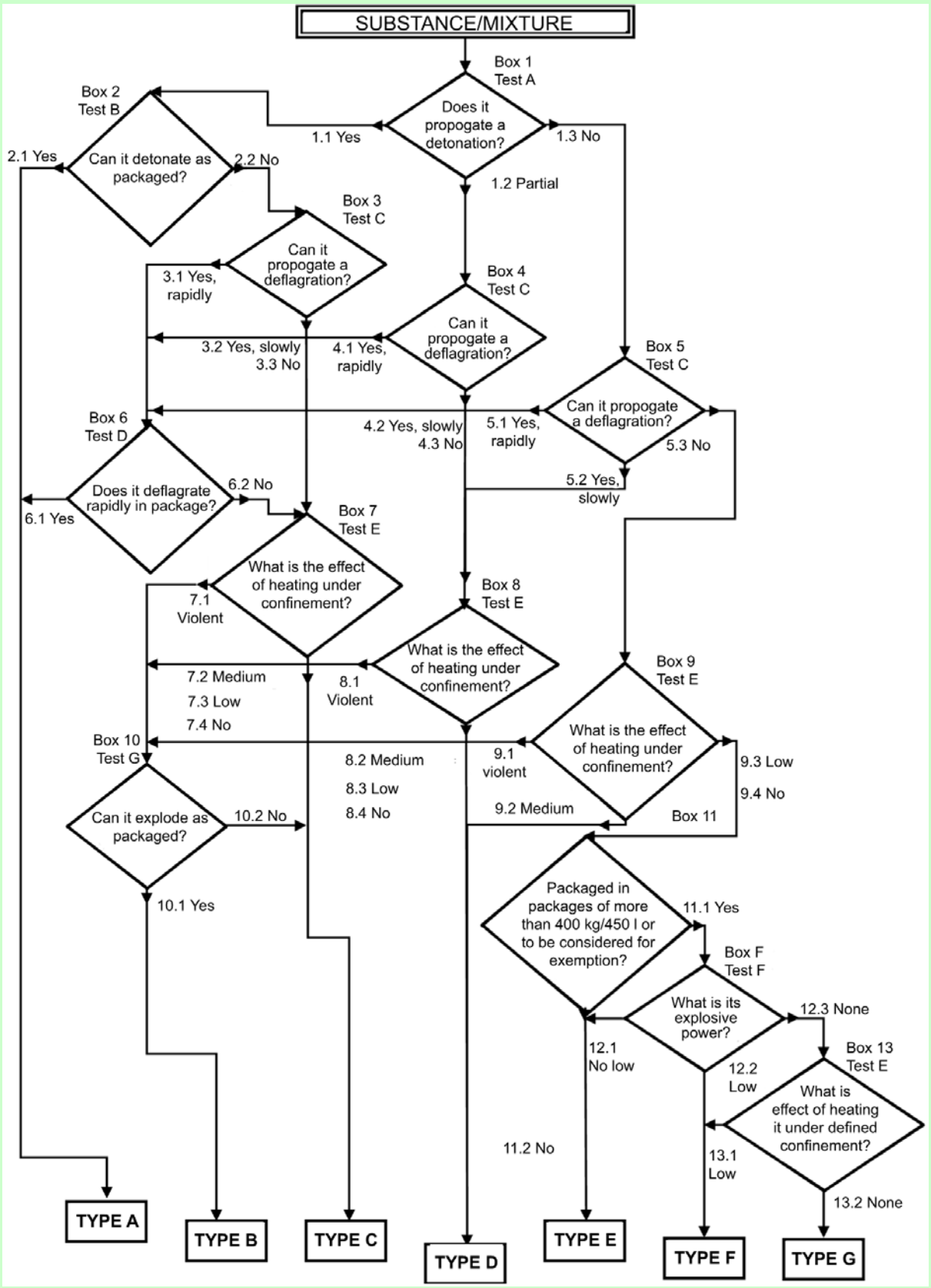
2.9.3.4 Decision logic

The following decision logic for self-reactive substances is applicable according to CLP.

NOTE: The person responsible for classification should study the criteria for classification before and during use of the decision logics.

Annex I: *Figure 2.8.1*

Self reactive substances and mixtures



2.9.4 Hazard communication for self-reactives

2.9.4.1 Pictograms, signal words, hazard statements and precautionary statements

According to CLP the following label elements shall be used for substances or mixtures meeting the criteria for this hazard class:

Annex I: 2.8.3. *Table 2.8.1*

Label elements for self-reactive substances and mixtures

Classification	Type A	Type B	Type C & D	Type E & F	Type G
GHS pictograms					There are no label elements allocated to this hazard category
Signal words	Danger	Danger	Danger	Warning	
Hazard Statement	H240: Heating may cause an explosion	H241: Heating may cause a fire or explosion	H242: Heating may cause a fire	H242: Heating may cause a fire	
Precautionary statement Prevention	P210 P220 P234 P280	P210 P220 P234 P280	P210 P220 P234 P280	P210 P220 P234 P280	
Precautionary statement Response	P370 + P378 P370 + P380 + P375	P370 + P378 P370 + P380 + P375	P370 + P378	P370 + P378	
Precautionary statement Storage	P403 + P235 P411 P420	P403 + P235 P411 P420	P403 + P235 P411 P420	P403 + P235 P411 P420	
Precautionary statement Disposal	P501	P501	P501	P501	

The wording of the Precautionary Statements is found in CLP Annex IV, Part 2.

2.9.5 Re-classification of substances and mixtures classified as self-reactives according to DSD or already classified for transport

2.9.5.1 Re-classification of substances and mixtures classified in accordance with DSD

In DSD no hazard class "self-reactive substances" is defined. In CLP self-reactive substances are a distinct hazard class. Self-reactivity is not a single "intrinsic property"; self-reactive substances are a group of substances that can release a certain amount of decomposition energy and which may be thermally unstable (see Section 2.9.1).

In DSD explosive properties and flammability are determined separately by the tests A14 (for explosive properties) and A9 or A10 (for flammable properties), as published in the Council Regulation (EC) No 440/2008.
Substances earlier listed under other hazard categories may now under CLP fulfil the criteria of a self-reactive substance. For the correct assignment of an individual self-reactive substance, the classification criteria as given in Section 2.9.3.2 should be applied. If necessary, expert advice should be sought.

Consequently the translation table in Annex VII to CLP is not applicable to this hazard class.

2.9.5.2 Relation to transport classification

A list of already classified self-reactive substances is included in RTDG, Section 2.4.2.3.2.3. This table includes self-reactive substances type B-type F.

2.9.6 Examples of classification for self-reactives

2.9.6.1 Examples of substances and mixtures fulfilling the classification criteria

Substance to be classified: NP

Molecular formula: n.a.

According to GHS 2.8.2.1, the substance has:

- an energy content of 1452 kJ/kg; and
- a SADT of 45 °C;

and consequently it has to be considered for classification in the hazard class Self-Reactive Substances.

Test results and classification according to CLP decision logic 2.8.1 for Self-Reactive Substances and the UN Recommendations on the transport of Dangerous Goods, Manual of Tests and Criteria, Part II, is as follows:

Classification test results

1.	Name of the Self-Reactive Substance	:	NP
2.	General data		
2.1.	Composition	:	NP, technically pure
2.2.	Molecular formula	:	n.a.
2.3.	Physical form	:	solid, fine powder
2.4.	Colour	:	brown
2.5.	Density (apparent)	:	460 kg/m^3
3.	Detonation (test series A)		
	Box 1 of the decision logic	:	Does the peroxide propagate a detonation?
3.1.	Method	:	UN Test A.1: BAM 50/60 steel tube test
3.2.	Sample conditions	:	technically pure substance
3.3.	Observations	:	fragmented part of the tube: 12, 18cm

3.4.	Result	:	No
3.6.	Exit	:	1.3
4.	Deflagration (test series C)		
	Box 5 of the decision logic	:	Does the peroxide propagate a deflagration?
4.1.	Method 1	:	Time/pressure test (test C.1)
4.1.1.	Sample conditions	:	ambient temperature
4.1.2.	Observations	:	498, 966, 3395 ms
4.1.3.	Result	:	Yes, slowly
4.2.	Method 2	:	Deflagration test (test C.2)
4.2.1.	Sample conditions	:	temperature: 20 °C
4.2.2.	Observations	:	deflagration rate: 0.90, 0.87 mm/s
4.2.3.	Result	:	Yes, slowly
4.3.	Final result	:	Yes, slowly
4.4.	Exit	:	5.2
5.	Heating under confinement (test series E)		
	Box 8 of the decision logic:		What is the effect of heating it under defined confinement?
5.1.	Method 1	:	Koenen test (test E.1)
5.1.1.	Sample conditions	:	-
5.1.2.	Observations	:	limiting diameter: < 1.0 mm
			fragmentation type "A"
5.1.3.	Result	:	Low
5.2.	Method 2	:	Dutch pressure vessel test
			(test E.2)
5.2.1.	Sample conditions	:	-
5.2.2.	Observations	:	limiting diameter: <1.0 mm (with 10 g), 1.0 mm (50 g)
5.2.3.	Result	:	low
5.3.	Final result	:	low
5.4.	Exit	:	8.3
6.	Thermal stability (outside of the decision logic)		
6.1.	Method	:	Heat accumulation storage test (test H.4)
6.2.	Sample conditions with	:	mass 232.5 g. Half life time of cooling of Dewar vessel
			400 ml water: 10.0 hrs.(representing substance in package)
6.3.	Observations	:	self-accelerating decomposition at 45 °C
			no self-accelerating decomposition at 40 °C
6.4.	Result	:	SADT 45 °C
7.	General remarks	:	The decision logic is given in figure 1
8.	Final classification		
	Hazard / hazard class:		Self-Reactive Substance, Type D, solid, temperature controlled
Label		:	Flame
Signal word		:	Danger
Hazard statement		:	Heating may cause a fire

Temperature control	:	Needed based on SADT (45 °C, in package)
Control temperature*	:	35°C (in package)
Emergency temperature*	:	40°C (in package)

*see UN-TDG, manual of tests and criteria, table 28.2

Additional remarks

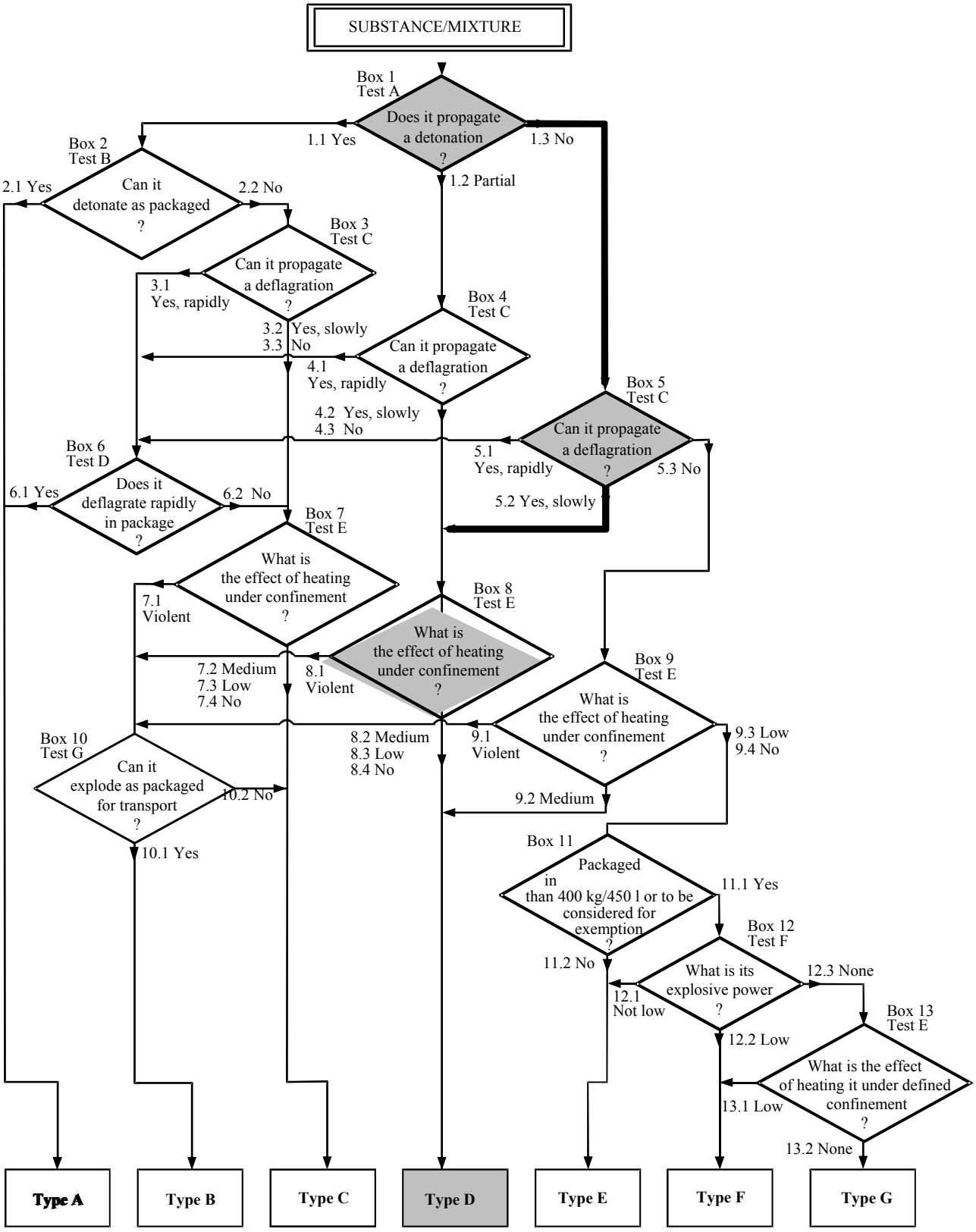
(1) *Control and emergency temperature*

The Control and Emergency temperatures are based on the SADT as determined by UN test H.4. The Dewar vessel used in the UN H.4 test was representative for the substance handled in packages. For handling of the substance in larger quantities (IBCs/tanks/vessels etc.) and/or in better (thermally) insulated containers under more thermal insulated conditions, the SADT has to be determined for that quantity with the given that degree of insulation factor. From that SADT the Control and Emergency temperatures can be derived (see also section 2.3)

(2) Explosive properties

The explosive properties do not have to be determined according to Annex I, Chapter 2.1 for explosives, because this is incorporated in the decision logic. Substance may have explosive properties when handled under more confined conditions of greater confinement.

Figure 2.9.6.1: *Decision logic for self reactive substance example: NP, technically pure*



2.10 PYROPHORIC LIQUIDS AND SOLIDS

2.10.1 Introduction

Pyrophoricity, i.e. the ability to spontaneously ignite in air, is the result of a reaction of a substance or mixture with the oxygen in the air. The reaction is exothermic and has the particularity that it starts spontaneously, i.e. without the aid of a supplied spark, flame, heat or other energy source. Another way of saying this is that the auto-ignition temperature for a pyrophoric substance is lower than room (ambient) temperature.

Organo-metals and organo-metalloids may be suspected of being pyrophores, as well as their derivatives. Also organo-phosphines and their derivatives, hydrides and their derivatives, haloacetylene derivatives, and complex acetylides may show pyrophoricity (Urben, 1995). Furthermore, powders or fine particles of metals could be pyrophoric. However, although many solid metallic substances, like e.g. aluminium, would be suspected of being pyrophoric when considering their general reactivity, they form a protective oxide-coat upon reaction with air. This thin coat of metal oxide prevents the metal from reacting further, and hence such substances may not show pyrophoric behaviour in reality.

There are also pyrophoric substances that do not belong to the above mentioned groups of chemicals, i.e. the list above is not exhaustive. Since pyrophoric substances ignite *spontaneously* in air, pyrophoricity is a very dangerous property. In case of doubt it should therefore be thoroughly investigated whether a given substance or mixture is pyrophoric. More information on pyrophoric substances can e.g. be found in Bretherick's Handbook of Reactive Chemical Hazards (Urben, 1995).

2.10.2 Definitions and general considerations for the classification pyrophoric liquids and solids

The definitions in CLP for pyrophoric liquids and pyrophoric solids are as follows:

Annex I: 2.9.1. Pyrophoric liquid means a liquid substance or mixture which, even in small quantities, is liable to ignite within five minutes after coming into contact with air.

2.10.1. Pyrophoric solid means a solid substance or mixture which, even in small quantities, is liable to ignite within five minutes after coming into contact with air.

Special consideration on particle size for solids

The finer the particle size of a solid substance or mixture, the greater the area exposed to air will be, and since pyrophoricity is a reaction with the oxygen in air, the particle size will greatly influence the ability to spontaneously ignite. Hence it is very important that pyrophoric properties for solids are investigated on the substance/mixture as it is actually presented (including how it can reasonably be expected to be used, see Article 8(6) of CLP). This is indicated by the Note cited in CLP Annex I, 2.10.2.1.

Annex I; 2.10.2.1. Note: The test shall be performed on the substance or mixture in its physical form as presented. If for example, for the purposes of supply or transport, the same chemical is to be presented in a physical form different from that which was tested and which is considered likely to materially alter its performance in a classification test, the substance shall also be tested in the new form.

2.10.3 Relation to other physical hazards

Pyrophoric substances will react spontaneously with air already in small amounts and more or less instantaneously (within minutes). This differentiates them from self-heating substances, which also react spontaneously with air but only when in larger amounts and after an

extended period of time (hours or days). A substance that is not classified as a Pyrophoric Liquid or Pyrophoric Solid may thus belong to the hazard class Self-heating Substances and Mixtures, and should be considered for classification in that hazard class.

Pyrophoricity may be expected for certain reactive metals and some of their compounds (e.g. hydrides and other organo-metal compounds). Many of these substances will also react vigorously with water under the production of flammable gases. Such substances may thus be classified in the hazard class Substances and Mixtures which in Contact with Water Emit Flammable Gases, as well as in the hazard class Pyrophoric Solids or Pyrophoric Liquids. It should be noted in this context that water-reactive substances may also to some extent react with the humidity in air, although such a reaction is seldom vigorous. A substance that spontaneously ignites in air in accordance with the test procedures is to be considered pyrophoric, regardless of the reaction mechanism.

Solids not classified as pyrophoric may still be able to burn rapidly if subjected to enough initiating energy, such as the flame from a gas burner, to start the reaction. Therefore they may be subject to classification in the hazard class flammable solids, i.e. they may be 'readily combustible solids'.

Liquids not classified as pyrophoric but that can burn may belong to the hazard class flammable liquids depending on their flash point and ability to sustain combustion.

2.10.4 Classification of substances and mixtures as pyrophoric liquids and solids

2.10.4.1 Identification of hazard information

Since the tests to determine pyrophoricity are simple and require no special equipment, see Section 2.10.4.4 below, there is in general no reason to go to data sources instead of performing tests. Furthermore, the possibilities of waiving tests are ample both for known pyrophores and for substances and mixtures known not to be pyrophoric, see Section 2.10.4.2 below. If information anyway is taken from literature or other data sources, it is of utmost importance that the correct physical form is considered, see Section 2.1.4. Naturally, all data sources should be carefully evaluated with regard to reliability and scientific validity.

2.10.4.2 Screening procedures and waiving of testing

In case a substance or mixture is known from practical handling to be pyrophoric no testing is necessary. Such liquids and solids are classified as pyrophoric without testing. This would also be the case if the substance or mixture spontaneously ignites upon opening of the receptacle when trying to perform the tests for classification.

According to the additional classification considerations in CLP Annex I, 2.9.4 and 2.10.4, the classification procedure for pyrophoric solids or liquids need not be applied when experience in manufacture or handling shows that the substance or mixture does not ignite spontaneously on coming into contact with air at normal temperatures (i.e. the substance is known to be stable at room temperature for prolonged periods of time (days)).

2.10.4.3 Classification criteria

Sections 2.9.2.1 and 2.10.2.1 of Annex I of CLP specify the classification criteria:

Annex I: 2.9.2. *Table 2.9.1* **Criteria for pyrophoric liquids**	
Category	**Criteria**

1	The liquid ignites within 5 min when added to an inert carrier and exposed to air, or it ignites or chars a filter paper on contact with air within 5 min.

Annex I: 2.10.2. *Table 2.10.1* **Criteria for pyrophoric solids**	
Category	**Criteria**
1	The solid ignites within 5 minutes of coming into contact with air.

2.10.4.4 Testing and evaluation of hazard information

In Section 2.9.2.1 and 2.10.2.1 of Annex I of CLP reference to the test-methods are made:

Annex I: 2.9.2.1. A pyrophoric liquid shall be classified in a single category for this class using test N.3 in part III, sub-section 33.3.1.5 of the UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria.

2.10.2.1. A pyrophoric solid shall be classified in a single category for this class using test N.2 in part III, sub-section 33.3.1.4 of the UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria.

The N.2 and N.3 tests for pyrophoricity are quite simple and are sufficiently described in Part 3 Section 33 of the UN-MTC. No special equipment is needed. Essentially the substance or mixture is exposed to air to see if it ignites. For liquids which do not spontaneously ignite when poured, the surface in contact with air is increased using a filter paper. Ignition or charring of the filter paper is regarded as a positive response in the test, i.e. such a liquid is considered to be pyrophoric.

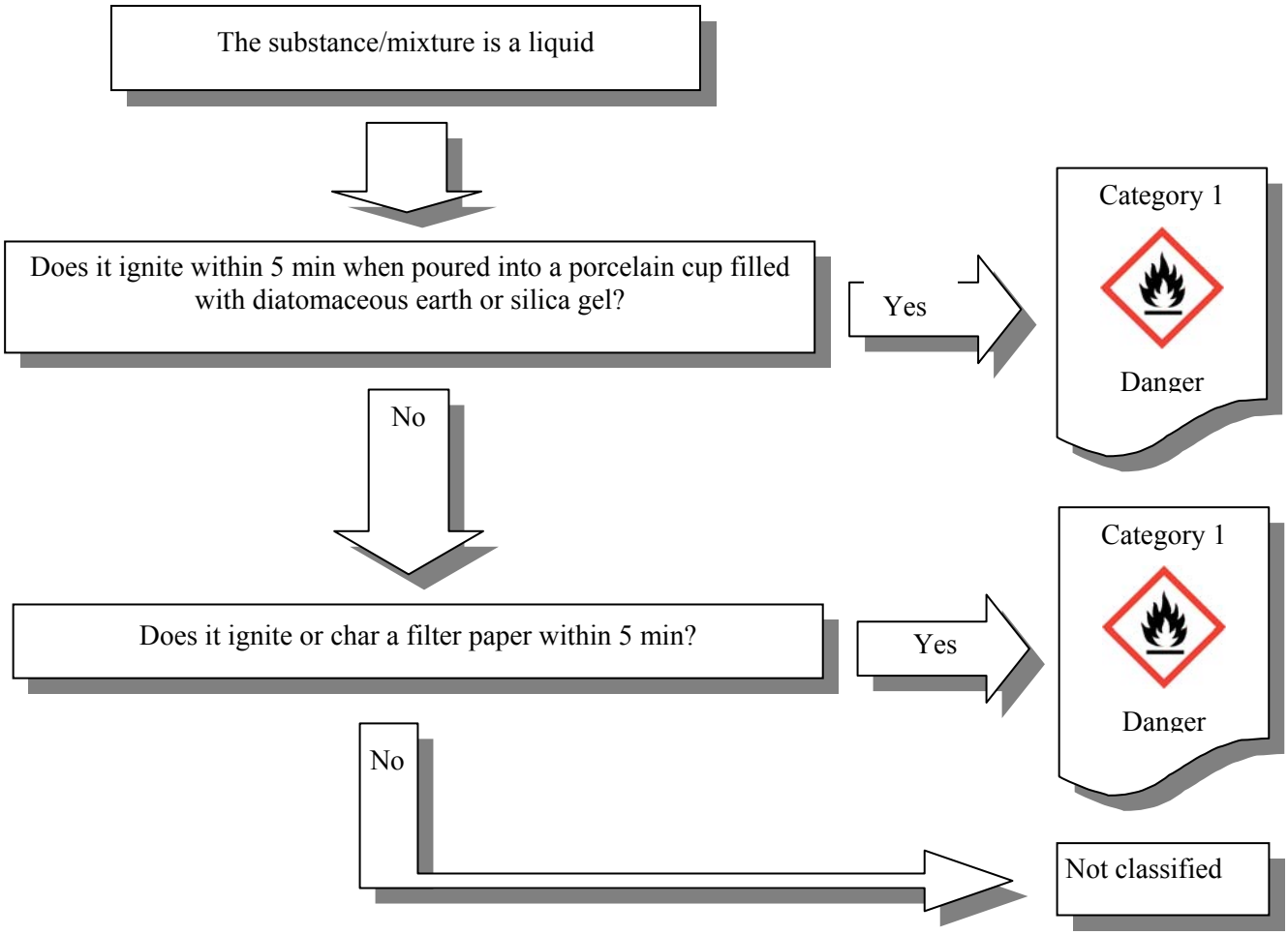
It is important that samples for testing of pyrophoric properties are carefully packed and sealed. Furthermore, the material offered for testing should be freshly prepared, since the reactive properties may diminish due to aging or agglomeration. Whenever experiments are to be done one should be careful – a pyrophoric substance may well ignite already upon opening the receptacle!

It should be noted that the mechanism of oxidation is, in general, very complex, and that the humidity of air might influence the rate of reaction. It is known that certain metals will not react in dry air, whereas in the presence of moisture the reaction is almost instantaneous (often even trace amounts of moisture are sufficient). Therefore a false negative may result when performing the tests in an extremely dry environment, and this condition must be avoided when performing the tests for classification for pyrophoricity.

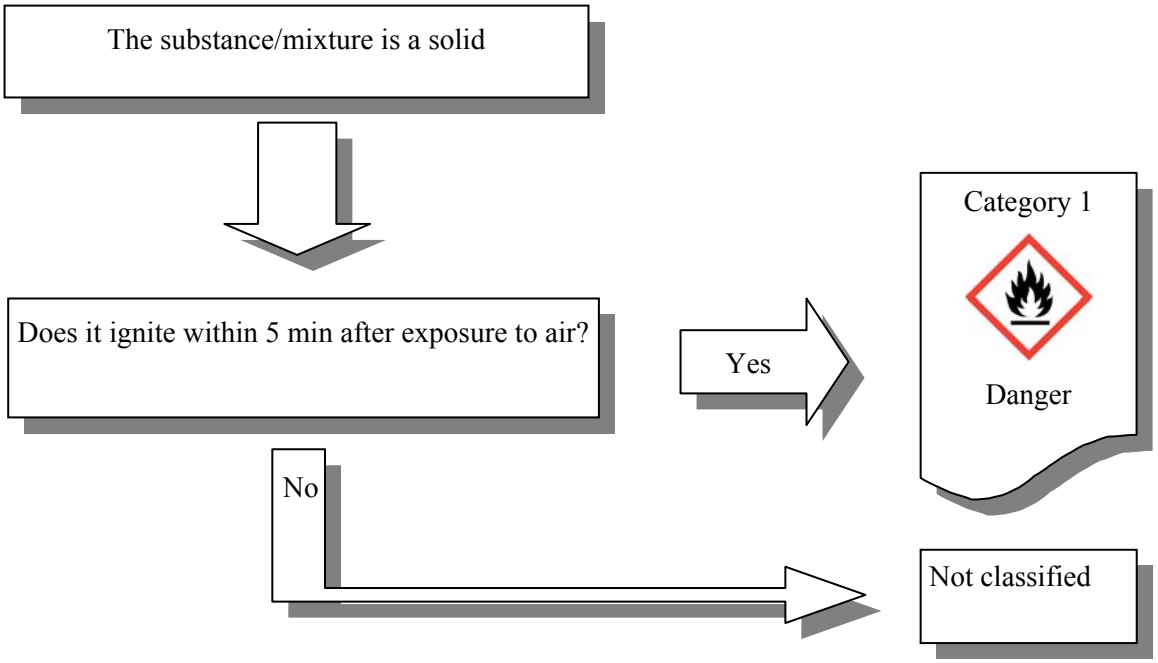
2.10.4.5 Decision logic

NOTE: The person responsible for classification should study the criteria for classification before and during use of the decision logics.

Decision logic for pyrophoric liquids (taken from GHS Rev. 2):



Decision logic for pyrophoric solids (taken from GHS Rev. 2):



2.10.5 Hazard communication for pyrophoric liquids and solids

2.10.5.1 Pictograms, signal words, hazard statements and precautionary statements

The hazard communication is the same for liquids and for solids, except for one of the precautionary statements (P335 for solids and P302 for liquids):

Annex I: 2.9.3 & 2.10.3 **Label elements for pyrophoric liquids (Table 2.9.2) and solids (Table 2.10.2)**		
Classification	**Category 1, liquids**	**Category 1, solids**
GHS Pictogram		
Signal word	Danger	Danger
Hazard statement	H250: Catches fire spontaneously if exposed to air	H250: Catches fire spontaneously if exposed to air
Precautionary Statement Prevention	P210 P222 P280	P210 P222 P280
Precautionary Statement Response	P302 + P334 P370 + P378	P335 + P334 P370 +P378
Precautionary Statement Storage	P422	P422
Precautionary Statement Disposal		

The wording of the Precautionary Statements is found in CLP Annex IV, Part 2.

2.10.6 Re-classification of substances and mixtures classified as pyrophoric liquids and solids according to DSD or already classified for transport

2.10.6.1 Re-classification of substances and mixtures classified in accordance with DSD

According to the DSD, the A.13 test in EC-Regulation 440/2008 is used to characterise the pyrophoric properties of solids and liquids. Substances or mixtures reacting positively in the A.13-test are assigned the risk phrase R17 – 'Spontaneously flammable in air'.

The test methods used to determine pyrophoric properties in CLP are methods N.2 (for solids) and N.3 (for liquids) as described in Part 3 Section 33 of the UN-MTC. These tests methods are identical to the A.13-test used in the DSD, apart from details in the environmental conditions. The A.13-test specifies a temperature of circa 20°C, but does not specify the air humidity. In the N.2 and N.3 tests on the other hand, specific environmental conditions are only given for the filter paper test (25 ± 2°C and relative humidity 50 ± 5 %).

A small difference in temperature or humidity could possibly result in a slight change in reaction rate or a delayed effect, but unless extreme environmental parameters have been applied (such as an extremely low air humidity or extreme temperatures) this is unlikely to have any effect on the outcome as far as classification is concerned. Therefore the N.2 and

N.3 test methods can be regarded the same as the A.13 test method as described in Council Regulation (EC) No 440/2008 for both solids and liquids in virtually all cases.

The CLP hazard classes pyrophoric solids and pyrophoric liquids each contain only a single hazard category (Category 1), and the classification criteria for this category are identical to that for assignment of the R17 risk phrase for both solids and liquids. So in virtually all cases, substances and mixtures that have been assigned the risk phrase R17 on the basis of the result of the A.13-test fall into Category 1 of the hazard class Pyrophoric Solids if they are solid and Category 1 of the hazard class Pyrophoric Liquids if they are liquid. Normally no re-testing is thus required. The straight translation from R17 is also reflected in Annex VII to CLP.

2.10.6.2 Relation to transport classification

The tests N.2 and N.3 that are used for classification for pyrophoricity according to CLP are also those used for classification in the subdivision pyrophoric substances in Class 4.2 (Substances liable to spontaneous combustion) according to the RTDG. The criteria for Category 1 according to CLP (which is the only category for pyrophoric liquids and pyrophoric solids) and for packing group I in Class 4.2 according to the ADR are also exactly the same. Furthermore, all pyrophoric substances and mixtures are assigned to packing group I, which is also used exclusively for pyrophoric substances and mixtures.

Therefore, any substance or mixture assigned to Class 4.2 packing group I according to ADR will be classified in Category 1 of the hazard classes pyrophoric liquids or pyrophoric solids according to CLP. Naturally, if the substance or mixture is a liquid it belongs to pyrophoric liquids, and if it is a solid it belongs to pyrophoric solids.

2.10.7 Examples of classification for pyrophoric liquids and solids

Please note that the substance names in this chapter are fictitious.

2.10.7.1 Examples of substances and mixtures fulfilling the classification criteria

Example 1:

Name: Pyroferil

Physical state: Solid

Pyrophoric properties: Pyroferil is known to self-ignite upon contact with air at ambient conditions.

Classification: Pyrophoric solid Category 1

Example 2:

Name: Zorapyrole

Physical state: Solid

Pyrophoric properties: Unknown, therefore the N.2-test of the UN RTDG – Manual of Tests and Criteria was applied.

Test result: When poured from one meter height according to the test procedure, Zorapyrole self-inited after two minutes already in the first trial.

Classification: Pyrophoric solid Category 1

Example 3:

Name: Pyrpherdine

Physical state: Liquid

Pyrophoric properties: Unknown, therefore the N.3-test of the UNRTDG – Manual of Tests and Criteria was applied. However, when opening the receptacle in order to perform the test, Pyrpherdine self-ignited.

Classifiction: Pyrophoric liquid Category 1

Example 4:

Name: Qulipyr

Physical state: Liquid

Pyrophoric properties: Unknown, therefore the N.3-test of the UN-MTC was applied.

Test result: When poured according to the test procedure, nothing happened. The procedure was repeated six times, each time giving a negative result (i.e. no ignition). Therefore Qulipyr was supplied to a filter paper in accordance with the test method. In the second trial the filter paper was charred within five minutes.

Classification: Pyrophoric liquid Category 1

2.10.7.2 Examples of substances and mixtures not fulfilling the classification criteria

Example 1:

Name: Nonopyr

Physical state: Solid

Pyrophoric properties: Nonopyr has been handled extensively in air and has never self-ignited. From the chemical structure no pyrophoricity is expected.

Classification: Not a pyrophoric solid

Example 2:

Name: Pyronot

Physical state: Solid

Pyrophoric properties: Unknown, therefore test N.3 of the UN-MTC was applied.

Test result: When poured from one meter height according to the test procedure no ignition occurred within five minutes. The procedure was repeated six times and each time the result was negative.

Classification: Not a pyrophoric solid

Example 3:

Name Notpyratal

Physical state: Liquid

Pyrophoric properties: Unknown, therefore test N.3 of the UN-MTC was applied.

Test result: When poured according to the test procedure nothing happened in either of six trials. Therefore Notpyratal was supplied to a filter paper in accordance with the test method, whereupon no ignition or charring occurred in either of three trials.

Classification: Not a pyrophoric liquid

2.10.8 References

Urben, P.G. (ed), Bretheric's Handbook of Reactive Chemical Hazards, 5:th ed., Butterworth-Heinemann, Oxford (1995)

2.11 SELF-HEATING SUBSTANCES AND MIXTURES

2.11.1 Introduction

Self-heating is the result of an exothermic reaction of a substance or mixture with the oxygen in the air. Initially, the reaction rate may be very small. However, when the heat produced cannot be removed rapidly enough (i.e. heat accumulation), the substance or mixture will self-heat, with the possible consequence of self-ignition. The phenomenon can occur only where a large surface of substance or mixture is in contact with air or oxygen (for example, piles of powders, crystals, splinters, any other rough surface etc.). The initiation occurs usually at or near the centre of the substance pile with the available air in the interspace between the particles.

2.11.2 Definitions and general considerations for the classification of self-heating substances and mixtures

The definitions in CLP for self-heating substances and mixtures are as follows:

Annex I: 2.11.1.1. A self-heating substance or mixture is a liquid or solid substance or mixture, other than a pyrophoric liquid or solid, which, by reaction with air and without energy supply, is liable to self-heat; this substance or mixture differs from a pyrophoric liquid or solid in that it will ignite only when in large amounts (kilograms) and after long periods of time (hours or days).

2.11.1.2. Self-heating of substances or mixtures, leading to spontaneous combustion, is caused by reaction of the substance or mixture with oxygen (in the air) and the heat developed not being conducted away rapidly enough to the surroundings. Spontaneous combustion occurs when the rate of heat production exceeds the rate of heat loss and the auto-ignition temperature is reached.

2.11.3 Relation to other physical hazards

Pyrophoric solids and liquids should not be considered for classification as self-heating substances and mixtures.

2.11.4 Classification of self-heating substances and mixtures

2.11.4.1 Identification of hazard information

Self-heating is a very complex phenomenon which is influenced by many parameters (some of them being volume, temperature, particle shape and size, heat conductivity and bulk density). Therefore, self-heating behaviour cannot be predicted from any theoretical model. In some cases, properties might even differ between producers of seemingly very similar substances or mixtures. Differences in self-heating behaviour are especially to be anticipated where surface treatment occurs in the production process. Hence, all data sources should be carefully evaluated with regard to reliability and scientific validity.

It is of utmost importance that in compliance with Articles 5 and 6 of CLP authentic and representative material in the correct form and physical state be used for testing. In many cases, a simple screening test (see Section 2.11.4.2) can be used to determine whether self-heating occurs or not.

2.11.4.2 Screening procedures and waiving of testing

Annex I: 2.11.4.2. The classification procedure for self-heating substances or mixtures need not be applied if the results of a screening test can be adequately correlated with the classification test and an appropriate safety margin is applied. Examples of screening tests are:

(a) The Grewer Oven test (VDI guideline 2263, part 1, 1990, Test methods for the De-termination of the Safety Characteristics of Dusts) with an onset temperature 80 K above the reference temperature for a volume of 1 l;

(b) The Bulk Powder Screening Test (Gibson, N. Harper, D.J. Rogers, R. Evaluation of the fire and explosion risks in drying powders, Plant Operations Progress, 4 (3), 181-189, 1985) with an onset temperature 60 K above the reference temperature for a volume of 1 l.

Test method A.16 as described in Council Regulation (EC) No 440/2008 checks for self-heating properties. However, the method used is generally inappropriate for a sound assessment, and the findings do not lead to a classification. Therefore, special care must be taken if results from A.16 testing are interpreted towards a CLP classification for self-heating substances and mixtures.

In general, liquids are not classified as self-heating since the phenomenon applies only to solids (i.e. the surface for reaction with air is not large enough) and the test method is not applicable to liquids. However, if liquids are absorbed on a large surface (e.g. on powder particles), a self-heating hazard should be considered.

Substances with a low melting point (< 160 °C) should not be considered for classification in this class since the melting process is endothermic and the substance-air surface is drastically reduced. However, this criterion is only applicable if the substance or mixture is **completely molten** up to this temperature.

2.11.4.3 Classification criteria

A self-heating substance or mixture shall be classified in one of the two categories for this class if, in a test performed in accordance with test method N.4 in Part III, sub-section 33.3.1.6 of the UN-MTC, the result meets the criteria according to following table:

Annex I: *Table 2.11.1*

Criteria for self-heating substances and mixtures

Category	Criteria
1	A positive result is obtained in a test using a 25 mm sample cube at 140°C
2	(a) a positive result is obtained in a test using a 100 mm sample cube at 140°C and a negative result is obtained in a test using a 25 mm cube sample at 140°C and the substance or mixture is to be packed in packages with a volume of more than 3 m^3; or (b) a positive result is obtained in a test using a 100 mm sample cube at 140°C and a negative result is obtained in a test using a 25 mm cube sample at 140°C, a positive result is obtained in a test using a 100 mm cube sample at 120°C and the substance or mixture is to be packed in packages with a volume of more than 450 litres; or (c) a positive result is obtained in a test using a 100 mm sample cube at 140°C and a negative result is obtained in a test using a 25 mm cube sample at 140°C and a positive result is obtained in a test using a 100 mm cube sample at 100°C.

2.11.2.3. Substances and mixtures with a temperature of spontaneous combustion higher than 50°C for a volume of 27 m³ shall not be classified as a self-heating substance or mixture.

2.11.2.4. Substances and mixtures with a spontaneous ignition temperature higher than 50°C for a volume of 450 litres shall not be assigned to Category 1 of this class.

2.11.2.2. Note: The test shall be performed on the substance or mixture in its physical form as presented. If, for example, for the purposes of supply or transport, the same chemical is to be presented in a physical form different from that which was tested and which is considered likely to materially alter its performance in a classification test, the substance shall also be tested in the new form.

2.11.4.4 Testing and evaluation of hazard information

A self-heating substance or mixture shall be classified in one of the two categories for this class using test method N.4 in Part III, sub-section 33.3.1.6 of the UN-MTC.

2.11.4.4.1 General remarks

If self-heating behaviour cannot be ruled out by a screening test, further testing becomes necessary. UN test method N.4 as described in the latest version of the UN-MTC should be used.

Explosive substances should not be tested according to this method. For safety reasons, it is advisable to test for explosive and self-reactive properties and to rule out pyrophoric behavior before performing this test. The oven should be equipped with an appropriate pressure-relief device in case an energetic decomposition is triggered by a temperature rise. For samples containing flammable solvents explosion protection measures have to be taken.

The tests may be performed in any order. It is suggested to start with the 25 mm sample cube at 140 °C. If a positive result is obtained, the substance or mixture shall be classified as a self-heating substance or mixture, Category 1, and no further testing is necessary.

The test procedure need not be applied if the substance or mixture is completely molten at 160 °C.

2.11.4.4.2 Sample preparation

The sample (powder or granular) in its commercial form should be used. The material should not be milled or ground. It should be filled to the brim of the sample container and the container tapped several times. If the sample settles, more is added. If the sample is heaped it should be levelled to the brim. The sample container is placed in the oven as described in the UN Manual.

2.11.4.4.3 Criteria and evaluation

A positive result is obtained if spontaneous ignition occurs or if the temperature of the sample exceeds the oven temperature by 60 K. The testing time is 24 hours. The time count starts when the temperature in the centre of the sample has reached a value of 2 K below the oven temperature. This is especially important when the sample contains solvents which evaporate under the test conditions or when larger test volumes are used for extrapolation purposes (see below).

Before starting test series UN N.4, the decomposition behaviour of the sample should be known. In general, it is sufficient to perform a screening with Differential Scanning Calorimetry. Special care with respect to the interpretation of the test data is necessary when exothermic decomposition may occur at the test temperatures. In such cases, a test under an inert atmosphere (i.e. nitrogen) should be run to determine the temperature rise due to

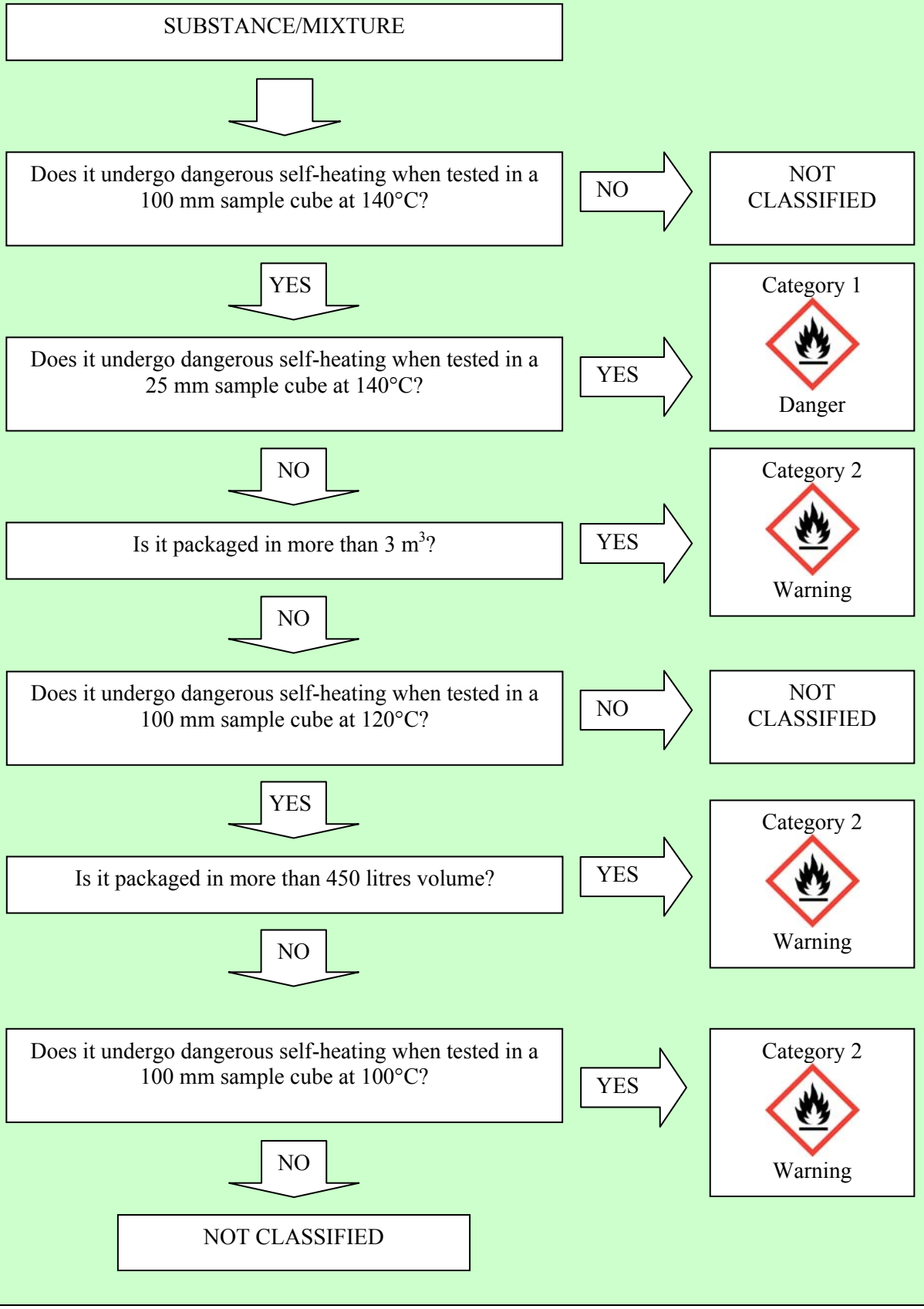
decomposition. Careful flushing is essential since otherwise much air may be retained between the crystals of the sample in the container.

2.11.4.5 Decision logic

NOTE: The person responsible for classification should study the criteria for classification before and during use of the decision logics.

Annex I: *Figure 2.11.1.*

Self-heating substances and mixtures



2.11.4.6 Exemption

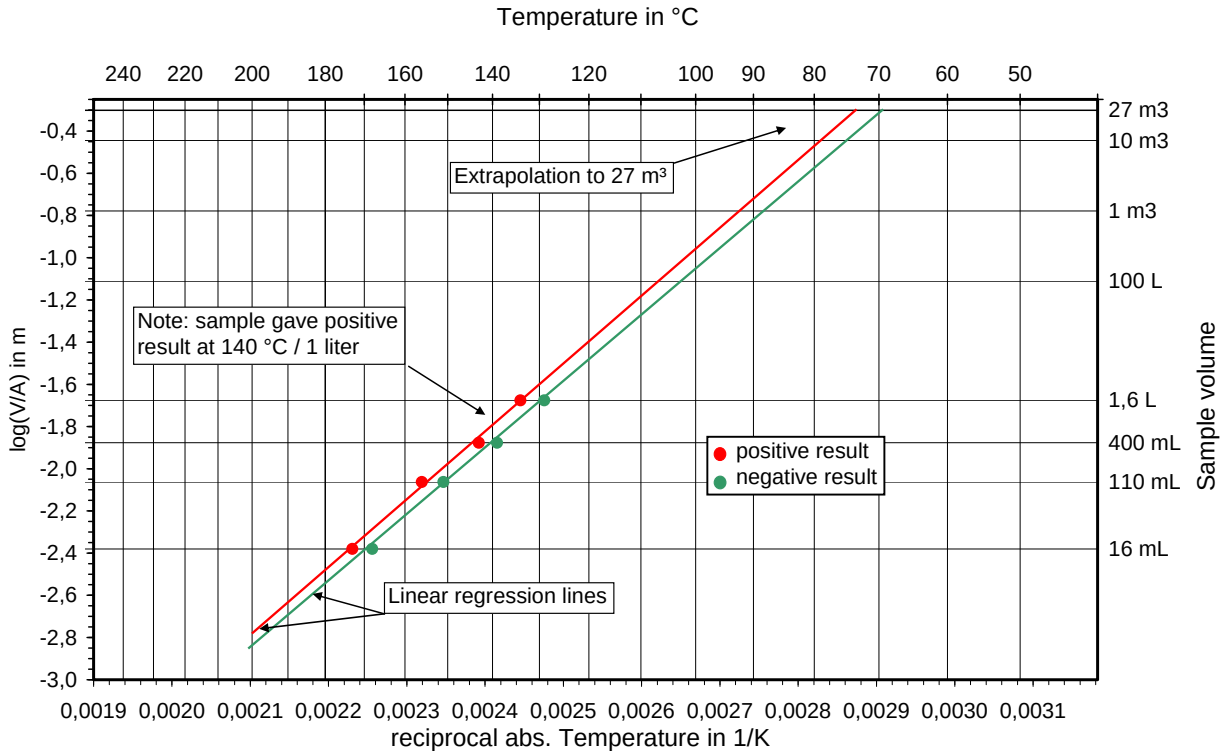
The following exemptions apply (see Section 1.11.4.3):

- Substances and mixtures with a temperature of spontaneous combustion higher than 50°C for a volume of 27 m³ shall not be classified as a self-heating substance or mixture.
- Substances and mixtures with a spontaneous ignition temperature higher than 50°C for a volume of 450 litres shall not be assigned to Category 1 of this class.

However, the UN-MTC does not provide any guidance how these values should be determined. The UN test regime is based on the silent assumption of a cubic sample shape. For the extrapolation to larger volumes, an improved model has to be used. According to Grewer, plotting (Grewer, 1994) the logarithm of the volume to surface ratio (log (V/A)) versus the reciprocal temperature gives good results without knowledge of the Frank-Kamenetzskii (Frank-Kamenetzskii, 1969) shape factor.

The critical temperature for a volume of 450 l or 27 m³ can be found by extrapolation of the critical temperature in a log (V/A) vs. 1/T plot (see Figure 2.11.4.6):

Figure 2.11.4.6 *Extrapolation towards large volumes*



The test setup is essentially the same as in test N.4 of the UN-MTC but now the sample size and possibly the shape are systematically varied. The criteria of Section 2.11.4.3 apply as well.

The critical temperature must be determined for at least four different volumes covering at least two decades and with a volume not smaller than 16 ml. If possible, larger volumes

should be also tested. The borderline temperature should be determined as precisely as possible. For small volumes (< 1 litre), the temperature rise due to self-heating may be considerably less than 60 K; in this case a noticeable temperature rise is interpreted as a positive result.

A conservative approach is required for the evaluation. The uncertainty of measurement must be taken into account. The extrapolation shall be based on a linear regression of the negative and positive borderline data sets in the log (V/A) vs. 1/T diagram. The maximum permissible difference between a positive and a negative result should be 5 K. An exemption may be claimed if the more conservative endpoint for the particular volume is well beyond 50 °C (i.e. 55 °C or higher).

2.11.5 Hazard communication for self-heating substances and mixtures

2.11.5.1 Pictograms, signal words, hazard statements and precautionary statements

Annex I: 2.11.3. *Table 2.11.2* **Label elements for self-heating substances and mixtures**		
Classification	Category 1	Category 2
GHS Pictograms		
Signal Word	Danger	Warning
Hazard Statement	H251: Self-heating; may catch fire	H252: Self-heating in large quantities; may catch fire
Precautionary Statement Prevention	P235 + P410 P280	P235 + P410 P280
Precautionary Statement Response		
Precautionary Statement Storage	P407 P413 P420	P407 P413 P420
Precautionary Statement Disposal		

The wording of the Precautionary Statements is found in CLP Annex IV, Part 2.

2.11.6 Re-classification of substances and mixtures classified according to DSD or already classified for transport

2.11.6.1 Re-classification of substances and mixtures classified in accordance with DSD

The DSD used the A.16 test to determine the "relative self-ignition temperature for solids". However, the method used is generally inappropriate for a sound assessment and has never had any relevance for classification. The A.16 test determines the oven temperature at which the sample temperature reaches 400 °C by self-ignition, and this criterion cannot be correlated with the CLP classification. Therefore, special care must be taken if results from A.16 testing

are interpreted towards a CLP classification for self-heating substances and mixtures. In some cases, the original test data may be used as a screening test and may be interpreted in analogy to the Grewer Oven Test (VDI guideline 2263, part 1, 1990, Test methods for the Determination of the Safety Characteristics of Dusts).

2.11.6.2 Relation to transport classification

In transport, Division 4.2 – substances liable to spontaneous combustion – comprises the following entries

(a) Pyrophoric substances

(b) Self-heating substances

Whereas pyrophoric substances in transport are assigned to packing group I, self-heating substances are assigned to packing groups II and III. In cases where a substance (or mixture) is classified in Division 4.2, packing group II or III, the translation into the CLP system is straightforward.

It should be kept in mind that transport classification is based on prioritisation of hazards (see ADR, section 2.1.3.5.3) and that self-heating substances have a relatively low rank in the precedence of hazards. Therefore, the translation from transport classification to CLP using the above table should be only done if a transport classification as shown is explicitly available. The conclusion that a substance or mixture not classified as self-heating for transport should not be classified as self-heating substance or mixture according to CLP is, in general, not correct.

2.11.7 Examples of classification for self-heating substances and mixtures

2.11.7.1 Examples of substances and mixtures fulfilling the classification criteria

- Many organometallic compounds, especially substances or mixtures containing transition metals
- Many organic substances or mixtures; the tendency to self-heat increases with decreasing particle size
- Many metals, especially catalysts

2.11.7.2 Examples of substances and mixtures not fulfilling the classification criteria

In general, liquids show no self-heating behaviour unless absorbed on a large surface.

Scientific background

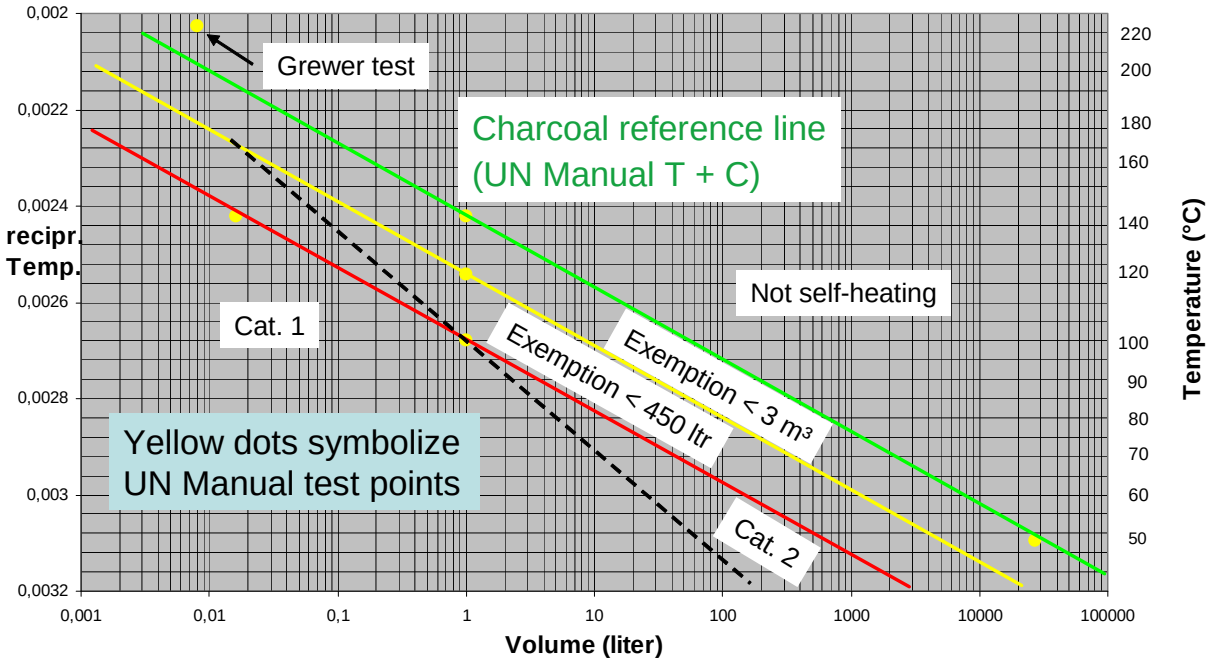
A basic model for the thermal explosion of solids was first developed by Frank-Kamenetzskii. It is based on the assumption that only the heat loss by thermal conduction is relevant for the phenomenon. In this case, the critical criterion for a thermal runaway reaction can be described as a linear relationship between the reciprocal absolute temperature and the logarithm of volume.

The classification scheme of the UN for self-heating substances and mixtures is based on charcoal as a reference system. The critical temperature for a 1 litre cube of charcoal is 140 °C and for a cube of 27 m³ 50 °C. When a parallel line is drawn in the 1/T vs. logarithm of volume diagram from the reference points 1 litre / 120 °C and 1 litre / 100 °C, the

corresponding volumes for a critical temperature of 50 °C are found to be 3 m³ and 450 l, respectively (see Figure 2.11.7.2). The black dotted line in Figure 2.11.7.2 separates Category 1 from Category 2.

However, the slope of the line in the 1/T vs. volume diagram depends on the individual activation energy of the substance or mixture, and therefore it may vary within certain limits. It must be born in mind that this test regime has been developed to facilitate classification and that it may not suffice to solve safety issues in storage.

Figure 2.11.7.2 *Volume dependency of the critical temperature for charcoal*



2.11.8 References

Grewer, T., Thermal hazards of chemical reactions, Elsevier, Amsterdam – London - New York – Tokyo 1994.

Frank-Kamenetzski, D.A., Diffusion and heat transfer in chemical kinetics, 2nd edition, Plenum Press, New York, London 1969.

2.12 SUBSTANCES AND MIXTURES WHICH, IN CONTACT WITH WATER, EMIT FLAMMABLE GASES

2.12.1 Introduction

Depending on the chemical structure and/or the physical state (e.g. particle size) substances or mixtures may be able to react with water (even water damp / air humidity) under normal ambient temperature conditions. Sometimes this reaction can be violent and/or with significant generation of heat. Especially if gases are evolved this reaction may become very dangerous during use. In addition, it is important to know whether a substance emits

flammable gases after contact with water because special precautions are necessary especially with regard to explosion protection.

Examples are demonstrated in the following table.

Table 2.12.1 *Examples of hazards, depending on the property of the emitted gas, when substances and mixtures are in contact with water*

Type of emitted gas	Example of the hazard	CLP Reference
Gas (in general)	• Heating up of the substance • Splashing of the substance and thus e.g. contact with skin etc. or additional risk during fire fighting • Pressure rise and bursting of e.g. the packaging, tank	Annex II, 1.1.3: Supplemental hazard information: EUH014*
Flammable gas	• Ignition • Flash of fire	Annex I, 2.12: H260/H261
Toxic gas	• Damage to health: intoxication (acute)	Annex II, 1.2.1: Supplemental hazard information: EUH029*

* For supplemental hazard information: see Section 2.12.4.2

For substances and mixtures which, in contact with water, emit flammable gases the general classification principles of GHS and CLP are widely comparable.

2.12.2 Definitions and general considerations for the classification of substances and mixtures which, in contact with water, emit flammable gases

The following definition is given in CLP for substances and mixtures which, in contact with water, emit flammable gases (CLP Annex I, 2.12).

Annex I: 2.12.1. Substances or mixtures which, in contact with water, emit flammable gases means solid or liquid substances or mixtures which, by interaction with water, are liable to become spontaneously flammable or to give off flammable gases in dangerous quantities.

2.12.3 Classification of substances and mixtures which, in contact with water, emit flammable gases

2.12.3.1 Identification of hazard information

For the classification of substances and mixtures which, in contact with water, emit flammable gases the following data are needed, if applicable:

- Chemical structure
- Water solubility
- Chemical identity and flammability of the emitted gas
- Pyrophoric properties of the tested substance or mixture
- Particle size in case of solids
- Friability in case of solids
- Hazard properties in general

– Information concerning the experience in production or handling

Information about the chemical structure is used to check whether the substance or mixture contains metals and/or metalloids (see the following chapter 2.1.1 on non-testing data).

The water solubility is used to decide whether the substance or mixture is soluble in water to form a stable mixture. This may also be decided based on information concerning experience in handling or use, e.g. the substance is manufactured with water or washed with water (see Section 2.12.3.4.1).

The chemical identity of the emitted gas is used to decide whether the evolved gas is flammable or not. If the chemical identity of the emitted gas is unknown, the gas shall be tested for flammability (see Section 2.3).

In case of pyrophoric substances and mixtures the test UN N.5 of the UN-MTC, Part III, section 33.4.1.4 shall be executed under nitrogen atmosphere. Therefore, in regard to CLP data about pyrophoric properties are needed.

Melting point, boiling point and information about viscosity are necessary to identify the physical state of the substance or mixture. Even though the UN N.5 test can be applied to both, solids and liquids, these data are necessary to decide whether information concerning the friability (for solids) in accordance with the test method is necessary.

The particle size and the friability of a solid substance or mixture are crucial parameters for the classification of substances and mixtures which, in contact with water, emit flammable gases. These parameters have a significant effect on the test result. Thus specific requirements regarding the particle size and the friability are prescribed in the test method UN N.5. For further details regarding the test procedure see Section 2.12.3.4.1.

The following references generally provide good quality data on physical hazards (see Section 2.7.8 for full references):

(a) Bretherick's Handbook of Reactive Chemical Hazards (Urben, 1999)

(b) ChemFinder (ChemFinder, database)

(c) CHEMSAFE (contains evaluated/recommended data) (CHEMSAFE, database)

(d) CRC Handbook of Chemistry and Physics (CRC, 2005)

(e) GESTIS-database on hazardous substances (GESTIS database)

(f) The Merck Index (Merck, 2001)

2.12.3.2 Screening procedures and waiving of testing

For the majority of substances, flammability as a result of contact with water is not a typical property and testing can be waived based on a consideration of the structure and experiences in handling and use.

Annex I: 2.12.4.1. The classification procedure for this class need not be applied if:

a) The chemical structure of the substance or mixture does not contain metals or metalloids; or

b) Experience in handling and use shows that the substance or mixture does not react with water, e.g. the substance is manufactured with water or washed with water; or

c) The substance or mixture is known to be soluble in water to form a stable mixture.

2.12.3.3 Classification criteria

Annex I: *Table 2.12.1* **Criteria for substances or mixtures which in contact with water emit flammable gas**	
Category	Criteria
1	Any substance or mixture which reacts vigorously with water at ambient temperatures and demonstrates generally a tendency for the gas produced to ignite spontaneously, or which reacts readily with water at ambient temperatures such that the rate of evolution of flammable gas is equal to or greater than 10 litres per kilogram of substance over any one minute.
2	Any substance or mixture which reacts readily with water at ambient temperatures such that the maximum rate of evolution of flammable gas is equal to or greater than 20 litres per kilogram of substance per hour, and which does not meet the criteria for Category 1.
3	Any substance or mixture which reacts slowly with water at ambient temperatures such that the maximum rate of evolution of flammable gas is equal to or greater than 1 litre per kilogram of substance per hour, and which does not meet the criteria for Categories 1 and 2.
Note: The test shall be performed on the substance or mixture in its physical form as presented. If for example, for the purposes of supply or transport, the same chemical is to be presented in a physical form different from that which was tested and which is considered likely to materially alter its performance in a classification test, the substance must also be tested in the new form. **2.12.2.2.** A substance or mixture shall be classified as a substance or mixture which in contact with water emits flammable gases if spontaneous ignition takes place in any step of the test procedure.	

2.12.3.4 Testing and evaluation of hazard information

2.12.3.4.1 Testing procedure

Care shall be taken during testing as the emitted gas might be toxic as well.

The testing procedure for substances and mixtures which in contact with water emit flammable gases is sensitive to a number of influencing factors and therefore should be carried out by experienced personnel. Some of these factors are described in the following:

1. Apparatus / measuring technique

In test method UN N.5 no special laboratory apparatus / measuring technique to determine gas evolving flow is required and no reference material is prescribed. As demonstrated in the past by a round robin test, the gas evolution rate measured by different apparatuses may vary in a wide range. Therefore in order to avoid measuring and classification errors adequate quality control measures are necessary to validate the results and should be noted in the test report.

2. Particle size and/or friability

The particle size of a solid has a significant effect on the test result. Therefore, if for solids the percentage of powder with a particle size of less than 500 µm constitutes more than 1 % of the total mass, or if the substance is friable, then the complete sample shall be ground to a powder before testing to consider a possible reduction in particle size during handling and transport.

In other cases, a grinding procedure may not be applicable and/or the sample cannot be ground completely to a particle size of less than 500 µm (e.g. metal granules).

Information on these pre-treatments and the respective procedures, the particle size and the friability has to be mentioned in the test report.

3. Atmospheric parameters

Variations of the atmospheric parameters (mainly air pressure and temperature) during the test have a considerable influence on the test result. Therefore the substance or mixture shall be tested at 20 °C, i.e. make sure that the test apparatus is acclimatised to 20 °C.

On the other hand it is difficult to regulate and stabilise the air pressure during the testing. To characterise this influencing factor and to avoid false positive results, an additional "blank test" is strictly recommended. The results of the blank test should be noted in the test report.

4. Test with demineralised (distilled) water

The UN N.5 test is performed with demineralised (distilled) water. In practice, contact with water can be to water in the liquid state (fresh water, sea water) or humid air, respectively. Note that the reactivity and thus the gas evolution rate observed in practice may differ from the gas evolution rate value measured by demineralised water. This circumstance should be taken into account when handling substances which in contact with water emit flammable gases.

5. Stirring procedures during the test

Stirring of the sample/water mixture during the test may have a considerable effect on the test result (e.g. significant increase or decrease of the gas evolution rate). Therefore, the sample/water mixture should not be stirred continuously during the test, e.g. by an automatic magnetic stirrer, even if the test sample has hydrophobic properties and the moistening of the sample becomes impossible.

6. Spontaneous ignition

This term means spontaneous ignition of the evolved gas in the air but without contact to an additional ignition source, i.e. without the flame of the gas burner.

2.12.3.4.2 Evaluation of hazard information

In order to evaluate test results the evaluator person shall have sufficient experience in the application of the test methods and in the disturbing / influencing factors as described above.

The evaluation of data comprises two steps

- Evaluation of all available data and
- Identification of the study or studies giving rise to the highest concern (key studies).

The criterion for the gas evolution rate for assignment to Category 2 or 3 amounts to 20 or 1 litre per kilogram of substance per hour, respectively, but for Category 1 the relevant criterion is 10 litres per kilogram of substance over any one minute period. This has to be considered while testing and for correct evaluation of the test results.

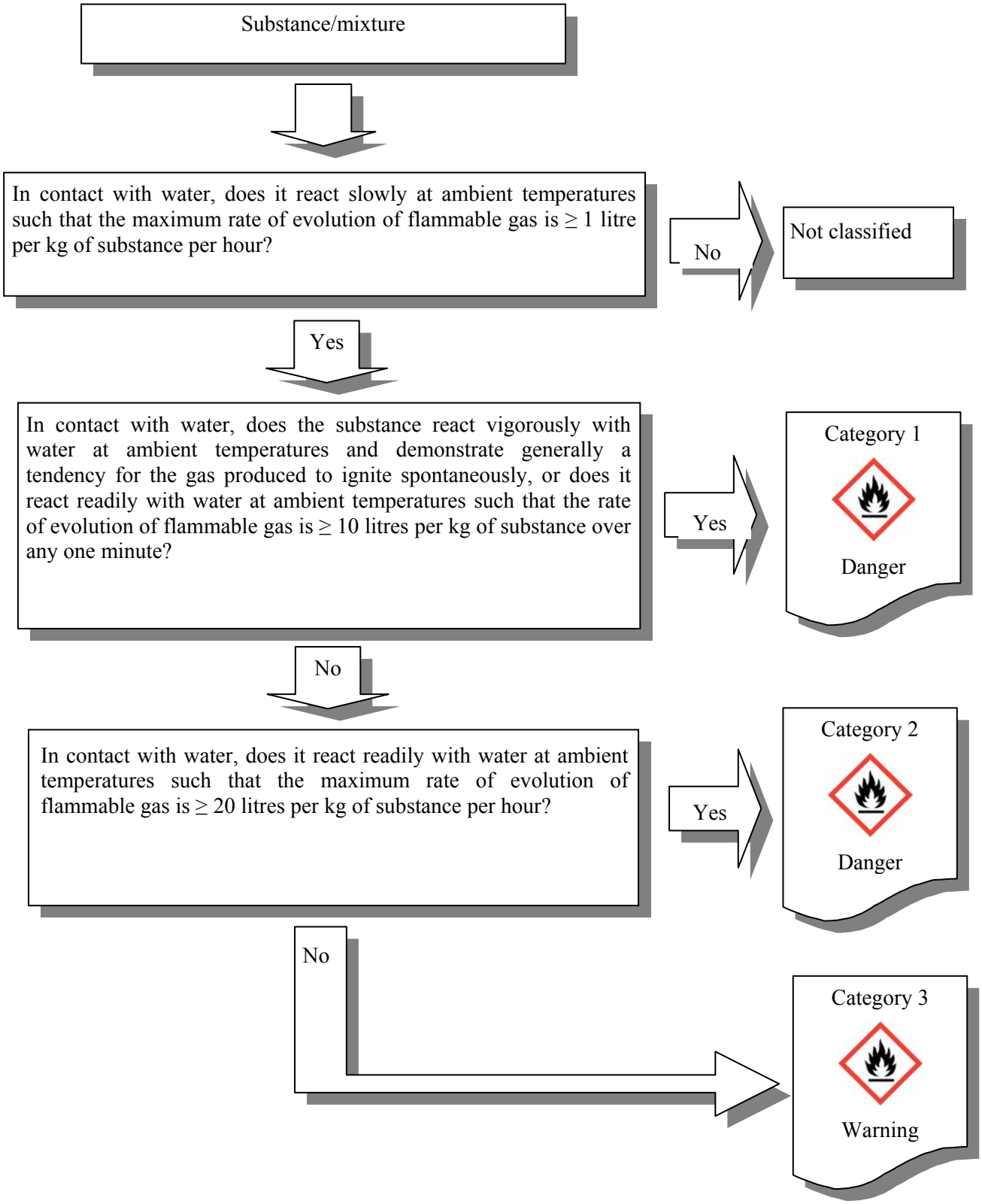
The assignment to the respective hazard class / category will further determine the technical means to be taken to avoid dangerous events which, in combination with other endpoints such as i) explosion limits, ii) flash points (applicable only for liquids) or iii) self-ignition temperature, can lead to clear restrictions in the conditions of use.

2.12.3.5 Decision logic

The decision logic and guidance which follow, are not part of the harmonized classification system, but have been provided here as additional guidance.

NOTE: The person responsible for classification should study the criteria for classification before and during use of the decision logics.

Figure 2.12.3.5 *Decision logic for substances and mixtures which, in contact with water, emit flammable gases (Taken from GHS, Revision 2)*



2.12.4 Hazard communication for substances and mixtures which, in contact with water, emit flammable gases

2.12.4.1 Pictograms, signal words, hazard statements and precautionary statements for substances and mixtures

Annex I: 2.12.3. *Table 2.12.2* **Label elements for substances or mixtures which in contact with water emit flammable gases**			
Classification	**Category 1**	**Category 2**	**Category 3**
GHS Pictograms			
Signal word	Danger	Danger	Warning
Hazard statement	H260: In contact with water releases flammable gases which may ignite spontaneously	H261: In contact with water releases flammable gases	H261: In contact with water releases flammable gases
Precautionary Statement Prevention	P223 P231 + P232 P280	P223 P231 + P232 P280	P231 + P232 P280
Precautionary Statement Response	P335 + P334 P370 + P378	335 + P334 P370 + P378	P370 + P378
Precautionary Statement Storage	P402 + P404	P402 + P404	P402 + P404
Precautionary Statement Disposal	P501	P501	P501

The wording of the Precautionary Statements is found in CLP Annex IV, Part 2.

2.12.4.2 Additional labelling provisions

Annex II of CLP provides the following additional labelling provisions for water-reactive substances. These statements shall be assigned in accordance with CLP, Article 25 (1), to substances and mixtures classified for physical, health or environmental hazards. There are no criteria or test methods provided for these EUH statements.

Annex II: 1.1.3. EUH014 – *'Reacts violently with water'*

For substances and mixtures which react violently with water, such as acetyl chloride, alkali metals, titanium tetrachloride.

Annex II: 1.2.1. EUH029 - *'Contact with water liberates toxic gas'*

For substances and mixtures which in contact with water or damp air, evolve gases classified for acute toxicity in category 1, 2 or 3 in potentially dangerous amounts, such as aluminium phosphide,

phosphorus pentasulphide.

2.12.5 Re-classification of substances and mixtures which, in contact with water, emit flammable gases according to DSD or already classified for transport

2.12.5.1 Re-classification of substances and mixtures classified in accordance with DSD

2.12.5.1.1 Differences in classification and labelling

The differences between the classification principles of CLP and DSD are relevant and a direct translation is not possible in all cases.

All substances and mixtures with F, R15 are classified as substances and mixtures which, in contact with water, emit flammable gases under CLP. The assignment of the correct category can be done in accordance with the transport classification on the basis of the UN N.5 test results.

Substances and mixtures with F; R15 where spontaneous ignition was observed in any step of the test procedure EC A.12 are classified in Category 1. In all other cases a re-evaluation of the EC A.12 test report data is not giving all relevant information (due to the missing value of the gas evolution rate of the minute intervals) and the assignment of the correct Category 1, 2 or 3 can be done only on the basis of the UN N.5 test results (see section 2.12.3.4.2).

Attention! According to DSD in case of pyrophoric substances and mixtures (F; R17) the test EC A.12 was not to be performed (see instruction of test method A.12 as described in in Council Regulation (EC) No 440/2008) and no additional classification with R15 was required. On the other hand, the CLP (and GHS) stipulate an additional classification as a substance and mixture which, in contact with water, emit flammable gases, even for pyrophoric substances or mixtures (F; R17). In case of pyrophoric substances and mixtures the UN N.5 test shall be executed under nitrogen atmosphere (see Table 2.12.5.1.2). Therefore, for pyrophoric substances or mixtures a direct translation with respect to their reaction with water is not possible.

2.12.5.1.2 Differences in the test procedures

There are relevant methodological differences between the test method EC A.12 of the Council Regulation (EC) No 440/2008 and the UN Test N.5 as described in Part III, sub-section 33.4.1 of the UN-MTC. The main differences are listed in the following table.

Table 2.12.5.1.2 *Differences between the method EC A.12 and UN N.5*

Parameter	EC A.12	CLP and UN N.5
Testing of pyrophoric substances and mixtures	not required	yes, required under nitrogen atmosphere
Gas evolution rate interval	1-hour interval: yes, required 1-minute-interval: not required	1-hour interval: yes, required 1-minute-interval: yes, required (with respect to Category 1)
Amount of sample	10 g	…enough (up to a maximum mass of 25 g) to produce between 100 ml and 200 ml of gas
Amount of water	10 to 20 ml	no instruction
Division into categories	no	yes, Category 1, 2, or 3

If no spontaneous ignition of the evolved gas was observed in step 1 to 3 of the procedure, then the gas evolution rate must be determined. In contrast to test UN N.5 the method EC A.12 does not require to determine the gas evolution rate at the 1-minute interval. Thus, a classification based on an A.12 test report is not possible if the gas evolution rate is greater than 1 litre per kilogram of substance per hour. In this case the assignment of the correct category shall be done in accordance with the transport classification on the basis of the UN N.5 test results.

For substances and mixtures with F; R15 a re-evaluation of the test will lead to a classification in Category 1 if a spontaneous ignition was observed in any step of the test procedure EC A.12. In all other cases a re-evaluation of the EC A.12 test report data is not giving all relevant information (due to the missing value of the gas evolution rate of the minute intervals) and the assignment of the correct Category 1, 2 or 3 can be done only on the basis of the UN N.5 test results (see chapter 4.1).

Attention! Special care is required in those cases where the gas evolution rate depends on the relative amounts of sample and water. However, the requirements for the sample and water amounts are different in the test methods EC A.12 and UN N.5. Thus, significant differences between the test results of different methods and/or amounts may occur.

For these reasons, the person responsible for classification shall have sufficient experience in the differences of both test methods.

In addition, it has to be mentioned that the lower criteria of both methods are different:

According to CLP (and GHS) the criterion for the gas evolution rate is:

"**equal to or greater than** 1 litre per kilogram of substance per hour".

According to EC test method A.12 and the UN Test Manual it is "**greater than** 1 litre per kilogram of substance per hour"

2.12.5.2 Relation to transport classification

Substances which are classified as class 4.3 for transport or are labelled with 4.3 in addition to class 4.2, class 8 or class 6.1 are classified as substances and mixtures which, in contact with water, emit flammable gases under CLP.

2.12.6 Examples of classification for substances and mixtures which, in contact with water, emit flammable gases

2.12.6.1 Example of a substance fulfilling the classification criteria

Substances and mixtures which, in contact with water, emit flammable gases may belong to many different classes of substances, for example, alkali metals, alkyl aluminium derivatives, alkyl metals, metal hydrides, metal phosphides, certain metal powders. A comprehensive list can be found in Bretherick's Handbook of Reactive Chemical Hazards (Urben P (editor 2007) and Urben P, 1999).

Example: Pyrophoric substance fulfilling the criteria for CLP classification

Substance:	Magnesium alkyls (Index No. 012-001-00-4)
Chemical structure:	R_2Mg
Flammable gas:	Hydrogen
Gas evolution rate:	not applicable
Spontaneous ignition:	not possible due to the nitrogen atmosphere during the UN N.5 test

EU classification:	F; R14-17
Transport classification:	-
Reference:	Former Annex I to DSD and Annex VI to CLP
⇒ CLP Classification:	H260 Water-react. 1 H250 Pyr. Sol. 1 EUH014

2.12.6.2 Example of a substance not fulfilling the classification criteria

Example: Manganese ethylene bis (dithiocarbamate) complex with zinc salt 88% (Mancozeb)

Gas evolution rate:	0 litre per kilogram of substance per hour.
Spontaneous ignition:	not applicable
Transport classification:	not class 4.3
Reference:	Method UN N.5, Table 33.4.1.4.5, United Nations (2003)
⇒ CLP Classification:	not classified as substances and mixtures which, in contact with water, emit flammable gases

2.12.7 References

ChemFinder (database): http://chemfinder.cambridgesoft.com

CHEMSAFE (database): http://www.dechema.de/en/chemsafe.html

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2.13 OXIDISING LIQUIDS AND OXIDISING SOLIDS

2.13.1 Introduction

The hazard classes "oxidising liquids" (CLP Annex I, 2.13) and "oxidising solids" (CLP Annex I, 2.14) comprise substances and mixtures whose hazard is characterised by the fact that, in contact with other materials, they are able to cause or contribute to the combustion of those materials. The other materials do not necessarily have to belong to a certain hazard class in order to be able to be affected by the presence of oxidising materials. For example, when

coming into contact with an oxidising material, a solid that is not classified into the hazard category "flammable solids" (CLP Annex I, 2.7) may upon ignition behave like a flammable solid. This is for example the case when a solid material (e.g. wood) is soaked with an oxidising liquid or when a liquid fuel (e.g. gas oil) mixes with an oxidising solid. Certain combinations of combustible materials and oxidising materials may even result in spontaneous combustion, thermal instability or form an explosive mixture, this means that they may have explosive properties or may be regarded as self-reactive substances.

The oxidising properties of a solid depend on its particle size. Smaller particles enable a more intimate contact between the solid oxidiser and a combustible solid. The smaller the particle size, the higher the oxidising capability of the solid. As a consequence, it may happen that large particles of a certain solid are considered to be non-hazardous, while small particles of the same solid need to be classified into the hazard class of oxidising solids.

Although widely known as "oxidising materials", their hazard and behaviour might be better understood by considering them to be "fire enhancing substances".

The hazards communication of oxidising liquids and oxidising solids intends to communicate the property that it may cause fire or explosion or that it may intensify fire.

Apart from the combustion hazard, the production of toxic and/or irritating fumes may cause an additional hazard. For example, when nitrates are involved in a fire, nitrous fumes may be formed.

The classification procedure and criteria for oxidising substances is not applicable for organic peroxides. Under DSD organic peroxides were considered to be oxidising substances because of the presence of the –O–O– bond. The majority of the organic peroxides do not possess oxidising properties; their main hazards are reactivity and flammability. Under CLP organic peroxides are comprised in a separate hazard class (CLP Annex I, 2.15) and they must not be considered according to the procedures described for oxidising solids and oxidising liquids.

The testing procedure and criteria for oxidising substances do not work properly for ammonium nitrate, ammonium nitrate compounds, ammonium nitrate based fertilizers and ammonium nitrate emulsions, suspensions or gels.

Ammonium nitrate is not an oxidising substance, but by default it may be classified is an oxidising substance. The classification of ammonium nitrate or ammonium nitrate compounds is based on their composition and not on test results according to test O.1 or O.2 of the UN-MTC, Part III, sections 34.4.1 and 34.4.2, respectively. The procedure for the classification of ammonium nitrate emulsions, suspensions or gels is comprised in test series 8 of the UN-MTC.

For classification and labelling of materials containing ammonium nitrate, expert judgement should be sought.

2.13.2 Definitions and general considerations for the classification of oxidising liquids and oxidising solids

The CLP text comprises the following definitions for oxidising liquids and oxidising solids.

Annex I: 2.13.1 & 2.14.1 *Definitions*

An oxidising liquid or solid means a liquid or solid substance or mixture which, while in itself not necessarily combustible, may, generally by yielding oxygen, cause, or contribute to, the combustion of other material.

2.13.3 Classification of substances and mixtures as oxidising liquids and oxidising solids

2.13.3.1 Identification of hazard information

Oxidising liquids and oxidising solids may cause, or contribute to, the combustion of other material. Although the definition states that they generally do this by yielding oxygen, halogens can behave in a similar way. Therefore, any substance or mixture containing oxygen and/or halogen atoms should in principle be considered for inclusion into the hazard categories oxidising liquids or oxidising solids. This does not necessarily mean that every substance or mixture containing oxygen and/or halogen atoms should be subjected to the full testing procedure. Possibilities to waive testing are outlined in the next paragraph as well as paragraph 2.3.

2.13.3.1.1 Non-testing data

Experience in the handling and use of substances or mixtures which shows them to be oxidising is an important additional factor in considering classification as oxidising solid or oxidising liquid. In the event of divergence between test results and known experience, judgement based on known experience should take precedence over test results.

Before submitting a substance or a mixture to the full test procedure, an evaluation of its chemical structure may be very useful as it may prevent unnecessary testing. The person applying this procedure should have sufficient experience in testing and in theoretical evaluation of hazardous substances. The following text provides a guideline for the theoretical evaluation of potential oxidising properties on basis of its composition and chemical structure. In case of doubt, the full test shall be performed.

For organic substances or mixtures the classification procedure for these hazard classes need not to be applied if:

(a) The substance or mixture does not contain oxygen, fluorine or chlorine; or

(b) The substance or mixture contains oxygen, fluorine or chlorine and these elements are chemically bonded only to carbon or hydrogen.

For inorganic substances or mixtures, the classification procedure for these hazard classes need not be applied if they do not contain oxygen or halogen.

On basis of this theoretical evaluation only a distinction can be made between “potentially oxidising” (i.e. further testing required) and “non-oxidising” (i.e. no further testing for this hazard category required). It is not possible to assign a hazard category on basis of a theoretical evaluation.

Any substance or mixture that complies with the above evaluation criteria can be safely regarded to have no oxidising properties and, hence, needs not to be tested and needs not to be regarded as an oxidising liquid or an oxidising solid. However, such a substance or mixture may still possess other hazardous properties that require classification into another hazard class.

In case a mixture of an oxidising material and a non-hazardous inert material is offered for classification, the following should be taken into account.

An inert material by definition does not contribute to the oxidising capability of the oxidising material. Hence, the mixture can never be classified into a more severe hazard category.

If an oxidising material is mixed with an inert material, the oxidising capability of the mixture does not linearly decrease with decreasing content of oxidising substance. The relationship is

more or less logarithmic and depends on the characteristics of the oxidising material. For instance, a mixture containing 50% of a strong oxidiser and 50% of an inert material may retain 90% of the oxidising capability of the original oxidising component. Non-testing classification of mixtures based solely on test data for the original oxidising substance should therefore be done with extreme care and only, if sufficient experience in testing exists

The determination of the oxidising properties of an aqueous solution of solid oxidising substances and the classification as an oxidising preparation is not necessary provided that the total concentration of all solid oxidisers in the aqueous solution is less then or equal to 20%(w/w).

2.13.3.2 Classification criteria

2.13.3.2.1 General

The testing procedures for oxidising liquids and oxidising solids are based on the capability of an oxidising material to enhance the combustion of a combustible material. Therefore, oxidising solids and oxidising liquids that are submitted for classification testing are mixed with a combustible material. In principle, dried fibrous cellulose is used as a combustible material. The mixture of the potentially oxidising material and cellulose is then ignited and its behaviour is observed and compared to the behaviour of reference materials.

For liquids the mixture with cellulose is ignited under confinement in an autoclave and the pressure rise rate that is caused by the ignition and the subsequent reaction is recorded. The pressure rise rate is compared to that of three reference materials. The higher the pressure rise rate, the stronger the oxidising capability of the liquid tested.

For solids the mixture with cellulose is ignited at atmospheric conditions and the time necessary for the combustion reaction to consume the mixture is recorded. The faster the combustion rate, the stronger the oxidising capability of the solid tested.

The classification criteria as included in CLP are copied in sections 2.2.2 and 2.2.3.

2.13.3.2.2 Oxidising liquids

Annex I: 2.13.2.1. An oxidising liquid shall be classified in one of the three categories for this class using test O.2 in Part III, sub-section 34.4.2 of the *UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria* in accordance with Table 2.13.1:

Table 2.13.1

Criteria for oxidising liquids

Category	Criteria
1	Any substance or mixture which, in the 1:1 mixture, by mass, of substance (or mixture) and cellulose tested, spontaneously ignites; or the mean pressure rise time of a 1:1 mixture, by mass, of substance (or mixture) and cellulose is less than that of a 1:1 mixture, by mass, of 50% perchloric acid and cellulose.
2	Any substance or mixture which, in the 1:1 mixture, by mass, of substance (or mixture) and cellulose tested, exhibits a mean pressure rise time less than or equal to the mean pressure rise time of a 1:1 mixture, by mass, of 40% aqueous sodium chlorate solution and cellulose; and the criteria for Category 1 are not met.
3	Any substance or mixture which, in the 1:1 mixture, by mass, of substance (or mixture) and cellulose tested, exhibits a mean pressure rise time less than or equal to the mean pressure rise time of a 1:1 mixture, by mass, of 65% aqueous nitric acid and cellulose; and

	the criteria for Category 1 and 2 are not met.

2.13.3.2.3 Oxidising solids

Annex I: 2.14.2.1. An oxidising solid shall be classified in one of the three categories for this class using test O.1 in Part III, sub section 34.4.1 of the UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria, in accordance with Table 2.14.1:

Table 2.14.1

Criteria for oxidising solids

Category	Criteria
1	Any substance or mixture which, in the 4:1 or 1:1 sample-to-cellulose ratio (by mass) tested, exhibits a mean burning time less than the mean burning time of a 3:2 mixture, by mass, of potassium bromate and cellulose.
2	Any substance or mixture which, in the 4:1 or 1:1 sample-to-cellulose ratio (by mass) tested, exhibits a mean burning time equal to or less than the mean burning time of a 2:3 mixture (by mass) of potassium bromate and the criteria for Category 1 are not met.
3	Any substance or mixture which, in the 4:1 or 1:1 sample-to-cellulose ratio (by mass) tested, exhibits a mean burning time equal to are less than the mean burning time of a 3:7 mixture (by mass) of potassium bromate and cellulose and the criteria for Categories 1 and 2 are not met.

Note 1:
Some oxidising solids also present explosion hazards under certain conditions (when stored in large quantities). Some types of ammonium nitrate may give rise to an explosion hazard under extreme conditions and the 'Resistance to detonation test' (BC Code, Annex 3, Test 5) can be used to assess this hazard. Appropriate information shall be made available in the SDS.

Note 2:
The test shall be performed on the substance or mixture in its physical form as presented. If for example, for the purposes of supply or transport, the same chemical is to be presented in a physical form different from that which was tested and which is considered likely to materially alter its performance in a classification test, the substance shall also be tested in the new form.

Note 1 may also apply to other oxidising ammonium salts. Experience indicates that the conditions required for ammonium nitrate to present an explosion hazard involve a combination of factors: storage in large volumes (multiple tonnes) and either contamination of the material (e.g. with metals, acids, organics) or excessive heat (e.g. under conditions of fire). The resistance to detonation (RTD) test is extensively described in Regulatioin 2003/2003/EC for ammonium nitrate.

Testing and evaluation of hazard information see Section 2.13.3.3 regarding the application of non-testing data. See Urben, 2007 for additional information regarding the use of non-testing data.

Testing can be waived in the following cases where the tests are not applicable: gases, explosive or highly flammable substances, organic peroxides.

2.13.3.3 Testing and evaluation of hazard information

The test methods for oxidising liquids and oxidising solids are designed to give a final decision regarding their classification. Apart from testing, also experience in the handling and use of substances or mixtures which shows them to be oxidising is an important additional factor in considering classification in these hazard classes. In the event of divergence between test results and known experience, judgement based on known experience should take

precedence over test results. However, on basis of experience only a substance or mixture shall never be classified into a category of a less severe hazard.

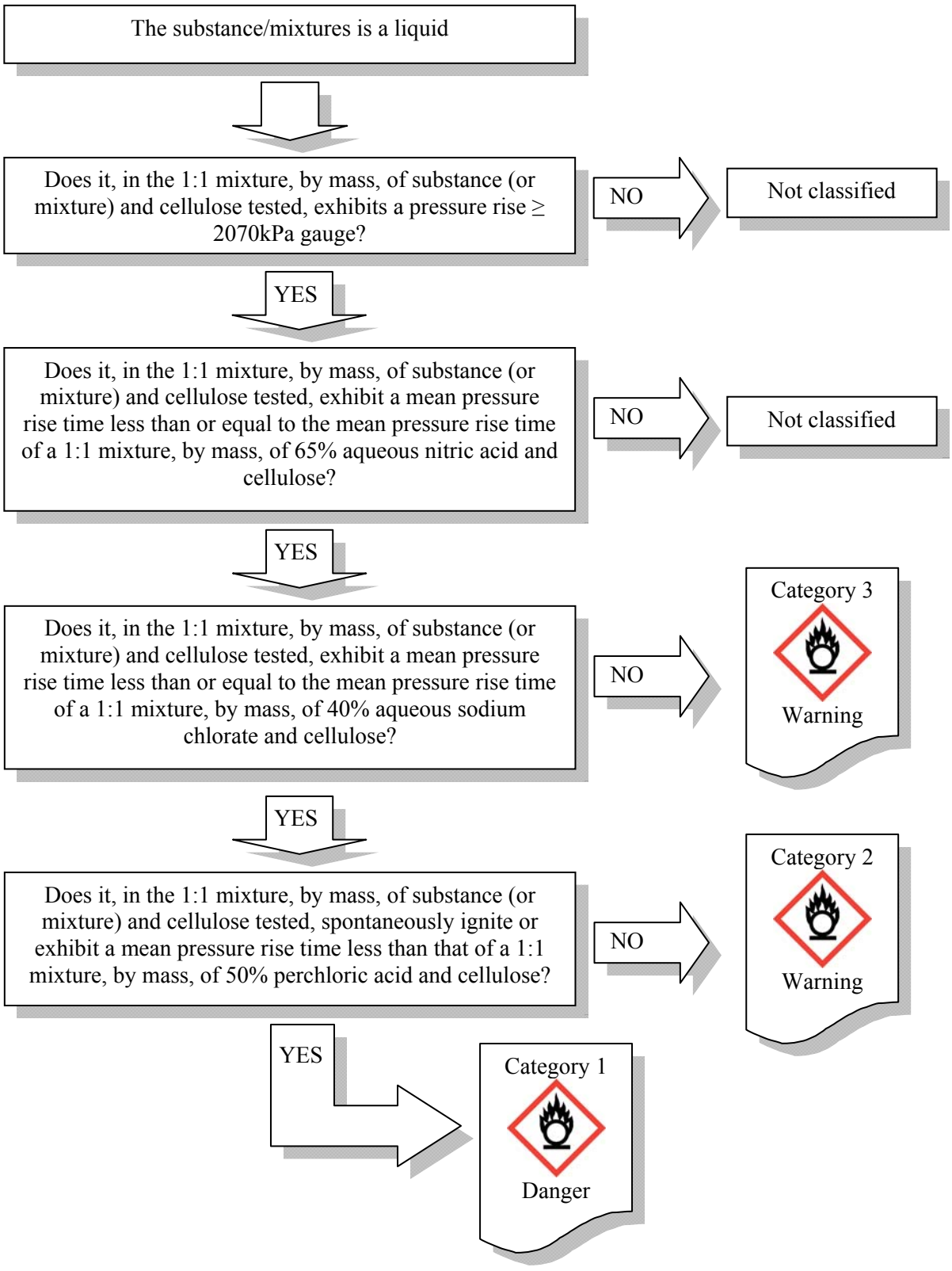
If the evaluation according to the appropriate criteria shows that the classification criteria are fulfilled, one or more hazard categories and the corresponding hazard statements shall be assigned (see Section 2.13.3.2).

2.13.3.4 Decision logic

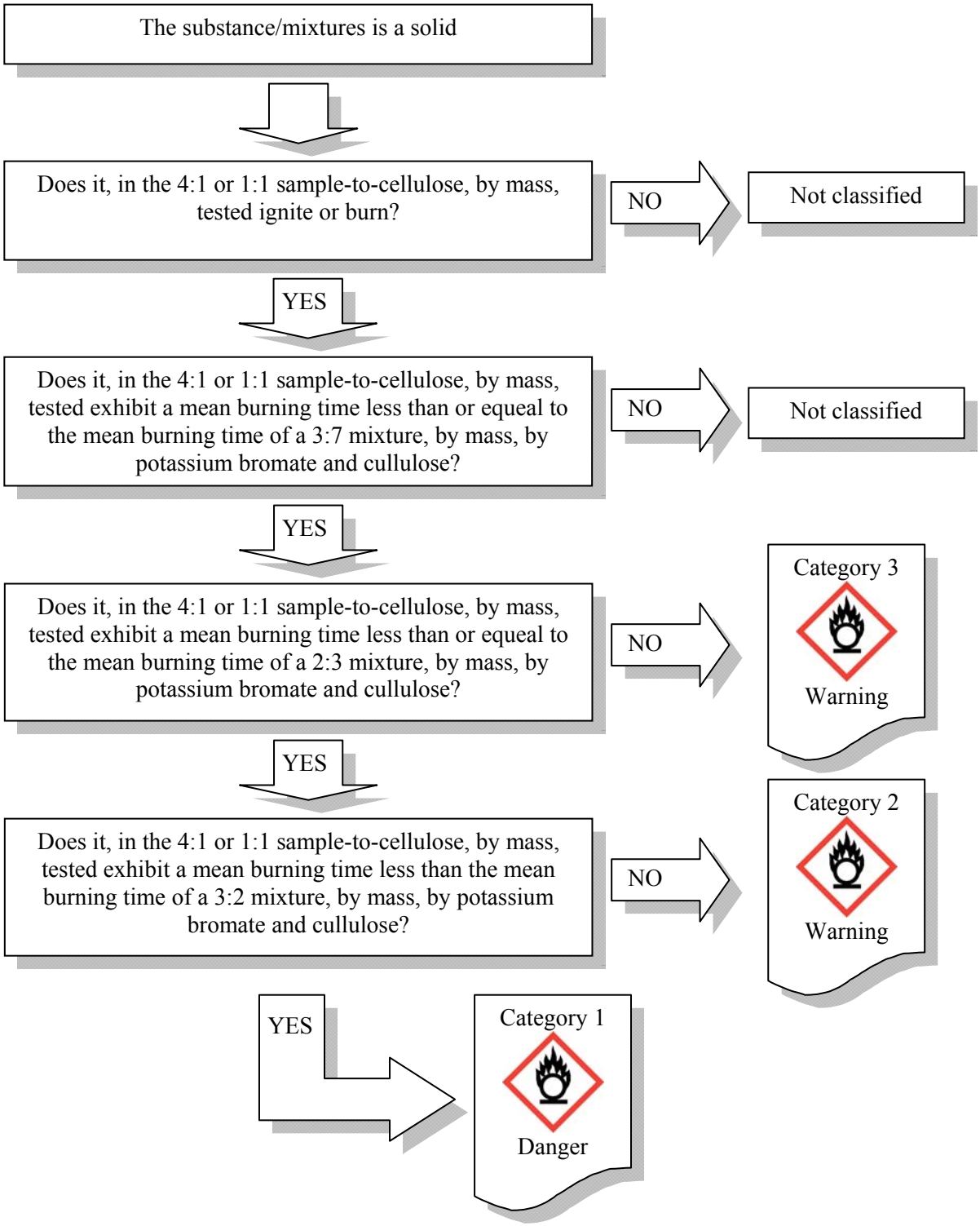
Classification of oxidising liquids and oxidising solids is done according to decision logics 2.13 and 2.14 as included in the GHS.

NOTE: The person responsible for classification should study the criteria for classification before and during use of the decision logics.

2.13.3.4.1 Decision logic 2.13 for oxidising liquids



2.13.3.4.2 Decision logic 2.14 for oxidising solids



Hazard communication for oxidising liquids and oxidising solids

2.13.3.5 Pictograms, signal words, hazard statements and precautionary statements

The symbols and hazard statements are designed to indicate that oxidising materials may cause or contribute to fire or explosion and therefore in principle should be separated from combustible materials.

According to CLP, the same label elements must be used for liquid and solid oxidising substances and mixtures (Tables 2.13.2 and 2.14.2 of CLP are equal).

Annex I, 2.13.3. & 2.14.3. *Tables 2.13.2 (liquids) & 2.14.2 (solids)* **Label elements for oxidising liquids and solids**			
	Category 1	**Category 2**	**Category 3**
Symbol			
Signal word	Danger	Danger	Warning
Hazard statement	H271: May cause fire or explosion; strong oxidiser	H272: May intensify fire; oxidiser	H272: May intensify fire; oxidiser
Precautionary Statement Prevention	P210 P220 P221 P280 P283	P210 P220 P221 P280	P210 P220 P221 P280
Precautionary Statement Response	P306 + P360 P371 + P380 + P375 P370 + P378	P370 + P378	P370 + P378
Precautionary Statement Storage			

The wording of the Precautionary Statements is found in CLP Annex IV, Part 2.

2.13.4 Re-classification of substances and mixtures classified as oxidising liquids and oxidising solids according to DSD or already classified for transport

2.13.4.1 Re-classification of substances and mixtures classified in accordance with DSD

2.13.4.1.1 Liquids

Substances that have been classified as oxidising liquids according to DSD can be re-classified to the GHS classification according to CLP. The test method that was used under DSD was included as Test Guideline A.21 in Council Regulation (EC) No 440/2008. The principle and criteria of this method are equivalent to those of the GHS method. However, previously it was only used to indicate whether or not the material had oxidising properties. Classification into hazard categories was possible but not necessary.

Since the cut-off limit is equivalent, substances that were classified as oxidising liquids according to DSD do also meet the CLP criteria. If no hazard category was assigned previously, re-testing will be necessary.

2.13.4.1.2 Solids

Substances that have been classified as oxidising solids according to DSD cannot be re-classified straightforward to the CLP classification. The test method that was used under DSD was included as Test Guideline A.17 of Council Regulation (EC) No 440/2008 for oxidising solids. Although the principle of this method was quite similar to that of the GHS method, the set-up and the criteria of the test method were very different. Moreover, the previous method was only designed to indicate whether or not the material had oxidising properties. No classification into hazard categories was possible.

In general, substances that were classified as oxidising solids according to DSD will also meet the criteria for GHS classification according to CLP. If no hazard category was assigned previously, re-testing will be necessary.

2.13.4.2 Relation to transport classification

Substances or mixtures which are classified as class 5.1 for transport are classified as oxidising liquids or solids under CLP.

2.13.5 Examples of classification for oxidising liquids and oxidising solids

2.13.5.1 Examples of substances and mixtures fulfilling the classification criteria

The list of substances and mixtures fulfilling the criteria for classification is only presented for information purposes. This list is not exhaustive.

2.13.5.1.1 Liquids

Ferric nitrate, saturated aqueous solution

Lithium perchlorate, saturated aqueous solution

Magnesium perchlorate, saturated aqueous solution

Perchloric acid, 55%

Sodium nitrate, 45% aqueous solution

2.13.5.1.2 Solids

Calcium nitrate, anhydrous

Chromium trioxide

Potassium nitrite

Potassium perchlorate

Potassium permanganate

Sodium chlorate

Sodium nitrite

Sodium nitrate

Strontium nitrate, anhydrous

2.13.5.2 Examples of substances and mixtures not fulfilling the classification criteria for

2.13.5.2.1 Liquids

Nickel nitrate, saturated aqueous solution

Potassium nitrate, 30% aqueous solution

Silver nitrate, saturated aqueous solution

2.13.5.2.2 Solids

Calcium nitrate, tetrahydrate

Cobalt nitrate, hexahydrate

2.13.6 Reference

Urben, P.G., Bretherick's Handbook of Reactive Chemical Hazards, Seventh Edition, 2007, Academic Press, Elsevier, Amsterdam.

2.14 ORGANIC PEROXIDES

2.14.1 Introduction

The hazard class "Organic Peroxides" is unique in the respect that it is the only category to which chemicals are assigned on the basis of their chemical structure. Organic peroxides cannot be seen as an "intrinsic property"; it is a family of chemical substances which may have various properties. However, the type of peroxide is determined by testing.

2.14.2 Definitions and general considerations for the classification of organic peroxides

Annex I: 2.15.1. *Definition*

Organic peroxides means liquid or solid organic substances which contain the bivalent –O-O-structure and may be considered derivatives of hydrogen peroxide, where one or both of the hydrogen atoms have been replaced by organic radicals. The term organic peroxide includes organic peroxide mixtures (formulations) containing at least one organic peroxide. Organic peroxides are thermally unstable substances or mixtures, which can undergo exothermic self-accelerating decomposition. In addition, they can have one or more of the following properties:

(i) be liable to explosive decomposition;

(ii) burn rapidly;

(iii) be sensitive to impact or friction;

(iv) react dangerously with other substances.

2.15.1.2. An organic peroxide is regarded as possessing explosive properties when in laboratory testing the mixture (formulation) is liable to detonate, to deflagrate rapidly or to show a violent effect when heated under confinement.

In CLP, the following definition is given for organic peroxides.

2.14.3 Relation to other physical hazards

In addition to the definition (CLP Annex I, 2.15.1), organic peroxides may:

(v) Be flammable.

(vi) Emit flammable gas when heated,

In general, organic peroxides do not have or have only weak oxidising properties.

The additional (subsidiary) labelling, as indicated in the list of classified organic peroxides included in the RTDG section 2.5.3.2.4, represents the additional hazardous properties.

Neither the burning properties nor the sensitivity to impact and friction form part of the classification procedure for organic peroxides in CLP. These properties may be of importance for the safe handling of organic peroxides (see Section 2.14.4.3.2, additional testing).

In addition, the hazard statement for flammable properties for liquid organic peroxides should be based on the appropriate category for flammable liquids, as long as the flashpoint is relevant, (see Section 2.14.4.3.2). The translation table in Annex VII to CLP can be used for this.

2.14.4 Classification of substances and mixtures as organic peroxides

2.14.4.1 Identification of hazard information

The classification of an organic peroxide in one of the seven categories “Types A to G” is dependent on its detonation, thermal explosion and deflagrating properties, its response to heating, the concentration and the type of diluent added to desensitize the substance. Specifications of acceptable diluents that can be used safely are given in the UN Recommendations on the Transport of Dangerous Goods, 2.5.3.5. The classification of an organic peroxide as Type A, B or C is dependent on the type of packaging in which the substance is tested as it affects the degree of confinement to which the substance is subjected. This has to be considered when handling the substance; stronger packaging may result in more violent reactions when the substance decomposes. This is why it is important that storage and transport is done in packaging, allowed for the type of organic peroxide, that conforms the requirements of the UN-packaging or IBC instruction (P520/IBC520) or tank instruction (T23).

The traditional aspects of explosive properties, such as detonation, deflagration and thermal explosion, are incorporated in the decision logic Figure 2.15.1 of CLP. Consequently, explosive property determination as prescribed for the hazard class ‘explosives’ needs not to be conducted for organic peroxides.

A list of currently classified organic peroxides is included in the RTDG section 2.5.3.2.4.

2.14.4.2 Classification criteria

In CLP, organic peroxides are not classified as oxidisers but they are a distinct hazard class.

Annex I: 2.15.2.1. Any organic peroxide shall be considered for classification in this class, unless it contains:

a) not more than 1,0 % available oxygen from the organic peroxides when containing not more than

1,0 % hydrogen peroxide; or

b) not more than 0,5% available oxygen from the organic peroxides when containing more than 1,0 % but not more than 7,0 % hydrogen peroxide.

Determination of the explosive properties is incorporated in the classification decision logic. Flammability is not incorporated into the decision flow chart (see Section 2.14.4.4).
In CLP decision logic Annex I, Figure 2.15.1, classification of organic peroxides is based on performance based testing both small scale tests and, where necessary, some larger scale test with the substance in its packaging. The concept of "intrinsic properties" is, therefore, not applicable to this hazard class.
Organic peroxides are classified into one of the seven categories of "Types A to G" according to the classification criteria of CLP. The classification principles are given in decision logic Figure 2.15.1 of CLP and the test series A to H, as described in the Part II of the UN-MTC, should be performed.

Annex I: 2.15.2.2. Organic peroxides shall be classified in one of the seven categories of 'Types A to G' for this class, according to the following principles:

(a) any organic peroxide which, as packaged, can detonate or deflagrate rapidly shall be defined as organic peroxide TYPE A;

(b) any organic peroxide possessing explosive properties and which, as packaged, neither detonates nor deflagrates rapidly, but is liable to undergo a thermal explosion in that package shall be defined as organic peroxide TYPE B;

(c) any organic peroxide possessing explosive properties when the substance or mixture as packaged cannot detonate or deflagrate rapidly or undergo a thermal explosion shall be defined as organic peroxide TYPE C;

(d) any organic peroxide which in laboratory testing:

(i) detonates partially, does not deflagrate rapidly and shows no violent effect when heated under confinement; or

(ii) does not detonate at all, deflagrates slowly and shows no violent effect when heated under confinement; or

(iii) does not detonate or deflagrate at all and shows a medium effect when heated under confinement;

shall be defined as organic peroxide TYPE D;

(e) any organic peroxide which, in laboratory testing, neither detonates nor deflagrates at all and shows low or no effect when heated under confinement shall be defined as organic peroxide TYPE E;

(f) any organic peroxide which, in laboratory testing, neither detonates in the cavitated state nor deflagrates at all and shows only a low or no effect when heated under confinement as well as low or no explosive power shall be defined as organic peroxide TYPE F;

(g) any organic peroxide which, in laboratory testing, neither detonates in the cavitated state nor deflagrates at all and shows no effect when heated under confinement nor any explosive power, provided that it is thermally stable, i.e. the SADT is 60 °C or higher for a 50 kg package[44], and, for liquid mixtures, a diluent having a boiling point of not less than 150 °C is used for desensitisation, shall be defined as organic peroxide TYPE G. If the organic peroxide is not thermally stable or a diluent having a boiling point less than 150 °C is used for desensitisation, the organic peroxide shall be defined as organic peroxide TYPE F.

Where the test is conducted in the package form and the packaging is changed, a further test shall be conducted where it is considered that the change in packaging will affect the outcome of the test.

[44] See UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria, sub-sections 28.1, 28.2, 28.3 and Table 28.3.

A list of currently classified organic peroxides is included in the UN RTDG, Section 2.5.3.2.4.

2.14.4.3 Testing and evaluation of hazard information

2.14.4.3.1 Thermal stability tests and temperature control

In addition to the classification tests given in decision logic Figure 2.15.1 of CLP, the thermal stability of the organic peroxide has to be assessed in order to determine the Self-Accelerating Decomposition Temperature (SADT). For the determination of the SADT, the testing method in UN-MTC, Part II, section 28, may be used.

The SADT is defined as the lowest temperature at which self-accelerating decomposition may occur with a substance in the packaging as used in transport, handling and storage. The SADT is a measure of the combined effect of the ambient temperature, decomposition kinetics, package size and the heat transfer properties of the substance and its packaging.

There is no relation between the SADT of an organic peroxide and its classification in one of the seven categories "Types A to G". The SADT is used to derive safe handling, storage and transport temperatures (control temperature) and alarm temperature (emergency temperature).

Depending on its SADT an organic peroxide needs temperature control and the rules as given in CLP Annex I, 2.15.2.3, are the following two elements:

1) Criteria for temperature control

The following organic peroxides need to be subjected to temperature control:

(a) Organic peroxide types B and C with a SADT ≤ 50° C;

(b) Organic peroxide type D showing a medium effect when heated under confinement with a SADT ≤ 50° C or showing a low or no effect when heated under confinement with a SADT ≤ 45° C; and

(c) Organic peroxide types E and F with a SADT ≤ 45° C.

2) Derivation of control and emergency temperatures:

Type of receptacle	SADT[a)]	Control temperature	Emergency temperature
Single packagings and IBC's	20 °C or less	20 °C below SADT	10 °C below SADT
	over 20 °C to 35 °C	15 °C below SADT	10 °C below SADT
	over 35 °C	10 °C below SADT	5 °C below SADT
Tanks	< 50 °C	10 °C below SADT	5 °C below SADT

a) i.e. the SADT of the substance as packaged for transport, handling and storage.

It should be emphasized that the SADT is dependent on the nature of the organic peroxide itself, together with the volume and heat-loss characteristics of the packaging or vessel in which the substance is handled. The temperature at which self-accelerating decomposition occurs falls:

- as the size of the packaging or vessel increases; and
- with increasing efficiency of the insulation on the package or vessel.

The SADT is only valid for the substance as tested and when handled properly. Mixing the organic peroxide with other chemicals, or contact with incompatible materials (including incompatible packaging or vessel material) may reduce the thermal stability due to catalytic

decomposition, and lower the SADT. This may increase the risk of decomposition and has to be avoided.

2.14.4.3.2 Additional testing

The sensitivity of organic peroxides to impact (solids and liquids) and friction (solids only) may be of importance for the safe handling of the substances, in the event that these substances have pronounced explosive properties (e.g. rapid deflagration and/or violent heating under confinement). Test methods to determine these properties are described in test series 3 of the UN-MTC. This information should be part of the hazard communication in safety data sheets.

In national storage guidelines burning rate is commonly used for classification and consequential storage requirements. Test methods are incorporated in these national storage regulations.
The flashpoint for liquid organic peroxides is only relevant in the temperature range where the product is thermally stable. Above the SADT of the product flashpoint determination is not relevant because decomposition products are evolved.

Note: In case a flashpoint determination seams reasonable (expected flashpoint below the SADT) a test method using small amount of sample is recommended. In case the organic peroxide is diluted or dissolved, the diluent may determine the flashpoint

The determination of the auto ignition temperature is not relevant for organic peroxides, because the vapours decompose during the execution of the test. Available test methods are for non-decomposing vapour phases. Auto ignition of organic peroxide vapours when they decompose, can never be excluded. This information should be part of the hazard communication in safety data sheets.

Also self-ignition temperature determination (test applicable for solids) is not relevant. The thermal stability of organic peroxides is quantitatively given by the SADT test.

2.14.4.3.3 Additional classification considerations

Currently the following properties are not incorporated in CLP:

- mechanical sensitivity i.e. impact and friction sensitivity (for handling purposes);
- burning tests (for storage purposes); and
- flammability aspects (definition of label and relevance of flashpoint).

Furthermore:

2.15.4.2. Mixtures of already classified organic peroxides may be classified as the same type of organic peroxide as that of the most dangerous component. However, as two stable components can form a thermally less stable mixture, the SADT of the mixture shall be determined.

Note: The sum of the individual parts can be more hazardous than the individual components.

Formulated commercial organic peroxides are classified according to their SADT.

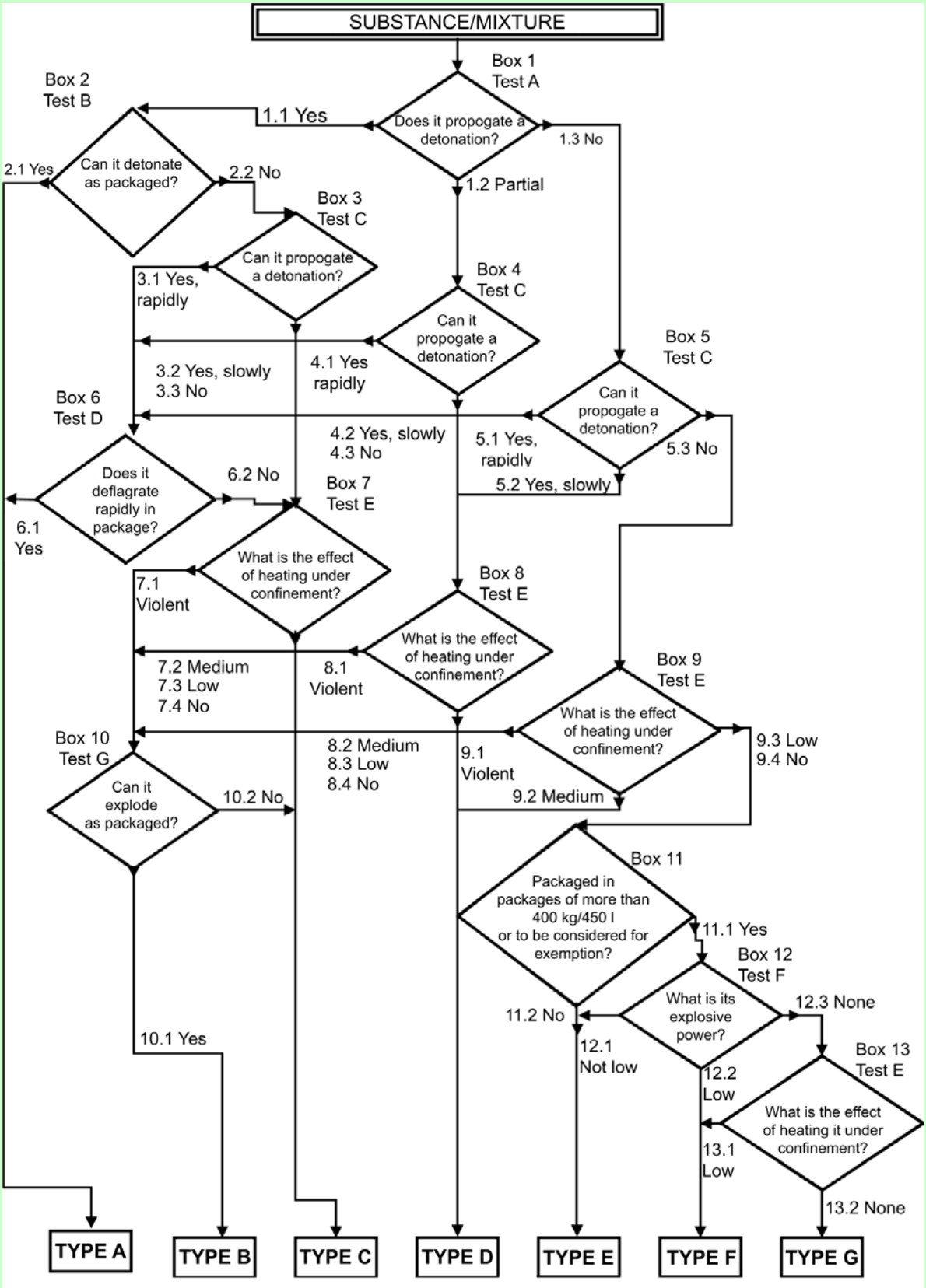
2.14.4.4 Decision logic

The following decision logic for organic peroxides is applicable according to CLP.

NOTE: The person responsible for classification should study the criteria for classification before and during use of the decision logics.

Annex I: *Figure 2.15.1*

Organic Peroxides



2.14.5 Hazard communication for organic peroxides

2.14.5.1 Pictograms, signal words, hazard statements and precautionary statements

According to CLP the following label elements shall be used for substances or mixtures meeting the criteria for this hazard class:

Annex I: *Table 2.15.1*

Label elements for organic peroxides

Classification	Type A	Type B	Type C & D	Type E & F	Type G
GHS pictograms					There are no label elements allocated to this hazard category
Signal words	Danger	Danger	Danger	Warning	
Hazard Statement	H240: Heating may cause an explosion	H241: Heating may cause a fire or explosion	H242: Heating may cause a fire	H242: Heating may cause a fire	
Precautionary statement Prevention	10 20 34 80	P210 P220 P234 P280	P210 P220 P234 P280	P210 P220 P234 P280	
Precautionary statement Response					
Precautionary statement Storage	P411 + P235 P410 P420	P410 P420	P410 P420	P410 P420	
Precautionary statement Disposal	P501	P501	P501	P501	

The wording of the Precautionary Statements is found in CLP Annex IV, Part 2.

Although CLP does not provide any precautionary statements for response, it is recommended to consider the same statements as for the hazard class self-reactive substances.

Precautionary statement Response	P370 + P378 P370 + P380 + P375	P370 + P378 P370 + P380 + P375	P370 + P378	P370 + P378

2.14.5.2 Additional labelling provisions for organic peroxides

Additional hazardous properties, resulting in additional (subsidiary) labelling, are indicated in the list of classified organic peroxides included in the RTDG, section 2.5.3.2.4.

2.14.6 Re-classification of substances and mixtures classified as organic peroxides according to DSD or already classified according to transport

2.14.6.1 Re-classification of substances and mixtures classified in accordance with DSD

According to the DSD, organic peroxides are classified as oxidising substances or mixtures, on basis of their structure and composition. In CLP organic peroxides are **NOT** classified as oxidisers but they are a distinct hazard class. The classification procedure is described in Section 2.14.4. Under DSD, explosive properties and flammability were determined separately by the EU tests A14 (for explosive properties) and A9 (for flammable properties).

Annex VII to CLP provides direct translations from DSD to CLP classifications. For organic peroxides a translation from symbol O and R-phrases, to a dedicated organic peroxide Type A-F is not possible. For the correct assignment of an individual organic peroxide substance or mixture, to the relevant Type B-F, the tables of the UN RTDG, 2.5.3.2.4, IBC 520 and T23 can be used. For Type A organic peroxides the classification principles of CLP should be applied.

2.14.6.2 Relation to transport classification

A list of currently classified organic peroxides is included in the UN RTDG, Section 2.5.3.2.4. This table includes organic peroxides Type B-Type F (and some formulations Type G, so-called exempted organic peroxides).

An exceptional case in this respect is a peroxyacetic acid formulation, as currently classified in the RTDG under UN 3149, with the following description: HYDROGEN PEROXIDE AND PEROXYACETIC ACID MIXTURE with acid(s), water and not more than 5% peroxyacetic acid, STABILISED. In the classification procedure for organic peroxides, see decision logic in Section 2.14.4.4, this formulation will be assigned to organic peroxide Type G, and consequently no label elements are allocated. In view of the above, this formulation can be classified, also in accordance with CLP, as an oxidising liquid, Category 2.

2.14.7 Examples of classification for organic peroxides

2.14.7.1 Examples of substances and mixtures fulfilling the classification criteria

Substance to be classified: BE

Molecular formula: n.a.

According to GHS 2.15.2.1, the substance has an active oxygen content of 7.40 % and thus has to be considered for classification in the hazard class organic peroxides.

Test results and classification according to CLP decision logic 2.15.1 for organic peroxides and the UN-MTC, Part II, is as follows:

Classification test results

1. Name of the organic peroxide : BE

2. General data

2.1.	Composition :	BE, technically pure (97%)
2.2.	Molecular formula:	n.a.
2.3.	Active oxygen content:	7.18 %
2.4.	Physical form:	liquid
2.5.	Colour:	colourless
2.6.	Density (apparent):	900 kg/m^3

3. Detonation (test series A)

Box 1 of the decision logic: Does the peroxide propagate a detonation?

3.1.	Method:	UN Test A.1: BAM 50/60 steel tube test
3.2.	Sample conditions:	peroxide assay 97 %
3.3.	Observations:	fragmented part of the tube: 18 cm
3.4.	Result:	No
3.6.	Exit:	1.3

4. Deflagration (test series C)

Box 5 of the decision logic:		Does the peroxide propagate a deflagration?
4.1.	Method 1:	Time/pressure test (test C.1)
4.1.1.	Sample conditions:	ambient temperature
4.1.2.	Observations:	4000 ms
4.1.3.	Result:	Yes, slowly
4.2.	Method 2:	Deflagration test (test C.2)
4.2.1.	Sample conditions:	temperature: 25 °C
4.2.2.	Observations:	deflagration rate: 0.74 mm/s
4.2.3.	Result:	Yes, slowly
4.3.	Final result:	Yes, slowly
4.4.	Exit:	5.2

5. Heating under confinement (test series E)

Box 8 of the decision logic:		What is the effect of heating it under defined confinement?
5.1.	Method 1:	Koenen test (test E.1)
5.1.1.	Sample conditions:	-
5.1.2.	Observations:	limiting diameter: 2.0 mm fragmentation type "F"
5.1.3.	Result:	Violent
5.2.	Method 2:	Dutch pressure vessel test (test E.2)
5.2.1.	Sample conditions:	-
5.2.2.	Observations:	limiting diameter: 6.0 mm (with 10 g)
5.2.3.	Result:	Medium

5.3.	Final result:	Violent
5.4.	Exit:	8.1
6. Explosion test in package (test series G)		
Box 10 of the decision logic:		What is the effect of heating it under defined confinement?
6.1.	Method:	Thermal explosion test in package (test G.1)
6.2.	Sample conditions:	30 litre packaging,
6.3.	Observations:	no fragmentation (N.F.)
6.4.	Result:	No
6.5.	Exit:	10.2
7. Thermal stability (outside of the decision logic)		
7.1.	Method:	Heat accumulation storage test (test H.4)
7.2.	Sample conditions:	mass 380 g. Half life time of cooling of Dewar vessel with 400 ml DMP: 10.0 hrs.(representing substance in package)
7.3.	Observations:	self-accelerating decomposition at 35 °C no self-accelerating decomposition at 30 °C
7.4.	Result:	SADT 35 °C
8.	General remarks:	The decision logic is given in figure 1
9.	Final classification	
Hazard hazard class:		organic peroxide, Type C, liquid, temperature controlled
Label:		Flame over circle
Signal word: Danger		
Hazard statement:		Heating may cause a fire
Temperature control:		Needed based on SADT (35 °C, in package)
Control temperature*:		20°C (in package)
Emergency temperature* :		25°C (in package)

*see UN-TDG, manual of tests and criteria, table 28.2

2.14.8 Additional remarks

Control and emergency temperature

The Control and Emergency temperatures are based on the SADT as determined by UN test H.4. The Dewar vessel used in the UN H.4 test was representative for the substance handled in packages. For handling the substance in larger quantities (IBCs/tanks/vessels etc.) and/or in (thermally) insulated containers, the SADT has to be determined for that quantity with that degree of insulation. From that SADT the Control and Emergency temperatures can be derived (see also Section 2.14.4.3.1)

Explosive properties

The explosive properties do not have to be determined according to CLP Annex I, 2.1 for explosives, because this is incorporated in the decision logic, see also Section 2.14.4.4.

Substance may have explosive properties when handled under greater confinement than is afforded by the packaging in which it was tested in UN test G.1 (see 6 of classification test results).

The appropriate precautionary statement should be assigned to indicate the hazard of thermal explosion under confined conditions.

Because the substance shows propagation [marked [mass] explosive] properties in test series E (see, 5 of the classification test results) the sensitivity to impact and friction (friction only for solids) are of importance for safe handling (see Section 2.14.4.3.2). Impact sensitivity according to UN test series 3, test 3 (a) (ii), BAM Fallhammer of the substances is 20 J. The appropriate precautionary statement should be assigned to indicate the hazard of impact sensitivity.

Burning properties

Together with the classification of the organic peroxide, the burning properties are of importance for storage classification (see Section 2.14.4.3.2). For example the burning properties as determined by the test method described in the storage guidelines, currently in place in France, Germany, Netherlands and Sweden, is 7.0 kg/min/m². Based on this figure and the classification as organic peroxide type C, the storage classification can be assigned in those countries.

Flashpoint

The substance thermally decomposes before the temperature at which the vapour can be ignited is reached (see Section 2.14.4.3.2).

2.15 CORROSIVE TO METALS

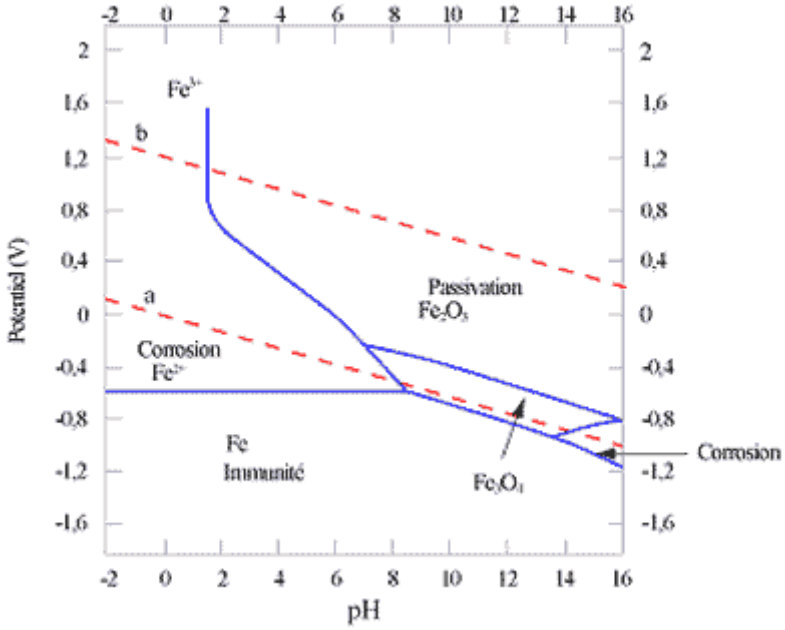
2.15.1 Introduction

The hazard class “corrosive to metals” (CLP AnnexI, 2.16) is a physico-chemical property that is new in the EU classification scheme and appears for the first time in CLP. So far, only the health hazard “corrosivity to skin” was considered in the classification scheme. To some extent, both properties relate to each other and, in the context of transport of dangerous goods, have been considered for classification in class 8, despite the different nature of the hazard (material damage versus living tissue damage).

A substance or a mixture that is corrosive to metal under normal conditions is a substance or a mixture liable to undergo an irreversible electrochemical reaction with metals that leads to significant damage or, in some cases, even to full destruction of the metallic components. The “corrosive to metal” property is a quite complex property, since it is a substance (or mixture) related as well as a material (metal) related property. This means a corrosive substance or mixture leads to corroded material (metal), according to a number of external conditions. From the material side, many types of corrosion processes may occur, according to configurations, liquid or fluid media inducing the corrosion process, nature of metal, potential passivation occuring by oxide formation during corrosion.

From the substance or mixture side, many parameters may influence the corrosion properties of a substance or mixture, such as the nature of the substance or the pH. From an electochemistry point of view, corrosion conditions are often studied using Pourbaix diagrams, which plot the electrochemical potential (in Volt) that develops according to electrical charges transfer versus the pH-value. Such a diagram is shown for the case of iron and applies only for carbon steel corrosion (Jones, 1996).

Figure 2.15.1 *Potential pH (also called Pourbaix) diagram for iron in water at 25°C, indicating stable form of the Fe element and implicitly, corrosion domains*



For the purposes of CLP, corrosion to metal will only be considered, by pure convention, for substances that are liable to attack carbon steel or aluminum, two of the most common metals that may come in contact with chemical substances (containment material, reactor material). The classification scheme applied here shall not be considered as a material (metal) classification method for metals regarding resistance to corrosion. By no means steel or aluminium specimens that are treated to resist to corrosion, shall be selected for testing.

2.15.2 Definitions and general considerations for the classification of substances and mixtures corrosive to metals

CLP comprises the following definition for substances and mixtures that are corrosive to metal.

Annex I: 2.16.1. *Definition*

A substance or a mixture that is corrosive to metals means a substance or a mixture which by chemical action will materially damage, or even destroy, metals.

2.15.3 Classification of substances and mixtures as corrosive to metals

2.15.3.1 Identification of hazard information

Importance of the physical state of the test substance or mixture

There is no reference in the definition (CLP Annex I, 2.16.1) to the physical state of the substances or mixtures that needs consideration for potential classification in this hazard class. According to the test method to be employed for considering classification under this hazard class, we may state at least that gases are out of the scope of the "corrosive to metal" hazard class. The hazard related to the formation of corrosive gases is not currently covered by the criteria for physical hazards in CLP. Corrosivity of gases (to metal) is assumed not to represent an actual physico-chemical hazard, and is therefore not applicable here.

According to the classification criteria (CLP Annex I, 2.16.2.1) only substances and mixtures for which the application of the test "C.1"described in part III, section 37 of the UN-MTC (4th

revised edition) is relevant and needs to be considered. This means that non soluble solids are excluded, while "liquids and solids that may become liquids (during transport)", as mentioned in this reference text, have to be considered for such a classification.

The wording "solids that may become liquids" was developed for TDGs classification purposes, and needs further explanation.

Solids may become liquids by melting (due to increase in temperature). Solids having a melting point lower than 55°C (which is the test temperature required in test C.1) must then be taken into consideration. The other physical way to transform a solid into liquid is by dissolution in water or another solvent. Classification of solid substances that may become liquids by dissolution is subject to further expert judgement, and may need adaptation of the classification criteria or test protocol (see Section 2.15.3.4.2). Interaction with liquids may come from air moisture or unintentional contact with water. Other solvent traces may result from the extraction process during manufacturing and these may induce corrosion in practice.

Substances and mixtures in a liquid state must be tested without any modification before testing, by using the C.1 test protocol. For other cases (solids that may become liquids), appropriate testing procedures require further work by the Committees of experts in charge of developing and updating the GHS at UN level. It needs to be further specified how such substances or mixtures shall be prepared (transformed into liquids) to be able to determine their corrosivity to metals. As an example, it is thought that the quantity of solvent (water or any other solvent) to liquefy the test substance before testing would greatly influence results of the C.1 test and may not necessarily represent the real life situation of a product during transport, handling or use.

Non-testing data

Following parameters are helpful to evaluate corrosive properties before testing:

- Melting points for solids,
- Chemical nature of the substances and mixtures under evaluation (e.g. strong acids),
- pH values (liquids),

Literature may also provide information on widely used substances and liquids "compatibility tables", taking account of the corrosiveness of the products that may serve to decide whether testing must be conducted before assigning the "corrosive to metals" hazard class, on basis of expert judgement.

The following substances and mixtures should be considered for classification in this class:

– Substances and mixtures having acidic or basic functional groups;
– Substances or mixtures containing halogen;
– Substances able to form complexes with metals and mixtures containing such substances.

2.15.3.2 Screening procedures and waiving of testing

Experience may have proven the corrosivity of given substances and mixtures. In such case no more testing is needed (see examples in Section 2.15.6).

Generally extreme pH-values point to a higher likelihood that the substance is corrosive. However, it can not lead to immediate classification in the hazard class "corrosive to metals". As a proof of that, Figure 2.15.1 shows that immunity zones (where steel does not corrode) still exist on the full spectrum of pH values as far as carbon steel is concerned.

Corrosivity is so complex that the evaluation of a mixture cannot be extrapolated from similar behaviour of constituents of a mixture. However, if one significant component of a mixture is corrosive to metals the mixture is likely to be corrosive to metals as well. Testing the actual mixture is therefore highly recommended. As already mentioned, solids are currently difficult to test according to the current CLP requirements, as the C.1 test has obviously been designed for liquids.

Where an initial test on either steel or aluminium indicates the substance or mixture being tested is corrosive, the follow up test on the other metal is not required.

2.15.3.3 Classification criteria

Substances and mixtures of hazard class 'corrosive to metals' are classified in a single hazard category on the basis of the outcome of the UN Test C.1 (UN-MTC, part III, section 37, paragraph 37.4).

Annex I, 2.16.2. *Table 2.16.1*

Criteria for substances and mixtures corrosive to metals

Category	Criteria
1	Corrosion rate on steel or aluminium surfaces exceeding 6.25 mm per year at a test temperature of 55°C

2.15.3.4 Testing and evaluation of hazard information

2.15.3.4.1 General considerations

It is important to point out that the criteria of corrosion rate will never be applied in an absolute way, but by extrapolating the measured rate of corrosion over the test period to the annual assumed correlating corrosion rate. This exercise has to take account of the fact that the corrosion rate is not necessarily constant over time. Expert judgement may be required to consolidate the optimum test duration and to ascertain test results. However, the possibility of increasing the testing period from minimum one week to four weeks as well as the use of two different metals in the test protocol C.1 act as barriers against erroneous classification.

Whatever the result of the classification may be, the classification as "corrosive to metals" relates to steel and/or aluminium only and does not provide information with regard to the corrosivity potential to other metals than those tested.

Two types of corrosion phenomena need to be distinguished for classification of substances and mixtures in this hazard class, although not reported in CLP: the uniform corrosion attack and the localised corrosion (e.g. pitting corrosion, shallow pit corrosion).

Table 1 (Section 37.4.1.4.1 of the UN Manual of test and criteria) translates the corresponding minimum mass loss rates leading to classify the test substance as corrosive to metals for standard metal specimens (2 mm of thickness), according to time of exposure, for reasons of uniform corrosion process. In case of use of metal plates of a thickness that differs from the specified 2 mm (see comments in 2.4.2), the values in tables 1 and 2 need adjustments due to the fact that the corrosion process depends on the surface of specimen.

Table 2.15.3.4.1(a): *Minimum mass loss of specimens after different exposure times (corresponding to the criterion of 6.25 mm/year)*

Exposure time	Mass loss
7 days	13.5%

14 days	26.5%
21 days	39.2%
28 days	51.5%

Table 2 (Section 37.4.1.4.2 of the UN-MTC) indicates the criteria leading to classification of the test substance as corrosive to metals for standard metal specimens, according to time of exposure, for reasons of localised corrosion process.

Table 2.15.3.4.1(a): *Minimum intrusion depths after exposure times (corresponding to the the criterion of localized corrosion of 6.25 mm/year)*

Exposure time	Min. intrusion depth
7 days	120µm
14 days	240µm
21 days	360µm
28 days	480µm

It is not mentioned explicitly in the text that localised corrosion as well as uniform corrosion has also be taken into account. However, localised corrosion, that is entirely part of test C.1 protocol, has actually to be taken into account. In addition, although the type of corrosion is not reflected in the classification result, this valuable information should be given in the SDS.

2.15.3.4.2 Additional notes on best practice for testing

Competence required for testing

The overall evaluation of appropriate data for considering the corrosion properties of a substance or a mixture and in particular for testing it according to the mentioned criteria for this hazard class, requires certain qualifications and experience. Expertise is often needed for this hazard class, which relates to a complex and multi-faceted hazardous phenomenon.

Selection of metal specimens

CLP refers to two types of metals (carbon steel and aluminium) meeting accurate specifications (technical characteristics of metal sheets and plate thickness). Thicker metal sheets, such as cast materials, of which the thickness is reduced by any form of mechanical treatment, may never be used. Mechanical reduction of sheet (metal) thickness could induce corrosion enhanced process due to cross section heterogeneity in metal grain and impurities. It is far better to use slightly different specifications of metal in the correct thickness or slightly different specimen plate thicknesses. It is recognised that it will not always be easy to obtain metal specimens with the profile as described above.

Regarding the type of aluminium or steel to be used for this test see UN Manual of Tests and Criteria, sub-section 37.4.1.2.

Minimum corrosive media volume

In order to prevent any limitation on the corrosion process due to full consumption of the corrosive media before the end of the testing period, a minimum volume of substance (1.5 L, according to the UN Manual) has to be used. (Note: volume/surface ratio of 10 mL/cm² is stated in DIN 50905, similar in ASTM G31–72.)

Adjustment of the test temperature

Corrosion processes are temperature dependent. In the context of CLP, the property "corrosive to metals" is assessed through testing metal specimens at a specified temperature of 55°C ± 1°C. In practice, it may be difficult with standard testing equipment to stay within

the temperature window (55°C ± 1°C) of the gas phase, all over the test period. In such case, the test can be performed conservatively at a slightly higher temperature and somewhat lower accuracy (e.g. 57°C ± 3°C).

Selecting the appropriate test duration

The evaluation of the criterion of 6.25 mm/year is generally based on a test duration not exceeding 1 month. There is, however, the option to stop the test procedure already after 1 week (see table 1). For the decision on test duration, the non linear behaviour of the corrosion process must be taken due account of. In borderline cases a non-appropriate test duration may result in either false positive or false negative results.

Specimen cleaning

Attention must be paid to the correct cleaning of the corroded residue before measurement of the corrosion characteristics. In case of adhesive corroded layer, the same cleaning process needs to be carried out on a non corroded sample to verify if the cleaning procedure is not significantly abrasive. For further information see UN-MTC, sub-section 37.4.1.3.

Testing soluble solids

As said in Section 2.15.3.1, for solids that may become liquids through dissolution in water or in a solvent, the adequate testing procedure is more complex (not explicitly describe in the C.1 test protocol). In no case will simple dilution of the solid substance in any quantity of water lead to satisfactory testing of the substance for corrosion to metals. It is recommended to perform the test with solutions containing extreme concentrations of the solid substance or mixture in water (very diluted e.g. 0.1% or saturated).

For the specific case where the corrosion potential is linked to the presence of solvent traces (other than water), expert judgement is needed to determine if further testing must be performed (where the solid is put in interaction with the metallic part considered).

Example of equipment relevant for the performance test C.1

Figure 2.15.3.4.2: *Example of testing equipment available on the market to perform test C.1*

2.15.4 Hazard communication for substances and mixtures corrosive to metals

2.15.4.1 Pictograms, signal words, hazard statements and precautionary statements

Table 2.16.2 of CLP Annex I provides the label elements for hazard class 'corrosive to metals'. The hazard statement H290, using the wording "may", reflects that classification under this hazard class does not cover all metals (testing only considers carbon steel and aluminium). Thus we may find examples of substances that are classified in this hazard class 'corrosive to metals' but will not induce corrosive action on other more corrosive resistant metals than those serving as reference materials (e.g. platinium).

Label elements shall be used for substances and mixtures meeting the criteria for classification in this hazard class in accordance with Table 2.16.2.

Annex I: 2.16.3. *Table 2.16.2* **Label elements for substances and mixtures corrosive to metals**	
Classification	Category 1
GHS Pictogram	

Signal Word	Warning
Hazard Statement	H290: May be corrosive to metals
Precautionary Statement, Prevention	P234
Precautionary Statement, Response	P390
Precautionary Statement, Storage	P406
Precautionary Statement, Disposal	

The wording of the Precautionary Statements is found in CLP Annex IV, Part 2.

2.15.5 Re-classification of substances and mixtures classified as corrosive to metals according to DSD

2.15.5.1 Re-classification of substances and mixtures classified in accordance with DSD

The hazard class 'corrosive to metals' was not included in the DSD. Therefore, re-classification is not applicable.

Only the substances and mixtures presenting the health related property "Skin corrosive" were included (Symbol C with R-phrases 34 or 35). These substances generally present a significant potential for the "corrosive to metals" property and should be considered for testing.

2.15.5.2 Relation to transport classification

Valuable information can be obtained from TDG regulation. Transport class 8 covers substances that are classified for corrosivity to skin, metals or both. Existing test results obtained in the context of transport may be applied since the C.1 test serves as reference for testing in both classification systems.

2.15.6 Examples of classification for substances and mixtures corrosive to metals

The following table lists some examples of substances and mixtures that should be classified or not in class 2.16 (according to known test C.1 results) in comparison with predicted results for skin corrosion hazard.

Table 2.15.6: *Examples of classified and non classified substances and mixtures in class 2.16*

Note: "corroded" means corrosion attack in the sense of test C.1;

"non corroded" means corrosion resistant in the sense of test C.1;

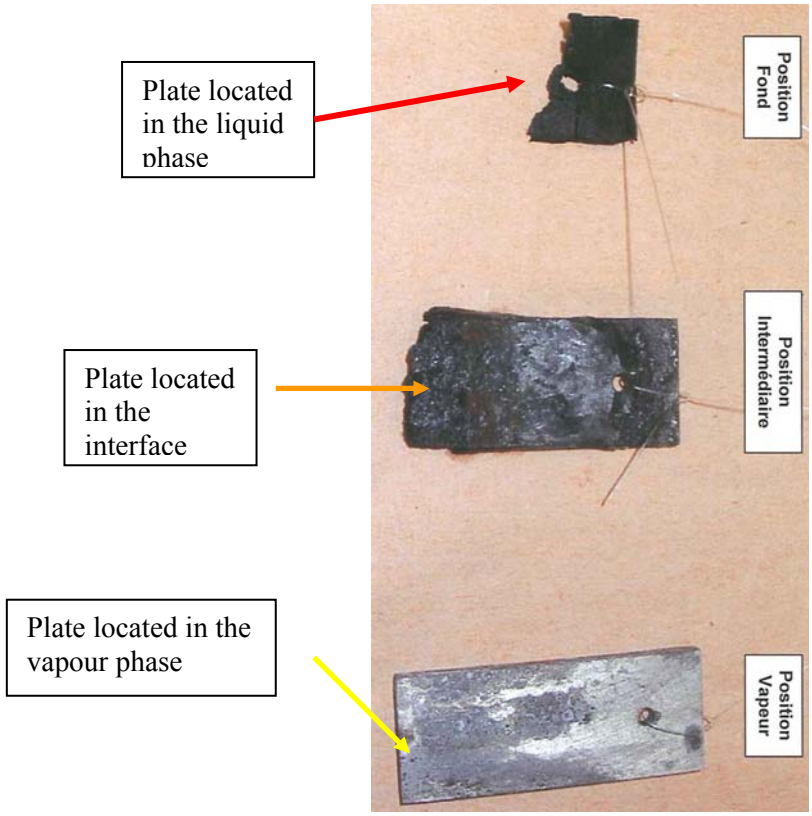
"positive or negative" are results from skin corrosion.

Substance or mixture	Steel	Aluminium	CLP Annex I, 2.16 classification	Skin (for comparison)
Hydrofluoric acid > 70% (UN1790)	Not corroded	Corroded	Classified	Positive
Highly concentrated nitric acid (97%) (UN2031)	Not corroded	Corroded	Classified	Positive

HNO_3 red fuming (UN2032)	Not corroded	Not corroded	Not classified	Positive
Hydrochloric acid (diluted) (UN1789)	Corroded	Corroded	Classified	Negative
NaOH solutions (UN1824)	Not corroded	Corroded	Classified	Positive

2.15.6.1 Example of metal specimen plates after exposure to a corrosive mixture

Figure 2.15.6.1: *Example of corroded metal plates after testing according to C.1 test for a classified mixture*



This example shows that the corrosion may develop at different rates according to the accurate position of the specimen related to the corroding mixture (sunk in the liquid, placed in the gas phase above liquid or at the liquid/gas interface).

2.15.7 References

ASTM G31-72(2004) Standard Practice for Laboratory Immersion Corrosion Testing of Metals.

Jones, D.A., Principles and Prevention of Corrosion, 2nd edition, 1996, Prentice Hall, Upper Saddle River, NJ. ISBN 0-13-359993-0 Page 50-52.

DIN 50905-1: 2007, Corrosion of metals - Corrosion testing - Part 1: General guidance (Korrosion der Metalle - Korrosionsuntersuchungen - Teil 1: Grundsätze).

3 HEALTH HAZARDS[45]

3.1 ACUTE TOXICITY

3.1.1 Definitions and general considerations for acute toxicity

Annex I: 3.1.1.1. Acute toxicity means those adverse effects occurring following oral or dermal administration of a single dose of a substance or a mixture, or multiple doses given within 24 hours, or an inhalation exposure of 4 hours.

Acute toxicity relates to effects occurring after a single or relatively brief exposure to a substance. The definition in CLP reflects the fact that the evidence for acute toxicity is usually obtained from animal testing. In particular, acute toxicity is usually characterised in terms of lethality and exposure times are based around those used in experimental protocols. However, classification for acute toxicity can also be based on human evidence which shows lethality following human exposure.

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

Acute toxicity classification is generally assigned on the basis of evident lethality (e.g. an LD_{50}/LC_{50} value), or, where the potential to cause lethality can be concluded from evident toxicity (e.g. from the fixed dose procedure). STOT-SE should be considered where there is clear evidence of toxicity to a specific organ, especially when it is observed in the absence of lethality (see Chapter 3.8).

For more details see IR/CSA, Section R.7.4.1.1.

Annex I: 3.1.1.2. The hazard class Acute Toxicity is differentiated into:

- Acute oral toxicity;
- Acute dermal toxicity;
- Acute inhalation toxicity.

The classification shall be considered for each route of exposure, using the appropriate approach as described in Section 3.1.2.2. If different hazard categories are assigned, the more severe hazard category will be used for the classification for acute toxicity, with the appropriate pictogram and signal word. For each relevant route of exposure, the hazard statement will correspond to the classification of this specific route.

[45] The guidance provided in this chapter is based on the classification criteria from the original version of the CLP Regulation (EC) No 1272/2008. This chapter is currently being updated based on the 2nd ATP to the CLP Regulation and planned for a future update of this document in 2013.

3.1.2 Classification of substances for acute toxicity

3.1.2.1 Identification of hazard information

3.1.2.1.1 Identification of human data

Relevant information with respect to acute toxicity may be available from case reports, epidemiological studies, medical surveillance and reporting schemes and national poison centres. Human data to be considered for acute toxicity should report severe effects after single exposure or exposure of less than 24h, but data on severe effects after a few exposures over a few days can also be considered on a case by case basis.

For more details see IR/CSA, Section R.7.4.3.2.

3.1.2.1.2 Identification of non-human data

Non-testing data:

Physicochemical data

Physico-chemical properties, such as pH, physical state, form, solubility, vapour pressure and particle size, can be important parameters in evaluating toxicity studies and in determining the most appropriate classification. This is especially valid with respect to inhalation where physical form and particle size can have a significant impact on toxicity (see Section 3.1.2.3.2).

(Q)SAR models, expert systems and grouping methods

"Non-testing data can be provided by the following approaches: a) structure-activity relationships (SARs) and quantitative structure-activity relationships (QSARs), collectively called (Q)SARs; b) expert systems incorporating (Q)SARs and/or expert rules; and c) grouping methods (read-across and categories. These approaches can be used to assess acute toxicity if they provide relevant and reliable (adequate) data for the chemical of interest. …. Compared with some endpoints, there are relatively few (Q)SAR models and expert systems capable of predicting acute toxicity." (IR/CSA, Section R.7.4.3.1).

Testing data:

In vitro data

There are currently no *in vitro* tests that have been officially adopted by the EU or OECD for assessment of acute toxicity (IR/CSA, Section R.7.4.3.1). Any available studies should be assessed by using expert judgement.

Animal data

A number of different types of studies have been used to investigate acute toxicity. Older standard studies were designed to determine lethality and estimate the LD_{50}/LC_{50}. In contrast, contemporary study protocols, such as the fixed dose procedure, use signs of overt ("evident") toxicity rather than lethality as indications of acute toxicity. These studies are generally conducted using preferred species, i.e. the rat for acute oral and inhalation toxicity studies, and in addition rabbit for dermal toxicity studies.

The animal studies are listed in IR/CSA, Section R.7.4.3.1.

3.1.2.2 Classification criteria

Annex I: 3.1.2.1. Substances can be allocated to one of four toxicity categories based on acute toxicity by the oral, dermal or inhalation route according to the numeric criteria shown in Table 3.1.1. Acute toxicity values are expressed as (approximate) LD50 (oral, dermal) or LC50 (inhalation) values or as acute toxicity estimates (ATE). Explanatory notes are shown following Table 3.1.1.

Table 3.1.1

Acute toxicity hazard categories and acute toxicity estimates (ATE) defining the respective categories

Exposure Route	Category 1	Category 2	Category 3	Category 4
Oral (mg/kg bodyweight) See Note (a)	ATE ≤ 5	5 < ATE ≤ 50	50 < ATE ≤ 300	300 < ATE ≤ 2000
Dermal (mg/kg bodyweight) See Note (a)	ATE ≤ 50	50 < ATE ≤ 200	200 < ATE ≤ 1000	1000 < ATE ≤ 2000
Gases (ppmV[1]) see: Note (a) Note (b)	ATE ≤ 100	100 < ATE ≤ 500	500 < ATE ≤ 2500	2500 < ATE ≤ 20000
Vapours (mg/l) see: Note (a) Note (b) Note (c)	ATE ≤ 0.5	0.5 < ATE ≤ 2.0	2.0 < ATE ≤ 10.0	10.0 < ATE ≤ 20.0
Dusts and Mists (mg/l) see: Note (a) Note (b)	ATE ≤ 0.05	0.05 < ATE ≤ 0.5	0.5 < ATE ≤ 1.0	1.0 < ATE ≤ 5.0

[1]Gas concentrations are expressed in parts per million per volume (ppmV)

Notes to Table 3.1.1:

(a) The acute toxicity estimate (ATE) for the classification of a substance or ingredient in a mixture is derived using:

- the LD50/LC50 where available,

- the appropriate conversion value from Table 3.1.2 that relates to the results of a range test, or

- the appropriate conversion value from Table 3.1.2 that relates to a classification category.

(b) Generic concentration limits for inhalation toxicity in the table are based on 4 hour testing exposures. Conversion of existing inhalation toxicity data which have been generated using a 1 hour exposure can be carried out by dividing by a factor of 2 for gases and vapours and 4 for dusts and mists.

(c) For some substances or mixtures the test atmosphere will not just be a vapour but will consist of a mixture of liquid and vapour phases. For other substances or mixtures the test atmosphere may consist of a vapour which is near the gaseous phase. In these latter cases, classification shall be based on ppmV as follows: Category 1 (100 ppmV), Category 2 (500 ppmV), Category 3 (2500 ppmV), Category 4 (20 000 ppmV).

The terms 'dust', 'mist' and 'vapour' are defined as follows:

- Dust: solid particles of a substance or mixture suspended in a gas (usually air);

- Mist: liquid droplets of a substance or mixture suspended in a gas (usually air);

- Vapour: the gaseous form of a substance or mixture released from its liquid or solid state.

Dust is generally formed by mechanical processes. Mist is generally formed by condensation of supersaturated vapours or by physical shearing of liquids. Dusts and mists generally have sizes ranging from less than 1 to about 100 µm.

Comment to Table 3.1.1, Note (b):

The classification criteria for acute inhalation toxicity relate to a 4-hour experimental exposure period. Where LC_{50} values have been obtained in studies using exposure durations shorter or longer than 4 hours values these may be adjusted to a 4-hour equivalent using Haber's law ($C^n \cdot t=k$) for direct comparison with the criteria. The value of n, which is specific to individual substances, should be chosen using expert judgement. If an appropriate value of n is not available in the literature then it may sometimes be derived from the available mortality data using probits (i.e.the inverse cumulative distribution functions associated with the standard normal distribution). Alternatively, some default values are recommended (IR/CSA, Section R.7.4.4.1).

Particular care should be taken when using Haber's law to assess inhalation data on substances which are corrosive or locally active. In all cases, Haber's law should only be used in conjunction with expert judgement.

It is noted that the statements in IR/CSA, Section R.7.4.4.1, with respect to Haber's law are not consistent with those of CLP. However the CLP approach must be used for classification and labelling.

Comment to Table 3.1.1, Note (c):

The term "aerosol" is commonly used for "dust and mists".

3.1.2.3 Evaluation of hazard information

3.1.2.3.1 Evaluation of human data

The evaluation of human data often becomes difficult due to various limitations frequently found with the types of studies and data highlighted in Section 3.1.2.1.1. These include uncertainties relating to exposure assessment (i.e. unreliable information on the amount of substance the subjects were exposed to) and uncertain exposure to other substances. As such, human data needs careful expert evaluation to properly judge the reliability of the findings. It should be acknowledged that human data often do not provide sufficiently robust evidence on their own to support classification. They may however contribute to a weight of evidence assessment with other available information such as data from animal studies.

The classification for acute toxicity is based primarily on the dose/concentration that causes mortality (the Acute Toxicity Estimate, ATE), which is then related to the numerical values in the classification criteria according to CLP Annex I, Table 3.1.1 (See Section 3.1.2.2) for substances or for use in the additivity formula in CLP Annex I, 3.1.3.6.1 and 3.1.3.6.2.3 for mixtures (See Section 3.1.3.3). The ATE is usually obtained from animal studies but in principle suitable human data can also be used if available. Where human data are available they should be used to estimate the ATE which can be used directly for classification as described above.

The minimum dose/concentration or range shown or expected to cause mortality after a single human exposure can be used to derive the human ATE directly, without any adjustments or uncertainty factors. See Example 1 (methanol).

If there are no exact/quantitative lethal dose data the procedure described in CLP Annex I, 3.1.3.6.2.1.(b) (See Section 3.1.3.3.4) would have to be followed using Table 3.1.2, (See Section 3.1.3.3.3) with an assessment of the available information on a semi-quantitative or qualitative basis.

Expert judgement is needed in a total weight of evidence approach taking relevance, reliability, and adequacy of the information into account. See Example 2 (N,N-dimethylaniline).

If the available human data alone are too limited to support a classification they may still provide supporting evidence in the overall weight of evidence assessment.

3.1.2.3.2 Evaluation of non-human data

Annex I: 3.1.2.2. *Specific considerations for classification of substances as acutely toxic*

3.1.2.2.1. The preferred test species for evaluation of acute toxicity by the oral and inhalation routes is the rat, while the rat or rabbit are preferred for evaluation of acute dermal toxicity. When experimental data for acute toxicity are available in several animal species, scientific judgement shall be used in selecting the most appropriate LD_{50} value from among valid, well-performed tests.

Evaluation of non-testing and *in vitro* data:

Results of (Q)SAR, grouping and read-across may be used instead of testing, and substances will be classified and labelled on this basis if the method fulfils the criteria described in Annex XI of REACH. See also IR/CSA, Section R.7.4.4.1.

ATE – establishing:

- Basis LD_{50}/LC_{50}: An available LD_{50}/LC_{50} is an ATE at first stage.

- Results from a range test: According to CLP Annex I, Table 3.1.2 results from range tests (i.e. doses/exposure concentrations that cause acute toxicity in the range of numeric criteria values) can be assigned to the four different categories of acute toxicity for each possible route of exposure (centre column). Further, Table 3.1.2 allows allocating a single value, the converted acute toxicity point estimate (cATpE), to each experimentally obtained acute toxicity range estimate or classification category (right column), see Note (a) to Table 3.1.1. This cATpE can be used in the additivity formulae (Annex I, 3.1.3.6.1 and 3.1.3.6.2.3) to calculate the acute toxicity of mixtures.

- In case of multiple LD_{50}/LC_{50}s or from several species:

Where several experimentally determined ATE values (i.e. LD_{50}, LC_{50} values or ATE derived from studies using signs of non-lethal toxicity) are available, expert judgement needs to be used to choose the most appropriate value for classification purposes. Each study needs to be assessed for its suitability in terms of study quality and reliability, and also for its relevance to the substance in question in terms of technical specification and physical form. Studies not considered suitable on reliability or other grounds should not be used for classification.

In general, classification is based on the lowest ATE value available i.e. the lowest ATE in the most sensitive appropriate species tested. However, expert judgement may allow another ATE value to be used in preference, provided this can be supported by a robust justification. If there is information available to inform on species relevance, then the studies conducted in the species most relevant for humans should normally be given precedence over the studies in other species. If there is a wide range of ATE values from the same species, it may be informative to consider the studies collectively, to understand possible reasons for the different results obtained. This would include consideration of factors such as the animal strains used, the experimental protocols, the purity of the substance and form/phase in which it was tested (e.g. the particle size distribution of any aerosols or dusts tested), as well as exposure mode and numerous technical factors in inhalation studies. This assessment may aid selection of the most appropriate study on which to base the classification.

If there are different LD_{50} values from tests using different vehicles e.g. water vs. corn oil or neat substance vs. corn oil), generally the lowest valid value would be the basis for classification. It is not considered appropriate to combine or average the available ATE values. The studies may not be equivalent (in terms of experimental design such as protocol, purity of material tested, species of animal used etc) making such a collation or combination unsound.

If there is a study available with a post-observation period of only ca 7 days (instead of the 14 days according to the OECD guidelines) and there are effects still observed at the end of the study, the resulting LD_{50} might be misleading. A long persistency of effects may be indicative of cumulative toxicity, sometimes coinciding with flat dose-response relationships, sometimes with species differences. Such information should be included in the weight of evidence consideration.

Annex I: 3.1.2.3. *Specific considerations for classification of substances as acutely toxic by the inhalation route*

3.1.2.3.1 Units for inhalation toxicity are a function of the form of the inhaled material. Values for dusts and mists are expressed in mg/l. Values for gases are expressed in ppmV. Acknowledging the difficulties in testing vapours, some of which consist of mixtures of liquid and vapour phases, the table provides values in units of mg/l. However, for those vapours which are near the gaseous phase, classification shall be based on ppmV.

Conversions:

Differentiation between vapour and mist will be made on the basis of the saturated vapour concentration (SVC) for a volatile substance, which can be calculated by the following equation:

SVC [mg/l] = 0.0412 x MW x vapour pressure in hPa at 20°C.

The conversion from mg/l to ppm assuming an ambient pressure of 1 at = 101.3 kPa and 25°C is: ppm=0.0245 mg/l x 1/MW.

An LC_{50} well below the SVC will be considered for classification according to the criteria for vapours; whereas an LC_{50} close to or above the SVC will be considered for classification according to the criteria for mists (see also Draft OECD TG 39).

Considerations with respect to physical forms or states / bioavailability:

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

For further details see Sections 1.2 and 1.3.

Special considerations concerning aerosols:

The test guidelines for acute inhalation toxicity with aerosols require rodents to be exposed to an aerosol containing primarily respirable particles (with a Mass Median Aerodynamic Diameter (MMAD) of 1 – 4 μm), so that particles can reach all regions of the respiratory tract. The use of such fine aerosols helps to avoid partial overloading of extra-thoracic airways in obligate nasal breathing species like rats. Results from studies in which substances with particle size with a MMAD > 4 μm have been tested can generally not be used for classification, but expert judgement is needed in cases where there are indications of high toxicity.

The use of highly respirable aerosols is ideal to fully investigate the potential inhalation hazard of the substance. However, it is acknowledged that these exposures may not necessarily reflect realistic conditions. For instance, solid materials are often micronised to a highly respirable form for testing, but in practice exposures will be to a dust of much lower respirability. Similarly, pastes or highly viscous materials with low vapour pressure need strong measures to be taken to generate airborne particulates of sufficiently high respirability, whereas for other materials this may occur spontaneously. In such situations, specific problems may arise with respect to classification and labelling, as these substances are tested in a form (i.e. specific particle size distribution) that is different from all the forms in which these substances are placed on the market and in which they can reasonably be expected to be used.

A scientific concept has been developed as a basis for relating the conditions of acute inhalation tests to those occurring in real-life, in order to derive an adequate hazard classification. This concept is applicable only to substances or mixtures which are proven to cause acute toxicity through local effects and do not cause systemic toxicity (Pauluhn, 2008).

Corrosive substances

It is presumed that corrosive substances (and mixtures) will cause toxicity by inhalation exposure. In cases where no acute inhalation test has been performed special consideration should be given to the need to communicate this potential hazard.

Corrosive substances (and mixtures) may be acutely toxic after inhalation to a varying degree and by different modes of action. Therefore, it is not possible to estimate the acute inhalation toxicity from the corrosivity data alone.

There are special provisions for hazard communication of acutely toxic substances by a corrosive effect, see Section 3.1.4.2.

3.1.2.3.3 Weight of evidence

In cases where there is sufficient human evidence that meets the criteria given in Section 3.1.2.2 then this will normally lead to classification for acute toxicity, irrespective of other information available.

If there are human data indicating no classification but there are also non-human data indicating classification then the classification is based on the non-human data unless it is shown that the human data cover the exposure range of the non-human data or that the non-human data are not relevant for humans. If the human and non-human data both indicate no classification then classification is not required.

If there are no human data then the classification is based on the non-human data.

For the role and application of expert judgement and weight of evidence determination, see CLP Annex I, 1.1.1.

3.1.2.4 Decision on classification

The classification has to be performed with respect to all routes of exposure (oral, dermal, inhalation) on the basis of all adequate and reliable available information.

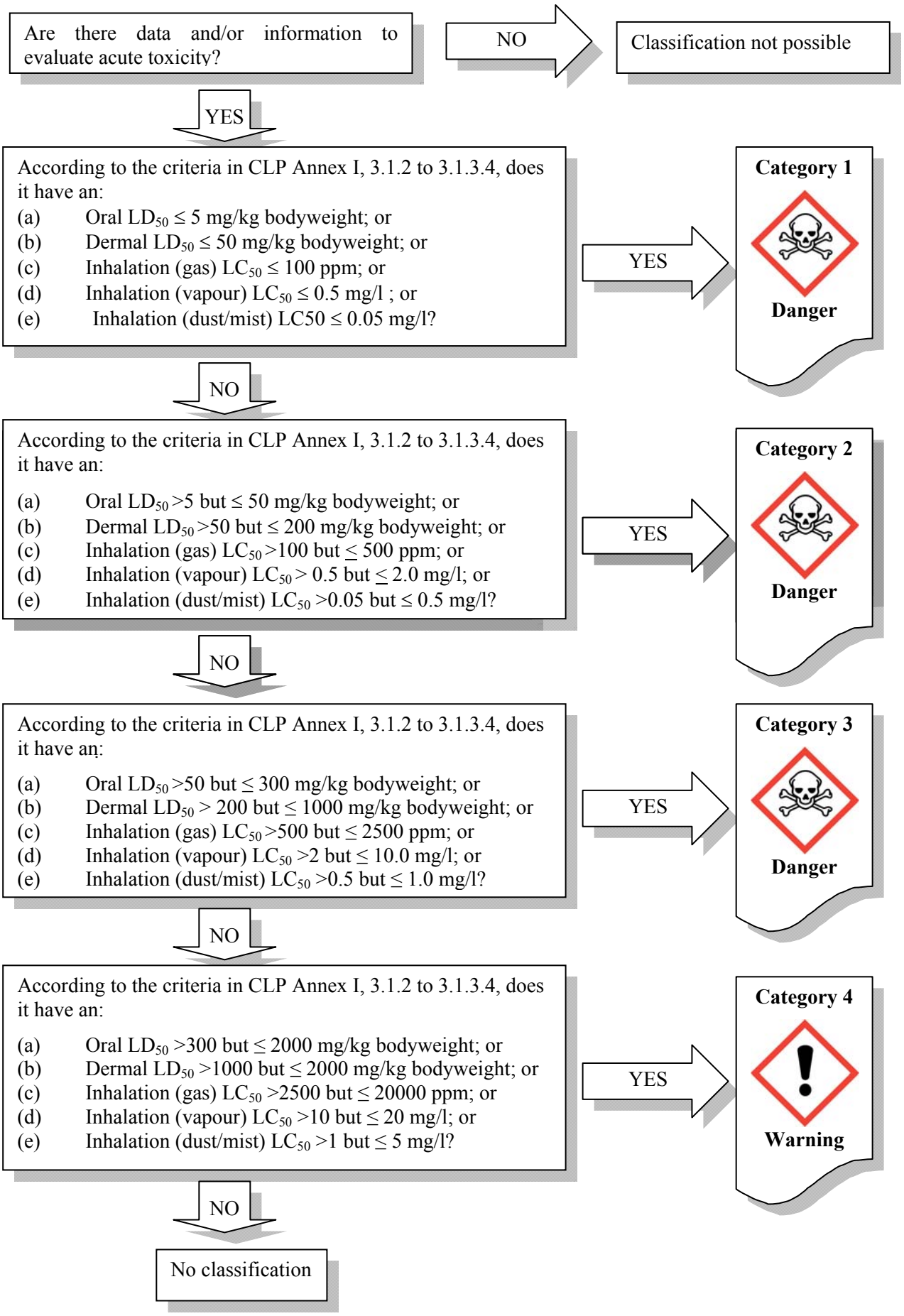
3.1.2.5 Setting of specific concentration limits

Specific concentration limits are not applicable for acute toxicity classification. Rather, the relative potency of substances is implicitly taken into account in the additivity formula (see Section 3.1.3.3.3). For this reason specific concentration limits for acute toxicity will not appear in CLP Annex VI, Table 3.1 or in the classification and labelling inventory (CLP Article 42).

3.1.2.6 Decision logic

The decision logic below is provided as additional guidance. It is strongly recommended that the person responsible for classification is fully familiar with the criteria for acute toxicity classification before using the decision logic.

For a complete classification of a substance, the decision logic must be worked out for each route of exposure for which data and/or information is available. For example, if a certain substance is classified in Category 1 based on an oral $LD_{50} \leq 5$ mg/kg bodyweight (the answer was 'Yes' in box 2 for item (a)), it is still necessary to go back to box 2 in the decision logic and complete the classification for the dermal (b) and inhalation (c)-(e) route of exposure, when data is available for one or both of these routes of exposure. In case there are data for all three routes of exposure, the classification for acute toxicity of the substance will include the three differentiations of the hazard class, which might end up in three different categories. The route of exposure will then be specified in the corresponding hazard statement.


Are there data and/or information to evaluate acute toxicity?
NO
Classification not possible
YES
According to the criteria in CLP Annex I, 3.1.2 to 3.1.3.4, does it have an:
(a) Oral LD_{50} ≤ 5 mg/kg bodyweight; or
(b) Dermal LD_{50} ≤ 50 mg/kg bodyweight; or
(c) Inhalation (gas) LC_{50} ≤ 100 ppm; or
(d) Inhalation (vapour) LC_{50} ≤ 0.5 mg/l ; or
(e) Inhalation (dust/mist) LC50 ≤ 0.05 mg/l?
YES
Category 1
Danger
NO
According to the criteria in CLP Annex I, 3.1.2 to 3.1.3.4, does it have an:
(a) Oral LD_{50} >5 but ≤ 50 mg/kg bodyweight; or
(b) Dermal LD_{50} >50 but ≤ 200 mg/kg bodyweight; or
(c) Inhalation (gas) LC_{50} >100 but ≤ 500 ppm; or
(d) Inhalation (vapour) LC_{50} > 0.5 but ≤ 2.0 mg/l; or
(e) Inhalation (dust/mist) LC_{50} >0.05 but ≤ 0.5 mg/l?
YES
Category 2
Danger
NO
According to the criteria in CLP Annex I, 3.1.2 to 3.1.3.4, does it have an:
(a) Oral LD_{50} >50 but ≤ 300 mg/kg bodyweight; or
(b) Dermal LD_{50} > 200 but ≤ 1000 mg/kg bodyweight; or
(c) Inhalation (gas) LC_{50} >500 but ≤ 2500 ppm; or
(d) Inhalation (vapour) LC_{50} >2 but ≤ 10.0 mg/l; or
(e) Inhalation (dust/mist) LC_{50} >0.5 but ≤ 1.0 mg/l?
YES
Category 3
Danger
NO
According to the criteria in CLP Annex I, 3.1.2 to 3.1.3.4, does it have an:
(a) Oral LD_{50} >300 but ≤ 2000 mg/kg bodyweight; or
(b) Dermal LD_{50} >1000 but ≤ 2000 mg/kg bodyweight; or
(c) Inhalation (gas) LC_{50} >2500 but ≤ 20000 ppm; or
(d) Inhalation (vapour) LC_{50} >10 but ≤ 20 mg/l; or
(e) Inhalation (dust/mist) LC_{50} >1 but ≤ 5 mg/l?
YES
Category 4
Warning
NO
No classification

3.1.3 Classification of mixtures for acute toxicity

3.1.3.1 General considerations for classification

Annex I: 3.1.3.1. The criteria for classification of substances for acute toxicity as outlined in section 3.1.2 are based on lethal dose data (tested or derived). For mixtures, it is necessary to obtain or derive information that allows the criteria to be applied to the mixture for the purpose of classification. The approach to classification for acute toxicity is tiered, and is dependent upon the amount of information available for the mixture itself and for its ingredients.

The procedure for classifying mixtures is a tiered i.e. a stepwise approach based on a hierarchy principle and depending on the type and amount of available data/information. If valid test data are available for the whole mixture they have precedence. If no such data exist, the so called bridging principles have to be applied if possible. If the bridging principles are not applicable an assessment on the basis of ingredient information will be applied (see Sections 3.1.3.3.3, 3.1.3.3.4 and 3.1.3.5).

3.1.3.2 Identification of hazard information

Where toxicological information from human evidence and animal studies is available on a mixture, this should be used to derive the appropriate classification. Such information may be available from the mixture manufacturer. Where such information on the mixture itself is not available, information on similar mixtures and/or the component substances in the mixture must be used, as described in Section 3.1.3.3.

Alternatively, the hazard information on all individual components in the mixture could be identified as described in Section 3.1.2.2.

3.1.3.3 Classification criteria

Annex I: 3.1.3.2. For acute toxicity each route of exposure shall be considered for the classification of mixtures, but only one route of exposure is needed as long as this route is followed (estimated or tested) for all ingredients. If the acute toxicity is determined for more than one route of exposure, the more severe hazard category will be used for classification. All available information shall be considered and all relevant routes of exposure shall be identified for hazard communication.

The classification shall be considered for each route of exposure, using the appropriate approach as described in Section 3.1.2.3. If different hazard categories are assigned, the more severe hazard category will be used for the classification for acute toxicity, with the appropriate pictogram and signal word. For each relevant route of exposure, the hazard statement will correspond to the classification of this specific route.

3.1.3.3.1 When data are available for the complete mixture

Annex I: 3.1.3.4.1. Where the mixture itself has been tested to determine its acute toxicity, it shall be classified according to the same criteria as those used for substances, presented in Table 3.1.1.

In general, where a mixture has been tested those data should be used to support classification according to the same criteria as used for substances. However, there should be some consideration of whether the test is appropriate. For instance, if the mixture contains a substance for which the test species is not considered appropriate (for instance a mixture containing methanol tested in rats which are not sensitive to methanol toxicity), then the appropriateness of these data for classification should be considered using expert judgement.

With respect to the classification of mixtures in the form of dust for acute inhalation toxicity, the particle size can affect the toxicity and the resulting classification should take this into account (see Section 3.1.2.3.2).

3.1.3.3.2 When data are not available for the complete mixture: bridging principles

Annex I: 3.1.3.5.1. Where the mixture itself has not been tested to determine its acute toxicity, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterise the hazards of the mixture, these data shall be used in accordance with the bridging rules set out in section 1.1.3.

3.1.3.3.3 When data are available for all components or only for some components

Annex I: 3.1.3.6. *Classification of mixtures based on ingredients of the mixture (Additivity formula)*

3.1.3.6.1. Data available for all ingredients

In order to ensure that classification of the mixture is accurate, and that the calculation need only be performed once for all systems, sectors, and categories, the acute toxicity estimate (ATE) of ingredients shall be considered as follows:

(a) Include ingredients with a known acute toxicity, which fall into any of the acute toxicity categories shown in Table 3.1.1;

(b) Ignore ingredients that are presumed not acutely toxic (e.g., water, sugar);

(c) Ignore ingredients if the oral limit test does not show acute toxicity at 2000 mg/kg bodyweight.

Ingredients that fall within the scope of this paragraph are considered to be ingredients with a known acute toxicity estimate (ATE).

The ATE of the mixture is determined by calculation from the ATE values for all relevant ingredients according to the following formula below 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.

The additivity formula cannot be used directly for mixtures containing substances tested for inhalation toxicity as vapours and others as dust, because it is unclear when the numeric values for vapours or dusts must be used. Therefore for acute inhalation toxicity the additivity formula should be used separately for each relevant physical form (i.e. gas, vapour and/or dust/mist), using the appropriate categories in Table 3.1.1. In case of different outcomes, the most severe classification applies.

Annex I: *Table 3.1.2*
Conversion from experimentally obtained acute toxicity range values (or acute toxicity hazard categories) to acute toxicity point estimates for classification for the respective routes of exposure

Exposure routes	Classification category or experimentally	Converted acute toxicity point estimate

	obtained acute toxicity range estimate	(see Note 1)
Oral (mg/kg bodyweight)	0 < Category 1 ≤ 5	0.5
	5 < Category 2 ≤ 50	5
	50 < Category 3 ≤ 300	100
	300 < Category 4 ≤ 2000	500
Dermal (mg/kg bodyweight)	0 < Category 1 ≤ 50	5
	50 < Category 2 ≤ 200	50
	200 < Category 3 ≤ 1000	300
	1000 < Category 4 ≤ 2000	1100
Gases (ppmV)	0 < Category 1 ≤ 100	10
	100 < Category 2 ≤ 500	100
	500 < Category 3 ≤ 2500	700
	2500 < Category 4 ≤ 20000	4500
Vapours (mg/l)	0 < Category 1 ≤ 0.5	0.05
	0.5 < Category 2 ≤ 2	0.5
	2.0 < Category 3 ≤ 10.0	3
	10.0 < Category 4 ≤ 20.0	11
Dust/mist (mg/l)	0< Category 1 ≤ 0.05	0.005
	0.05 < Category 2 ≤ 0.5	0.05
	0.5 < Category 3 ≤ 1.0	0.5
	1.0 < Category 4 ≤ 5.0	1.5
Note 1: These values are designed to be used in the calculation of the ATE for classification of a mixture based on its components and do not represent test results.		

Some converted Acute Toxicity point Estimates (cATpEs) are equal to the upper limit of the next lower category, for example the cATpE of oral Category 2 (5 mg/kg) is equal to the upper limit of oral Category 1 (also 5 mg/kg).

This can lead to a problem when using the cATpE values for calculating the acute toxicity of mixtures. For instance, using the cATpEs for a mixture containing only substances classified in Category 2 actually results in a Category 1 classification for the mixture. Similarly, a mixture containing substances classified as Category 3 for dust/mist results in a Category 2 classification. Clearly these outcomes are incorrect and are an unintended side-effect of the approach. To address this problem the following proposal has been endorsed at UN SCE-GHS: "If the acute toxicity range values (or acute toxicity hazard classification categories) for all ingredients of a mixture are within the same range or category, then the mixture should be classified in that category." Applying this to the cases highlighted above, these mixtures would be classified in Category 2 and 3, respectively.

Annex I: 3.1.3.3.(b) where a classified mixture is used as an ingredient of another mixture, the actual or derived acute toxicity estimate (ATE) for that mixture may be used, when calculating the classification of the new mixture using the formulas in section 3.1.3.6.1 and paragraph 3.1.3.6.2.3.

It is important that the downstream user has sufficient information in order to enable him to perform a correct classification of mixtures.

3.1.3.3.4 When data are not available for all components

Annex I: 3.1.3.6.2.1. Where an ATE is not available for an individual ingredient of the mixture, but available information such as that listed below can provide a derived conversion value such as those laid out in Table 3.1.2, the formula in paragraph 3.1.3.6.1 shall be applied.

This includes evaluation of:

(a) extrapolation between oral, dermal and inhalation acute toxicity estimates ([1]). Such an evaluation could require appropriate pharmacodynamic and pharmacokinetic data;

(b) evidence from human exposure that indicates toxic effects but does not provide lethal dose data;

(c) evidence from any other toxicity tests/assays available on the substance that indicates toxic acute effects but does not necessarily provide lethal dose data; or

(d) data from closely analogous substances using structure/activity relationships.

_____

([1]) For ingredients with acute toxicity estimates available for other than the most appropriate exposure route, values may be extrapolated from the available exposure route(s) to the most appropriate route. Dermal and inhalation route data are not always required for ingredients. However, in case data requirements for specific ingredients include acute toxicity estimates for the dermal and inhalation route, the values to be used in the formula need to be from the required exposure route.

Derivation of ATEs from available information:

When ingredients have a known acute toxicity (LC_{50} or LD_{50} values), this value has to be used in the additivity formula. However, for many substances, acute toxicity data will not be available for all exposure routes.

CLP allows for two ways of deriving acute toxicity conversion values. One option is to use the converted acute toxicity point estimates supplied in Annex I, Table 3.1.2. The other option, expert judgement would recommend in substantiated cases the use of the directly derived ATE values.

a) Route-to-route extrapolation (CLP Annex I, 3.1.3.6.2.1.(a)):

Route-to-route extrapolation is defined as the prediction of the total amount of a substance administered by one route that would produce the same systemic toxic response as that obtained by a given amount of a substance administered by another route. Thus, route-to-route extrapolation is only applicable for the evaluation of systemic effects. It is not appropriate to assess direct local effects.

This extrapolation is possible if certain conditions are met, which substantiate the assumption that an internal dose causing a systemic effect at the target is related to an external dose/concentration; preferably the absorption can be quantified. Therefore information on the physico-chemical and biokinetic properties should be available and assessed in order to allow such a conclusion and performing an extrapolation across routes. In the absence of any information on absorption, 100% absorption has to be presumed as a worst case for the dermal and inhalation route. Extrapolating from the oral route to other routes, the assumption of absorption of 100% for the oral route is, however, not a worst case. Absorption of less than

100% by the oral route will lead to lower ATEs. Another important factor is the local and systemic metabolic pathways; in particular it must be assured that no route-specific metabolism/degradation of substance occurs.

If extrapolating from oral data, the influence of first-pass metabolism in the stomach/intestines and the liver should be considered, especially if the substance is detoxified. Such first pass metabolism is unlikely to occur to any significant extent by the dermal or inhalation routes, and so this would lead to an underestimate of toxicity by these routes. Thus if based on kinetic or (Q)SAR data a specific first-pass effect is excluded, oral data may be used for extrapolation purposes.

For an extrapolation to the dermal route, information on the potential skin penetration may be derived from the chemical structure (polar vs. nonpolar structure elements, Log P_{ow}, molecular weight) if kinetic data are not available which would allow a quantitative comparison. When no such information is available 100% dermal absorption should be presumed.

Similarly for an extrapolation to the inhalation route if there is no quantitative information on absorption then 100% absorption should be presumed. Inhalation volatility is an important factor which on one hand may increase the exposure, but on the other hand may reduce absorption due to higher exhalation rates. The solubility (in water and non-polar solvents) has to be considered, as well as particle size, which plays a particularly important role in inhalation toxicity.

Route-to-route extrapolation is not always appropriate. For example where there is a substantial difference in absorption between oral and inhalation uptake (e.g. poorly soluble particles, substances that decompose within the gastro intestinal-tract), or where the substance causes local effects, the toxicity by different routes may be significantly different, and route-to-route extrapolation may not be appropriate (ECETOC TR 86, 2003).

i: Extrapolation oral → inhalation:

If the mentioned conditions are met an extrapolation from oral data would be performed as follows:

Incorporated dose = concentration x respiratory volume x exposure time

1 mg/kg bw = 0.0052 mg/l/4h

using a respiratory volume for a 250 g rat of 0.20 l/min and 100 % absorption and postulating 100% deposition and absorption (IR/CSA, Chapter R7C, Table R.7.12-10).

Valid information that the deposition and/or absorption rate for the extrapolated route is lower would allow a higher equivalent derived ATE (see Section 3.1.6.1.9 Example 9).

ii: Extrapolation oral → dermal

If based on kinetic or SAR data a high penetration rate can be assumed and a specific first pass-effect is excluded, oral and dermal toxicity might be regarded as equivalent. This is rarely the case.

Solids themselves may have a very low absorption rate, but if diluted in an appropriate solvent there may be appreciable absorption. Thus depending on the kinetic and physico-chemical properties and kind of mixture varying ATEs will result. An example for these differences is butyn-1,4-diol which dermally applied as solid shows no mortality in rats at 5000 mg/kg, whereas the aqueous solution giving LD_{50} of 659 and 1,240 mg/kg, the oral LD_{50} are in the range of 200 mg/kg.

For more details on inter-route extrapolation see IR/CSA, Section R.7C.12.1.5. Example 9 and 10 illustrate this approach.

b) Evidence from human exposure:

Human evidence can be used to derive an appropriate ATE to use in the additivity approach for mixtures (CLP Annex I, 3.1.3.6.1 and 3.1.3.6.2.3). Therefore it is necessary to extrapolate from adequate and reliable data and taking the potency (i.e. the magnitude of the lethal dose reported) of the effects in humans into account. Thus an equivalent ATE may be derived on the basis of valid human toxicity data (minimum dose/concentration) and used directly in the additivity formulae (see Section 3.1.6.1.1 Example 1). The alternative to the derivation of an equivalent ATE is the allocation to a category. The category should be justified by semi-quantitative or qualitative data and a subsequent derivation of a converted ATE (cATpE) according to CLP Annex I, Table 3.1.2 and subsequently use in the formulae (see Section 3.1.6.1.2 Example 2). See also Section 3.1.2.3.1 for more details.

c) Evidence from other toxicity tests:

Information from other types of studies can sometimes be useful in deriving an acute toxicity classification. (see Section 3.1.2.2). These studies will not usually provide an LD_{50}/ATE value that can be used directly for classification, but they may provide enough information to allow an estimate of acute toxicity to be made, which would be sufficient to support a decision on classification.

Example:

Available information: In a range finding study with respect to repeated dose toxicity daily oral doses of 1000 mg/kg over 5 days prove to be neither lethal nor cause serious symptoms in rats at the end of the observation period of 14 days.

Conclusion: the LD_{50}=ATE is >2000 mg/kg since 2 doses following (within roughly) 24 h are not lethal (see Section 3.1.2.2). Thus this ingredient can be ignored in the additivity procedure.

d) Use of (Q)SAR:

LD_{50}/LC_{50} values predicted by a highly reliable model (see Section 2.1.2) may be used according to Note (a) to Annex I, Table 3.1.1 directly as LD_{50}/LC_{50}=ATE in the additivity formula CLP Annex I, 3.1.3.6.1. If the assessment using (Q)SARs gives a more general result a cATpE acc. to Table 3.1.2 may be derived. It has to be emphasised that these approaches generally require substantial technical information, and expert judgement, to reliably estimate acute toxicity.

Annex I: 3.1.3.6.2.2. In the event that an ingredient without any useable information at all is used in a mixture at a concentration of 1% or greater, it is concluded that the mixture cannot be attributed a definitive acute toxicity estimate. In this situation the mixture shall be classified based on the known ingredients only, with the additional statement that x percent of the mixture consists of ingredient(s) of unknown toxicity.

Further guidance on how to apply this provision is given in Section 3.1.3.3.5.

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:

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

3.1.3.3.5 Components that should be taken into account for the purpose of classification

Annex I: 3.1.3.3.(a) the 'relevant ingredients' of a mixture are those which are present in concentrations of 1 % (w/w for solids, liquids, dusts, mists and vapours and v/v for gases) or greater, unless there is a reason to suspect that an ingredient present at a concentration of less than 1 % is still relevant for classifying the mixture for acute toxicity (see Table 1.1).

When a mixture contains a "relevant" ingredient (i.e. constituting ≥ 1%; Annex I, 3.1.3.3 (a)) for which there is inadequate acute toxicity data then the mixture must be classified on the basis of the ingredients with known toxicity, with an additional statement to indicate that the mixture contains ingredients of unknown toxicity (CLP Annex I, 3.1.3.6.2.2). The determination of the classification depends on what proportion of the mixture such ingredients of unknown toxicity constitute. If these ingredients constitute ≤10% of the total mixture, the additivity formula in 3.6.1.1 may be used. However, in cases where these ingredients constitute over 10%, a modified additivity formula, which adjusts for the presence of a significant proportion of ingredients of unknown toxicity, is used. This reflects the greater uncertainty as to the true toxicity of the mixture (CLP Annex I, 3.3.3.2.4).

Annex I: *Table 1.1*
Generic cut-off values

Hazard class	Generic cut-off values to be taken into account
Acute Toxicity:	
Category 1-3	0,1 %
Category 4	1 %

Note: Generic cut-off values are in weight percentages except for gaseous mixtures where they are in volume percentage.

As indicated in CLP Annex I, Table 1.1, when components are present in low concentrations they do not need to be taken into account when determining the classification of the mixture, according to the approaches detailed in CLP Annex I, 3.1.3.6.1 and 3.1.6.2.3 (see Section 3.1.6.3.1 Example 11). Accordingly, all components classified in Categories 1-3 at a concentration <0.1 % and Category 4 <1% are not taken into account. Similarly unknown ingredients present at <1% are not taken into account.

3.1.3.4 Generic concentration limits for substances triggering classification of mixtures

Generic concentration limits as such are not applicable for acute toxicity classification; therefore specific concentration limits are also not applicable (see Section 3.1.2.5). Nevertheless, according to CLP Annex VI, 1.2.1 the classification for entries with the reference * in the column specific concentration limits is of special concern; the* means that those entries have an SCL in CLP Annex VI, Table 3.2 originating from Annex I to DSD. Therefore when assessing a mixture according to the procedure set out in CLP Annex I, a thorough search for the data (animal, human experience or other information) which had been the basis for the respective SCL in Annex I of DSD is indicated as being necessary. The assessment shall take all available information into account using a weight of evidence approach and expert judgement with special emphasis on possibly available human

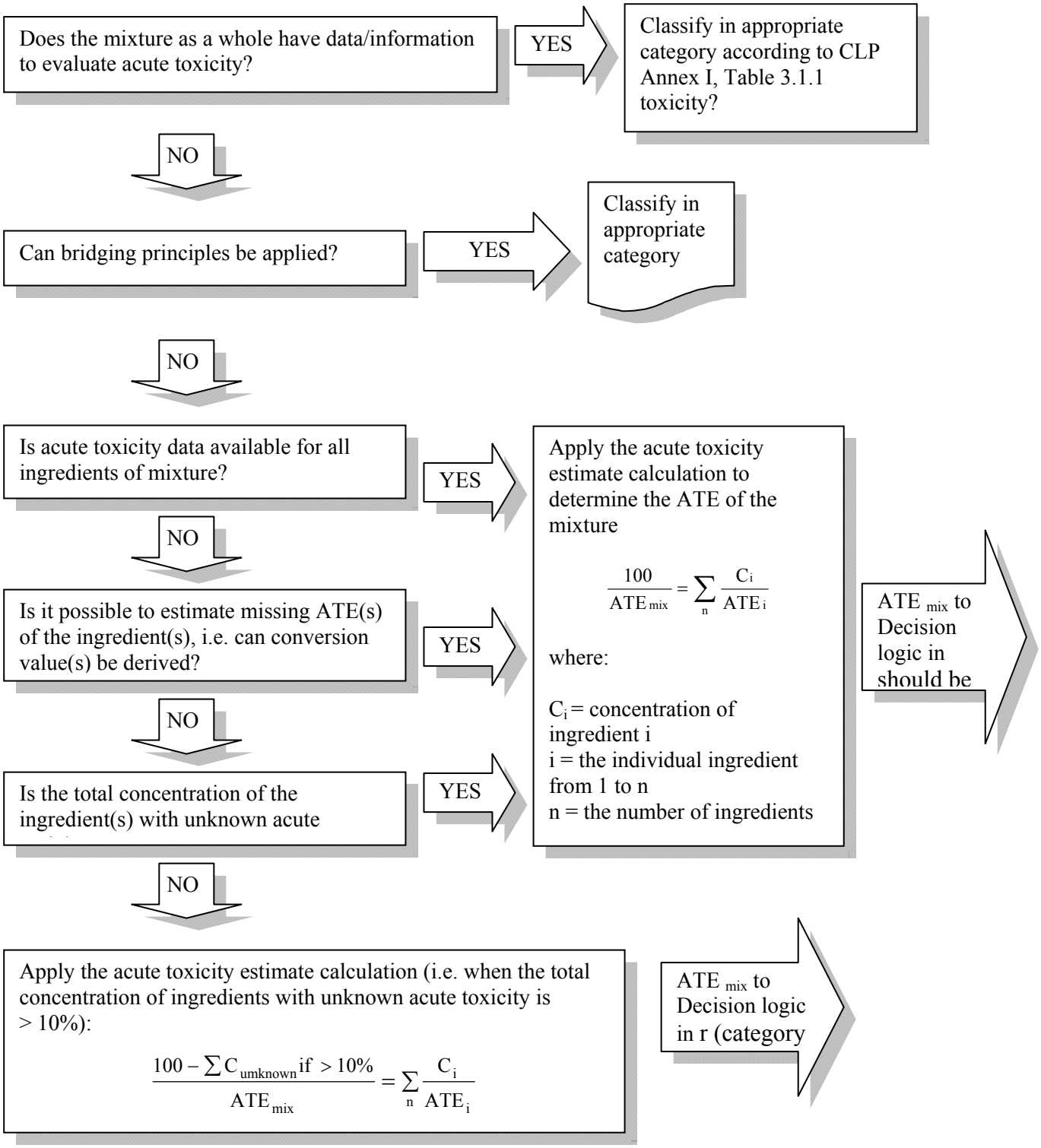
experience or information. These validated data will then be used in the additivity formula in Annex I, 3.1.3.6.1 as ATEs or cATpEs (Annex I, Table 3.1.2).

3.1.3.5 Decision on classification

The assessment on classification has to be performed with respect to the relevant routes of exposure (oral, dermal, inhalation) on the basis of all adequate reliable data. If a classification is warranted in different categories for different routes, then the mixture has to be classified in the more severe category, the other routes fulfilling the criteria for a classification are taken care by allocating the corresponding hazard statement(s) and appropriate precautionary statement(s). If for example, a mixture fulfils the criteria for oral toxicity Category 3 and for inhalation Category 2, then the mixture will be classified in Category 2, the corresponding hazard statements for both inhalation Category 2 and oral Category 3 will be assigned.

3.1.3.6 Decision logic

The decision logic is provided as additional guidance. It is strongly recommended that the person responsible for classification, study the criteria for classification before and during use of the decision logic.



3.1.4 Hazard communication in form of labelling for acute toxicity

3.1.4.1 Pictograms, signal words, hazard statements and precautionary statements

Annex I: *Table 3.1.3* **Acute toxicity label elements**				
Classification	Category 1	Category 2	Category 3	Category 4
GHS Pictograms				
Signal Word	Danger	Danger	Danger	Warning
Hazard Statement: – Oral	H300: Fatal if swallowed	H300: Fatal if swallowed	H301: Toxic if swallowed	H302: Harmful if swallowed
– Dermal	H310: Fatal in contact with skin	H310: Fatal in contact with skin	H311: Toxic in contact with skin	H312: Harmful in contact with skin
– Inhalation (see Note 1)	H330: Fatal if inhaled	H330: Fatal if inhaled	H331: Toxic if inhaled	H332: Harmful if inhaled
Precautionary Statement Prevention (oral)	P264 P270	P264 P270	P264 P270	P264 P270
Precautionary Statement Response (oral)	P301 + P310 P321 P330	P301 + P310 P321 P330	P301 + P310 P321 P330	P301 + P312 P330
Precautionary Statement Storage (oral)	P405	P405	P405	
Precautionary Statement Disposal (oral)	P501	P501	P501	P501
Precautionary Statement Prevention (dermal)	P262 P264 P270 P280	P262 P264 P270 P280	P280	P280

Precautionary Statement Response (dermal)	P302 + P350 P310 P322 P361 P363	P302 + P350 P310 P322 P361 P363	P302 + P352 P312 P322 P361 P363	P302 + P352 P312 P322 P363
Precautionary Statement Storage (dermal)	P405	P405	P405	
Precautionary Statement Disposal (dermal)	P501	P501	P501	P501
Precautionary Statement Prevention (inhalation)	P260 P271 P284	P260 P271 P284	P261 P271	P261 P271
Precautionary Statement Response (inhalation)	P304 + P340 P310 P320	P304 + P340 P310 P320	P304 + P340 P311 P321	P304 + P340 P312
Precautionary Statement Storage (inhalation)	P403 + P233 P405	P403 + P233 P405	P403 + P233 P405	
Precautionary Statement Disposal (inhalation)	P501	P501	P501	

Note 1

In addition to classification for inhalation toxicity, if data are available that indicates that the mechanism of toxicity is corrosivity, the substance or mixture shall also be labelled as EUH071: 'corrosive to the respiratory tract' — see advice at 3.1.2.3.3. In addition to an appropriate acute toxicity pictogram, a corrosivity pictogram (used for skin and eye corrosivity) may be added together with the statement 'corrosive to the respiratory tract'.

Note 2

In the event that an ingredient without any useable information at all is used in a mixture at a concentration of 1 % or greater, the mixture shall be labelled with the additional statement that 'x percent of the mixture consists of ingredient(s) of unknown toxicity' — see advice at 3.1.3.6.2.2.

EUH071 can also be applied to inhaled corrosive substances not tested for acute inhalation toxicity according to CLP Annex II, Section 1.2.6

If a mixture fulfils the classification criteria with respect to different routes the classification will be based on the more severe one. This and other routes have then to be addressed with the respective hazard statements to CLP Annex I, Table 3.1.3.

3.1.4.2 Additional labelling provisions

Annex I: 3.1.3.6.2.2. In the event that an ingredient without any useable information at all is used in a mixture at a concentration of 1 % or greater, it is concluded that the mixture cannot be attributed a definitive acute toxicity estimate. In this situation the mixture shall be classified based on the known ingredients only, with the additional statement that x percent of the mixture consists of ingredient(s) of unknown toxicity.

Though there is no standardised statement with respect to the requirement of CLP Annex I, 3.1.3.6.2.2 the following statement would be appropriate, specifying that the information gap refers only to acute toxicity: "This mixture contains x % of ingredients of unknown acute (…….*) toxicity (* to be specified on a case by case basis if appropriate: oral, dermal, inhalation)", to be included in the section for supplemental information on the label.

Corrosivity:

Annex I: 3.1.2.3.3. In addition to classification for inhalation toxicity, if data are available that indicates that the mechanism of toxicity was corrosivity, the substance or mixture shall also be labelled as 'corrosive to the respiratory tract' (see note 1 in 3.1.4.1). Corrosion of the respiratory tract is defined by destruction of the respiratory tract tissue after a single, limited period of exposure analogous to skin corrosion; this includes destruction of the mucosa. The corrosivity evaluation can be based on expert judgment using such evidence as: human and animal experience, existing (*in vitro*) data, pH values, information from similar substances or any other pertinent data.

In addition to the application of the classification for acute inhalation toxicity, the mixture shall also be labelled as EUH071 where data are available which indicate that the mode of toxic action was corrosivity (see Note 1 to Table 3.1.3). Such information can be derived from data which warrant classification as corrosive according to the hazard skin corrosion/irritation (see Chapter 3.2). In this case the substance or mixture has to be classified and labelled for skin corrosion with the pictogram for corrosivity, GHS05, hazard statement H314 and also labelling with EUH071 (for criteria, see CLP Annex II) is required.

Corrosive mixtures may be acutely toxic after inhalation to a varying degree, although this is only occasionally proved by testing. In case no acute inhalation study is available for a corrosive mixture, it is strongly recommended to apply the precautionary statement P260: Do not breathe dust/fume/gas/mist/vapours/spray.

Toxic by eye contact:

In cases where a substance or mixture has shown clear signs of severe systemic toxicity or mortality in an eye irritation study a supplemental labelling phrase EUH070 "Toxic by eye contact" is required. This additional labelling, based on relevant data, is independent of any classification in an acute toxicity category.

3.1.5 Re-classification of substances and mixtures classified for acute toxicity according to DSD and DPD

3.1.5.1 Is direct "translation" of classification and labelling possible?

The CLP allows a minimum classification of substances and mixtures classified according to DSD and DPD, by use of a translation table in Annex VII (Table 1.1) into the corresponding classification under CLP. For more details see Chapter 1.7 on the application of Annex VII.

3.1.5.2 Re-evaluation of data

If there is new information which might be relevant with respect to classification a re-evaluation has to be performed. Classified gases should be re-evaluated because the guidance values changed from general guidance values in mg/l for aerosols, vapours and gases to a specific guidance value for gases in ppm. Often the values for classification are higher according to CLP compared to DSD which may require a re-evaluation on a case by case basis.

3.1.6 Examples of classification for acute toxicity

Remark: The classification proposals for the examples refer only to Acute Toxicity.

3.1.6.1 Examples of substances fulfilling the criteria for classification

3.1.6.1.1 Example 1: Methanol

Application	Use of adequate and reliable human data allowing derivation of an equivalent ATE according to CLP Annex I, Table 3.1.1. Animal data not appropriate.		
	Test Data	**Classification**	**Rationale**
Available information	**Animal data:** Oral LD_{50} rat ≥ 5000 mg/kg	Classification not possible	The rat is known to be insensitive to the toxicity of methanol and is thus not considered to be a good model for human effects (different effect/mode of action)
	Human experience: Methanol is known to cause lethal intoxications in humans (mostly via ingestion) in relatively low doses: "…minimal lethal dose in the absence of medical treatment is between 300 and 1000 mg/kg" (IPCS, Environmental Health Criteria 196, Methanol, WHO, 1997)	Category 3	The minimum lethal dose reported of 300 mg/kg is used as equivalent ATE; according to Table 3.1.1 the resulting classification is Category 3 in Table 3.1.1
Remarks	Test data in rats from mixtures containing methanol should not be used directly in additivity formula.		

3.1.6.1.2 Example 2: N,N-Dimethylaniline

Application	Use of qualitative human data and of SAR information with extrapolation to an ATE (CLP Annex I, 3.1.3.6.2.1(b) and Table 3.1.2. Animal data are not appropriate.		
	Test Data	**Classification**	**Rationale**
Available information	**Animal data:** Acute dermal toxicity: LD_{50} values > 1690 mg/kg bw rabbit.	Category 4	

	Human experience: Broad human experience, reported in many case reports, demonstrating death from MetHB following relatively low oral/dermal/inhalation exposure to aromatic amines such as N,N-dimethylaniline. For N,N-Dimethyl - aniline itself no exact human toxicity values are available.	Category 3 (oral, dermal, inhalation)	The extensive and consistent human experience is considered to be sufficiently robust by expert judgement to be used for classification into Category 3. The rabbit LD_{50} suggests lower sensitivity to MetHB formation than humans which is consistent with what is known from other rabbit tests with substances known to induce MetHB in humans. The rabbit data are therefore not considered to be adequate for acute toxicity classification. Therefore the human data on this and structurally related substances are used to give a converted Acute Toxicity point Estimate (cATpE) according to Table 3.1.2 for Category 3; e.g. cATpE dermal = 300 mg/kgbw, which is then falling in a higher category than the rabbit data.
Remarks			

3.1.6.1.3 Example 3

Application	No exact LD_{50} value available. Expert judgement needed.		
	Test Data	**Classification**	**Rationale**
Available information	Corrosive volatile liquid. **Animal data:** In a GLP-compliant acute oral toxicity study in rats, the following results were observed: At a test dose of 200 mg/kg bw: no mortality, only transient symptoms and no necropsy findings. At a test dose of 500 mg/kg: 100% mortality, symptoms: poor general state; necropsy findings: hyperemia in stomach (due to local irritation /corrosivity), no other organs affected	Category 4	Since at a dose of 200 mg/kg bw no mortality and only slight transient symptoms without necropsy findings were observed, and at 500 mg/kg bw the high amount/concentration of the corrosive substance caused serious effect only at the site of action and mortality, based on expert judgement it can be assumed that the likely LD_{50} is > 300 mg/kg bw. Therefore, the Acute Toxicity Estimate (ATE) value for classification purpose is between 300 and 500 mg/kg bw, corresponding to Category 4 classification for acute toxicity.

Remarks	Labelling: C (pictogram optional) Additional Hazard statement: EUH071 Corrosive to the respiratory tract

3.1.6.1.4 Example 4

Application	Use of non-standard-guideline test data.		
	Test Data	**Classification**	**Rationale**
Available information	**Animal data:** A study to evaluate the acute dermal (percutaneous) toxicity was performed in rabbits. The following test data results were reported: - At the dose level of 50 mg/kg bw: no mortality was observed - At 200 mg/kg bw: 100% mortality Therefore, LD_{50} was estimated to be between 50mg/kg bw and 200mg/kg bw	Category 2	Rationale for classification: Since the dermal LD_{50} is above 50 mg/kg bw and less than 200 mg/kg bw, Category 2 classification is warranted (see Table 3.1.2)
Remarks			

3.1.6.1.5 Example 5

Application	Use of Table 3.1.1 and experimentally obtained LC_{50} value		
	Test Data	**Classification**	**Rationale**
Available information	A gas **Animal data**: A GLP-compliant test for acute inhalation toxicity (gaseous form) was performed in accordance with test guideline 403 in rats. The following LC_{50} was calculated: LC_{50}: 4500ppm/4h	Category 4	Rationale for classification: LC_{50} = 4500 ppm is considered an Acute Toxicity Estimate (ATE) for classification purposes; according to the classification criteria for acute inhalation toxicity for gases (Table 3.1.1), this value corresponds to Category 4. Therefore Category 4 Acute Inhalation Toxicity classification is warranted.
Remarks			

3.1.6.1.6 Example 6

Application	Time extrapolation; Note (b) in Table 3.1.1; Haber's law		
	Test Data	**Classification**	**Rationale**
Available	Solid substance	Category 3	The classification criteria for acute inhalation toxicity in

information	**Animal data**: The acute inhalation toxicity was studied in rats in a GLP-compliant study performed in principle according to test guideline 403, but with respect for transport only with 1-h exposure. The LC_{50} (1-h) of 3 mg/l was calculated.		Table 3.1.1 refer to a 4h exposure time; therefore to classify a substance, existing inhalation toxicity data generated from 1-hour exposure should be converted accordingly: LC_{50} values with 1h have to be converted by dividing by 4 (Haber's rule/law, dusts and mists) LC_{50} (4-h) = (LC_{50} (1-h) **:** 4) = (3mg/l **:** 4) = 0.75 mg/l, thus Category 3 classification is warranted according to Table 3.1.1.
Remarks			

3.1.6.1.7 Example 7: 2,3-Dichloropropene

Application	Discrimination from STOT-SE		
	Test Data	**Classification**	**Rationale**
Available information	**Animal data**: - Oral LD_{50}, rat 250-320 mg/kg (assumption: results from different tests; lowest LD 50 is valid) - Inhalation LC_{50} rat 2.3 mg/l/4h (vapour) Observations: extensive liver and kidney damage following oral and inhalation exposure to lethal doses (insufficient information)	Category 3 oral and Category 3 inhalation	
Remarks	The substance is classified for acute toxicity and not for STOT-SE, since the observed organ toxicity is clearly the cause of the lethality.		

3.1.6.1.8 Example 8

Application	Route-to-route extrapolation: oral to inhalation (Section 3.1.3.3.4). Expert judgement.		
	Test Data	**Extrapolated inhalation ATE/CATpE**	**Rationale**
Available information	**Animal data:** LD_{50} oral rat: 250 mg/kg bw (Category 3) a) No specific kinetic information	0.5 mg/l/4h (cATpE)	a) Using the extrapolation formula 1mg/kgbw = 0.0052

	b) Robust kinetic information allows the conclusion that only 50% is absorbed due to an exhalation rate of 50 %.	2.6 mg/l/4h (ATE)	mg/l/4h: 250 x 0.0052 mg/l/4h = 1.3 mg/l/4h → Category 2 according to Table 3.1.2 b)Based on the 50% inhalation absorption rate the equivalent ATE would be 2.6 (2 x 1.3) → Category 3 according to Table 3.1.2
Remarks	Robust kinetic and other information would allow the use of directly derived ATEs in the additivity formulae by expert judgement		

3.1.6.1.9 Example 9

Application	Route-to-route extrapolation: oral to dermal (Section 3.1.3.3.4). Expert judgement		
	Test Data	**Extrapolated dermal ATE/cATpE**	**Rationale**
Available information	**Animal data:** LD_{50} rat oral: 270 mg/kg bw; 100 % oral absorption assumed a) Assumed dermal absorption rate: 100% b) Dermal absorption rate based on robust kinetic/SAR information: 25%	300 mg/kg LD 50 dermal 1080 mg/kg	a) Based on the assumption of 100 % dermal absorption the converted dermal ATE will be derived by using Table 3.1.2 for Category 3 → 300 mg kg/bw as cATpE. b) Since dermal absorption is only 25%, the dermal ATE has to be accordingly increased → 4x270 mg/kg bw = 1080 mg/kg bw. This is regarded as an equivalent ATE which can be directly used in the additivity formulae.
Remarks	Robust kinetic and other information would allow the use of directly derived ATEs in the additivity formulae by expert judgement		

3.1.6.2 Examples of substances not fulfilling the criteria for classification

3.1.6.2.1 Example 10

Application	Available data are of different quality. Expert judgement. WoE		
	Test Data	**Classification**	**Rationale**
Available information	A liquid **Animal data**: Three studies for acute	No classification	With 3 different available values a validity check proved that the study with LC_{50} = 19 mg/l is not fully valid in

	inhalation toxicity (vapour) in rats are described. Two studies were performed in accordance with test guideline 403 and were GLP-compliant. One study has deficiencies with respect to study methodology and description of study performance and documentation of the test results; no GLP-compliance. The LC_{50} were as follows: – LC_{50}: 19 mg/l/4h (no GLP) – LC_{50}: 23 mg/l/4h (TG 403, GLP) – LC_{50}: 28 mg/l/4h (TG 403, GLP)		contrast to the two others; thus in a weight of evidence approach it is concluded that the LC_{50} = ATE > 20 mg/l/4h. The criteria for Category 4 are not fulfilled.
Remarks			

3.1.6.3 Examples of mixtures fulfilling the criteria for classification

3.1.6.3.1 Example 11

Application	Application of the "Relevant ingredient" (Annex I, 3.1.3.3 (a)) and "Generic cut-off values to be taken into account" concepts (Annex I, Table 1.1) for mixtures with data gaps using the equation in Annex I, 3.1.3.6.2.3.		
	Test Data	**Classification (ingredient)**	**Rationale**
Available information	**Animal data (oral rat):**		
Ingredient 1 (4%)	LD_{50}: 125 mg/kg	Oral Category 3	Apply the equation in Annex I, 3.1.3.6.2.3: $\frac{100-(\sum C_{unknown} if > 10\%)}{ATE_{mix}} = \sum_n \frac{C_i}{ATE_i}$ $\frac{100-92}{ATE_{mix}} = \frac{4}{125} + \frac{3}{1500} + \frac{0.2}{10} =$ $= 0.032 + 0.002 + 0.02 = 0.054$ ATEmix = 148 mg/kg → Category 3
Ingredient 2 (92%)	No data available	-	
Ingredient 3 (3 %)	LD_{50}: 1500 mg/kg	Oral Category 4	
Ingredient 4 (0.9%)	No data available	-	
Ingredient 5 (0.2%)	LD_{50}: 10 mg/kg	Oral Category 2	
Remarks	Rationale for classification of the mixture in Category 3: 1. Classification via application of substance criteria is not possible since acute toxicity test data was not provide for the complete mixture (Annex I, 3.1.3.4). 2. Classification via the application of bridging principles is not possible since data on a similar mixture was not provided (Annex I, 3.1.3.5.1).		

	3. Classification based on ingredient data for the mixture can be considered (Annex I, 3.1.3.6). 4. Applying the "relevant ingredients" concept from Annex I, 3.1.3.3 a) means that Ingredient 4 is excluded from the ATE_{mix} calculation since its concentration is < 1%. The same reasoning cannot apply to Ingredient 5, though its concentration is below the "relevant ingredients" threshold of 1% but it is higher than the cut-off value of 0.1% for a Category 2 ingredient in Annex I, Table 1.1. 5. The total concentration of ingredients with unknown acute toxicity (i.e., Ingredient 2) is 92%; therefore, the ATE_{mix} equation in Annex I, 3.1.3.6.2.3 must be used. This calculation corrects for relevant ingredients with unknown acute toxicity above 10% of the mixture. 6. Ingredients 1, 3 and 5 are included in the ATE_{mix} calculation because they have data that fall within a CLP acute toxicity category, Annex I, 3.1.3.6.1 (a). 7. Applying the guidance in Note (a) to Table 3.1.1 results in using the actual LD_{50} data for Ingredients 1, 3 & 5 in the ATE_{mix} calculation since data is available. **Additional Labelling**: "The mixture contains 92% of ingredients of unknown acute oral toxicity"

3.1.6.3.2 Example 12 a

Application	Different phases in inhalation exposure. Extrapolation		
	Test Data	**Classification**	**Rationale**
Available information	Use /exposure as **aerosol** (mist) Animal data (rat): LC_{50} (mg/l/4h)		
Ingredient 1 solid (6%)		Category 4	Conv. ATE (mg/l/4h) = 1.5 mg/1/4h
Ingredient 2 solid (11%)	0.6	Category 3	ATE = LC_{50}
Ingredient 3 solid (10%)	6 (dust)	-	Neglected, since not classified in any acute category.
Ingredient 4 liquid (40 %)	11 (vapour)	Category 4	Conv. ATE (mg/l/4h) = 1.5 mg/1/4h, assuming identical category for vapour and mist by expert judgement
Ingredient 5 (33%)		-	Water; neglected
Remarks	**Classification:** Category 4 No test data available for the whole mixture. Bridging principles not applicable since no test data on similar mixtures available. Classification therefore based on ingredients. Use additivity formula in Annex I, 3.1.3.6.1, as information is available for all		

	ingredients. $100/ATE_{mix} = 6/1.5+11/0.6+0+40/1.5+0 = 49$ → $ATE_{mix} = 2.04$ mg/l/4h →Category 4

Conclusion: The mixture Example 12a) has to be classified formally in Category 4 with respect to inhalation toxicity. It is notable that this classification is only derived from the calculation for the aerosol phase, not for the vapour phase.

3.1.6.4 Examples of mixtures not fulfilling the criteria for classification

3.1.6.4.1 Example 12 b

Application	Different phases in inhalation exposure. Extrapolation		
	Test Data	**Classification**	**Rationale**
Available information	Use / exposure as vapour Animal data (rat): LC_{50} (mg/l/4h)		
Ingredient 1 solid (6%)		Category 4	A solid with no sublimation, therefore not present in the vapour phase; neglected.
Ingredient 2 solid (11%)	0.6 (dust)	Category 3	As Ingredient 1
Ingredient 3 solid (10%)	6 (dust	-	Neglected, since not classified in any acute category.
Ingredient 4 liquid (40%)	11 (vapour)	Category 4	ATE = LC_{50}
Ingredient 5 (33%)		-	Water; not relevant
Remarks	**Classification:** NC Inhalation is appropriate route since one hazardous ingredient with appreciable vapour pressure. No test data on the whole mixture. Bridging principles not applicable since no test data on similar mixtures available. Classification is therefore based on ingredients. Use additivity formula in Annex I, 3.1.3.6.1 as information is available for all ingredients. There is no contributions from ingredients 1 and 2 in the formula since the diluted solid ingredients do not sublime, and thus are not present in the vapour phase; ingredient 3 is in addition not classified in any acute toxicity category. Ingredient 5 does not show acute toxicity. 100/ATEmix = 0+0+0+40/11+0 = 3.64→ATEmix = 27.5 27.5 mg/l/4h is above the upper generic concentration limit for vapour → NC		

3.1.7 References

Draft OECD TG 39. Draft guidance document on acute inhalation toxicity testing, OECD, 28 November 2008.

ECETOC TR 86, 2003: European centre for ecotoxicology and Toxicology of Chemicals, Brussels, Belgium, Technical report N°86.

Pauluhn, J. (2008) Inhalation toxicology: methodological and regulatory challenges. Exp Toxicol Pathol. **60**(2-3):111-24.

3.2 SKIN CORROSION/IRRITATION

3.2.1 Definitions for classification for skin corrosion/irritation

Annex I: 3.2.1.1. Skin Corrosion means the production of irreversible damage to the skin; namely, visible necrosis through the epidermis and into the dermis, following the application of a test substance for up to 4 hours. Corrosive reactions are typified by ulcers, bleeding, bloody scabs, and, by the end of observation at 14 days, by discolouration due to blanching of the skin, complete areas of alopecia, and scars. Histopathology shall be considered to evaluate questionable lesions.

Skin Irritation means the production of reversible damage to the skin following the application of a test substance for up to 4 hours.

3.2.2 Classification of substances for skin corrosion/irritation

3.2.2.1 Identification of hazard information

3.2.2.1.1 Identification of human data

CLP Article 7.3 specifies that testing on humans is not allowed for the purposes of CLP; however it does acknowledge that existing data obtained from other sources can be used for classification purposes.

Human data may be retrieved from a number of sources, e.g. epidemiological studies, clinical studies, well-documented case reports, poison information units and accident databases or occupational experience.

In this context the quality and relevance of existing human data for hazard assessment should be critically reviewed. There may be a significant level of uncertainty in human data due to poor reporting and lack of specific information on exposure. Diagnosis confirmed by expert physicians may be missing. Confounding factors may not have been accounted for. Small group sizes may flaw the statistical strength of evidence. Many other factors may compromise the validity of human data. In clinical studies the selection of individuals for the test and the control groups must be carefully considered. A critical review of the value of human studies is provided in IR/CSA Section R.4.3.3 and more specific considerations for skin corrosion/irritation are given in IR/CSA Section R.7.2.4.2.

Data indicates that human skin is, in most cases, less sensitive than rabbits (ECETOC, 2002).

3.2.2.1.2 Identification of non human data

Non human data include physico-chemical properties, results from (Q)SARs and expert systems, and results from *in vitro* and *in vivo* tests. Available skin corrosion/irritation

information on substances may include existing data generated by the test methods in the Test Methods Regulation or by methods based on internationally recognised scientific principles.

Several of the following non-testing methods and *in vitro* methods have been validated against the DSD criteria but not against CLP criteria for classification. As the criteria differ slightly between DSD and CLP, it should be checked whether the method is sufficiently validated for classification according to CLP.

3.2.2.1.2.1 Consideration of physico-chemical properties

Substances with oxidising properties can give rise to highly exothermic reactions in contact with other substances and human tissue. High temperatures thus generated may damage/destroy biological materials. This applies, for example, to organic peroxides, which can be assumed to be skin irritants, unless evidence suggests otherwise (IR/CSA Section R.7.2.3.1).

For a hydro peroxide classification as Skin Corrosive Category 1B should be considered, whereas Skin Irritation Category 2 should be considered for peroxides. Appropriate evidence must be provided in order to consider non-classification of substances with oxidising properties.

3.2.2.1.2.2 Non-testing methods: (Q)SARs and expert systems

Non-testing methods such as (Q)SARs and expert systems may be considered on a case-by-case basis. (Q)SAR systems that also account for skin effects are for example TOPKAT, TerraQSAR, and the BfR-DSS. These systems go beyond the structural similarity considerations encompassing also other parameters such as topology, geometry and surface properties. For full guidance consult IR/CSA Sections R.6 and R.7.2.3.1.

The BfR-DSS has been recommended in IR/CSA Section R.7.2.4 since there is no other model that sufficiently describes the absence of effects. The BfR rules to predict skin irritation and corrosion have been integrated in the internet tool “toxtree”, http://ecb.jrc.ec.europa.eu/qsar.

Conclusion on no classification can be made if the (Q)SAR or expert system has been shown to adequately predict the absence of the classified effect (IR/CSA Figure R.7.2-2, footnote f).

Since a formal adoption procedure for those non-testing methods is not foreseen and no formal validation process is in place, appropriate documentation is very important. In order to achieve acceptance under REACH the documentation must conform the so-called QSAR Model Reporting Format (QMRF). For more details consult the IR/CSA Section R.6.1.

3.2.2.1.2.3 Testing-methods: pH and acid/alkaline reserve

Annex I: 3.2.2.2. Likewise, pH extremes like ≤ 2 and ≥ 11,5 may indicate the potential to cause skin effects, especially when buffering capacity is known, although the correlation is not perfect. Generally, such substances are expected to produce significant effects on the skin. If consideration of alkali/acid reserve suggests the substance may not be corrosive despite the low or high pH value, then further testing shall be carried out to confirm this, preferably by use of an appropriate validated in vitro test.

The acid/alkaline reserve is a measure of the buffering capacity of chemicals. For details of the methodology, see Young *et al*, 1988, and Young and How, 1994.

3.2.2.1.2.4 Testing methods: *in vitro* methods

Table R.7.2-2 in IR/CSA lists the status of validation and regulatory acceptance for *in vitro* test methods for skin corrosion and skin irritation.

In vitro methods for skin corrosion

In recent years, the OECD has accepted new guidelines for *in vitro* skin corrosion tests as alternatives for the standard *in vivo* rabbit skin test (OECD TG 404). Accepted *in vitro* tests for skin corrosivity are found in the Test Methods Regulation (TM) and in OECD Test Guidelines (TG):

The transcutaneous electrical resistance (TER; using rat skin) test (TM B.40; OECD TG 430)

Human skin model (HSM) tests (TM B.40 bis; OECD TG 431)

The *in vitro* membrane barrier test method (OECD TG 435)

Positive *in vitro* results do not generally require further testing and can be used for classification. Negative *in vitro* corrosivity responses must be subject to further evaluation.

Whereas the TER test and the human skin models at present only allow a classification into Skin Corrosion Category 1A, the membrane barrier test allows for the differentiation into the three Categories 1A, 1B and 1C. The applicability domain of the three tests outlined here (TER-, HSM- and membrane barrier test) with regard to the alkalinity and acidity of the tested substance should be carefully considered to decide which data are most appropriate for the actual substance.

The TER and the HSM assays have been validated for the classification of skin corrosion. The results of this validation are well founded, because the CLP criteria for skin corrosion are identical with the ones referred to in the past validation study.

The membrane barrier method has been endorsed as a scientifically validated test for a limited range of substances - mainly acids, bases and their derivatives (ECVAM, 2000).

In vitro methods for skin irritation

Three *in vitro* skin irritation test methods based on reconstructed human epidermis (RHE) technology are currently under review by the OECD for regulatory acceptance as test methods able to reliably distinguish non-irritants from irritant substances using one single irritant category. The three assays are the EpiSkin™, the modified EpiDerm™ and the SkinEthic RHE™ test method. The EpiSkin and EpiDerm assays have undergone formal ECVAM validation from 2003 – 2007 (Spielmann *et al*, 2007). In 2007 the EpiSkin was considered valid by ESAC as a full replacement test (ECVAM/ESAC, 2007). Originally validated for use in a testing strategy for the identification of positives only (ECVAM/ESAC, 2007), the EpiDerm test methods protocol was subsequently modified. In November 2008, also the modified EpiDerm and the SkinEthic assay were found reliable and relevant test methods capable of distinguishing non-irritants from irritants and may therefore fully replace the traditional skin irritation test (ECVAM/ESAC, 2008). It should be noted that conclusions on the applicability domain of the three methods rest mainly on the optimisation and validation data set. All three methods are valid for the classification of substances for skin irritancy according to CLP criteria (ECVAM/ESAC, 2009).

The Skin integrity function test (SIFT) is also listed in IR/CSA, Table R.7.2-2. This test has only undergone prevalidation so far and the applicability domain is limited to surfactants. Positive data from SIFT may be used in a weight of evidence approach to consider classification for irritation, while negative data are not conclusive for a non - classification.

Other suitable in vitro methods

Positive data from other suitable *in vitro* methods may be used in a weight of evidence approach to determine classification as irritant, while negative data are not conclusive for a non-classification. In this context 'suitable' means sufficiently well developed according to internationally agreed development criteria (see REACH Annex XI, section 1.4).

3.2.2.1.2.5 Testing methods: *In vivo* data

The *in vivo* test in rabbits according to TM B.4 (OECD TG 404) is the standard test for the hazard assessment and classification required under the REACH Annex VIII provisions (10 tons per year and more). However it should be noted that according to REACH (Annexes VII to X) *in vivo* testing of corrosive substances at concentration/dose levels causing corrosivity shall be avoided.

Until 1987 the OECD standard protocol used occlusive patching for the application of the test substance, which resulted in more rigorous test conditions compared to the semi-occlusive patching used today. Especially in borderline cases of classification the method of application should be accounted for in the evaluation of effects.

Studies performed according to the USA Federal Hazardous Substances Act (US-FHSA) may be used for classification purposes although they deviate in their study protocol from the OECD TG 404. They do not include a 48-hour observation time and involve a 24-hour test material exposure followed by observations at 24 hour and 72 hours. Moreover, the test material is patched both on abraded and on intact skin of six rabbits. Studies usually are terminated after 72 hours. In case of no or minimal responses persisting until the 72 hours time points it is feasible to use such data for classification by calculating the mean values for erythema and oedema on the basis of only the 24 and 72 hours time points. Calculation of mean scores should normally be restricted to the results obtained from intact skin. In case of pronounced responses at the 72 hours time point an expert judgement is needed as to whether the data is appropriate for classification.

Data on skin effects on animals may be available from tests that were conducted for other primary purposes than the investigation of skin corrosion / irritation. Such information may be gained from acute or repeated dose dermal toxicity studies on rabbits or rats (TM B.3, OECD TG 402; TM B.9, OECD TG 410), guinea pig skin sensitisation studies (TM B.6, OECD guideline 406) and from irritation studies in hairless mice.

3.2.2.2 Classification criteria

Annex I: 3.2.2.6. *Corrosion*

3.2.2.6.1. On the basis of the results of animal testing a substance is classified as corrosive, as shown in Table 3.2.1. A corrosive substance is a substance that produces destruction of skin tissue, namely, visible necrosis through the epidermis and into the dermis, in at least 1 tested animal after exposure up to a 4 hour duration. Corrosive reactions are typified by ulcers, bleeding, bloody scabs and, by the end of observation at 14 days, by discoloration due to blanching of the skin, complete areas of alopecia and scars. Histopathology shall be considered to discern questionable lesions.

3.2.2.6.2. Three subcategories are provided within the corrosive category: subcategory 1A – where responses are noted following up to 3 minutes exposure and up to 1 hour observation; subcategory 1B – where responses are described following exposure between 3 minutes and 1 hour and observations up to 14 days; and subcategory 1C – where responses occur after exposures between 1 hour and 4 hours and observations up to 14 days.

3.2.2.6.3. The use of human data is discussed in paragraphs 3.2.2.1 and 3.2.2.4 and also in paragraphs 1.1.1.3, 1.1.1.4 and 1.1.1.5.

Table 3.2.1

Skin Corrosive category and subcategories

		Corrosive in ≥ 1 of 3 animals*	
	Corrosive subcategory	Exposure	Observation

Category 1: Corrosive	1A	≤ 3 minutes	≤ 1 hour
	1B	> 3 minutes - ≤ 1 hour	≤ 14 days
	1C	> 1 hour - ≤ 4 hours	≤ 14 days

3.2.2.7. *Irritation*

3.2.2.7.1. Using the results of animal testing a single irritant category (Category 2) is presented in Table 3.2.2. The use of human data is discussed in paragraphs 3.2.2.1 and 3.2.2.4 and also in paragraphs 1.1.1.3, 1.1.1.4 and 1.1.1.5. The major criterion for the irritant category is that at least 2 of 3 tested animals have a mean score of ≥ 2,3 - ≤ 4,0.

Table 3.2.2

Skin irritation category

Category	Criteria
Category 2: Irritant	(1) Mean value of ≥ 2,3 - ≤ 4,0 for erythema/eschar or for oedema in at least 2 of 3 tested animals from gradings at 24, 48 and 72 hours after patch removal or, if reactions are delayed, from grades on 3 consecutive days after the onset of skin reactions; or (2) Inflammation that persists to the end of the observation period normally 14 days in at least 2 animals, particularly taking into account alopecia (limited area), hyperkeratosis, hyperplasia, and scaling; or (3) In some cases where there is pronounced variability of response among animals, with very definite positive effects related to chemical exposure in a single animal but less than the criteria above.

3.2.2.8. *Comments on responses obtained in skin irritation tests in animals*

3.2.2.8.1. Animal irritant responses within a test can be quite variable, as they are with corrosion. The major criterion for classification of a substance as irritant to skin, as shown in paragraph 3.2.2.7.1, is the mean value of the scores for either erythema/eschar or oedema calculated in at least 2 of 3 tested animals. A separate irritant criterion accommodates cases when there is a significant irritant response but less than the mean score criterion for a positive test. For example, a test material might be designated as an irritant if at least 1 of 3 tested animals shows a very elevated mean score throughout the study, including lesions persisting at the end of an observation period of normally 14 days. Other responses could also fulfil this criterion. However, it should be ascertained that the responses are the result of chemical exposure.

3.2.2.8.2. Reversibility of skin lesions is another consideration in evaluating irritant responses. When inflammation persists to the end of the observation period in 2 or more test animals, taking into consideration alopecia (limited area), hyperkeratosis, hyperplasia and scaling, then a material shall be considered to be an irritant.

* *Note*: In Table 3.2.1 it should read "Corrosive in ≥ 1 of 3 animals". There is a misprint in the BG, CS, ET, EL, EN, LV, PT, and RO versions of CLP published in the Official Journal 31.12.2008.

3.2.2.3 Evaluation of hazard information

Annex I: 3.2.2.4.

…

Although information might be gained from the evaluation of single parameters within a tier (see paragraph 3.2.2.5), e.g. caustic alkalis with extreme pH shall be considered as skin corrosives, there is merit in considering the totality of existing information and making an overall weight of evidence determination. This is especially true when there is information available on some but not all parameters. Generally, primary emphasis shall be placed upon existing human experience and data, followed by animal experience and testing data, followed by other sources of information, but case-

by-case determinations are necessary.

3.2.2.5. A tiered approach to the evaluation of initial information shall be considered, where applicable, recognising that all elements may not be relevant in certain cases.

3.2.2.3.1 Evaluation of human data

The usefulness of human data for classification purposes will depend on the extent to which the effect, and its magnitude, can be reliably attributed to the substance of interest. Further guidance on evaluation of human data for skin corrosion/irritation can be found in IR/CSA Section R.7.2.4.2.

The criteria in Annex I, Table 3.2.2 are not applicable to human data.

3.2.2.3.2 Evaluation of non human data

3.2.2.3.2.1 In vitro data

In evaluation of data from *in vitro* tests the applicability domain has to be taken into account. The *in vitro* membrane barrier test method e.g. is mainly applicable for acids and bases and is not applicable for solutions with pH values between 4.5 and 8.

3.2.2.3.2.2 In vivo data

Tests in albino rabbits (OECD TG 404)

Evaluation criteria for local effects on the skin are *severity* of the damage and *reversibility*.

For the *severity* of damage the responses are evaluated according to the Draize score ranking from "0" (no response") up to "4" (severe response"). Evaluation takes place separately for erythema and oedema.

Reversibility of skin lesions is the other decisive factor in evaluating responses in the animal test. The criteria are fulfilled if, for

- *corrosion*
- the full thickness of the skin is destroyed resulting in ulcers, bleeding, bloody scabs discoloration, complete areas of alopecia and scars. In questionable cases a pathologist should be consulted. One animal showing this response at the end of the observation period is sufficient for the classification as corrosive.
- *irritation*
  - a limited degree of alopecia, hyperkeratosis, hyperplasia and scaling occurs. Two animals showing this response are sufficient for the classification as irritant.
  - very elevated mean scores throughout the study are revealed, including lesions persisting at the end of an observation period of normally 14 days. One animal showing this response throughout and at the end of the observation period is sufficient for the classification as irritant (In cases of suspected corrosives, existing test data may only be available for one animal due to testing restrictions, see Example 2.).

With regard to severity the main criterion for classification of a substance as irritant to skin, is the mean score per animal for either erythema/eschar or oedema. During the observation period following the removal of the patch each animal is scored on erythema and oedema. For each of the three test animals the average scores for three consecutive days (usually 24, 48 and 72 hours) are calculated separately for oedema and erythema. If 2/3 animals exceed the cut-off-values defined in the CLP, the classification has to be done accordingly.

With regard to reversibility the test report must prove that these effects are transient i.e. the affected sites are repaired within the observation period of the test (see Example 1).

Non-classification as corrosive can be only justified, if the test was performed with at least three animals and the test results were negative for all three animals.

Tests that have been conducted with more than three animals

Current guidelines foresee a sequential testing of rabbits until a response is confirmed. Typically, up to 3 rabbits may be used. The basis for a positive response is the individual rabbit value averaged over days 1, 2, and 3. The mean score for each individual animal is used as a criterion for classification. The Skin Irritant Category 2 is used if at least 2 of 3 animals show a mean score of 2.3 or above. Other test methods, however, have been using up to 6 rabbits. This is also the case for the studies performed according to the US-FSHA.

For existing test data with more than three animals, specific provisions need to be applied. For the sake of flexibility basically two approaches can be accepted for evaluation**:**

- the overall average over all animals will be used (see Example 3a). This has been common practice under the DSD.
- According to the second approach the average score is determined per animal (see Example 3b). In this case Skin Irritant Category 2 is assigned if 4 of 6 rabbits show a mean score of 2.3 or above. Likewise, if the test was performed with 4 or 5 animals, for at least 3 individuals the mean score must exceed the value of 2.3 to classify as Skin Irritant Category 2.

The more stringent result has to be used if the evaluation according to the method shown under Example 3a is different to that under Example 3b.

Other dermal tests in animals

Relevant data may also be available from animal studies that were conducted for other primary purposes than the investigation of skin corrosion/irritation. However, due to the different protocols and the interspecies differences in sensitivity, the use of such data in general needs to be evaluated on a case-by-case basis. These are considered significant if the effects seen are comparable to those described above. For further guidance how to evaluate data from studies on dermal toxicity or skin sensitisation, see IR/CSA Figure R.7.2-2 footnotes d) and e), respectively.

3.2.2.3.3 Weight of evidence

Where the criteria cannot be applied directly to available identified information, a weight of the evidence determination using expert judgement shall be applied in accordance with CLP Article 9(3).

A weight of the evidence determination means that all available and scientifically justified information bearing on the determination of hazard is considered together, such as physico-chemical parameters (e.g., pH, reserve alkalinity/acidity), information from the application of the category approach (grouping, read-across), (Q)SAR results, the results of suitable *in vitro* tests, relevant animal data, skin irritation information/data on other similar mixtures, 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. Both positive and negative results shall be assembled together in a single weight of evidence determination.

Evaluation must be performed on a case-by-case basis and with expert judgement. However, normally positive results that are adequate for classification should not be overruled by negative findings.

Annex I: 1.1.1.4. For the purpose of classification for health hazards (Part 3) established hazardous effects seen in appropriate animal studies or from human experience that are consistent with the criteria for classification shall normally justify classification. Where evidence is available from both humans and animals and there is a conflict between the findings, the quality and reliability of the evidence from both sources shall be evaluated in order to resolve the question of classification. Generally, adequate, reliable and representative data on humans (including epidemiological studies, scientifically valid case studies as specified in this Annex or statistically backed experience) shall have precedence over other data. However, even well-designed and conducted epidemiological studies may lack a sufficient number of subjects to detect relatively rare but still significant effects, to assess potentially confounding factors. Therefore, positive results from well-conducted animal studies are not necessarily negated by the lack of positive human experience but require an assessment of the robustness, quality and statistical power of both the human and animal data.

For further guidance, if both human and animal data are available, see IR/CSA Section R.7.2.3.2.

3.2.2.4 Decision on classification

Where the substance is classified as a skin corrosive but the data used for classification does not allow differentiation between the skin corrosion subcategories 1A/1B/1C, then the substance should be assigned skin corrosive Category 1.

3.2.2.5 Setting of 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.

It is more difficult to prove the absence of a hazardous property; the legal text states that:

Article 10(1)

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.

A specific concentration limit (SCL) set in accordance with the above mentioned provisions shall take precedence over the generic concentration limit (GCL) set out in Tables 3.2.3 and 3.2.4 of Annex I to CLP (Article 10(6)). Furthermore, an SCL is substance-specific and should be applicable to all mixtures containing the substance, instead of any GCL that otherwise would apply to a mixture containing the substance.

What type of information may be the basis for setting a specific concentration limit?

Existing human data may in certain cases (especially if dose-response information is available) indicate that the threshold for the irritation hazard in humans for a substance in a mixture, would be higher or lower than the GCL. A careful evaluation of the usefulness and the validity of such human data, as well as their representativeness and predictive value (IR/CSA, sections R.4.3.3. and R.7.2.4.2), should be performed. As pointed out in 1.1.1.4 (Annex I to CLP), positive results from well-conducted animal studies are not necessarily negated by the lack of positive human experience but require an assessment of robustness, quality and a degree of statistical certainty of both the human and animal data.

The aim of the standard test method for "Acute Dermal Irritation/Corrosion" TM B.4/OECD TG 404[46] is to **identify** potential skin corrosion or irritation. The test material is generally administered undiluted, thus, no dose-response relationship can be obtained from an individual test.

However, if there are adequate, reliable, relevant and conclusive existing data from other already performed animal studies with a sufficient number of animals tested to ensure a high degree of certainty, and with information on dose-response relationships, such data may be considered for setting a lower or, in exceptional cases, a higher SCL on a case-by-case basis.

It should be noted that any additional animal testing to set SCLs (of dilutions) of substances already classified as a skin corrosive or skin irritant, is strongly discouraged and may only take place on a case-by-case basis if there are no alternatives providing adequate reliability and quality of data (see CLP Articles 7(1) and 8(1)). The possibilities to use *in vitro* test methods are being explored as a basis for setting SCLs, but an accepted common approach is not yet available. Thus, at the present point in time, it is not possible to provide guidance for the use of *in vitro* methods for the purpose of setting SCLs. However, this does not exclude that a method to set SCLs based on *in vitro* tests could be developed in the future, as they provide a promising option for SCL setting.

An SCL should apply to any mixture containing the substance instead of the GCL (that otherwise would apply to the mixture containing the substance). Thus, if the SCL is based on data derived from tests with dilutions of the substance in a specific solvent, it has to be considered that the derived concentration should be applicable to all mixtures for which the SCL should apply.

Annex VI Part 3 (Table 3.2) to CLP includes examples of substances for which a higher or lower SCL was set under Directive 67/548/EEC (old DSD system).

3.2.2.6 Decision logic for classification of substances

The decision logic, which is based on IR/CSA Figure R.7.2-2 is revised to meet CLP requirements. It is strongly recommended that the person responsible for classification, study the criteria for classification, as well as the guidance above, before and during use of the decision logic.

Step		
1a	Is the substance an organic hydro peroxide or an organic peroxide? **YES** ➔ **NO** ↓	Consider to classify as – corrosive (Skin Corr. 1B) if the substance is a hydro peroxide, or – irritating (Skin Irrit. 2) if the substance

[46] TO NOTE: In OECD TG 404 *test substance* refers to the test material, test article or test item. The term *substance* may be used differently from the REACH/CLP definition.

		is a peroxide. OR Provide evidence for the contrary and proceed to step 1b
1b	Is the pH of the substance ≤ 2 or ≥ 11.5? **YES ➔** **NO** **↓**	Consider to classify as corrosive. – Where classification is based upon consideration of pH alone (i.e. buffering capacity is not known), Skin Corr. 1A should be applied. – Where consideration of alkali/acid reserve suggests that the substance is not corrosive, this has to be confirmed (preferably by use of an appropriate *in vitro* test). Proceed to step 1c
1c	Are there other physical or chemical properties that indicate that the substance is irritating / corrosive? **YES ➔** **NO** **↓**	Use this information for weight of evidence (WoE) determination (step 7). Proceed to step 2
2	Are there adequate existing human data which provide evidence that the substance is corrosive or irritant? **YES ➔** **NO** **↓**	Classify accordingly.
3	Are there data from existing studies *on irritation and corrosion* in laboratory animals, which provide sound conclusive evidence that the substance is a corrosive, irritant or non-irritant? **YES ➔** **NO** **↓**	Classify accordingly (either Skin Corr. 1A/1B/1C or Skin Irrit. 2 or no classification).
4a	Has the substance proven to be a corrosive, irritant or non-irritant in a suitable acute dermal toxicity test? **YES ➔** **NO** **↓**	If test conditions are consistent with OECD TG 404, classify accordingly (Skin Corr. 1A/ 1B/1C or Skin Irrit. 2 or no classification) If test conditions are not consistent with OECD TG 404, use this information in the WoE determination (step 7) and proceed to step 4b
4b	Has the substance proven to be a corrosive or an irritant in sensitisation studies or after repeated exposure? **YES ➔** NO	Classification cannot be considered directly. Use this information for WoE determination (step 7). Proceed to step 5a

	↓	
5a	Are there structurally related substances (suitable "read-across" or grouping), which are classified as corrosive (Skin Cat. 1) on the skin, or do suitable (Q)SAR methods indicate corrosive potential of the substance? **YES** → **NO** ↓	Consider to classify as Skin Corr. 1. Proceed to step 5b
5b	Are there structurally related substances (suitable "read-across" or grouping), which are classified as irritant on the skin (Skin Cat. 2), or do suitable (Q)SAR methods indicate the presence of irritating potential of the substance? **YES** → **NO** ↓	Consider to classify as Skin Irrit. 2. Proceed to step 6a
6a	Has the substance demonstrated corrosive properties in an OECD adopted *in vitro* test? **YES** → **NO** ↓	Classify as corrosive. If discrimination between Skin Corr. 1A/1B/1C is not possible, Skin Corr. 1 must be chosen.
6b	Are there acceptable data from a validated *in vitro* test (adopted by OECD or not), which provide evidence that the substance is an irritant or non-irritant? **YES** → **NO** ↓	Consider to classify accordingly (Skin Irrit. 2 or no classification). Proceed to step 6c
6c	Are there data from a suitable *in vitro* test, which provide sound conclusive evidence that the substance is an irritant? **YES** → **NO** ↓	Consider to classify as Skin Irrit. 2 Proceed to step 7
7	Taking all existing and relevant data (steps 1-6) into account, is there sufficient information to make a decision on classification? **YES** → **NO** ↓	Classify accordingly (Skin Corr. 1A or Skin Corr. 1B or Skin Corr. 1C or Skin Irrit. 2 or no classification)
Unable to classify substance for skin corrosion/irritation		Decision to undertake generation of new test data should be made in compliance with REACH and Article 8 of CLP. It is recommended that IR/CSA R.7.2.6 should also be considered.

3.2.3 Classification of mixtures for skin corrosion/irritation

3.2.3.1 Identification of hazard information

The procedure for classifying mixtures is a tiered, i.e. a stepwise, approach based on a hierarchy principle and depending on the type and amount of available data/information starting from evaluating existing human data on the mixture, followed by a thorough examination of the existing *in vivo* data, physico-chemical properties, and finally *in vitro* data available on the mixture. For mixtures that have been on the market for a long time, human data and experience may exist that may provide useful information on the skin irritation potential of the respective mixtures. See Section 3.2.2.1.1 for further information on the identification of human data.

If valid test data are available for the whole mixture they have precedence. If no such data exist, the so called bridging principles have to be applied if possible. If the bridging principles are not applicable an assessment on the basis of data for the components of the mixture will be applied.

Where it is decided to base the classification of a mixture upon consideration of pH alone, Skin corrosion Category 1A should be applied. In this case no further retrieval of information on the mixture itself is needed.

3.2.3.2 Classification criteria

3.2.3.2.1 When data are available for the complete mixture

Annex I: 3.2.3.1.1. The mixture will be classified using the criteria for substances, and taking into account the testing and evaluation strategies to develop data for these hazard classes.

3.2.3.1.2. Unlike other hazard classes, there are alternative tests available for skin corrosivity of certain types of substances and mixtures that can give an accurate result for classification purposes, as well as being simple and relatively inexpensive to perform. When considering testing of the mixture, classifiers are encouraged to use a tiered weight of evidence strategy as included in the criteria for classification of substances for skin corrosion and irritation (paragraph 3.2.2.5), to help ensure an accurate classification as well as avoid unnecessary animal testing. A mixture is considered corrosive to skin (Skin Category 1) if it has a pH of 2 or less or a pH of 11.5 or greater. If consideration of alkali/acid reserve suggests the substance or mixture may not be corrosive despite the low or high pH value, then further testing shall be carried out to confirm this, preferably by use of an appropriate validated in vitro test.

There are a range of available *in vitro* test systems that have been validated for their suitability in assessing skin corrosion/irritation potential of substances. Some but not all test systems have been validated for mixtures and not all available *in vitro* test systems work equally well for all types of mixtures. Prior to testing a mixture in a specific *in vitro* assay for classification purposes, it has to be assured that the respective test has been previously shown to be suitable for the prediction of skin corrosion/irritation properties for the type of mixture to be evaluated.

3.2.3.2.1.1 Mixtures with extreme pH

As a general rule, mixtures with a pH of ≤ 2 or ≥ 11.5 should be considered as corrosive. However, assessment of the buffering capacity of the mixture indicated by its acid or alkali reserve should be considered. If the additional consideration of the acid/alkaline reserve according to Young *et a*l. (1987, 1994) suggests that classification for corrosion or even irritation may not be warranted, then further *in vitro* testing to confirm final (or no)

classification shall be carried out. The consideration of acid/alkali reserve should not be used alone to exonerate mixtures from classification.

Where the mixture has an extreme pH value but the only corrosive/irritant ingredient present in the mixture is an acid or base with an assigned SCL (either in CLP Annex VI or set by supplier), then the mixture should be classified according to the SCL. In this instance, pH of the mixture should not be considered a second time since it would have already been taken into account when deriving the SCL for the substance.

If this is not the case, then the steps to be taken into consideration when classifying a mixture with pH ≤ 2 or ≥ 11.5 are described in the following decision logic:

Mixture without *in vivo* data on skin corrosion or relevant data from similar tested mixtures, **pH is ≤ 2 or ≥ 11.5**	
Does the acid alkaline reserve indicate that the mixture may not be corrosive? **NO** ➔ **YES** ⬇	Classify as corrosive, Skin Corr. Cat. 1A.
Is the mixture tested in an OECD adopted *in vitro* test for skin corrosion? **NO** ➔ **YES** ⬇	Classify as corrosive, Skin Corr. Cat. 1A.
Does the mixture demonstrate corrosive properties in an OECD adopted *in vitro* test? **YES** ➔ **NO** ⬇	Classify as corrosive. If discrimination between Skin Corr. 1A/1B/1C is not possible, Skin Corr. 1 must be chosen.
Apply methods in Annex I, sections 3.2.3.3.2 (Table 3.2.3) / 3.2.3.3.4 (Table 3.2.4) ➔ (When validated *in vitro* skin irritation test methods are available, these may be used to generate data to classify the mixture instead of using the summation method.)	Classify accordingly.

The mixture must be classified as Skin corrosion Category 1 should the supplier decide not to carry out the required confirmatory testing.

It is also important to note that the pH-acid/alkali reserve to change classification from corrosive to irritant or from irritant to not classified assumes that the potential corrosivity or irritancy is due to the effect of the ionic entities. When this is not the case, especially when the mixture contains non-ionic (non-ionisable) substances themselves classified as corrosive or irritant, then the pH-reserve method cannot be a basis for modifying the classification but should be considered in a weight of evidence analysis.

3.2.3.2.2 When data are not available for the complete mixture: bridging principles

Annex I: 3.2.3.2.1. Where the mixture itself has not been tested to determine its skin irritation/corrosion hazards, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterise the hazards of the mixture, these data shall be used in accordance with the bridging rules set out in section 1.1.3.

In order to apply bridging principles, there needs to be sufficient data on similar tested mixtures as well as the components of the mixture.

When the available identified information is inappropriate for the application of the bridging principles then the mixture should be classified using the methods described in Section 1.6.3.2.

3.2.3.2.3 When data are available for all components or only for some components

3.2.3.2.3.1 Components that should be taken into account for the purpose of classification

Annex I: 3.2.3.3.1. …..Assumption: the 'relevant ingredients' of a mixture are those which are present in concentrations of 1% (w/w for solids, liquids, dusts, mists and vapours and v/v for gases) or greater, unless there is a presumption (e.g., in the case of corrosive ingredients) that an ingredient present at a concentration of less than 1% can still be relevant for classifying the mixture for skin irritation/corrosion.

3.2.3.2.3.2 The additivity approach is applicable

Annex I: 3.2.3.3.2. In general, the approach to classification of mixtures as irritant or corrosive to skin when data are available on the components, but not on the mixture as a whole, is based on the theory of additivity, such that each corrosive or irritant component contributes to the overall irritant or corrosive properties of the mixture in proportion to its potency and concentration. A weighting factor of 10 is used for corrosive components when they are present at a concentration below the generic concentration limit for classification with Category 1, but are at a concentration that will contribute to the classification of the mixture as an irritant. The mixture is classified as corrosive or irritant when the sum of the concentrations of such components exceeds a concentration limit.

3.2.3.3.3. Table 3.2.3 provides the generic concentration limits to be used to determine if the mixture is considered to be an irritant or a corrosive to the skin.

When the supplier is unable to derive the classification using either data on the mixture itself or bridging principles, he must determine the skin corrosion/irritation properties of the mixture using data on the individual ingredients. The supplier must ascertain whether the additivity approach is applicable, the first step in the process being to identify all the ingredients in the mixture (i.e. their name, chemical type, concentration level, hazard classification and any SCLs) and the pH of the mixture. In addition to for example surfactant interaction, neutralisation of acids/bases could also occur in a mixture, which also makes it important to consider effects of the entire mixture (i.e. pH and the acid/alkaline reserve) rather than considering contributions of individual ingredients. Additivity may not apply where the mixture contains substances mentioned in Annex I, 3.2.3.3.4, see Section 3.2.3.2.3.3.

Application of SCLs when applying the additivity approach

The generic concentration limits (GCLs) are specified in Annex I, Table 3.2.3. However, according to CLP Article 10(5) SCLs take precedence over GCLs. Thus, if a given substance has a SCL, then this limit has to be taken into account when applying the summation (additivity) method for skin corrosion/irritation (see Examples 5 and 6).

In cases where additivity applies for skin corrosion/irritation to a mixture with two or more substances some of which may have SCLs assigned, then the following formula should be used:

The mixture is classified for skin corrosion/irritation if the

Sum of (ConcA / clA) + (ConcB / clB) + ….+ (ConcZ / clZ) is ≥ 1

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

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

ConcB = the concentration of substance B in the mixture;

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

This approach is similar to that used in the DPD where a substance SCL replaces the default limits in the conventional method equations.

3.2.3.2.3.3 The additivity approach is not applicable

Annex I: 3.2.3.3.4.1. Particular care must be taken when classifying certain types of mixtures containing substances such as acids and bases, inorganic salts, aldehydes, phenols, and surfactants. The approach explained in paragraphs 3.2.3.3.1 and 3.2.3.3.2 may not be applicable given that many of such substances are corrosive or irritant at concentrations < 1%.

3.2.3.3.4.2. For mixtures containing strong acids or bases the pH shall be used as a classification criterion (see paragraph 3.2.3.1.2) since pH is a better indicator of corrosion than the concentration limits of Table 3.2.3.

3.2.3.3.4.3. A mixture containing ingredients that are corrosive or irritant to the skin and that cannot be classified on the basis of the additivity approach (Table 3.2.3), due to chemical characteristics that make this approach unworkable, shall be classified as Skin Corrosive Category 1A, 1B or 1C if it contains ≥ 1% of an ingredient classified in Category 1A, 1B or 1C respectively or as Category 2 when it contains ≥ 3% of an irritant ingredient. Classification of mixtures with ingredients for which the approach in Table 3.2.3 does not apply is summarised in Table 3.2.4.

3.2.3.3.5. On occasion, reliable data may show that the skin corrosion/irritation hazard of an ingredient will not be evident when present at a level above the generic concentration limits mentioned in Tables 3.2.3 and 3.2.4. In these cases the mixture shall be classified according to that data (see also Articles 10 and 11). On other occasions, when it is expected that the skin corrosion/irritation hazard of an ingredient is not evident when present at a level above the generic concentration limits mentioned in Tables 3.2.3 and 3.2.4, testing of the mixture shall be considered. In those cases the tiered weight of evidence strategy shall be applied, as described in paragraph 3.2.2.5.

3.2.3.3.6. If there are data showing that (an) ingredient(s) is/are corrosive or irritant at a concentration of < 1 % (corrosive) or < 3 % (irritant), the mixture shall be classified accordingly.

3.2.3.3 Generic concentration limits for substances triggering classification of mixtures

3.2.3.3.1 When the additivity approach is applicable

Annex I: *Table 3.2.3*
Generic concentration limits of ingredients classified for skin corrosive/irritant hazard (Category 1 or 2)that trigger classification of the mixture as corrosive/irritant to skin

Sum of ingredients classified as:	Concentration triggering classification of a mixture as:	
	Skin Corrosive	Skin Irritant
	Category 1 (see note below)	Category 2
Skin corrosive Categories 1A, 1B, 1C	≥ 5%	≥ 1% but < 5%
Skin irritant Category 2		≥ 10%
(10 x Skin corrosive Category 1A,		≥ 10%

1B, 1C) + Skin irritant Category 2		
Note The sum of all ingredients of a mixture classified as Skin Corrosive Category 1A, 1B or 1C respectively, shall each be ≥ 5% respectively in order to classify the mixture as either Skin Corrosive Category 1A, 1B or 1C. If the sum of the Skin Corrosive Category 1A ingredients is < 5% but the sum of Category 1A+1B ingredients is ≥ 5%, the mixture shall be classified as Skin corrosive Category 1B. Similarly, if the sum of Skin corrosive Category 1A+1B ingredients is < 5% but the sum of Category 1A+1B+1C ingredients is ≥ 5% the mixture shall be classified as Skin Corrosive Category 1C.		

3.2.3.3.2 When the additivity approach is not applicable

Annex I: *Table 3.2.4*

Generic concentration limits of ingredients of a mixture for which the additivity approach does not apply, that trigger classification of the mixture as corrosive/irritant to skin

Ingredient:	Concentration:	Mixture classified as: Skin
Acid with pH ≤ 2	≥ 1%	Category 1
Base with pH ≥ 11,5	≥ 1%	Category 1
Other corrosive (Categories 1A, 1B, 1C) ingredients for which additivity does not apply	≥ 1%	Category 1
Other irritant (Category 2) ingredients for which additivity does not apply, including acids and bases	≥ 3%	Category 2

3.2.3.4 Decision logic for classification of mixtures

The decision logic, which is based on IR/CSA Figure R.7.2-2, is revised to meet CLP requirements. It is strongly recommended that the person responsible for classification, study the criteria for classification, as well as the guidance above, before and during use of the decision logic.

1. When data are available for the complete mixture		
1a	Is the pH of the mixture ≤ 2 or ≥ 11.5? **YES** ➔ **NO** ⬇	Consider to classify as corrosive. – Where classification is based upon consideration of pH alone (i.e. buffering capacity is not known), Skin Corr. 1A should be applied. – Where consideration of alkali/acid reserve suggests that the substance is not corrosive, this has to be confirmed (preferably by use of an appropriate *in vitro* test). Proceed to step 1b.

1b	Are there other physical or chemical properties that indicate that the mixture is corrosive/irritating? **YES** ➔ **NO** ⬇	Use this information for WoE analysis (step 6). Proceed to step 2
2	Is there adequate existing human experience which provides evidence that the mixture is corrosive or irritant? **YES** ➔ **NO** ⬇	Classify accordingly (Skin Corr. 1 or Skin Irrit. 2).
3	Are there data from existing studies *on irritation and corrosion* in laboratory animals, which provide sound conclusive evidence that the mixture is corrosive, irritant or non-irritant? **YES** ➔ **NO** ⬇	Classify accordingly (Skin Corr. 1A or Skin Corr. 1B or Skin Corr. 1C or Skin Irrit. 2 or no classification).
4a	Has the mixture proven to be a corrosive, irritant or non-irritant in a suitable acute dermal toxicity test? **YES** ➔ **NO** ⬇	– If test conditions are consistent with OECD TG 404, classify accordingly (Skin Corr. 1A/1B/1C or Skin Irrit. 2 or no classification). – If test conditions are not consistent with OECD TG 404, use this information in the WoE determination (step 6) and proceed to step 4b
4b	Has the mixture proven to be a corrosive or an irritant in sensitisation studies or after repeated exposure? **YES** ➔ **NO** ⬇	Classification cannot be considered directly. Use this information for WoE determination (step 6). Proceed to step 5a
5a	Has the mixture demonstrated corrosive properties in an OECD adopted *in vitro* test? **YES** ➔ **NO** ⬇	Classify as corrosive. If discrimination between Skin Corr. 1A/1B/1C is not possible, Skin Corr. 1 must be chosen.
5b	Are there acceptable data from a validated *in vitro* test (adopted by OECD or not), which provide evidence that the mixture is an irritant or non-irritant? **YES** ➔ **NO** ⬇	Consider to classify accordingly (Skin Irrit. 2 or no classification). Proceed to step 5c
5c	Are there data from a suitable *in vitro* test, which provide sound conclusive evidence that the mixture is an irritant? **YES** ➔	Consider to classify as Skin Irrit. 2.

	NO 🡻	Proceed to step 6
6	Taking all existing and relevant data (steps 1-5) into account including potential synergistic/antagonistic effects and bioavailability, is there sufficient information to make a decision on classification? **YES** ➔ **NO** 🡻	Classify accordingly (Skin Corr. 1A or Skin Corr. 1B or Skin Corr. 1C or Skin Irrit. 2 or no classification**)**
2. When data are not available for the complete mixture: bridging principles		
7a	Are existing sufficient skin corrosion/irritation data available on similar tested mixtures and on the individual ingredients? **NO** ➔ **YES** 🡻	Proceed to step 8
7b	Can bridging principles be applied? **YES** ➔ **NO** 🡻	Classify in appropriate category (Skin Corr. 1A or Skin Corr. 1B or Skin Corr. 1C or Skin Irrit. 2 or no classification)
3. When data are available for all components or only for some components of the mixture		
8a	Is pH of the mixture ≤ 2 or ≥ 11.5? **YES** ➔ **NO** 🡻	Follow decision logic in Section 3.2.3.2.1.1 and classify accordingly.
8b	Is there any indication that the additivity principle does not apply? **YES** ➔ **NO** 🡻	Annex I, section. 3.2.3.3.4 and Table 3.2.4 may apply. Take into account relevant ingredients (Annex I, 3.2.3.3.1. and SCLs as appropriate. Classify in appropriate category (Skin Corr. 1A/1B/1C or Skin Irrit. 2 or no classification)
	Annex I, section 3.2.3.3.2 and Table 3.2.3 applies. Take into account relevant ingredients (Annex I, 3.2.3.3.1. and SCLs as appropriate. Classify in appropriate category (Skin Corr. 1A/1B/1C or Skin Irrit. 2 or no classification)	Where the mixture is classified as corrosive but the data used for classification does not allow differentiation between the skin corrosion subcategories 1A/1B/1C, then the mixture should be assigned Skin corrosion Category 1.

3.2.4 Hazard communication in form of labelling for skin corrosion/irritation

3.2.4.1 Pictograms, signal words, hazard statements and precautionary statements

Annex I: 3.2.4.1. Label elements shall be used for substances or mixtures meeting the criteria for classification in this hazard class in accordance with Table 3.2.5.

Table3.2.5 **Label elements for skin corrosion/irritation**		
Classification	Category 1A / 1B / 1C	Category 2
GHS Pictograms		
Signal Word	Danger	Warning
Hazard Statement	H314: Causes severe skin burns and eye damage	H315: Causes skin irritation
Precautionary Statement Prevention	P260 P264 P280	P264 P280
Precautionary Statement Response	P301 + P330 + P331 P303 + P361 + P353 P363 P304 + P340 P310 P321 P305 + P351 + P338	P302 + P352 P321 P332 + P313 P362
Precautionary Statement Storage	P405	
Precautionary Statement Disposal	P501	

3.2.4.2 Additional labelling provisions

Annex II: 1.2.6. *EUH071 — Corrosive to the respiratory tract*
For substances and mixtures in addition to classification for inhalation toxicity, if data are available that indicate that the mechanism of toxicity is corrosivity, in accordance with section 3.1.2.3.3 and Note 1 of Table 3.1.3 in Annex I.

For substances and mixtures in addition to classification for skin corrosivity, if no acute inhalation test data are available and which may be inhaled.

Corrosive substances (and mixtures) may be acutely toxic after inhalation to a varying degree, which is only occasionally proved by testing. In case no acute inhalation study is available for a corrosive substance (or mixture) and such substance (or mixture) may be inhaled, a hazard of respiratory tract corrosion may exist. As a consequence, substances and mixtures have to be supplementary labelled with EUH071. Moreover, in such a case it is strongly recommended to apply the precautionary statement P260: "Do not breathe dust/fume/gas/mist/vapours/spray."

Annex II: 1.2.4. *EUH066 — Repeated exposure may cause skin dryness or cracking*
For substances and mixtures which may cause concern as a result of skin dryness, flaking or cracking but which do not meet the criteria for skin irritancy in section 3.2 of Annex I, based on either:
— practical observations; or
— relevant evidence concerning their predicted effects on the skin.

3.2.5 Re-classification of substances and mixtures classified for skin corrosion/irritation according to DSD and DPD

3.2.5.1 Is direct "translation" of classification and labelling possible?

A direct translation as indicated in the translation table in Annex VII to CLP is generally possible. Translation from classification according to DSD or DPD to the classification according to CLP is as follows:

- C; R35 is translated into Skin Corr. 1A; H314. The criteria in CLP and in DSD are identical.
- C; R34 is translated into Skin Corr. 1B; H 314 with the following note:

Annex VII: *Table 1.1*

Note 2
It is recommended to classify in Category 1B even if it also could be possible that 1C could be applicable for certain cases. Going back to original data, may not result in a possibility to distinguish between Category 1B or 1C, since the exposure period has normally been up to 4 hours according to Regulation (EC) No 440/2008. However, for the future, when data are derived from tests following a sequential approach as foreseen in the Regulation (EC) No 440/2008, Category 1C should be considered.

- Xi; R38 is translated into Skin Irrit. 2; H315. The criteria in CLP and DSD are almost identical.

It should be noted that where mixtures containing substances with risk phrase R34 have been classified on basis of the hazards of individual ingredients, the use of the translation table may lead to an under-classification of the mixture. This is because the general concentration limits, to be applied for mixtures, are lowered under CLP compared to DPD. For mixtures containing substances with this classification the use of the translation table may therefore not be appropriate and re-classification done by using the existing data would be more correct. For more details see Chapter 1.7.

3.2.5.2 Re-evaluation of data

If there is new information which might be relevant with respect to classification a re-evaluation has to be performed.

3.2.6 Examples of classification for skin corrosion/irritation

3.2.6.1 Examples of substances fulfilling the criteria for classification

3.2.6.1.1 Example 1: Standard test according to OECD TG 404 with three animals

In a guideline test according to OECD TG 404 the test substance was applied for three minutes and 1 hour. No scars or other irreversible effects were found. The scoring results obtained after 4 hours application time are listed in the following table:

Animal Nr.	Degree of erythema after …[observation time]						Degree of oedema after …[observation time]						**<u>∅ 24/48/72 h ≥2.3 ?</u>**	
	1h	24h	48 h	72 h	7d	14d	1h	24h	48 h	72 h	7d	14d	Erythe-ma	Oede-ma

1	3	3	3	2	0		1	2	2	2	0		Yes	No
		∅ 24/48/72 h = 2.7						**∅ 24/48/72 h = 2.0**					=>"positive Responder"	
2	3	3	3	3	0		1	2	2	1	0		Yes	No
		∅ 24/48/72 h = 3						**∅ 24/48/72 h = 1.7**					=>"positive Responder"	
3	1	1	1	0	0		1	1	1	1	0		No	No
		∅ 24/48/72 h = 0,66						**∅ 24/48/72 h = 1**						

Classification: Skin Irritant Category 2

The classification is made on basis of 2/3 "positive responder" exceeding 2.3 mean score for erythema.

3.2.6.1.2 Example 2: Test carried out with one animal with a test substance which is suspected as corrosive

Due to the unprecedented structure the biological effects of the substance cannot be anticipated. Therefore, the test according to OECD TG 404 was started with one animal only in line with testing restrictions. Exposure times were 3 min and 1h. The following scores/effects were observed:

Exposure time	Degree of erythema after ……[observation time]					Degree of oedema after ……[observation time]					Visible necrosis, irreversible skin damage
	1h	24h	48h	72h	...	1h	24h	48h	72h	...	After 14d
3 min	0	0	0	0		0	0	0	0		No
1h	0	1	2	3		0	2	2	3		Yes

Classification: Skin Corrosion Category 1B

Rationale for the classification is destruction of the tissue within 1 hour exposure.

3.2.6.1.3 Example 3a: Test carried out with more than three animals

A substance was tested on acute skin irritation / corrosion according to OECD TG 404. Contact time was 4 hours. No effects were seen after a contact time of 3 min and one hour. The following scores were obtained:

Animal Nr	Degree of erythema after …[observation time]						Degree of oedema after …[observation time]					
	1h	24h	48h	72h	7d	14d	1h	24h	48h	72h	7d	14d
1	3	3	2	2	1	0	2	3	2	2	1	0
2	3	2	2	2	1	0	2	2	2	2	1	0

3	2	2	1	1	1	0	2	2	2	2	1	0
4	2	2	1	1	1	0	2	2	2	2	1	0

Evaluation was made based on the arithmetic mean of all animals.

The arithmetic mean after 24/48/72 hours for erythema M_E= 21:12 = 1.8; and for oedema M_O = 25:12 = 2.1. Both values are below 2.3, i.e. no classification warranted for skin irritation.

3.2.6.1.4 Example 3b: Test carried out with more than three animals

A substance was tested on acute skin irritation / corrosion according to OECD TG 404. Contact time was 4 hours. No effects were seen after a contact time of 3 min and one hour. The following scores were obtained after a contact time of 4 hours:

	Observation time													
	1h	24h	48h	72h	7d	14d	1h	24h	48h	72h	7d	14d	Pos responder	
Animal Nr	Erythema						Oedema						Erythe-ma	Oed-ema
1	3	3	2	2	1	0	2	3	2	2	1	0	Yes	Yes
2	3	2	2	2	1	0	2	2	2	2	1	0	No	No
3	2	2	1	1	1	0	2	2	2	2	1	0	No	No
4	2	2	1	1	1	0	2	2	2	2	1	0	No	No

Evaluation was made based on the average score per animal.

Only 1/4 of the animals reached the cut-off value of 2.3, i.e. only animal No 1 is a positive responder. No classification is warranted with regard to skin irritation.

3.2.6.2 Examples of mixtures fulfilling the criteria for classification

Where the mixture is made up of ingredients with no assigned SCLs, then the appropriate summation(s) and generic concentration limits from CLP Annex I, Table 3.2.3 should be used.

3.2.6.2.1 Example 4

Ingredient	Skin corrosion / irritation classification	Concentration (% w/w)	SCL
Surfactant A	Skin Cat 2	1,8	Not assigned
Substance B	Not classified	0,5	
Substance C	Skin Cat 2	5,4	Not assigned
Substance D	Not classified	4	
Acid	Skin Cat 1A	2	Not assigned
Water	Not classified	86.3	

pH of the mixtureis is 9.0 – 10.0, thus extreme pH provisions do not apply. The mixture contains a surfactant and an acid but neither are corrosive/irritant below 1% (as identified by the absence of SCLs in either CLP Annex VI or the Classification and Labelling Inventory). Additivity is considered to apply.

Substance B, substance D and water can be disregarded as they are not classified for skin corrosion/irritation.

The mixture contains 2% acid, the only ingredient classified as Skin Corr. Cat 1. As this is below the 5% GCL, the mixture is not classified Skin Corr. Cat. 1 but is classified Skin Irrit. Cat. 2 (≥ 1% < 5%).

3.2.6.2.2 Example 5

Ingredient	Skin corrosion / irritation classification	Concentration (% w/w)	SCL
Surfactant A	Skin Cat 2	3,8	Not assigned
Substance B	Not classified	0,5	
Base E	Skin Cat 1B	5,4	C ≥ 10 %: Skin Cat 1B 5 % ≤ C < 10 %: Skin Cat 2
Substance D	Not classified	4	
Substance F	Skin Cat 1B	2	Not assigned
Water	Not classified	84.3	

pH of the mixture is 10.5 – 11.0, thus extreme pH provisions do not apply. The mixture contains a surfactant and a base but none are corrosive/irritant below 1% (as identified by absence of specific concentration limits in either CLP Annex VI or the Classification and Labelling Inventory). Additivity is considered to apply.

Substance B, substances D and water can be disregarded as they are not classified for skin corrosion/irritation.

SCLs are neither assigned to substance F nor surfactant A, thus GCLs apply for these ingredients. SCLs are assigned to Base E (see section 3.2.3.2.3.2 under *Application of SCLs when applying the additivity approach*).

Skin Cat 1:

(% substance F/GCL) + (% base E/SCL) = (2/5) + (5.4/10) = 0.94 ⇨ < 1, thus mixture is not classified as Skin Corr. Cat 1

Skin Cat 2:

(% substance F/GCL) + (% base E/SCL) + (% surfactant A/GCL) = (2/1) + (5.4/5) + (3.8/10) = 3.46 which is > 1, thus the mixture is classified Skin Irrit. Cat. 2

3.2.6.3 Examples of mixtures not fulfilling the criteria for classification

3.2.6.3.1 Example 6

Ingredient	Skin corrosion / irritation classification	Concentration (% w/w)	SCL
Surfactant C	Skin Cat 2	0,4	Not assigned
Surfactant G	Skin Cat 2	3.0	Not assigned
Surfactant A	Skin Cat 2	0,7	Not assigned
Substance H	Skin Cat 1A	3,0	C ≥ 70 %: Skin Cat 1A 50 % ≤ C < 70 %: Skin Cat 1B

			35 % ≤ C < 50 %: Skin Cat 2
Substance D	Not classified	2	
Water	Not classified	90.9	

pH of the mixture is: 2.5 – 3.0, thus extreme pH provisions do not apply. The mixture contains three surfactants but none are corrosive/irritant below 1% (as identified by the absence of specific concentration limits in either CLP Annex VI or the Classification and Labelling Inventory) Additivity is considered to apply.

Substance D and water can be disregarded as they are not classified for skin corrosion/irritation. Also surfactant C and surfactant A can be disregarded as both are present below 1%.

A SCL is not assigned to surfactant G, thus GCL apply for this ingredient.

Skin Cat 1:

The mixture contains 3% substance H, the only ingredient classified as Skin Corr. Cat. 1. As this is below the 50% SCL for substance H, the mixture is not classified as Skin Corr. Cat. 1.

Skin Cat 2:

(% substance H/SCL) + (% surfactant G/GCL) = (3/35) + (3/10) = 0.39 which is < 1, thus the mixture is not classified Skin Irrit. Cat. 2.

3.2.7 References

ECETOC (2002), Use of human data in hazard classification for irritation and sensitisation, Monograph No 32, Brussels ISSN 0773-6374-32

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Young J.R., How M.J., Walker A.P., Worth W.M.H. (1988): Classification as corrosive or irritant to skin of preparations containing acidic or alkaline substances, without test on animals. *Toxicology in Vitro* **2**, 19-26.

Young J.R., How M.J. (1994): Product classification as corrosive or irritant by measuring pH and acid / alkali reserve. In Alternative Methods in Toxicology vol. 10 - *In Vitro* Skin Toxicology: Irritation, Phototoxicity, Sensitization, eds. A.Rougier, A.M. Goldberg and H.I Maibach, Mary Ann Liebert, Inc. 23-27.

3.3 SERIOUS EYE DAMAGE/EYE IRRITATION

It should be noted that if a substance or mixture is classified as Skin corrosive Category 1 then serious damage to eyes is implicit and there is no need to proceed with classification for eye effects.

3.3.1 Definitions for classification for serious eye damage/eye irritation

Annex I: 3.3.1.1. Serious eye damage means the production of tissue damage in the eye, or serious physical decay of vision, following application of a test substance to the anterior surface of the eye, which is not fully reversible within 21 days of application.

Eye irritation means the production of changes in the eye following the application of test substance to the anterior surface of the eye, which are fully reversible within 21 days of application.

3.3.2 Classification of substances for serious eye damage/eye irritation

3.3.2.1 Identification of hazard information

3.3.2.1.1 Identification of human data

Existing data on eye effects in humans may include well-documented epidemiological studies, clinical studies, case reports, and data from poison information units and accident databases or occupational experience. Their quality and relevance for hazard assessment should be thoroughly reviewed. A critical review of the value of human studies is provided in IR/CSA Section R.4.3.3 and more specific considerations for eye damage/irritation are given in IR/CSA Section R.7.2.4.2.

3.3.2.1.2 Identification of non human data

Available serious eye damage/eye irritation information on substances may include existing data generated by the test methods in the Test Methods Regulation or by methods based on internationally recognised scientific principles.

Several of the following non-testing and *in vitro* methods have been validated against the DSD criteria but not against the CLP criteria for classification. Therefore it should be checked whether the method is sufficiently validated for classification according to CLP.

3.3.2.1.2.1 Consideration of physico-chemical properties

Substances with oxidising properties can give rise to highly exothermic reactions in contact with other substances and human tissue. High temperatures thus generated may damage/destroy biological materials. This applies, for example, to organic peroxides, which can be assumed to be eye irritants, unless evidence suggests otherwise (IR/CSA Section R.7.2.3.1).

For a hydro peroxide classification as Eye Damage Category 1 should be considered, whereas Eye Irritation Category 2 should be considered for peroxides. Appropriate evidence must be provided in order to consider non-classification of substances with oxidising properties.

3.3.2.1.2.2 Non-testing methods: (Q)SARs and expert systems

Non-testing methods such as (Q)SARs and expert systems may be considered on a case-by-case basis. (Q)SARs are in general not very specific for eye irritancy. In many cases rules are used in a similar manner to those used for skin irritation and corrosion. (Q)SAR systems that also account for eye effects are for example TOPKAT, Derek for Windows, and SICRET. For

full guidance, consult the IR/CSA Section R.6 ("QSAR and grouping of chemicals"), in which also the many shortcomings of the existing systems are discussed.

Since a formal adoption procedure for those non-testing methods is not foreseen and no formal validation process is in place, appropriate documentation is crucial. In order to achieve acceptance under REACH, the documentation must conform to the so-called QSAR Model Reporting Format (QMRF). For more details consult the IR/CSA Section R.6.1.

3.3.2.1.2.3 Testing-methods: pH and the acid/alkaline reserve

Annex I: 3.3.2.3. ….Likewise, pH extremes like ≤ 2 and ≥ 11,5 may produce serious eye damage, especially when associated with significant buffering capacity. Such substances are expected to produce significant effects on the eyes. Possible skin corrosion has to be evaluated prior to consideration of serious eye damage/eye irritation in order to avoid testing for local effects on eyes with skin corrosive substances…

Substances can be predicted to be corrosive, if the pH is ≤ 2 or ≥ 11.5. Where extreme pH is the only basis for classification as serious eye damage, it is important to take into consideration the acid/alkaline reserve, a measure of the buffering capacity (Young *et al*, 1988, and Young and How, 1994). However, lack of buffering capacity should not be used alone to exonerate from classification as corrosive.

If pH is < 3.2 or > 8.6, then consider the substance for severe eye damage/eye irritation (IR/CSA Section R.7.2.4.1). Further information and/or reasoning is needed to conclude whether the substance is causing severe eye damage or eye irritation. This model is not recommended for the stand-alone discrimination between eye irritants and non-irritants. However, it could be used in the context of a tiered testing strategy to identify eye irritants (due to its very low false positive rate) but not for non-irritants (due to its relatively high false negative rate).

3.3.2.1.2.4 Testing methods: *in vitro* methods

There are no OECD adopted *in-vitro*/*ex-vivo* tests for serious eye damage/eye irritation at present. However, there is regulatory acceptance in the EU that a substance can be considered a severe eye irritant (Serious eye damage Category 1) based on positive results in the Isolated Chicken Eye (ICE) test, the Bovine Corneal Opacity and Permeability (BCOP) test, the Isolated Rabbit Eye (IRE) test or the Hen's Egg Test on Chorio-allantoic Membrane (HET-CAM) test. Negative *in vitro* corrosivity responses in these tests must be followed by further testing (IR/CSA Section R.7.2.4.1)

There are no *in vitro* tests with regulatory acceptance for eye irritation at present, but the two human corneal epithelium models, EpiOcular™ and SkinEthic™, have been submitted to ECVAM for validation.

3.3.2.1.2.5 Testing methods: *In vivo* data

Testing for eye irritation would not be carried out on substances known or predicted to be corrosive to skin. Such substances are automatically considered to be severely damaging to the eye. A parallel classification with serious eye damage in addition to skin corrosion is not required.

The *in vivo* test in rabbits according to OECD TG 405 (B.5 in the Test Methods Regulation) is the standard test for the hazard assessment under the REACH.

The Low Volume Eye Test (LVET; Griffith *et al* 1980) is a modification of the standard OECD TG 405 test method, the differences being:

- the test material is placed directly on the cornea instead of introducing it in the conjunctival sac inside the lower lid;
- a reduction in the volume of test material applied (0.01 ml (or corresponding weight for solids) compared with the standard 0.1 ml).

Data from the LVET should be considered but must be carefully evaluated. The applicability domain up to now is limited to detergent and cleaning products. It is stated that positive data are a trigger for appropriate classification, but that negative data are not conclusive for a non-classification (IR/CSA R.7.2.4.1). However, they should be considered in a weight of evidence determination.

3.3.2.2 Classification criteria

Annex I: 3.3.2.6. *Irreversible effects on the eye/serious damage to eyes (Category 1)*

3.3.2.6.1. Substances that have the potential to seriously damage the eyes are classified in Category 1 (irreversible effects on the eye). Substances are classified in this hazard category on the basis of the results of animal testing, in accordance with the criteria listed in Table 3.3.1. These observations include animals with grade 4 cornea lesions and other severe reactions (e.g., destruction of cornea) observed at any time during the test, as well as persistent corneal opacity, discoloration of the cornea by a dye substance, adhesion, pannus, and interference with the function of the iris or other effects that impair sight. In this context, persistent lesions are considered those which are not fully reversible within an observation period of normally 21 days. Substances are also classified in Category 1 if they fulfil the criteria of corneal opacity ≥ 3 or iritis > 1,5 detected in a Draize eye test with rabbits, recognising that such severe lesions usually do not reverse within a 21 days observation period.

Table 3.3.1
Category for irreversible eye effects

Category	Criteria
Irreversible effects on the eye (Category 1)	If, when applied to the eye of an animal, a substance produces: – at least in one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days; and/or – at least in 2 of 3 tested animals, a positive response of: – corneal opacity ≥ 3 and/or – iritis > 1.5 calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material.

Annex I: 3.3.2.7. *Reversible effects on the eye (Category 2)*

3.3.2.7.1. Substances that have the potential to induce reversible eye irritation are classified in Category 2 (irritating to eyes).

Table 3.3 2
Category for reversible eye effects

Category	Criteria
Irritating to eyes (Category 2)	if, when applied to the eye of an animal, a substance produces: – at least in 2 of 3 tested animals, a positive response of: – corneal opacity ≥ 1 and/or – iritis ≥ 1, and/or – conjunctival redness ≥ 2 and/or

	– conjunctival oedema (chemosis) ≥ 2 – calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material, and which fully reverses within an observation period of 21 days
3.3.2.7.2. For those substances where there is pronounced variability among animal responses, this information shall be taken into account in determining the classification	

The classification criteria apply to the results of the OECD TG 405 and to the results of the LVET. Negative data from the LVET are not conclusive for non-classification, but should be considered in a weight of evidence determination.

3.3.2.3 Evaluation of hazard information

Annex I: 3.3.2.5. A tiered approach to the evaluation of initial information shall be considered where applicable, while recognising that all elements may not be relevant in certain cases.

3.3.2.4. ….Although information may be gained from the evaluation of single parameters within a tier (e.g. caustic alkalis with extreme pH shall be considered as local corrosives), the totality of existing information shall be considered in making an overall weight of evidence determination, particularly when there is information available on some but not all parameters. Generally, primary emphasis shall be placed upon expert judgement, considering human experience with the substance, followed by the outcome of skin irritation testing and of well-validated alternative methods.

3.3.2.3.1 Evaluation of human data

Quality data on substance-induced eye irritation in humans are likely to be rare. Where human data are available, the usefulness of such data for classification purposes will depend on the extent to which the effect, and its magnitude, can be reliably attributed to the substance of interest. The quality and relevance of such data for hazard assessment should be critically reviewed.

If a substance is diagnostically confirmed by a physician to be the cause for decay in vision with the effects not being transient but persistent this should lead to the most serious eye classification, i.e. Eye Damage Category 1.

Further information on the evaluation of human data for eye irritation can be found in IR/CSA Section R7.2.4.2.

3.3.2.3.2 Evaluation of non-human data

The results of the non-testing methods fulfilling the criteria of REACH Annex XI paragraphs 1.3 and 1.5 should be used instead of testing or as part of the weight of evidence approach.

3.3.2.3.2.1 In-vitro data

Only positive results in the BCOP, ICE, IRE and HET-CAM *in vitro* assays can be used for classification as severe eye irritants. Negative results are not conclusive for a non-classification.

There are currently no validated *in vitro* eye irritation test methods available. However, two reconstituted human tissue models (the EpiOcular™ and SkinEthic™ HCE models) are undergoing formal validation.

3.3.2.3.2.2 In-vivo data

Tests in albino rabbits (OECD TG 405)

Evaluation criteria for local effects on the eye are *severity* of the damage and *reversibility*.

For the *severity* of damage the degree of inflammation is assessed. Responses are graded according to the grading of ocular lesions in OECD TG 405.

Evaluation takes place separately for cornea, iris and conjunctiva (erythema and swelling). If the scoring meets the criteria in Annex I, Tables 3.3.1 / 3.3.2, the substances are classified as Category 1 for serious eye damage or Category 2 for eye irritation, respectively.

Reversibility of eye lesions is the other decisive factor in evaluating responses in the animal test. If the effects are not transient within the observation time of 21 days but cause persistent damage, they are considered irreversible and the test substance needs to be classified into Category 1. In the case of studies with a shorter observation period with irreversible effects, classification based on expert judgement should be considered.

With regard to reversibility the test report must prove that these effects are transient, i.e. the affected sites are repaired within the observation period of the test (see Example 1). Evaluation of reversibility or irreversibility of the observed effects does not need to exceed 21 days after instillation for the purpose of classification.

According to OECD TG 405, in cases of suspected serious eye damage, the test is started with one animal only. If effects in this animal are irreversible until the end of the observation period, sufficient information is available to classify the substance for serious eye damage. For a decision on no classification for serious eye damage and/or irritation or for a decision on classification as irritant, two additional animals have to be tested.

For each of the three test animals the average scores for three consecutive days (usually 24, 48 and 72 hours) are calculated separately for the cornea, iris and conjunctiva (erythema and swelling). If the mean scores for 2 out of 3 animals exceed the values in Tables 3.3.1 / 3.3.2, classification has to be assigned accordingly.

Tests that have been conducted with more than three animals

Older test methods, however, have been using up to six rabbits. The CLP does not provide criteria for the evaluation of such studies. The current US EPA/UN Recommendation may be considered (see Example 2):

*In case of **6** rabbits the following applies:*

Classification as serious eye damage – Category 1 if at least in one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days; and/or

at least 4 out of 6 rabbits show a mean score of

≥ 3 for the cornea and/or

≥ 1.5 for the iris

Classification as eye irritation – Category 2 if at least 4 out of 6 rabbits show a mean score of

≥ 1 for the cornea and/or

≥ 1 for the iris and/or

≥ 2 conjunctival erythema and/or

≥ 2 conjunctival swelling

*In case of **5** rabbits the following applies:*

Classification as serious eye damage – Category 1 if at least in one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days; and/or

at least 3 out of 5 rabbits show a mean score of

≥ 3 for the cornea and/or

≥ 1.5 for the iris

Classification as eye irritation – Category 2 if at least 3 out of 5 rabbits show a mean score of

≥ 1 for the cornea and/or

≥ 1 for the iris and/or

≥ 2 conjunctival erythema and/or

≥ 2 conjunctival swelling

*In case of **4** rabbits the following applies:*

Classification as serious eye damage – Category 1 if at least in one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days; and/or

at least 3 out of 4 rabbits show a mean score of

≥ 3 for the cornea and/or

≥ 1.5 for the iris

Classification as eye irritation – Category 2 if at least 3 out of 4 rabbits show a mean score of

≥ 1 for the cornea and/or

≥ 1 for the iris and/or

≥ 2 conjunctival erythema and/or

≥ 2 conjunctival swelling

In this case the irritant categories 1 and 2 are used if 4 of 6 rabbits show a mean score as outlined in the criteria. Likewise, if the test was performed with 4 or 5 animals, for at least 3 individuals the mean score must exceed the values laid down in the classification criteria. A single animal showing irreversible or otherwise serious effects consistent with corrosion will necessitate classification as serious eye damage Category 1 irrespective of the number of animals used in the test.

Other animal tests

The LVET uses the same scoring system as for results from the OECD TG 405, but data from the test is not .conclusive for a non-classification. However, they can be included in a weight of evidence determination.

Note that in case there are test data that originate from non-OECD tests and scoring has not been performed according to the Draize system, the values in Annex I, Tables 3.3.1 / 3.3.2 are no longer applicable for classification purposes. However these data from non-OECD tests should be considered in a weight of evidence determination.

3.3.2.3.3 Weight of evidence

Where the criteria cannot be applied directly to available identified information, a weight of the evidence determination using expert judgement shall be applied in accordance with CLP Article 9(3).

A weight of the evidence determination means that all available and scientifically justified information bearing on the determination of hazard is considered together, such as human experience (including occupational data and data from accident databases, epidemiological and clinical studies, and well-documented case reports and observations), relevant animal data, skin irritation information/data, physico-chemical parameters (e.g., pH, reserve alkalinity/acidity), the results of suitable *in vitro* tests, information from the application of the category approach (grouping, read-across), QSAR results. The quality and consistency of the data shall be given appropriate weight. Both positive and negative results shall be assembled together in a single weight of evidence determination. Evaluation must be performed on a case-by-case basis and with expert judgement. However, normally positive results that are adequate for classification should not be overruled by negative findings.

Annex I: 1.1.1.4. For the purpose of classification for health hazards (Part 3) established hazardous effects seen in appropriate animal studies or from human experience that are consistent with the criteria for classification shall normally justify classification. Where evidence is available from both humans and animals and there is a conflict between the findings, the quality and reliability of the evidence from both sources shall be evaluated in order to resolve the question of classification. Generally, adequate, reliable and representative data on humans (including epidemiological studies, scientifically valid case studies as specified in this Annex or statistically backed experience) shall have precedence over other data. However, even well-designed and conducted epidemiological studies may lack a sufficient number of subjects to detect relatively rare but still significant effects, to assess potentially confounding factors. Therefore, positive results from well-conducted animal studies are not necessarily negated by the lack of positive human experience but require an assessment of the robustness, quality and statistical power of both the human animal data.

For further guidance, if both human and animal data are available, see IR/CSA Section R.7.2.3.2.

3.3.2.4 Decision on classification

A skin corrosive substance is considered to also cause serious eye damage which is indicated in the hazard statement for skin corrosion (H 314: Causes severe skin burns and eye damage). Thus, in case a substance has to be classified for skin corrosion an additional classification with H318 “Causes serious eye damage” is not indicated.

3.3.2.5 Setting of 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.

It is more difficult to prove the absence of a hazardous property, the legal text states that:

Article 10(1)

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.

A specific concentration limit (SCL) set in accordance with the above mentioned provisions shall take precedence over the generic concentration limit (GCL) set out in Tables 3.2.3 and 3.2.4 of Annex I to CLP (Article 10(6)). Furthermore, an SCL is substance-specific and should be applicable to all mixtures containing the substance, instead of any GCL that otherwise would apply to a mixture containing the substance.

What type of information may be the basis for setting a specific concentration limit?

Existing human data may in certain cases (especially if dose-response information is available) indicate that the threshold for the irritation hazard in humans for a substance in a mixture, would be higher or lower than the GCL. A careful evaluation of the usefulness and the validity of such human data as well as their representativeness and predictive value (IR/CSA, sections R.4.3.3. and R.7.2.4.2) should be performed. As pointed out in Section 1.1.1.4 of Annex I, CLP, positive results from well-conducted animal studies are not necessarily negated by the lack of positive human experience but require an assessment of robustness, quality and a degree of statistical certainty of both the human and animal data.

The aim of the standard test method for "Acute Eye Irritation/Corrosion" TM B.5/OECD TG 405[47] is to **identify** potential serious eye damage or eye irritation. The test material is generally administered undiluted. Thus, no dose-response relationship can be obtained from an individual test.

However, if there are adequate, reliable, relevant and conclusive existing data from other already performed animal studies with a sufficient number of animals tested to ensure a high degree of certainty, and with information of dose-response relationships, such data may be considered for setting a lower or, in exceptional cases, a higher SCL on a case-by-case basis.

It should be noted that any additional animal testing to set SCLs (of dilutions) of substances already classified as causing serious eye damage or as an eye irritant, is strongly discouraged and may only take place on a case-by-case basis if there are no alternatives providing adequate reliability and quality of data (see CLP Articles 7(1) and 8(1)). The possibilities to use *in vitro* test methods as a basis for setting SCLs have not yet been explored and therefore, at the present point in time, it is not possible to provide guidance for the use of *in vitro* methods for the purpose of setting SCLs. However, this does not exclude that a method to set SCLs based on *in vitro* tests could be developed in the future, and these tests may provide a promising option for SCL setting.

An SCL should apply to any mixture containing the substance instead of the GCL (that otherwise would apply to the mixture containing the substance). Thus, if the SCL is based on data derived from tests with dilutions of the substance in a specific solvent, it has to be considered that the derived concentration, should be applicable to all mixtures for which the SCL should apply.

Annex VI Part 3 (Table 3.2) to CLP Regulation includes examples of substances for which a higher or lower SCL was set under Directive 67/548/EEC (old Dangerous Substances Directive (DSD) system).

[47] TO NOTE: In OECD TG 404 the term test substance refers to the test material, test article or test item. The term substance may be used differently from the REACH/CLP definition.

3.3.2.6 Decision logic

The decision logic which is based on IR/CSA Figure R.7.2-3 is revised to meet CLP requirements. It is strongly recommended that the person responsible for classification, study the criteria for classification before and during use of the decision logic.

Step		
0	Is the substance classified as a skin corrosive? **YES** ➔ **NO** ⬇	When classified as Skin Corr. 1, the risk of severe damage to eyes is considered implicit. No need to proceed.
1a	Is the substance an organic hydro peroxide or an organic peroxide? **YES** ➔ **NO** ⬇	– Consider to classify as serious eye damage (Eye Dam. 1) if the substance is a hydro peroxide, or – eye irritating (Eye Irrit. 2) if the substance is a peroxide. OR Provide evidence for the contrary and proceed to step 1b
1b	Is the pH of the substance ≤ 2 or ≥ 11.5? **YES** ➔ **NO** ⬇	– Where classification is based upon consideration of pH alone (i.e. buffering capacity not known), Eye Dam. 1 should be applied. When assigned Skin Corr. 1, the risk of severe damage to eyes is considered implicit. – Where consideration of the alkali/alkaline reserve suggests that the substance is not corrosive, this has to be confirmed (preferably by use of an appropriate *in vitro* test). Proceed to step 1c
1c	Are there other physical or chemical properties that indicate that the substance has the potential to cause serious eye damage or is irritating to the eye? **YES** ➔ **NO** ⬇	Use this information for weight of evidence (WoE) determination (step 6). Proceed to step 2
2	Is there adequate existing human experience which provides evidence that the substance has the potential to cause serious eye damage or is irritating to the eye? **YES** ➔ **NO** ⬇	Classify accordingly (Eye Dam. 1 or Eye Irrit. 2).
3	Are there data from existing studies *on eye irritation* in laboratory animals, which provide sound conclusive evidence that the substance has the potential to cause serious eye damage, is an eye irritant or non-irritant?	Classify accordingly (Eye Dam. 1 or Eye Irrit. 2 or no classification).

	YES ➔ **NO** ⬇	
4	Are there structurally related substances (suitable "read-across" or grouping), which are classified as serious eye damage or eye irritant, or do valid QSAR methods indicate the presence/absence of serious eye damage/eye irritation potential of the substance? **YES** ➔ **NO** ⬇	Consider to classify accordingly (Eye Dam. 1 or Eye Irrit. 2). If discrimination between Eye Dam. 1 and Eye Irrit. 2 is not possible, Eye Dam. 1 must be chosen. Proceed to step 5a
5a	Are there data from a validated *in vitro* test (adopted by OECD or not), which provide evidence that the substance is an eye irritant or non-irritant? **YES** ➔ **NO** ⬇	Consider to classify accordingly (Eye Dam. 1 or Eye Irrit. 2 or no classification). If discrimination between Eye Dam. 1 and Eye Irrit. 2 is not possible, Eye Cat. 1 must be chosen. Proceed to step 5b
5b	Are there acceptable data from a suitable *in vitro* test, which provide evidence that the substance is a severe eye irritant? **YES** ➔ **NO** ⬇	Consider to classify as Eye Dam. 1. Proceed to step 6
6	Taking all existing and relevant data) into account, is there sufficient information to make a decision on classification? **YES** ➔ **NO** ⬇	Classify accordingly (Eye Dam. 1 or Eye Irrit. 2 or no classification).
	Unable to classify substance for serious eye damage/eye irritation	Decision to undertake generation of new test data should be made in compliance with REACH and Article 8 of the CLP. It is recommended that ECHA guidance R.7.2.6 should also be considered.

3.3.3 Classification of mixtures for serious eye damage/eye irritation

3.3.3.1 Identification of hazard information

The procedure for classifying mixtures is a tiered i.e. a stepwise approach based on a hierarchy principle and depending on the type and amount of available data/information starting from evaluating existing human data on the mixture, followed by a thorough examination of the existing *in vivo* data, physico-chemical properties, and finally *in vitro* data available on the mixture. If valid test data are available for the whole mixture they have precedence. If no such data exist, the so called bridging principles have to be applied if possible. If the bridging principles are not applicable an assessment on the basis of data for the components of the mixture will be applied.

Where it is decided to base the classification of a mixture upon consideration of pH alone, Eye Damage Category 1 should be applied. In this case no further retrieval of information on the mixture itself is needed.

3.3.3.1.1 Identification of existing human data

For mixtures that have been on the market for a long time, some human data and experience may exist that could provide useful information on the eye irritation potential of the respective mixtures. However, lack of data on effects in humans may be due to, for example, poor reporting or adequate preventive measures. Therefore, lack of data cannot be taken as evidence of the mixture being non-hazardous. See Section 3.3.2.1.1 for further information on the identification of human data.

3.3.3.2 Classification criteria

3.3.3.2.1 When data are available for the complete mixture

Annex I: 3.3.3.1.1. The mixture will be classified using the criteria for substances, and taking into account the testing and evaluation strategies used to develop data for these hazard classes.

Unlike other hazard classes, there are alternative tests available for skin corrosivity of certain types of mixtures that give an accurate result for classification purposes, as well as being simple and relatively inexpensive to perform. When considering testing of the mixture classifiers are encouraged to use a tiered weight of evidence strategy as included in the criteria for classification of substances for skin corrosion and serious eye damage and eye irritation to help ensure an accurate classification, as well as avoid unnecessary animal testing. A mixture is considered to cause serious eye damage (Category 1) if it has a pH $\leq$ 2.0 or $\geq$ 11.5. If consideration of alkali/acid reserve suggests the mixture may not have the potential to cause serious eye damage despite the low or high pH value, then further testing needs to be carried out to confirm this, preferably by use of an appropriate validated in vitro test.

Where the criteria cannot be applied directly to available identified information, a weight of the evidence determination using expert judgement shall be applied in accordance with CLP Article 9(3). A weight of the evidence determination means that all available and scientifically justified information bearing on the determination of hazard is considered together, such as physico-chemical parameters, the results of suitable *in vitro* tests, relevant animal data, and human experience. The quality and consistency of the data shall be given appropriate weight. Both positive and negative results shall be assembled together in a single weight of evidence determination.

The integration of all information to come to a final hazard assessment based on weight of evidence in general requires in-depth toxicological expertise.

There are a number of available *in vitro* test systems that currently being validated for their suitability in assessing serious eye damage/eye irritation potential of substances and mixtures. When validated *in vitro* eye irritation test methods are available in the future the results from such tests can be used for classification. Then these results can also be used to classify the mixture. However, not all available in vitro test systems work equally well for all types of mixtures. Prior to testing a mixture in a specific in vitro assay for classification purposes, it has to be assured that the respective test has been previously shown to be suitable for the prediction of serious eye damage/eye irritation properties for the type of mixture to be evaluated.

3.3.3.2.1.1 Mixtures with extreme pH

Where the mixture has an extreme pH value but the only corrosive/irritant ingredient present in the mixture is an acid or base with an assigned SCL (either CLP Annex VI or set by supplier), then the mixture should be classified accordingly. In this instance, pH of the mixture should not be considered a second time since it would have already been taken into account when deriving the SCL for the substance.

If this is not the case, then the steps to be taken into consideration when classifying a mixture with pH ≤ 2 or ≥ 11.5 are described in the following decision logic:

<table>
<tr><td colspan="2">Mixture not classified as Skin Corr. 1 and without in vivo data on serious eye damage/eye irritation or relevant data from similar tested mixtures.
pH is ≤ 2 or ≥ 11.5</td></tr>
<tr><td>Does the acid/alkaline reserve indicate that the mixture may not be corrosive? NO ➔

YES
🡻</td><td>Classify as serious eye damaging, Eye Dam. 1.</td></tr>
<tr><td>Is the mixture tested for serious eye damaging properties in an accepted in vitro test? NO ➔

YES
🡻</td><td>Classify as serious eye damaging, Eye Dam. 1.</td></tr>
<tr><td>Does the mixture demonstrate serious eye damaging properties in an accepted in vitro test?
YES ➔
NO
🡻</td><td>Classify as serious eye damaging, Eye Dam. 1.</td></tr>
<tr><td>Apply methods in Annex I, 3.3.3.3.2 (Table 3.3.3) / 3.3.3.3.4 (Table 3.3.4) ➔
(When validated in vitro eye irritation test methods are available, these may be used to generate data to classify the mixture instead of using the summation method.)</td><td>Classify accordingly.</td></tr>
</table>

If consideration of extreme pH and acid/alkaline reserve indicates the mixture may not have the potential to cause serious eye damage, then the supplier should carry out further testing to confirm this (Annex I, Section 3.3.3.2.1). The mixture must be classified as Serious eye damage Category 1 if the supplier decide not to carry out the required confirmatory testing.

If further testing confirms that the mixture should not be classified for serious eye damage effects, then the supplier should assess the mixture for eye irritation either using *in vitro* eye irritation test methods when available or the summation method.

It must be note that the pH-acid/alkali reserve method assumes that the potential corrosivity or irritancy is due to the effect of the ionic entities. When this is not the case, especially when the mixture contains non-ionic (non-ionisable) substances themselves classified as corrosive or irritant, then the pH-reserve method cannot be a basis for modifying the classification.

Where the mixture has an extreme pH value and contains some other corrosive/irritant ingredients (some of which may have SCLs assigned) in addition to an acid or base with or without an assigned SCL, then the mixture shall follow the procedure described in the decision logic.

3.3.3.2.2 When data are not available for the complete mixture: bridging principles

Annex I: 3.3.3.2.1. Where the mixture itself has not been tested to determine its skin corrosivity or potential to cause serious eye damage or irritation, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterise the hazards of the mixture, these data shall be used in accordance with the bridging rules set out in section 1.1.3.

In order to apply bridging principles, there needs to be sufficient data on similar tested mixtures as well as the components of the mixture.

When the available identified information is inappropriate for the application of the bridging principles then the mixture should be classified using the methods described in Section 1.1.3.2.3.

3.3.3.2.3 When data are available for all components or only for some components of the mixture

3.3.3.2.3.1 Components that should be taken into account for the purpose of classification

Annex I: 3.3.3.3.1. ….. Assumption: The 'relevant ingredients' of a mixture are those which are present in concentrations of 1% (w/w for solids, liquids, dusts, mists and vapours and v/v for gases) or greater, unless there is a presumption (e.g. in the case of corrosive ingredients) that an ingredient present at a concentration of less than 1% is still relevant for classifying the mixture for eye irritation/serious eye damage.

3.3.3.2.3.2 The additivity approach is applicable

Annex I: 3.3.3.3.2. In general, the approach to classification of mixtures as eye irritant or seriously damaging to the eye when data are available on the components, but not on the mixture as a whole, is based on the theory of additivity, such that each corrosive or irritant component contributes to the overall irritant or corrosive properties of the mixture in proportion to its potency and concentration. A weighting factor of 10 is used for corrosive components when they are present at a concentration below the generic concentration limit for classification in Category 1, but are at a concentration that will contribute to the classification of the mixture as an irritant. The mixture is classified as seriously damaging to the eye or eye irritant when the sum of the concentrations of such components exceeds a concentration limit.

3.3.3.3.3. Table 3.3.3 provides the generic concentration limits to be used to determine if the mixture shall be classified as irritant or as seriously damaging to the eye.

When the supplier is unable to derive the classification using either data on the mixture itself or bridging principles, he must determine the serious eye damage/ eye irritation properties of his mixture using data on the individual ingredients. The supplier must ascertain whether the additivity approach is applicable, the first step in the process being to identify all the ingredients in the mixture (i.e. their name, chemical type, concentration level, hazard classification and any SCLs) and the pH of the mixture. In addition, for example surfactant interaction or neutralisation of acids/bases could occur in a mixture, which makes it important to consider not only the contribution of individual ingredients but also the effects of the entire mixture

Additivity may not apply where the mixture contains substances mentioned in Annex I, 3.3.3.3.4.1 which may be corrosive/irritant at concentrations below 1%, see Section 3.3.3.2.3.3.

Application of SCLs when applying the additivity approach

The generic concentration limits are specified in Table 3.3.3. However, Article 10.5 indicates that specific concentration limits (SCLs) take precedence over generic concentration limits. Thus, if a given substance has a SCL, then this specific concentration limit has to be taken into account when applying the summation (additivity) method for serious eye damage/eye irritation (see Examples 4 and 5).

In cases where additivity applies for serious eye damage/eye irritation to a mixture with two or more substances some of which may have SCLs assigned, then the following formula should be used:

The mixture is classified for serious eye damage/eye irritation if the

Sum of (ConcA / clA) + (ConcB / clB) + ….+ (ConcZ / clZ) is ≥ 1

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

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

ConcB = the concentration of substance B in the mixture;

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

This approach is similar to that used in the DPD where a substance SCL can replace the default limits in the conventional method equations.

3.3.3.2.3.3 The additivity approach is not applicable

Annex I; 3.3.3.3.4.1. Particular care must be taken when classifying certain types of mixtures containing substances such as acids and bases, inorganic salts, aldehydes, phenols, and surfactants. The approach explained in paragraphs 3.3.3.3.1 and 3.3.3.3.2 might not work given that many of such substances are corrosive or irritant at concentrations < 1 %.

3.3.3.3.4.2. For mixtures containing strong acids or bases the pH shall be used as classification criteria (see paragraph 3.3.2.3) since pH will be a better indicator of serious eye damage than the generic concentration limits of Table 3.3.3.

3.3.3.3.4.3. A mixture containing corrosive or irritant ingredients that cannot be classified based on the additivity approach (Table 3.3.3), due to chemical characteristics that make this approach unworkable, shall be classified as Category 1 for effects on the eye if it contains ≥ 1 % of a corrosive ingredient and as Category 2 when it contains ≥ 3 % of an irritant ingredient. Classification of mixtures with ingredients for which the approach in Table 3.3.3 does not apply is summarised in Table 3.3.4.

3.3.3.3.5. On occasion, reliable data may show that the reversible/irreversible eye effects of an ingredient will not be evident when present at a level above the generic concentration limits mentioned in Tables 3.3.3 and 3.3.4. In these cases the mixture shall be classified according to those data. On other occasions, when it is expected that the skin corrosion/irritation hazards or the reversible/irreversible eye effects of an ingredient will not be evident when present at a level above the generic concentration limits mentioned in Tables 3.3.3 and 3.3.4, testing of the mixture shall be considered. In those cases, the tiered weight of evidence strategy shall be applied.

3.3.3.3.6. If there are data showing that (an) ingredient(s) may be corrosive or irritant at a concentration of < 1 % (corrosive) or < 3 % (irritant), the mixture shall be classified accordingly.

3.3.3.3 Generic concentration limits for substances triggering classification of mixtures

3.3.3.3.1 When the additivity approach is applicable

Annex I: *Table 3.3.3* **Generic concentration limits of ingredients of a mixture classified as Skin corrosive Category 1 and/or eye Category 1 or 2 for effects on the eye that trigger classification of the mixture for effects on the eye (Category 1 or 2)**		
Sum of ingredients classified as:	Concentration triggering classification of a mixture as:	
	Irreversible Eye Effects	Reversible Eye Effects
	Category 1	Category 2
Eye effects Category 1 or Skin corrosive Category 1A, 1B, 1C	≥ 3 %	≥ 1 % but < 3 %
Eye Effects Category 2		≥ 10 %
(10 x Eye Effects Category 1) + Eye effects Category 2		≥ 10 %
Skin Corrosive Category 1A, 1B, 1C + Eye effects Category 1	≥ 3 %	≥ 1 % but < 3 %
10 x (Skin corrosive Category 1A, 1B, 1C + Eye Effects Category 1) + Eye Effects Category 2		≥ 10 %

3.3.3.3.2 When the additivity approach is not applicable

Annex I: *Table 3.3.4* **Generic concentration limits of ingredients of a mixture for which the additivity approach does not apply, that trigger classification of the mixture as hazardous to the eye**		
Ingredient	Concentration	Mixture classified as: Eye
Acid with pH ≤ 2	≥ 1%	Category 1
Base with pH ≥ 11,5	≥ 1%	Category 1
Other corrosive (Categories 1) ingredients for which additivity does not apply	≥ 1%	Category 1
Other irritant (Category 2) ingredients for which additivity does not apply, including acids and bases	≥ 3%	Category 2

There are ongoing discussions at UN level whether 'Other irritant (Category 2) ingredients' in Table 3.3.4 (last row) include skin and eye irritants or only eye irritants.

3.3.3.4 Decision logic

The decision logic which is based on IR/CSA Figure R.7.2-3 is revised to meet CLP requirements. It is strongly recommended that the person responsible for classification, study the criteria for classification before and during use of the decision logic.

1. When data are available for the complete mixture		
0	Is the mixture classified as a skin corrosive? **YES ➔** **NO** **🡻**	When assigned Skin Corr. 1, the risk of severe damage to eyes is considered implicit. No need to proceed.
1a	Is the pH of the mixture ≤ 2 or ≥ 11.5? **YES ➔** **NO** **🡻**	– Where classification is based upon consideration of pH alone (i.e. buffering capacity not known), Eye Dam. 1 should be applied. When assigned Skin Corr. 1, the risk of severe damage to eyes is considered implicit. – Where consideration of the acid/alkaline reserve suggests that the substance is not corrosive, this has to be confirmed (preferably by use of an appropriate in vitro test). Proceed to step 1b.
1b	Are there other physical or chemical properties that indicate that the mixture has the potential to cause serious eye damage or is irritating to the eye? **YES ➔** **NO** **🡻**	Use this information for weight of evidence (WoE) determination (step 6). Proceed to step 2.
2	Are there adequate existing human experience data which provide evidence that the mixture has the potential to cause serious eye damage or is irritating to the eye? **YES ➔** **NO** **🡻**	Classify accordingly (Eye Dam. 1 or Skin Irrit. 2).
3	Are there data from existing studies *on eye irritation* in laboratory animals, which provide sound conclusive evidence that the mixture has the potential to cause serious eye damage, is an eye irritant or non-irritant? **YES ➔** **NO** **🡻**	Classify accordingly (Eye Dam. 1 or Eye Irrit. 2 or no classification).
4a	Are there data from a validated *in vitro* or *ex vivo* test (adopted by OECD or not), which provide evidence that the mixture is an eye irritant or non-irritant? **YES ➔** **NO** **🡻**	Consider to classify accordingly (Eye Dam. 1 or Eye Irrit. 2 or no classification). If discrimination between Eye Dam. 1 and Eye Irrit. 2 is not possible, Eye Dam. 1 must be chosen. Proceed to step 4b
4b	Are there acceptable data from a suitable *in vitro* test, which provide evidence that the mixture is an irritant to the eye? **YES ➔** **NO**	Consider to classify accordingly (Eye Dam. 1 or Eye Irrit. 2). If discrimination between Eye Dam. 1 and Eye Irrit. 2 is not possible, Eye Dam. 1 must be chosen.

	↓	Proceed to step 5
5	Taking all existing and relevant data (steps 1-4) into account including potential synergistic/antagonistic effects and bioavailability, is there sufficient information to make a decision on classification? **YES** → **NO** ↓	Classify accordingly (Eye Dam. 1 or Eye Irrit. 2 or no classification)
2. When data are not available for the complete mixture: bridging principles		
6a	Are existing eye irritation data available on similar tested mixtures and on the individual ingredients? **NO** → **YES** ↓	Proceed to step 7a
6b	Can bridging principles be applied? **YES** → **NO** ↓	Classify in appropriate category (Eye Dam. 1 or Eye Irrit. 2 or no classification)
3. When data are available for all components or only for some components of the mixture		
7a	Is pH of the mixture ≤ 2 or ≥ 11.5? **YES** → **NO** ↓	Follow decision logic in Section 3.3.3.2.1.1 and classify accordingly.
7b	Is there any indication that the additivity principle does not apply? **YES** → **NO** ↓	Section 3.3.3.3.4 and Table 3.3.4 may apply. Take relevant ingredients (Annex I, 3.2.3.3.1) and SCLs into account, as appropriate. Classify in appropriate category (Eye Dam. 1 or Eye Irrit. 2 or no classification)
	Section. 3.3.3.3.2 and Table 3.3.3 applies. Take relevant ingredients (Annex I, 3.2.3.3.1) and SCLs into account, as appropriate. Classify in appropriate category (Eye Dam. 1 or Eye Irrit. 2 or no classification).	

3.3.4 Hazard communication in form of labelling for serious eye damage/eye irritation

3.3.4.1 Pictograms, signal words, hazard statements and precautionary statements

Annex I; 3.3.4.1 Label elements shall be used for substances or mixtures meeting the criteria for classification in this hazard class in accordance with Table 3.3.5.

Table3.3.5
Label elements for serious eye damage/eye irritation

Classification	Category 1	Category 2
GHS Pictograms		
Signal Word	Danger	Warning
Hazard Statement	H318: Causes serious eye damage	H319: Causes serious eye irritation
Precautionary Statement Prevention	P280	P264 P280
Precautionary Statement Response	P305 + P351 + P338 P310	P305 + P351 + P338 P337 + P313
Precautionary Statement Storage		
Precautionary Statement Disposal		

A skin corrosive mixture is considered to also cause serious eye damage which is indicated in the hazard statement for skin corrosion, H 314: Causes severe skin burns and eye damage. Thus, in case a mixture has to be classified for skin corrosion an additional classification with H318: Causes serious eye damage is not indicated.

3.3.5 Re-classification of substances and mixtures classified for serious eye damage/eye irritation according to DSD and DPD

3.3.5.1 Is direct “translation” of classification and labelling possible?

A direct translation as indicated in the translation table in Annex VII to CLP is generally possible. However, an evaluation and classification must be carried out in accordance with CLP Articles 9 – 13 when data for the mixture are available. Translation from classification according to DSD to the classification according to CLP is as follows:

- Xi; R41 is translated into Eye Dam. 1; H318. The criteria in DSD are completely covered by the criteria in CLP.
- Xi; R36 is translated into Eye Irrit. 2; H 319. The criteria in DSD are completely covered by the criteria in CLP.

It should be noted that CLP eye irritation Category 2 will include more substances which are currently not classified under the DSD, but with values of cornea opacity >1 and <2 or values of conjunctival redness >2 and < 2.5, will be classified as eye irritants under CLP.

It should be noted that where mixtures containing substances with risk phrase R41 have been classified on basis of the hazards of individual ingredients, the use of the translation table may lead to an under-classification of the mixture. This is because the general concentration limits, to be applied for mixtures, are lowered under CLP compared to DPD. For mixtures containing substances with this classification the use of the translation table may therefore not be appropriate and re-classification done by using the existing data would be more correct. For more details see Chapter 1.7.

3.3.5.2 Re-evaluation of data

If there is new information which might be relevant with respect to classification a re-evaluation has to be performed.

3.3.6 Examples of classification for serious eye damage/eye irritation

3.3.6.1 Examples of substances fulfilling the criteria for classification

3.3.6.1.1 Example 1: Standard test according to OECD TG 405 with three animals

In a study according to OECD 405 the test substance was applied on the eyes of three rabbits. The scoring results obtained are listed in the following table:

Cornea:

Animal Nr	Evaluation after …					**Positive responder?** ∅ Score …	
	1 hr	24 hrs	48 hrs	72 hrs	21 days	≥ 1	≥ 3
1	0	2	2	2	0		
		∅ 24/48/72 h animal 1 is 2				Yes	No
2	2	2	2	2	0		
		∅ 24/48/72 h animal 2 is 2				Yes	No
3	2	2	1	1	0		
		∅ 24/48/72 h animal 3 is 1.3				Yes	No

Effects are reversible

Iris:

Animal Nr	Evaluation after …					**Positive responder?** ∅ Score …	
	1 hr	24 hrs	48 hrs	72 hrs	21 days	≥ 1	≥ 1,5
1	0	1	1	1	0		
		∅ 24/48/72 h animal 1 is 1				Yes	No
2	1	1	1	1	0		

		∅ 24/48/72 h animal 2 is 1				Yes	No
3	1	1	1	1	0		
		∅ 24/48/72 h animal 3 is 1				Yes	No

Effects are reversible

Conjunctiva – Erythema:

Animal #	Evaluation after …					**Positive responder?** ∅ Score …	
	1 hr	24 hrs	48 hrs	72 hrs	21 days	≥ 2	
1	2	2	2	2	0		
		∅ 24/48/72 h animal 1 is 2				Yes	
2	1	1	1	1	0		
		∅ 24/48/72 h animal 2 is 1				No	
3	1	1	1	1	0		
		∅ 24/48/72 h animal 3 is 1				No	

Effects are reversible

Conjunctiva – Swelling:

Animal #	Evaluation after …					**Positive responder?** ∅ Score …	
	1 hr	24 hrs	48 hrs	72 hrs	21 days	≥ 2	
1	0	3	3	3	0		
		∅ 24/48/72 h animal 1 is 3				Yes	
2	2	2	2	1	0		
		∅ 24/48/72 h animal 2 is 1.7				No	
3	2	3	2	2	0		
		∅ 24/48/72 h animal 3 is 2.3				Yes	

Effects are reversible

Classification according to CLP: Eye irritant Category 2

Rationale: Cornea and Conjunctiva ”positive responder” ≥ 2: 2/3 animals

Iris ”positive responder” ≥ 1: 3/3 animals

3.3.6.1.2 Example 2: Test carried out with more than 3 rabbits

Cornea:

Animal No.	Evaluation after …							**Positive responder?** ∅ Score …	
	1h	24h	48h	72h	7d	14d	21d	≥ 3	≥ 1
1	1	2	3	3	1	1	0		
		∅ 24/48/72h = 2.7						no	yes
2	1	2	2	3	1	1	0		
		∅ 24/48/72h = 2.3						no	yes
3	1	2	3	3	2	1	0		
		∅ 24/48/72h = 2.7						no	yes
4	1	2	4	4	2	1	0		
		∅ 24/48/72h = 3.3						yes	yes

Effects are reversible

Iris:

Animal No.	Evaluation after …							**Positive responder?** ∅ Score …	
	1h	24h	48h	72h	7d	14d	21d	≥ 1.5	≥ 1
1	0	0	0	0	0	0	0		
		∅ 24/48/72h = 0						no	no
2	0	0	0	0	0	0	0		
		∅ 24/48/72h = 0						no	no
3	0	1	1	1	1	0	0		
		∅ 24/48/72h = 1						no	yes
4	0	0	0	0	0	0	0		
		∅ 24/48/72h = 0						no	no

Effects are reversible

Conjunctiva – Erythema:

Animal No.	Evaluation after …							**Positive responder?** ∅ Score …	
	1h	24h	48h	72h	7d	14d	21d	≥ 2	

1	2	2	2	1	1	1	0		
		∅ 24/48/72h = 1.7						no	
2	2	2	2	1	1	0	0		
		∅ 24/48/72h = 1.7						no	
3	2	2	2	1	1	1	1		
		∅ 24/48/72h = 1.7						no	
4	2	2	2	1	0	0	0		
		∅ 24/48/72h = 1.7						no	

Effects are NON-reversible

Conjunctiva – Swelling:

Animal No.	Evaluation after …							**Positive responder?** ∅ Score …	
	1h	24h	48h	72h	7d	14d	21d	≥ 2	
1	2	2	2	1	1	1	0		
		∅ 24/48/72h = 1.7						no	
2	2	2	1	1	1	0	0		
		∅ 24/48/72h = 1.3						no	
3	2	2	2	1	1	1	1		
		∅ 24/48/72h = 1.7						no	
4	2	2	2	1	1	1	1		
		∅ 24/48/72h = 1.7						no	

Effects are NON-reversible

Classification according to CLP: Serious eye damage Category 1

Rationale: Conjunctiva with irreversible effects

3.3.6.2 Examples of mixtures fulfilling the criteria for classification

3.3.6.2.1 Example 3: Application of the additivity approach for mixtures containing ingredients without SCLs

Where the mixture is made up of ingredients with no assigned SCLs, then the appropriate summation(s) from Table 3.3.3 should be used.

Ingredient	Skin / eye classification	Concentration (% w/w)	SCL
Surfactant A	Eye Cat 1	1.8	Not assigned
Substance B	Eye Cat 2	0.5	Not assigned
Substance C	Eye Cat 1	5.4	Not assigned

Substance D	Not classified	4.0	
Acid E	Skin Cat 1A	2.0	Not assigned
Water	Not classified	86.3	

pH of the mixture is 9.0 – 10.0, thus extreme pH provisions do not apply. The mixture contains a surfactant and an acid but neither are corrosive/irritant below 1% (as identified by the absence of specific concentration limits in either CLP Annex VI or the Classification and Labelling Inventory). Additivity is considered to apply.
Substance D and water can be disregarded as they are not classified for serious eye damage/eye irritation. Substance B can also be disregarded as present below 1%.

Mixture contains 7.2% Eye Cat 1 ingredients as well as 2% acid E so the summation {Skin corrosion Cat 1A, 1B, 1C + Eye Cat 1} applies and is > 3%, thus mixture is classified Eye Cat 1.

3.3.6.2.2 Example 4: Application of the additivity approach for mixtures containing ingredients which may have SCLs

Ingredient	Skin / eye classification	Concentration (% w/w)	SCL
Surfactant A	Eye Cat 1	2.0	Not assigned
Substance B	Eye Cat 2	0.5	Not assigned
Substance C	Skin Cat 1B	5.4	C ≥ 10 %: Skin Cat 1B 5 % ≤ C < 10 %: Eye Cat 2
Substance D	Not classified	4.0	
Substance E	Skin Cat 1B	2.0	Not assigned
Water	Not classified	86.1	

pH of the mixture is 10.5 – 11.0, thus extreme pH provisions do not apply. The mixture contains a surfactant, an acid and a base but none are corrosive/irritant below 1% (as identified by the absence of specific concentration limits in either CLP Annex VI or the Classification and Labelling Inventory). Additivity is considered to apply.

Substance D and water can be disregarded as they are not classified for serious eye damage/eye irritation. Substance B can also be disregarded as present below 1%.

SCLs are not assigned to substance E or surfactant A, thus generic concentration limits (GCL) apply for these ingredients

Eye Cat 1

(% surfactant A / GCL) + (% Substance C / SCL) + (% Substance E / GCL) = (2/3) + (5.4/10) + (2/3) = 1.9 ⇨ > 1 thus mixture is classified Eye Cat 1

3.3.6.2.3 Example 5: Application of the additivity approach for mixtures containing ingredients which may have SCLs

Ingredient	Serious eye damage/ eye irritation classification	Concentration (% w/w)	SCL
Surfactant B	Eye Cat 1	0.7	Not assigned
Substance C	Eye Cat 2	74.9	Not assigned
Substance D	Eye Cat 1	8.5	C ≥ 25 %: Eye Cat 1

			10 % ≤ C < 25 %: Eye Cat 2
Substance E	Not classified	15.9	

pH of the mixture is 10.0 – 10.5 (10% solution), thus extreme pH provisions do not apply. The mixture contains a surfactant which is not corrosive/irritant below 1% (as identified by the absence of specific concentration limits in either CLP Annex VI or the Classification and Labelling Inventory). Additivity is considered to apply.

Substance E can be disregarded as it is not classified for serious eye damage/eye irritation. Surfactant B can also be disregarded as present below 1%.

SCLs are not assigned to substance C, thus GCL apply for this ingredient

Eye Cat 1

Mixture contains 8.5% substance D, the only 'relevant' ingredient classified as Eye Cat 1. As this is below the 25% SCL for substance D, the mixture is not classified Eye Cat 1

Eye Cat 2

(%substance D/ SCL) + (%substance C / GCL) = (8.5/10) + (74.9/10) which is > 1 thus mixture is classified Eye Cat 2

3.3.7 References

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3.4 RESPIRATORY OR SKIN SENSITISATION

3.4.1 Definitions and general considerations for respiratory or skin sensitisation

Annex I: 3.4.1.1. Respiratory sensitiser means a substance that will lead to hypersensitivity of the airways following inhalation of the substance.

3.4.1.2. Skin sensitiser means a substance that will lead to an allergic response following skin contact.

In terms of prevention it might be important to note that respiratory sensitisation may be induced not only by inhalation but also by skin contact.

Annex I: 3.4.1.3. For the purpose of section 3.4, sensitisation includes two phases: the first phase is induction of specialised immunological memory in an individual by exposure to an allergen. The second phase is elicitation, i.e. production of a cell-mediated or antibody-mediated allergic response by exposure of a sensitised individual to an allergen.

3.4.1.4. For respiratory sensitisation, the pattern of induction followed by elicitation phases is shared in common with skin sensitisation. For skin sensitisation, an induction phase is required in which the immune system learns to react; clinical symptoms can then arise when subsequent exposure is sufficient to elicit a visible skin reaction (elicitation phase). As a consequence, predictive tests usually follow this pattern in which there is an induction phase, the response to which is measured by a standardised elicitation phase, typically involving a patch test. The local lymph node assay is the exception, directly measuring the induction response. Evidence of skin sensitisation in humans normally is assessed by a diagnostic patch test.

3.4.1.5. Usually, for both skin and respiratory sensitisation, lower levels are necessary for elicitation than are required for induction. Provisions for alerting sensitised individuals to the presence of a particular sensitiser in a mixture can be found at section 3.4.4.

3.4.1.6. The hazard class Respiratory or Skin Sensitisation is differentiated into:

- Respiratory Sensitisation;
- Skin Sensitisation.

3.4.2 Classification of substances for respiratory or skin sensitisation

3.4.2.1 Identification of hazard information

There are no formally recognised and validated animal tests for respiratory sensitisation. However there may be data from human observation indicating respiratory sensitisation in exposed populations.

With respect to identification of relevant information for skin sensitisation see IR/CSA, Section R.7.3.3.

3.4.2.1.1 Identification of human data

Relevant information with respect to respiratory or skin sensitisation may be available from case reports, epidemiological studies, medical surveillance and reporting schemes. For more details see IR/CSA, Section R.7.3.3.2.

3.4.2.1.2 Identification of non human data

At present no validated non-testing systems exist to predict skin sensitising potential. The chemical structure of a molecule, when similar to that of known sensitisers, may form part of the weight of evidence for classification (see also IR/CSA, Section R.7.3.3).

The subject of *in vitro* testing for skin sensitisation has also been dealt with in IR/CSA, Section R.7.3.3. At present no validated *in vitro* methods exist to identify the sensitising potential of a chemical.

There are three animal test methods used to evaluate skin sensitisation for substances: the mouse local lymph node assay (LLNA), the guinea pig maximisation test (GPMT) and the Buehler occluded patch test. They are further described in IR/CSA, Section R.7.3.3, and in the context of classification in Section 3.4.2.3.4.

3.4.2.2 Classification criteria for substances

Annex I: 3.4.2.1. Respiratory sensitisers

Substances shall be classified as respiratory sensitisers (Category 1) in accordance with the criteria in Table 3.4.1:

Table 3.4.1

Hazard category for respiratory sensitisers

Category	Criteria
Category 1	Substances shall be classified as respiratory sensitisers (Category 1) in accordance with the following criteria: (a) if there is evidence in humans that the substance can lead to specific respiratory hypersensitivity and /or (b) if there are positive results from an appropriate animal test.

3.4.2.2. *Skin Sensitisers*

3.4.2.2.1. Substances shall be classified as skin sensitisers (Category 1) in accordance with criteria in Table 3.4.2:

Table 3.4.2

Hazard category for skin sensitisers

Category	Criteria
Category 1	Substances shall be classified as skin sensitisers (Category 1) in accordance with the following criteria: (i) if there is evidence in humans that the substance can lead to sensitisation by skin contact in a substantial number of persons, or (ii) if there are positive results from an appropriate animal test (see specific criteria in paragraph 3.4.2.2.4.1).

3.4.2.3 Evaluation of hazard information

3.4.2.3.1 Human data on respiratory sensitisation

Substances shall be classified as respiratory sensitisers if there is evidence in humans that the substance can lead to specific respiratory hypersensitivity.

3.4.2.3.2 Human data on skin sensitisation

Annex I: 3.4.2.2.2.1. For classification of a substance as a skin sensitiser, evidence shall include any or all of the following:

(a) positive data from patch testing, normally obtained in more than one dermatology clinic;
(b) epidemiological studies showing allergic contact dermatitis caused by the substance; Situations in which a high proportion of those exposed exhibit characteristic symptoms are to be looked at with special concern, even if the number of cases is small;
…
(d) positive data from experimental studies on humans (see Article 7(3));
(e) well documented episodes of allergic contact dermatitis, normally obtained in more than one dermatology clinic.

3.4.2.3.3 Non human data on respiratory sensitisation

No formally recognised and validated animal tests currently exist for respiratory sensitisation.

3.4.2.3.4 Non human data on skin sensitisation

Currently CLP allows classification of skin sensitisers in only one hazard category. Since it is possible to refine the evaluation of skin sensitisers on the basis of the potency of the sensitising effect, this guidance advises how to evaluate the potency on the basis of the recommended test methods. The potency considerations may be used as a basis for setting specific concentration limits (see Section 3.4.2.5) and it is also concluded in the GHS that this potency consideration will be included as further classification criteria in the future.

There are currently three recognised and officially accepted animal test methods for skin sensitisation defined by OECD Test Guidelines. These are the Mouse Local lymph Node Assay (LLNA), Guinea Pig Maximisation Test by Magnusson & Kligman (GPMT) and the Buehler occluded patch test in the guinea pig. The mouse and guinea pig methods differ fundamentally with respect to the endpoints used; whereas the mouse LLNA measures the responses provoked during the induction of sensitisation, the two guinea pig tests measure challenge induced elicitation reactions in previously sensitised animals. For new testing of substances the LLNA is now the method of first choice. In the exceptional circumstance that the LLNA is not appropriate, one of the alternative tests may be used (Buehler or GPMT), but justification shall be provided (see IR/CSA, Section R.7.3.2.1).

Test results from the LLNA, GPMT and the Buehler test could be used directly for classification. They may also be used for potency evaluation.

A sensitising potential of a substance is identified if a significant effect has been obtained in an acceptable *in vivo* test. A significant skin sensitising effect in each of the three recognised animal tests is defined as follows:

Table 3.4.2.3.4: *Definition of significant skin sensitising effect*

Test	Result
Mouse local lymph node assay (LLNA)	Stimulation Index ≥ 3
Guinea pig maximisation test (GPMT)	Redness in ≥ 30% of the test animals
Buehler occluded patch test	Redness in ≥ 15% of the test animals

A substance may be classified a skin sensitiser on the basis of a positive test result in one of the above described animal tests. A positive result obtained by another not officially recognised test method may also justify classification as a skin sensitiser, but can normally not overrule a negative result obtained in one of the three recognised, above described animal tests. A new animal study should not be conducted in an attempt to negate a clearly positive response in a not officially recognised test method particularly where there is other supporting evidence that the substance is a skin sensitiser.

3.4.2.3.4.1 Mouse Local Lymph Node Assay (LLNA, OECD TG 429)

The LLNA is used both for determination of skin sensitising potential (hazard identification) and for determination of relative skin sensitisation potency (hazard characterisation). In both instances the metric is cellular proliferation induced in draining lymph nodes following topical exposure to a chemical, lymph node cell proliferation being causally and quantitatively correlated with the acquisition of skin sensitisation (Basketter *et al*. 2002a, 2002b). A correlation has been demonstrated between the concentration of chemical required for the acquisition of skin sensitisation in humans according to historical predictive data and skin sensitisation potency as measured in the mouse LLNA (Schneider and Akkan 2004, Basketter *et al*. 2005b). Potency is measured as a function of derived EC3-values. The EC3-value is the amount of test chemical (% concentration, molar value or dose per unit area) required to elicit a stimulation index of 3 in the standard LLNA (Kimber *et al*. 2003). An

inverse relationship exists between EC3-value and potency meaning that extremely potent sensitisers have extremely low EC3-values. The relevance of potency derives from an appreciation that skin sensitisers vary by up to four or five orders of magnitude with respect to the minimum concentration required inducing skin sensitisation. Potency is graded on the basis of these minimum concentrations each grade reflecting a concentration range of approximately one order of magnitude.

The following scheme could be used for determination of potency categories for sensitisers. However, classification into potency categories is currently not a requirement in the classification of sensitisers.

Table 3.4.2.3.4.1: *Skin Sensitisation Potency in the Mouse Local Lymph Node Assay*

EC3-value (% w/v)	Potency
≤ 0.2	Extreme
> 0.2 - ≤ 2	Strong
> 2	Moderate

Potency may be considered when setting a specific concentration limit for a substance in mixtures (see Section 3.4.2.5).

3.4.2.3.4.2 Guinea Pig Maximisation Test (GPMT, OECD TG 406)

This test has been used for almost 40 years to detect the sensitising potential of chemicals through a test system maximizing the sensitivity by both intradermal and epidermal induction and use of an adjuvant (Freund's Complete Adjuvant). The intradermal induction is made by injection. Consequently the test is not suited for products which cannot be made up into a liquid formulation.

The GPMT was originally designed to maximise the ability to identify a sensitisation hazard, rather than to determine skin sensitisation potency. Yet, when only a GPMT test result is available, potency categorisation is possible on the basis of the concentration of test material used for intradermal induction and the percentage of guinea pigs sensitised. However, it should be recognised that there is often a degree of uncertainty associated with the derivation of allergenic potencies from the GPMT. If the test has been conducted in full compliance with OECD Test Guideline 406 and with the technical details ensuring proper data interpretation as specified by Schlede and Eppler (1995), the following scheme may be used.

The following scheme could be used for determination of potency categories for sensitisers. However, classification into potency categories is currently not a requirement in the classification of sensitisers.

Table 3.4.2.3.4.2: *Potency on basis of the Guinea Pig Maximisation Test*

Concentration for intradermal induction (% w/v)	Incidence sensitised guinea pigs (%)	Potency
≤ 0.1	≥ 60	Extreme
≤ 0.1	≥30 - <60	Strong
>0.1 - ≤1.0	≥60	Strong
>0.1 - ≤1.0	≥30 - <60	Moderate
> 1.0	≥ 30	Moderate

Potency may be considered when setting a specific concentration limit for a substance in mixtures (see Section 3.4.2.5).

3.4.2.3.4.3 Buehler occluded patch test (OECD TG 406)

This test has been in use for the last 40 years as a more realistic, although still a sensitive, test to detect skin sensitisers using epidermal occluded exposure. The skin barrier of the test species (guinea pig) is kept intact in this assay, thus providing for a more relevant exposure scenario for the human situation. Potency can be categorised using the results of the Buehler test on the basis of the number of animals sensitised and the concentration of the test material used for the epidermal induction. However, it should be recognised that there is often a degree of uncertainty associated with the derivation of allergenic potencies from the Buehler test. The following scheme could be used for determination of potency categories, if the test has been conducted in full compliance with OECD TG 406 and with the technical details ensuring proper data interpretation as specified by Robinson *et al* (1990).

Classification into potency categories is currently not a requirement in the classification of sensitisers.

Table 3.4.2.3.4.3: *Potency on basis of the Buehler Occluded Patch Test*

Concentration for intradermal induction (% w/v)	Incidence sensitised guinea pigs (%)	Potency
≤ 0.2	≥ 60	Extreme
≤ 0.2	≥15 - <60	Strong
>0.2 - ≤20	≥ 60	Strong
>0.2 - ≤20	≥15 - <60	Moderate
> 20	≥ 15	Moderate

Potency may be considered when setting a specific concentration limit for a substance in mixtures (see Section 3.4.2.5).

3.4.2.3.4.4 Non-compliant skin sensitisation tests

In vivo test methods which do not comply with recognised guidelines are strongly discouraged for the identification of skin sensitisers or assessment of skin sensitising potency. The results of such tests have to be evaluated carefully, but may provide supportive evidence. If doubts exist about the validity and the interpretation of the results, the evaluation needs to be taken by using a weight-of-evidence approach.

3.4.2.3.4.5 Animal test methods conducted for purposes other than sensitisation

Occasionally signs of skin sensitisation occur in repeated dose tests. These tests are often dermal toxicity tests on rats. Clearly, if signs of erythema/oedema occur in animals after repeated application, the possibility of skin sensitisation should be considered, and ideally assessed in an appropriate study.

3.4.2.3.5 Weight of evidence

Positive effects seen in either humans or animals for skin sensitisation will normally justify classification. Evidence from animal studies on skin sensitisation is usually more reliable than evidence from human exposure, although reliable human data is, of course, most relevant to man. In cases where evidence is available from both sources, and there is conflict between the results, the quality and reliability of the evidence from both sources must be assessed in order

to decide on the classification on a case-by-case basis. Negative human data should not normally negate positive findings in animal studies.

Since the data used in hazard or risk assessment should be relevant, reliable and sufficient for the regulatory purpose, it is necessary to base the assessment on the totality of available information, i.e. to apply Weight of Evidence (WoE) considerations.

The WoE assessment can be based on the total of experimental data, as well as post-market surveys and/or occupational experience data. In the case of mixtures, extrapolation from similar mixtures or from data available on the components may often provide reliable means of assessment. Estimated data might be used to supplement and increase confidence in the available experimental data, whereas in some others, such data might be used instead of experimental data.

WoE assessment can be divided into two stages:

a) Assessment of each single test result and, if needed, of other data. It may be helpful to apply criteria for reliability as defined by Klimisch *et al* (1997). These criteria include details on the recognition of the test method, reporting detail, method relevance, test parameters, etc.
b) Comparison of the weighed single test results.

Good quality data on the substance itself have more weight than such data extrapolated from similar substances.

3.4.2.4 Decision on classification

According to CLP Annex I, Section 3.4.2.1 substances fulfilling the criteria for respiratory sensitisation will be classified as such in Category 1, and according to CLP Annex I, Section 3.4.2.2 substances fulfilling the criteria for skin sensitisation will be classified as such in Category 1. In addition substances classified in Category 1 for skin sensitisation can be allocated specific concentration limits as described in Section 3.4.2.5.

3.4.2.5 Setting of specific concentration limits

Respiratory sensitisers cannot be identified reliably on the basis of animal tests as yet, since no recognised validated test exists to determine sensitising potential and potency by inhalation. Therefore specific concentration limits (SCLs) cannot be set on the basis of animal data. Moreover, there is no concept available to set SCLs on the basis of human data for respiratory sensitisers.

SCLs for skin sensitisation can be set based on the assumption that a substance can be categorised according to their skin sensitisation potency based on the results from animal testing as reported under Section 3.4.2.3.4.1, 3.4.2.3.4.2 and 3.4.2.3.4.3 above. SCL are set on the basis of testing of the substance and never on the basis of testing of a mixture containing the sensitising substance (see 3.4.3.1.1 of Annex I).

The generic concentration limit (GCL) for the classification of sensitisers in mixtures is 1% (CLP Annex I, Table 3.4.3). However, for certain sensitisers 1% is not sufficiently protective. Therefore a specific concentration limit (SCL) shall be set (CLP, Article 10) which will better reflect the hazard of mixtures containing that skin sensitiser.

SCLs shall be set when there is adequate and reliable scientific information available showing that the specific hazard is evident below the GCL, 1%, for classification. As such the SCL should normally be as suggested in Table 3.4.2.5. However, supported by reliable data the SCL could have some other value below 1%. Reliable data could be human data from e.g. work place studies where the exposure is defined.

It is more difficult to prove the absence of sensitising properties at certain concentration levels. Therefore an SCL above the GCL, 1%, may only be set in exceptional circumstances, if scientific information is adequate, reliable and conclusive for that particular skin sensitiser. However there is currently no guidance on how to set SCL above the GCL.

The concentration limits for skin sensitisers categorised according to their sensitisation potency in the Table 3.4.2.5 are recommendations from an EU expert group on skin sensitisation (Basketter *et al*., 2005a).

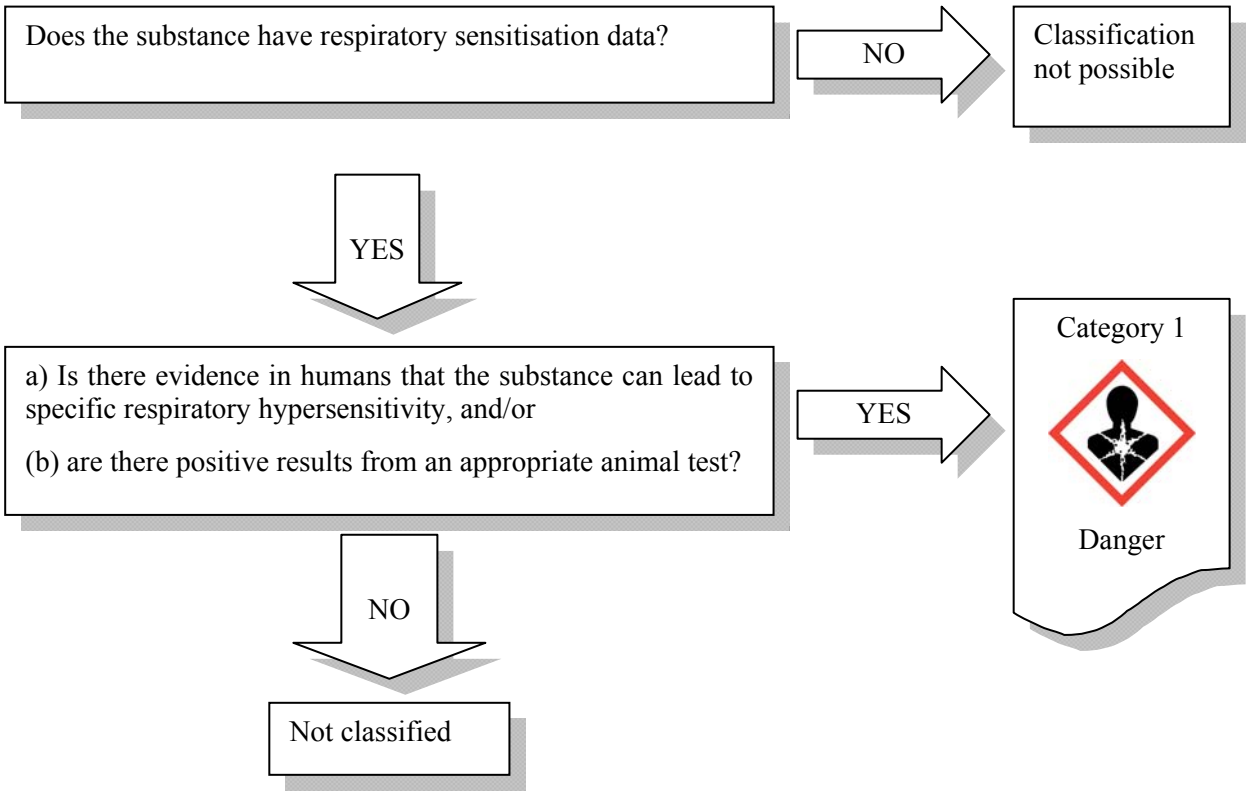
Table 3.4.2.5: Skin sensitising potency for substances and recommendations on specific concentration limits

Potency	Concentration Limit (% w/v)
Extreme	0.001 (SCL)
Strong	0.1 (SCL)
Moderate	1 (GCL)

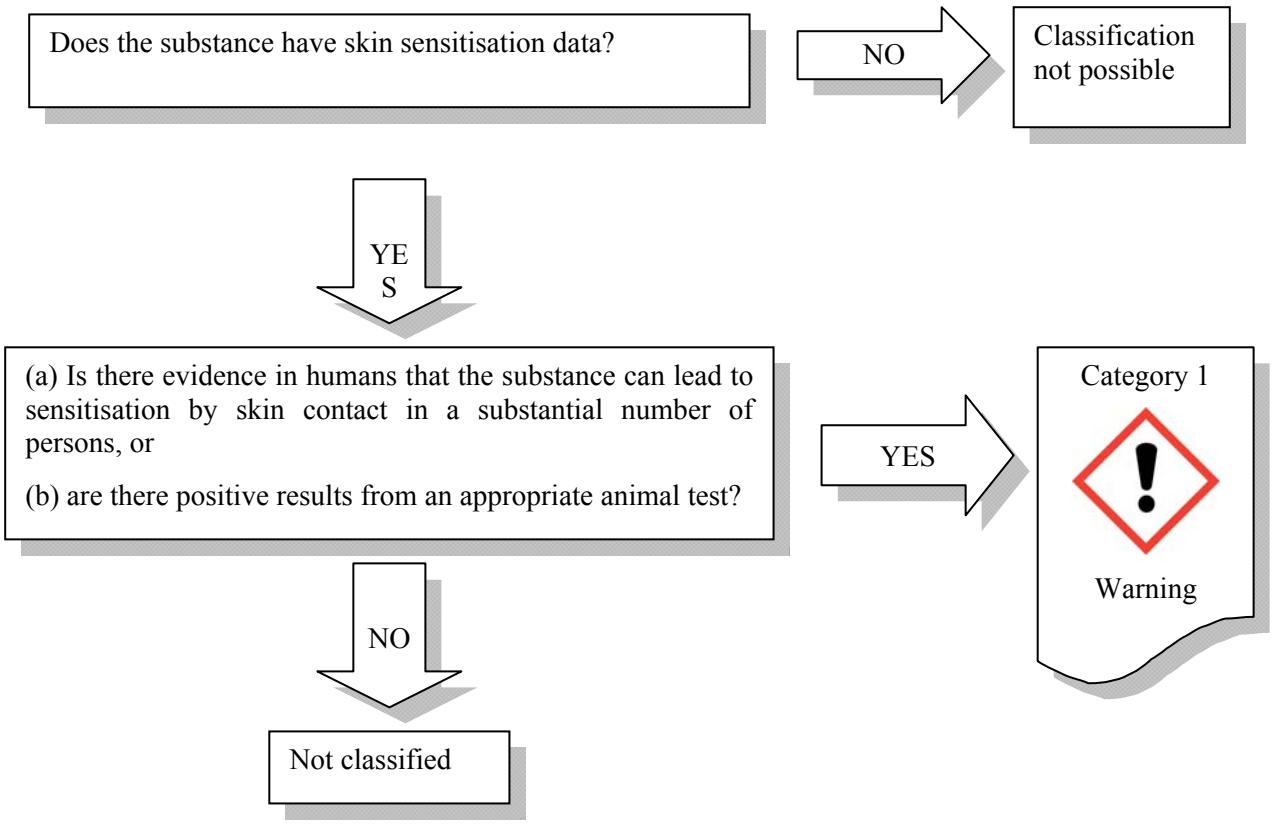
3.4.2.6 Decision logic for classification of substances

It is strongly recommended that the person responsible for classification study the criteria for classification before and during use of the decision logic.

Decision logic for respiratory sensitisation



Decision logic for skin sensitisation



3.4.3 Classification of mixtures for respiratory or skin sensitisation

3.4.3.1 General considerations for classification

The same principles apply as for substances (see Section 3.4.2).

3.4.3.2 Identification of hazard information for skin sensitisation

For identification of the sensitisation potential of a mixture the following information may be available:

(a) test results on one or more, preferably all of its potentially sensitising components; or
(b) test results on the mixture itself; or
(c) test results of a similar mixture.

Test methods are outlined in the Section 3.4.2.3.4. However, these animal tests have been developed to identify sensitising substances and not mixtures. Therefore the results obtained on mixtures need to be evaluated with care. For a mixture the cut-off in the mouse LLNA should be seen as a threshold for identification of a sensitiser rather than as a threshold for sensitisation. A conclusion on the absence of sensitising potential of a mixture based on the negative outcome in a test must be taken with great caution.

On the other hand test data on a mixture take into account effects of possible interactions of its components. For instance, it is known that presence of a vehicle may significantly influence the skin sensitising potency, by influencing the penetration of the sensitising component(s) through the skin, (Basketter *et al.* 2001, Dearman *et al*. 1996, Heylings *et al*. 1996) or through other mechanisms involved in the acquisition of sensitisation (Cumberbatch *et al*. 1993; Dearman *et al*. 1996).

Repeated exposure to mixtures, that are non-sensitising under standard LLNA exposure conditions, might induce skin sensitisation, if the sensitising component in this mixture has sufficient accumulation potential in the skin to reach the minimum concentration for a positive effect (De Jong et al. 2007). Uncertainty also exists about the effect of such mixture after exposure on a larger skin area. Therefore additional information is important, if the outcome of sensitisation tests on mixtures contrasts with the classification based on the content of sensitising component(s). For example, the validity of a well conducted LLNA on a mixture with a negative outcome can scientifically be confirmed by spiking the test mixture with another sensitiser (positive control) at different concentrations, or by showing a dose response relationship. Such LLNA tests could have been designed to provide such information without use of extra animals. Additional animal testing for the purpose of classification and labelling shall be undertaken only where no other alternatives, which provide adequate reliability and quality of data, are possible (CLP Article 7(1)).

3.4.3.3 Classification criteria

3.4.3.3.1 When data are available for all components or only for some components

Annex I: 3.4.3.3.1. The mixture shall be classified as a respiratory or skin sensitiser when at least one ingredient has been classified as a respiratory or skin sensitiser and is present at or above the appropriate generic concentration limit as shown in Table 3.4.3 below for solid/liquid and gas respectively.

3.4.3.3.2. Some substances that are classified as sensitisers may elicit a response, when present in a mixture in quantities below the concentrations established in Table 3.4.1, in individuals who are

already sensitised to the substance or mixture (see Note 1 to Table 3.4.3).

Table 3.4.3

Generic concentration limits of ingredients of a mixture classified as either skin sensitisers or respiratory sensitisers that trigger classification of the mixture

Ingredient classified as:	Concentration triggering classification of a mixture as:		
	Skin Sensitiser	Respiratory Sensitiser	
	All physical states	Solid/Liquid	Gas
Skin Sensitiser	≥ 0,1 % (Note 1)	–	–
	≥ 1,0 % (Note 2)	–	–
Respiratory Sensitiser	–	≥ 0,1 % (Note 1)	≥ 0,1 % (Note 1)
	–	≥ 1,0 % (Note 3)	≥ 0,2 % (Note 3)

Note 1
This concentration limit is generally used for the application of the special labelling requirements of Annex II section 2.8 to protect already sensitised individuals. A SDS is required for the mixture containing an ingredient above this concentration.

Note 2
This concentration limit is used to trigger classification of a mixture as a skin sensitiser.

Note 3
This concentration limit is used to trigger classification of a mixture as a respiratory sensitiser.

All sensitising components of a mixture at or above their generic or specific concentration limit should be taken into consideration for the purpose of classification. Specific concentration limits (see Section 3.4.2.5) will always take precedence over the generic concentration limits.

The additivity concept is not applicable for respiratory or skin sensitisation, i.e. if one single classified substance is present in the mixture above the generic concentration limit, the mixture must be classified for that hazard. If the mixture contains two substances each below the generic concentration limits, the mixture will not be classified, as far as no SCL has been set.

3.4.3.3.2 When data are available for the complete mixture

Annex I: 3.4.3.1.1. When reliable and good quality evidence from human experience or appropriate studies in experimental animals, as described in the criteria for substances, is available for the mixture, then the mixture can be classified by weight-of-evidence evaluation of these data. Care shall be exercised in evaluating data on mixtures, that the dose used does not render the results inconclusive.

In case classification of a mixture is based on test results for the mixture as a whole, this data must be shown to be conclusive. Especially it should be taken into account that in case of skin sensitisation current test methods are based on application of maximised dose, which only can be obtained using a substance by itself and not diluted in a mixture.

It is recognised that mixtures not showing sensitisation in a test, may still contain a low concentration of sensitising component.

For specific guidance on the test methods and evaluation of the results see Section 3.4.2.3.4, Section 3.4.3.1and CLP Annex I, 3.4.3.1.1.

3.4.3.3.3 When data are not available for the complete mixture: Bridging Principles

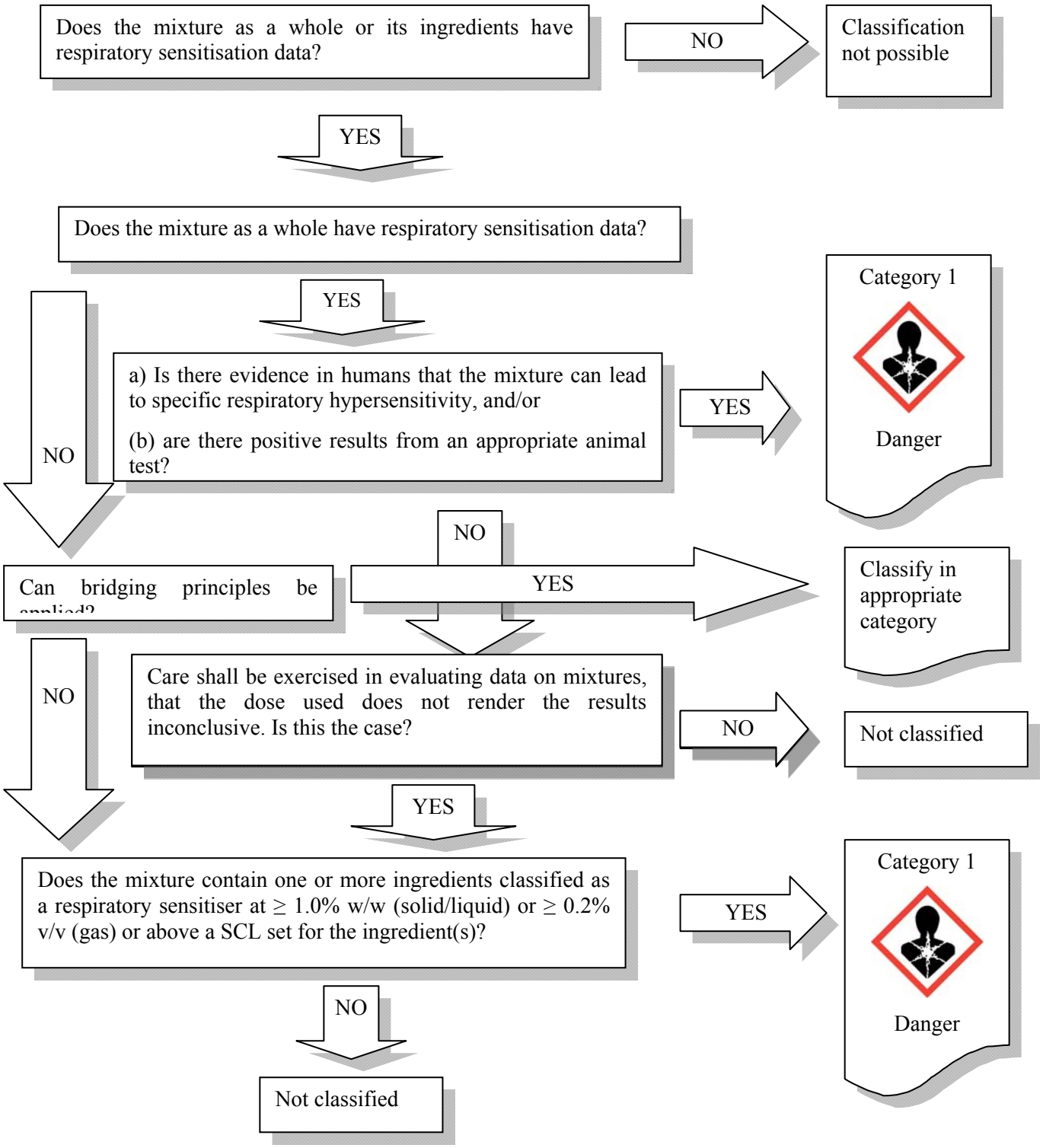
Annex I: 3.4.3.2.1. Where the mixture itself has not been tested to determine its sensitising properties, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterise the hazards of the mixture, these data shall be used in accordance with the bridging rules out in section 1.1.3.

In absence of a test on the mixture, data from tests on a similar mixture, i.e. containing the same sensitising component in a similar concentration, may be used for skin sensitising potential estimation.

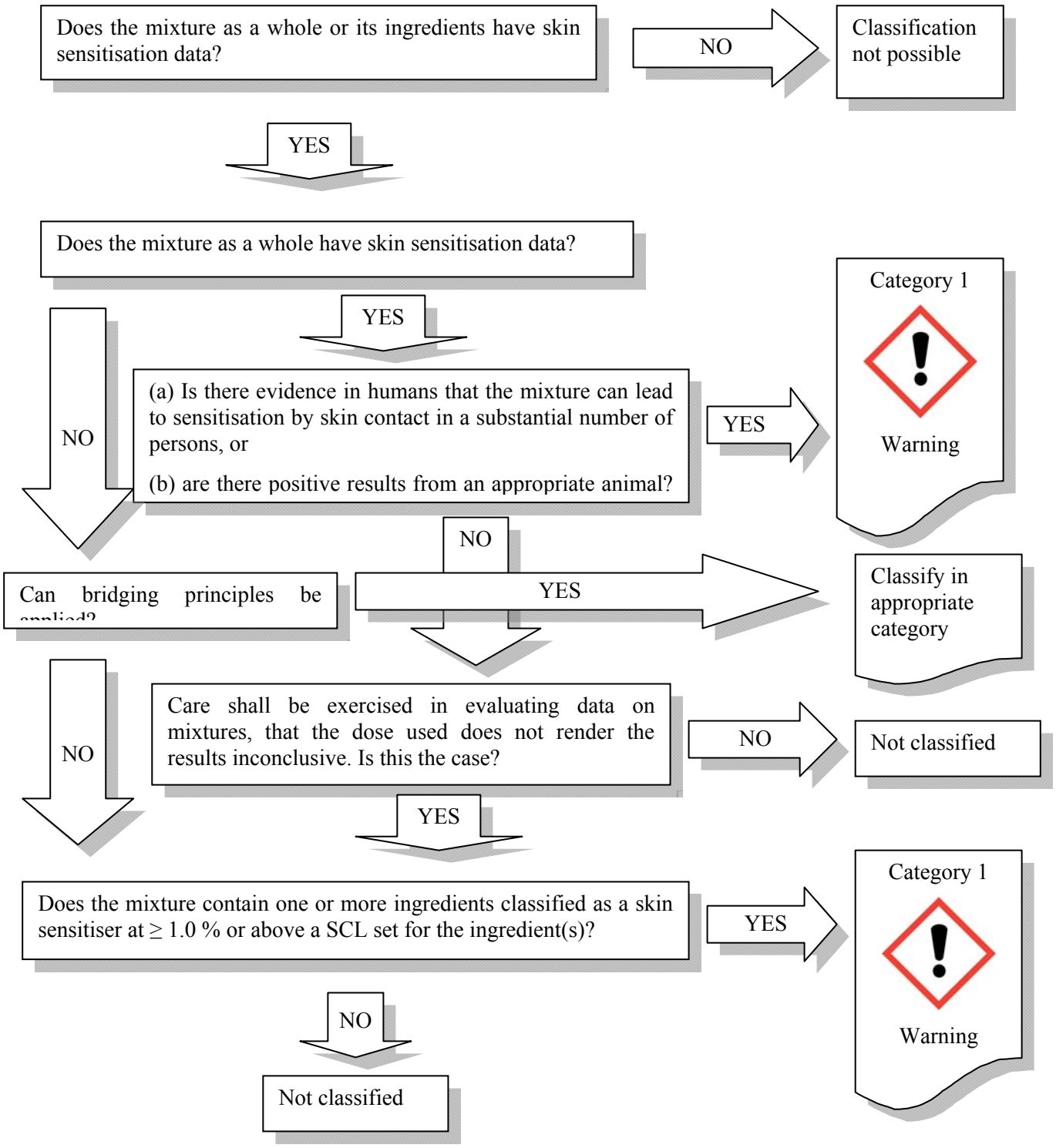
3.4.3.4 Decision logic for classification of mixtures

It is strongly recommended that the person responsible for classification study the criteria for classification before and during use of the decision logic.

Decision logic for respiratory sensitisation



Decision logic for skin sensitisation



3.4.4 Hazard communication for respiratory or skin sensitisation

3.4.4.1 Pictograms, signal words, hazard statements and precautionary statements

Annex I: 3.4.4.1. Label elements shall be used for substances or mixtures meeting the criteria for classification in this hazard class in accordance with Table 3.4.2

Table 3.4.4

Respiratory or skin sensitisation label elements

Classification	Respiratory sensitisation	Skin sensitisation
	Category 1	Category 1
GHS Pictograms		
Signal Word	Danger	Warning
Hazard Statement	H334: May cause allergy or asthma symptoms or breathing difficulties if inhaled	H317: May cause an allergic skin reaction
Precautionary Statement Prevention	P261 P285	P261 P272 P280
Precautionary Statement Response	P304 + P341 P342 + P311	P302 + P352 P333 + P313 P321 P363
Precautionary Statement Storage		
Precautionary Statement Disposal	P501	P501

If the hazard pictogram "GHS08" applies for respiratory sensitisation, the hazard pictogram "GHS07" shall not appear for skin sensitisation or for skin and eye irritation (CLP, Article 26).

In the SDS for a substance, information on the generic or specific concentration limit should be provided.

3.4.4.2 Additional labelling provisions

Annex II: 2.8. Mixtures not classified as sensitising but containing at least one sensitising substance
The label on the packaging of mixtures containing at least one substance classified as sensitising and present in a concentration equal to or greater than 0,1% or in a concentration equal to or

greater than that specified under a specific note for the substance in part 3 of Annex VI shall bear the statement:

EUH208 - "Contains (name of sensitising substance). May produce an allergic reaction"

3.4.5 Re-classification of substances and mixtures classified for respiratory or skin sensitisation according to DSD and DPD

3.4.5.1 Is direct "translation" of classification and labelling possible?

Direct translation from DSD to CLP is possible for sensitising substances.

Any existing SCLs may be transferred across to CLP and used for classification of mixtures. Where there is no existing SCL for an already classified substance, the substance shall be classified in the default Category 1, and a generic concentration limit of 1% applied.

3.4.5.2 Re-evaluation of the skin sensitisation data

Re-evaluation of non-tested mixtures has to be done on the basis of any relevant new data that might have become available after the time of the latest classification or if an SCL has been set.

3.4.6 Examples of classification for skin sensitisation

3.4.6.1 Example of substance fulfilling the criteria for classification for skin sensitisation

3.4.6.1.1 Example 1

Substance X gave a positive result in the LLNA with an EC3-value of 10.4%. As this EC3-value is above the cut-off of 2%, the substance is considered to be a moderate skin sensitiser, and should be classified as a Category 1 skin sensitiser. The GCL for classification of mixtures containing substance X is 1%.

3.4.6.1.2 Example 2

Substance Y tested positive in the LLNA with an EC3-value of 0.5%. In the GPMT a dermal induction concentration of 0.375% produced a positive response in 70% of the animals. On the basis of both these positive results, the substance is considered to be a strong sensitiser requiring classification as a Category 1 skin sensitiser. A specific concentration limit of 0.1% is suggested.

3.4.6.1.3 Example 3

Herby is a herbicide formulation containing 28 g/l substance X, a moderate skin sensitiser (see example 1). There is no sensitisation data for the formulation itself. As Herby contains more than the GCL (1%) of this sensitising a.i., and in the absence of any additional information, it should be classified as a Category 1 skin sensitiser. The label must also bear the statement EUH208.

3.4.6.1.4 Example 4

Methyl/Chloromethyl-isothiazolinone is an example of an extreme sensitiser. This substance is listed in CLP Annex VI (Index-No. 613-167-00-5) with harmonised classification. Being an extreme sensitiser it has a specific concentration limit with regard to skin sensitisation, and

due to this property any mixture containing the substance in a concentration ≥ 0.0015% must be classified with Skin Sens. 1. The label must also bear the statement EUH208.

3.4.6.2 Example of substances or mixtures not fulfilling the criteria for classification for skin sensitisation

3.4.6.2.1 Example 5

Substance A was tested in the LLNA and gave a maximum stimulation index of 2.4. On the basis of a stimulation index below 3, substance A is not considered to be a skin sensitiser, and does not require classification.

3.4.6.2.2 Example 6

Insecto super is an insecticide formulation containing 9 g/l substance X (see Example 1). Substance X is a moderate skin sensitiser (generic concentration limit in mixtures 1%). Based on the classification of substance X, the insecticide formulation shall not be classified as sensitising as the concentration of the a.i. is below the GCL of 1%. The label must bear the statement EUH208.

3.4.7 References

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3.5 GERM CELL MUTAGENICITY

3.5.1 Definitions and general considerations for classification for germ cell mutagenicity

Annex I: 3.5.1.1. A mutation means a permanent change in the amount or structure of the genetic material in a cell. The term "mutation" applies both to heritable genetic changes that may be manifested at the phenotypic level and to the underlying DNA modifications when known (including specific base pair changes and chromosomal translocations). The term "mutagenic" and "mutagen" will be used for agents giving rise to an increased occurrence of mutations in populations of cells and/or organisms.

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

Germ cell mutations are those that occur in the egg or sperm cells (germ cells) and therefore can be passed on to the organism's offspring. Somatic mutations are those that happen in cells other than the germ cells, and they cannot be transmitted to the next generation. This is an important distinction to keep in mind in terms of both the causes and the effects of mutation.

Annex I: 3.5.2.1 This hazard class is primarily concerned with substances that may cause mutations in the germ cells of humans that can be transmitted to the progeny. However, the results from mutagenicity or genotoxicity tests *in vitro* and in mammalian somatic and germ cells *in vivo* are also considered in classifying substances and mixtures within this hazard class.

Annex I: 3.6.2.2 *Specific considerations for classification of substances as carcinogens*

3.6.2.2.6. Mutagenicity: It is recognised that genetic events are central in the overall process of cancer development. Therefore evidence of mutagenic activity *in vivo* may indicate that a substance has a potential for carcinogenic effects.

Hazard classification for germ cell mutagenicity primarily aims to identify substances causing heritable mutations or being suspected of causing heritable mutations. A secondary aim is that the hazard class germ cell mutagenicity offers supporting information with respect to the classification of carcinogenic substances. This is expressed by the broad meaning of the hazard statements "H340: May cause genetic defects" and "H341: Suspected of causing genetic defects" which comprises heritable genetic damage as well as somatic cell

mutagenicity. Thus, classification as a germ cell mutagen (Category 1A, 1B, and.2) classifies for the hazard heritable genetic damage as well as providing an indication that the substance could be carcinogenic.

It is also warranted that where there is evidence of only somatic cell genotoxicity, substances are classified as suspected germ cell mutagens. Classification as a suspected germ cell mutagen may also have implications for potential carcinogenicity classification. This holds true especially for those genotoxicants which are incapable of causing heritable mutations because they cannot reach the germ cells (e.g. genotoxicants only acting locally, "site of contact" genotoxicants). This means that if positive results *in vitro* are supported by at least one positive local *in vivo*, somatic cell test, such an effect should be considered as enough evidence to lead to classification in Category 2. If there is also negative or equivocal data, a weight of evidence approach using expert judgement has to be applied.

3.5.2 Classification of substances for germ cell mutagenicity

3.5.2.1 Identification of hazard information

3.5.2.1.1 Identification of human data

Occasionally, studies of genotoxic effects in humans exposed by, for example, accident, occupation or participation in clinical studies (e.g. from case reports or epidemiological studies) may be available. Generally, cells circulating in blood are investigated for the occurrence of various types of genetic alterations; see alsoIR/CSA, Section R.7.7.3.2.

3.5.2.1.2 Identification of non human data

Animal data

Some test methods have an officially adopted EU/OECD guideline for the testing procedure, although for many test methods this is not the case. Furthermore, modifications to OECD protocols have been developed for various classes of substances and may serve to enhance the accuracy of test results. Use of such modified protocols is a matter of expert judgement and will vary as a function of the chemical and physical properties of the substance to be evaluated. Commonly used non-guideline *in vivo* tests employ methods by which any tissue of an animal can be examined for effects on the genetic material, giving the possibility to examine site-of-contact tissues (*i.e.,* skin, epithelium of the respiratory or gastro-intestinal tract) in genotoxicity testing. In addition, test methods developed over the past decades in *Drosophila* and in various species of plants and fungi are available; see also IR/CSA, Section R.7.7.3.

Other *in vivo* tests in somatic cells which provide supporting evidence on genotoxicity/mutagenicity may include, for example, a Comet single cell gel electrophoresis assay for DNA strand breaks, or a test for gene mutations in transgenic rodent models using reporter genes.

With the exception of *in vivo* studies proving "site of contact" effects, genotoxicity data from such non-standard *in vivo* studies are not sufficient but may offer supporting information for classification.

In vitro data

Typically, *in vitro* tests are performed with cultured bacterial cells, human or other mammalian cells. The sensitivity and specificity of tests will vary with different classes of substances; see alsoIR/CSA, Section R.7.7.3.

Use of other data

See IR/CSA, Section R.7.3.3.1.

Existing test methods

See IR/CSA, Section R.7.3.3.1.

3.5.2.2 Classification criteria for substances

Annex I: 3.5.2.2. For the purpose of classification for germ cell mutagenicity, substances are allocated to one of two categories as shown in Table 3.5.1.

Table 3.5.1
Hazard categories for germ cell mutagens

Categories	Criteria
CATEGORY 1:	Substances known to induce heritable mutations or to be regarded as if they induce heritable mutations in the germ cells of humans. Substances known to induce heritable mutations in the germ cells of humans.
Category 1A:	The classification in Category 1A is based on positive evidence from human epidemiological studies. Substances to be regarded as if they induce heritable mutations in the germ cells of humans.
Category 1B:	The classification in Category 1B is based on: − positive result(s) from in vivo heritable germ cell mutagenicity tests in mammals; or − positive result(s) from in vivo somatic cell mutagenicity tests in mammals, in combination with some evidence that the substance has potential to cause mutations to germ cells. It is possible to derive this supporting evidence from mutagenicity/genotoxicity tests in germ cells in vivo, or by demonstrating the ability of the substance or its metabolite(s) to interact with the genetic material of germ cells; or − positive results from tests showing mutagenic effects in the germ cells of humans, without demonstration of transmission to progeny; for example, an increase in the frequency of aneuploidy in sperm cells of exposed people.

CATEGORY 2:	Substances which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans.
	The classification in Category 2 is based on:
	− Positive evidence obtained from experiments in mammals and/or in some cases from in vitro experiments, obtained from:
	  − Somatic cell mutagenicity tests in vivo, in mammals; or
	  − Other *in vivo* somatic cell genotoxicity tests which are supported by positive results from in vitro mutagenicity assays.
	Note: Substances which are positive in in vitro mammalian mutagenicity assays, and which also show chemical structure activity relationship to known germ cell mutagens, shall be considered for classification as Category 2 mutagens.

3.5.2.3 Evaluation of hazard information

Annex I: 3.5.2.3.3 Classification for heritable effects in human germ cells is made on the basis of well conducted, sufficiently validated tests, preferably as described in Regulation (EC) No 440/2008 adopted in accordance with Article 13(3) of Regulation (EC) No 1907/2006 ('Test Method Regulation') such as those listed in the following paragraphs. Evaluation of the test results shall be done using expert judgement and all the available evidence shall be weighed in arriving at a classification.

3.5.2.3.1 Evaluation of human data

Human data have to be assessed carefully on a case-by-case basis. The interpretation of such data requires considerable expertise. Attention should be paid especially to the adequacy of the exposure information, confounding factors, co-exposures and to sources of bias in the study design or incident. The statistical power of the test may also be considered (See IR/CSA, Section R.7.4.4.2).

3.5.2.3.2 Evaluation of non human data

Evaluation of genotoxicity test data should be made with care. Regarding *positive* findings, responses generated only at highly toxic/cytotoxic concentrations should be interpreted with caution, and the presence or absence of a dose-response relationship should be considered. In case of *negativ*e findings *in vivo* toxicokinetic and other available information should be considered e.g. to verify whether the substance has reached the target organ (for detailed guidance see See IR/CSA, Section R.7.7.4.1).

3.5.2.4 Decision on classification

Annex I: 3.5.2.3.1. To arrive at a classification, test results are considered from experiments determining mutagenic and/or genotoxic effects in germ and/or somatic cells of exposed animals. Mutagenic and/or genotoxic effects determined in in vitro tests shall also be considered.

Annex I: 3.5.2.3.9. The classification of individual substances shall be based on the total weight of evidence available, using expert judgement (See 1.1.1). In those instances where a single well-conducted test is used for classification, it shall provide clear and unambiguously positive results. If new, well validated, tests arise these may also be used in the total weight of evidence to be considered. The relevance of the route of exposure used in the study of the substance compared to the most likely route of human exposure shall also be taken into account.

Classification as a Category 1A mutagen

Epidemiological studies have been to date unable to provide evidence to classify a substance as a Category 1A mutagen. Hereditary diseases in humans for the most part have an unknown origin and show a varying distribution in different populations. Due to the random distribution of mutations in the genome it is not expected that one particular substance would induce one specific genetic disorder. Therefore, it is unlikely that such evidence may be obtained by epidemiological studies to enable you to classify a substance as a Category 1A mutagen.

Classification as a Category 1B mutagen

Classification in Category 1B may be based on positive results of at least one valid *in vivo* mammalian germ cell mutagenicity test. In case there are also negative or equivocal data, a weight of evidence approach using expert judgement has to be applied.

If there are only positive results of at least one valid *in vivo* mammalian somatic mutagenicity test but no respective data on mammalian germ cells are available, additional evidence is required to be able to classify as mutagen in Category 1B. Such additional data must prove that the substance or its metabolite(s) interacts *in vivo* with the genetic material of germ cells. It is also possible to obtain supporting evidence in an *in vivo* genotoxicity test with mammalian germ cells. In addition, genetic damage to germ cells in exposed humans proven to be caused by substance exposure may offer respective information. In case of other supporting evidence or where there are also negative or equivocal data, a weight of evidence approach using expert judgement has to be applied.

It could be argued that in a case where *in vivo* mutagenicity/genotoxicity is proven and the substance under consideration is systemically available, then that substance should also be considered as a Category 1B mutagen. Germ cell mutagens as the spermatogonia are generally not protected from substance exposure by the blood-testes barrier formed by the Sertoli cells. In such circumstances the relevant criteria are as follows:

Annex I: 3.5.2.2. (extract from Table 3.5.1)

Category 1B

…

- positive result(s) from in vivo somatic cell mutagenicity tests in mammals, in combination with some evidence that the substance has potential to cause mutations to germ cells. It is possible to derive this supporting evidence from mutagenicity/genotoxicity tests in germ cells *in vivo*, or by demonstrating the ability of the substance or its metabolite(s) to interact with the genetic material of germ cells;

…

This wording expresses that supporting evidence in addition to an *in vivo* somatic cell mutagenicity test in mammals is needed to be able to classify a substance in a Category 1B mutagen. The second sentence in the green box above gives examples for such evidence, from these examples it is clear that such supporting evidence is experimental evidence. There has to be either data indicating that germ cell mutagenicity/genotoxicity is caused by the substance or data showing that the substance or its metabolite(s) interact with the genetic material of germ cells. Thus, in such circumstances, in addition to an *in vivo* somatic cell mutagenicity test, further experimental evidence is needed to be able to classify a substance as a Category 1B mutagen.

Classification as a Category 2 mutagen

Classification in Category 2 may be based on positive results of a least one *in vivo* valid mammalian somatic cell mutagenicity test, indicating mutagenic effects in somatic cells. A Category 2 mutagen classification may also be based on positive results of a least one *in vivo* valid mammalian genotoxicity test, supported by positive *in vitro* mutagenicity results. Genetic damage to somatic cells in exposed humans shown to be caused by substance exposure supported by positive *in vitro* mutagenicity results may also offer respective information warranting classification as a Category 2 mutagen. *In vitro* results can only lead to a Category 2 mutagen classification in a case where there is support by chemical structure activity relationship to known germ cell mutagens. In the case where there are also negative or equivocal data, a weight of evidence approach using expert judgement has to be applied.

In general, mutations can be differentiated into gene mutations (e.g. point or frame shift mutation), chromosome mutations (structural chromosome changes) and genome mutations (loss or gain of whole chromosomes). Different mutagenicity tests may detect different types of mutations and genotoxic effects which have to be taken into account in the weight of evidence determination. For instance, a substance which only causes chromosome mutations

may be negative in a test for detecting point mutations. A complex data situation with positive and negative results might still lead to classification. This is because all tests detecting a certain type of mutation (e.g. point mutations) have been positive and all tests detecting chromosome mutations have been negative. Such circumstances clearly warrant classification although several tests have been negative which is plausible in this case.

A positive result for somatic or germinal mutagenicity in a test using intraperitoneal administration only shows that the tested substance has an intrinsic mutagenic property, and the fact that negative results are exhibited by other routes of dosage may be related to factors influencing the distribution/ metabolism of the substance which may be characteristic to the tested animal species. It cannot be ruled out that a positive test result in intraperitoneal studies in rodents only may be relevant to humans.

If there are positive results in at least one valid *in vivo* mutagenicity test using intraperitoneal application, or from at least one valid *in vivo* genotoxicity test using intraperitoneal application plus supportive *in vitro* data, classification is warranted. In cases where there are additional data from further *in vivo* tests with oral, dermal or inhalative substance application, a weight of evidence approach using expert judgement has to be applied in order to to come to a decision. For instance, it may be difficult to reach a decision on whether or not to classify in the case where there are positive *in vivo* data from at least one *in vivo* test using intraperitoneal application but (only) negative test data from (an) *in vivo* test(s) using oral, dermal, or inhalative application. In such a case, it could be argued that mutagenicity/genotoxicity can only be shown at internal body substance concentrations which can not be achieved using application routes other than intraperitoneal. However, it also has to be taken into account that there is generally no threshold for mutagenicity unless there is specific proof for the existence of such a threshold as may be the case for aneugens. Thus, if mutagenicity/genotoxicity can only be demonstrated for the intraperitoneal route exclusively, then this may mean that the effect in the *in vivo* tests using application routes other than intraperitoneal may have been present, but it may not have been detected because it was below the detection limit of the oral, dermal, or inhalative test assays.

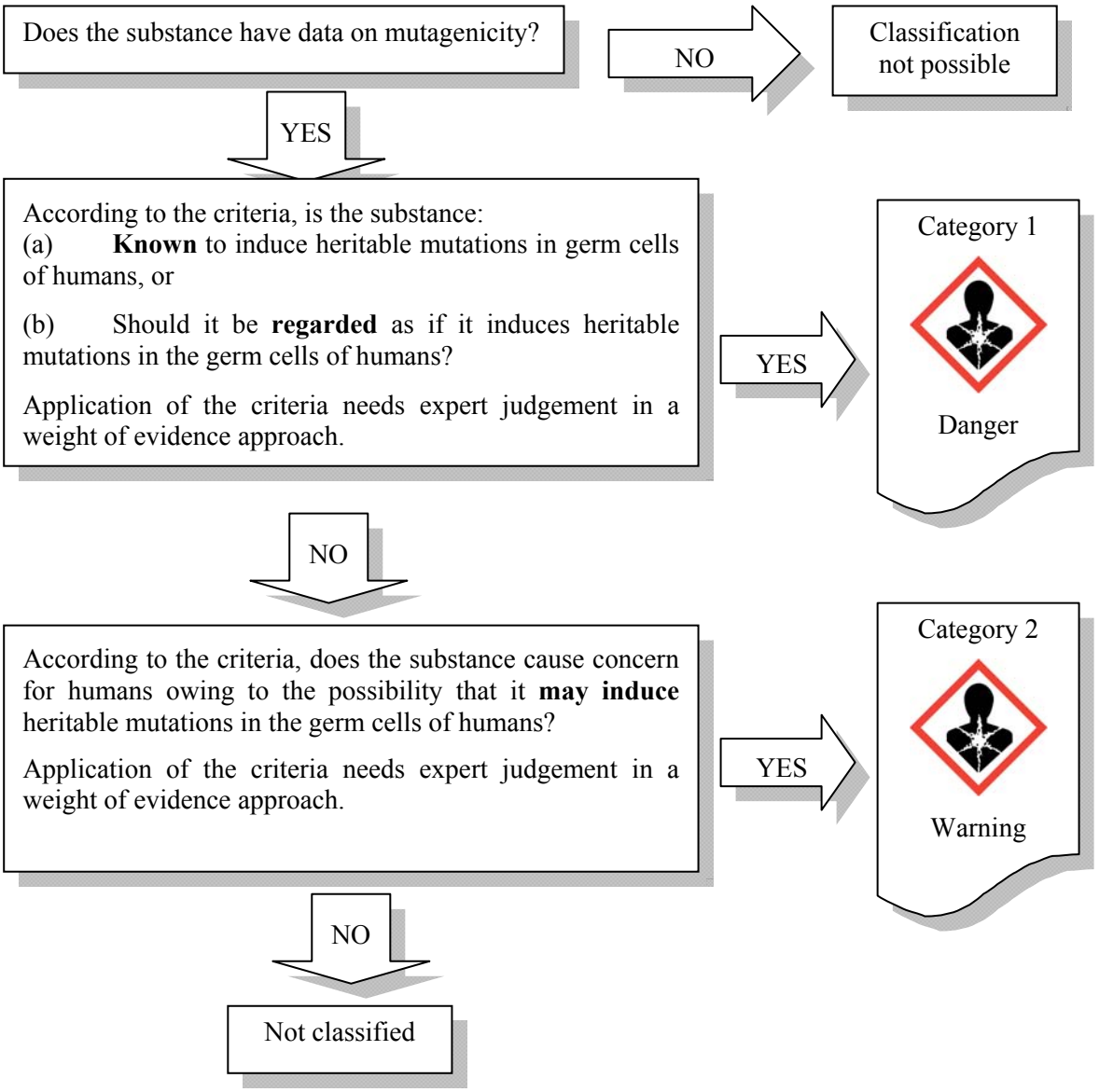
In summary, classification as a Category 2 mutagen would generally apply if only intraperitoneal *in vivo* tests show mutagenicity/genotoxicity and the negative test results from the *in vivo* tests using other routes of application are plausible. Factors influencing plausibility are e.g. the doses tested and putative kinetic data on the test substance. However, on a case-by-case analysis using a weight of evidence approach and expert judgement, non-classification may also result.

3.5.2.5 Setting of specific concentration limits

There is no detailed and accepted guidance developed for the setting of specific concentration limits (SCLs) for mutagenicity, as is the case for carcinogenic substances. Guidance such as the T_{25} concept for carcinogens covering all relevant aspects would need to be developed in order to derive SCLs for mutagens in a standardized manner. There are several reasons why it is considered impossible to set SCLs for mutagens without a comprehensive guidance, one of them being that mutagenicity tests have not been specifically developed for the derivation of a quantitative response. Moreover, different mutagenicity tests have different sensitivities in detecting mutagens. Thus, it is very difficult to describe the minimum data requirements which would allow a standardized SCL derivation. Another drawback in practice is that the results obtained for the most part do not offer sufficient information on dose-response, especially in the case for *in vivo* tests. In conclusion, the possibility to set SCL for germ cell mutagenicity is therefore not considered possible in the process of self-classification as there is no standardized methodical approach available which adequately takes into account all relevant information.

3.5.2.6 Decision logic for substances

The decision logic which follows is provided as additional guidance. It is strongly recommended that the person responsible for classification study the criteria before and during use of the decision logic.



3.5.3 Classification of mixtures for germ cell mutagenicity

3.5.3.1 Classification criteria for mixtures

Classification of mixtures will be based on the available test data for the individual ingredients of the mixture, using concentration limits for those ingredients. Under rare circumstances, the classification may be modified on a case-by-case basis based on the available test data for the mixture as a whole or based on bridging principles (see Article 6(3)).

3.5.3.1.1 When data are available for the complete mixture

Annex I: 3.5.3.2.1. Classification of mixtures will be based on the available test data for the individual ingredients of the mixture using concentration limits for the ingredients classified as germ cell mutagens. On a case-by-case basis, test data on mixtures may be used for classification when demonstrating effects that have not been established from the evaluation based on the individual ingredients. In such cases, the test results for the mixture as a whole must be shown to be conclusive taking into account dose and other factors such as duration, observations, sensitivity and statistical analysis of germ cell mutagenicity test systems. Adequate documentation supporting the classification shall be retained and made available for review upon request.

3.5.3.1.2 When data are not available for the complete mixture: bridging principles

Annex I: 3.5.3.3.1. Where the mixture itself has not been tested to determine its germ cell mutagenicity hazard, but there are sufficient data on the individual ingredients and similar tested mixtures (subject to paragraph 3.5.3.2.1), to adequately characterise the hazards of the mixture, these data shall be used in accordance with the applicable bridging rules set out in section 1.1.3.

3.5.3.2 Generic concentration limits for substances triggering classification of mixtures

Annex I: 3.5.3.1.1. The mixture shall be classified as a mutagen when at least one ingredient has been classified as a Category 1A, Category 1B or Category 2 mutagen and is present at or above the appropriate generic concentration limit as shown in Table 3.5.2 for Category 1A, Category 1B and Category 2 respectively.

Table 3.5.2

Generic concentration limits of ingredients of a mixture classified as germ cell mutagens that trigger classification of the mixture.

Ingredient classified as:	Concentration limits triggering classification of a mixture as:		
	Category 1A mutagen	Category 1B mutagen	Category 2 mutagen
Category 1A mutagen	≥ 0,1 %	—	—
Category 1B mutagen	—	≥ 0,1 %	—
Category 2 mutagen	—	—	≥ 1,0 %

Note

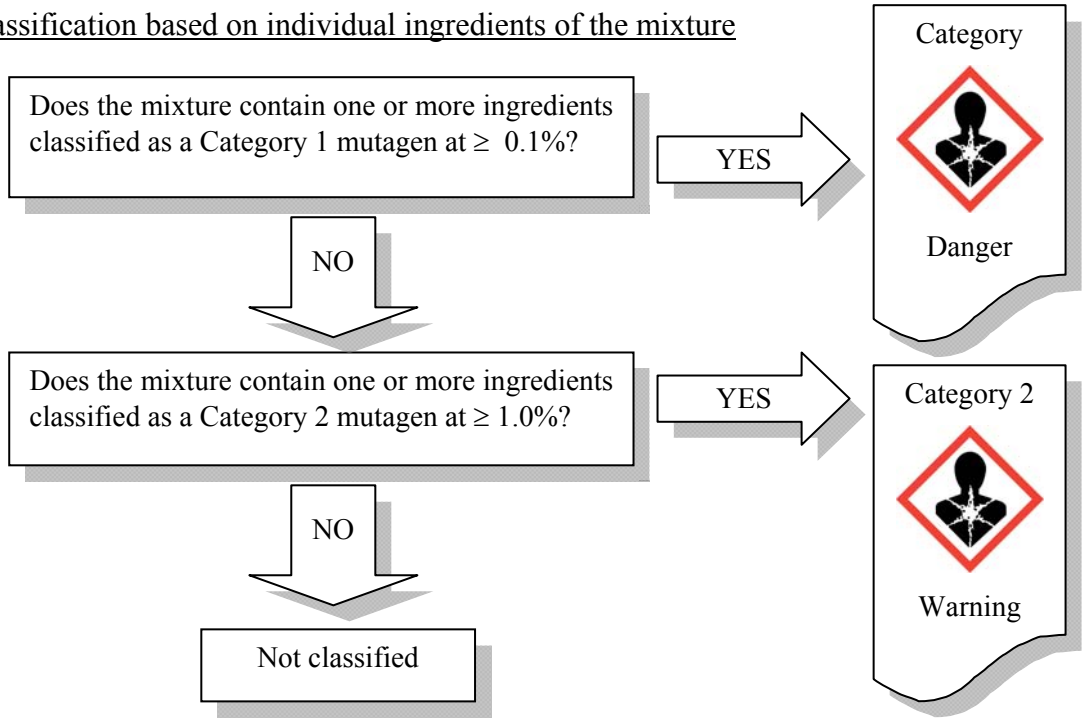
The concentration limits in the table above apply to solids and liquids (w/w units) as well as gases (v/v units).

The option to set SCL for germ cell mutagenicity is not considered possible in the process of self-classification as there is no standardized methodical approach available which adequately takes into account all relevant information (See Section 3.5.2.5).

3.5.3.3 Decision logic for mixtures

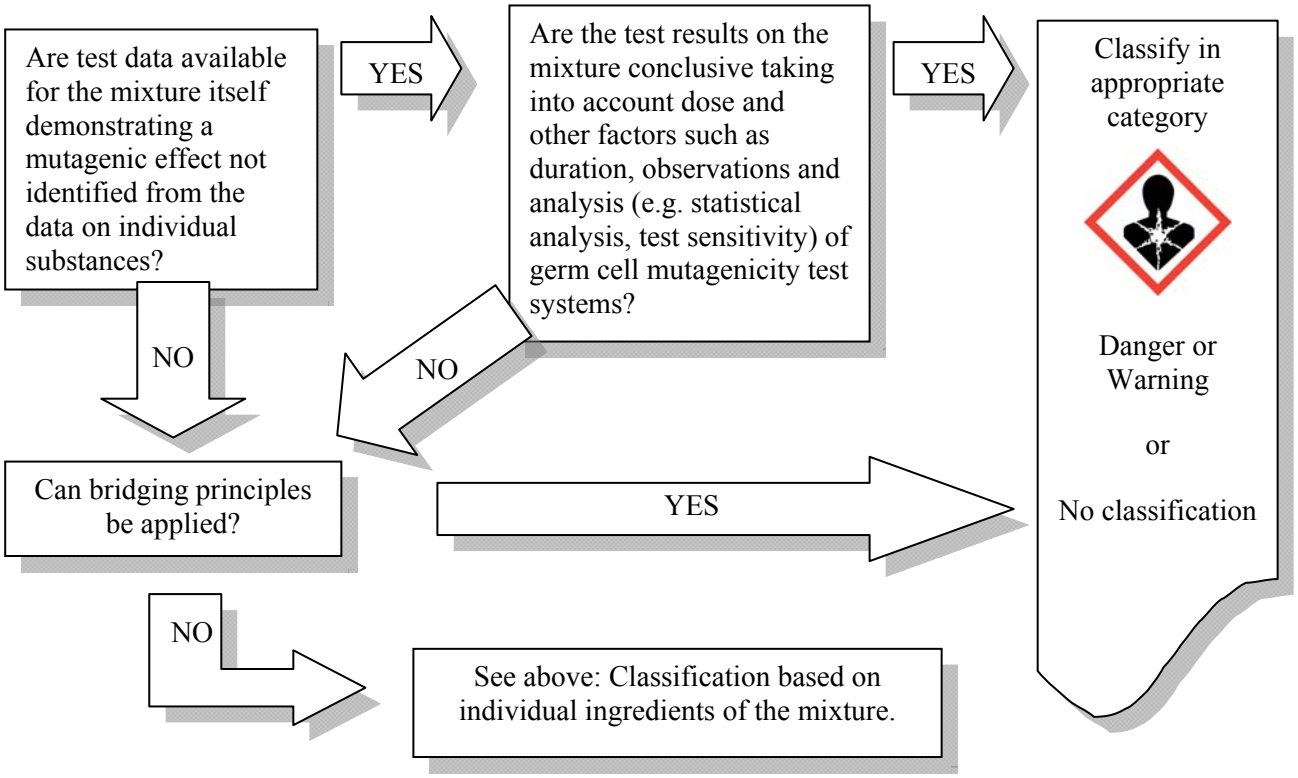
The decision logic which follows is provided as additional guidance. It is strongly recommended that the person responsible for classification study the criteria before and during use of the decision logic. This decision logic deviates (slightly) from the original GHS guidance, to meet CLP requirements.

Classification based on individual ingredients of the mixture



Modified classification on a case-by-case basis

Test data on mixtures may be used for classification when demonstrating effects that have not been established from the evaluation based on the individual ingredients (CLP Section 3.5.3.2.1, see also CLP Article 6(3)).



3.5.4 Hazard communication in form of labelling for germ cell mutagenicity

3.5.4.1 Pictograms, signal words, hazard statements and precautionary statements

Annex I: 3.5.4.1. Label elements shall be used in accordance with Table 3.5.3, for substances or mixtures meeting the criteria for classification in this hazard class.

Table 3.5.3

Label elements of germ cell mutagenicity

Classification	Category 1A or Category 1B	Category 2
GHS Pictograms		
Signal Word	Danger	Warning
Hazard Statement	H340: May cause genetic defects (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	H341: Suspected of causing genetic defects (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)
Precautionary Statement Prevention	P201 P202 P281	P201 P202 P281
Precautionary Statement Response	P308 + P313	P308 + P313
Precautionary Statement Storage	P405	P405
Precautionary Statement Disposal	P501	P501

The hazard statement to be applied for the classification germ cell mutagenicity has to be amended to state the route of exposure if it is conclusively proven that no other routes of exposure will lead to the respective effect. A conclusive proof means that valid *in vivo* test data need to be available for all three exposure routes clearly indicating that only one exposure route leads to positive results. Moreover, such findings should be plausible with respect to the mode of action. It is estimated that such circumstances rarely, if ever, exist. Therefore, amending the hazard statement with the route of exposure generally does not have to be considered.

3.5.4.2 Additional labelling provisions

There are no additional labelling provisions for substances and mixtures classified for germ cell mutagenicity in CLP, however there are provisions laid out in Annex XVII to REACH. The packaging of substances classified for germ cell mutagenicity Category 1A or Category 1B, and mixtures containing such substances, "must be marked visibly**,** legibly and indelibly as follows: ‘Restricted to professional users’." (REACH, Annex XVII, point 29).

3.5.5 Re-classification of substances classified for germ cell mutagenicity according to DSD and DPD

Direct translation of classification and labelling is generally possible for substances and mixtures classified as germ cell mutagens.

In CLP, there is clear discrimination of *in vivo* mutagenicity tests and *in vivo* genotoxicity tests with respect to their relevance for classification. Moreover, in some circumstances which are assumed to occur very rarely if at all, a different classification may be the consequence if expert judgement is not applied.

For instance, positive results from studies showing mutagenic effects in germ cells of exposed humans can lead to classification as a Category 1B mutagen under CLP. However, using the criteria in DSD it is not clear how to classify in such a case. Moreover, *in vivo* somatic cell genotoxicity tests need to be supported by *in vitro* data in order to classify as a Category 2 mutagen under CLP. In such circumstances under DSD, *in vivo* data do not necessarily need to be supported by *in vitro* data. However, it has to be taken into account that such circumstances will rarely occur as the testing strategy uses *in vitro* tests as a starting point.

3.6 CARCINOGENICITY

3.6.1 Definitions and general considerations for classification for carcinogenicity

Annex I: 3.6.1.1. Carcinogen means a substance or a mixture of substances which induce cancer or increase its incidence. Substances which have induced benign and malignant tumours in well performed experimental studies on animals are considered also to be presumed or suspected human carcinogens unless there is strong evidence that the mechanism of tumour formation is not relevant for humans.

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

Carcinogenic chemicals have conventionally been divided according to the presumed mode of action; genotoxic or non-genotoxic, see 3.6.2.3.2 (k).

Classification of a substance as a carcinogen is based on consideration of the strength of the evidence of available data for classification with considerations of all other relevant information (weight of evidence) being taken into account as appropriate. Strength of evidence involves the enumeration of tumours in human and animal studies and determination of their level of statistical significance. A number of other factors need to be considered that influence the overall likelihood that a substance poses a carcinogenic hazard in humans (weight of evidence determination). The list of factors for additional consideration is long and requires the most up-to-date scientific knowledge. It is recognised that, in most cases, expert judgement is necessary to be able to determine the most appropriate category for classification for carcinogenicity.

3.6.2 Classification of substances for carcinogenicity

3.6.2.1 Identification of hazard information

Carcinogens may be identified from epidemiological studies, from animal experiments and/or other appropriate means that may include (Quantitative) Structure-Activity Relationships ((Q)SAR) analyses and/or extrapolation from structurally similar substances (read-across). In addition some information on the carcinogenic potential can be inferred from *in vivo* and *in vitro* germ cell and somatic cell mutagenicity studies, *in vitro* cell transformation assays, and gap junction intercellular communication (GJIC) tests.

Extensive guidance on data requirements, information sources and strategies for the identification of potential carcinogens are given in Section R.7.7.9 (Information requirements on carcinogenicity) and Section R.7.7.10 (Information and its sources on carcinogenicity) and for potential mutagens Section R.7.7.3 (Information and its sources on mutagenicity), IR/CSA.

For more about non testing data see Section 3.6.2.3.4.

3.6.2.2 Classification criteria for substances

Substances are classified according to their potential to cause cancer in humans. In some cases there will be direct evidence on the carcinogenicity to humans from epidemiological studies. However, in most cases the available information on carcinogenicity will be primarily from animal studies. In this case the relevance of the findings in animals to humans must be considered.

Annex I: 3.6.2.1. For the purpose of classification for carcinogenicity, substances are allocated to one of two categories based on strength of evidence and additional considerations (weight of evidence). In certain instances, route-specific classification may be warranted, if it can be conclusively proved that no other route of exposure exhibits the hazard.

Table 3.6.1

Hazard categories for carcinogens

Categories	Criteria
CATEGORY 1:	Known or presumed human carcinogens A substance is classified in Category 1 for carcinogenicity on the basis of epidemiological and/or animal data. A substance may be further distinguished as:
Category 1A:	Category 1A, known to have carcinogenic potential for humans, classification is largely based on human evidence, or
Category 1B:	Category 1B, presumed to have carcinogenic potential for humans, classification is largely based on animal evidence.
	The classification in Category 1A and 1B is based on strength of evidence together with additional considerations (see section 3.6.2.2). Such evidence may be derived from: – human studies that establish a causal relationship between human exposure to a substance and the development of cancer (known human carcinogen); or – animal experiments for which there is sufficient ([1]) evidence to demonstrate animal carcinogenicity (presumed human carcinogen). In addition, on a case-by-case basis, scientific judgement may warrant a decision of presumed human carcinogenicity derived from studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals.
CATEGORY 2:	Suspected human carcinogens The placing of a substance in Category 2 is done on the basis of evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the substance in Category 1A or 1B, based on strength of evidence together with additional considerations (see section 3.6.2.2). Such evidence may be derived either from limited ([1]) evidence of carcinogenicity in human studies or from limited evidence of carcinogenicity in animal studies.

([1]) Note: See 3.6.2.2.4.

3.6.2.3 Evaluation of hazard information

Annex I: 3.6.2.2.1. Classification as a carcinogen is made on the basis of evidence from reliable and acceptable studies and is intended to be used for substances which have an intrinsic property to cause cancer. The evaluations shall be based on all existing data, peer-reviewed published studies and additional acceptable data.

3.6.2.2.2. Classification of a substance as a carcinogen is a process that involves two interrelated determinations: evaluations of strength of evidence and consideration of all other relevant information to place substances with human cancer potential into hazard categories.

Classification of a substance as a carcinogen requires expert judgement and consideration of many different factors (weight and strength of evidence) included in the hazard information on carcinogenicity. The guidance provides an approach to data analysis rather than hard and fast rules. A stepwise approach to the classification can be taken where all the factors, both weight and strength of evidence, that may influence the outcome are considered systematically. Such approach, including consideration of these factors is outlined, in McGregor *et al,* 2009 and Boobis *et al*, 2006. Also the IPCS "Conceptual Framework for Evaluating a Mode of Action for Chemical carcinogenesis" (2001), ILSI "Framework for Human Relevance Analysis of Information on Carcinogenic Modes of Action" (Meek *et al*., 2003; Cohen *et al*, 2003, 2004) and the International Agency for Research on Cancer (IARC, 2006 - Preamble Section B) provide a basis for systematic assessments which may be performed in a consistent fashion internationally; however they are not intended to provide lists of criteria to be checked off.

Specific considerations that are necessary are outlined in CLP, Annex I, Section 3.6.2.3 (see Section 3.6.2.3.1) and other important factors to consider in CLP, annex I, Section 3.6.6.2.6 (see Section 3.6.2.3.2). Further guidance on these important factors is given in this document.

3.6.2.3.1 Specific considerations for classification

There is a strong link between CLP and the IARC classification criteria. The definitions for sufficient and limited evidence as defined by IARC are part of the criteria (Annex I, section 3.6.2.2.3). IARC, however, understands the criteria of "sufficient" and "limited" as follows: 'It is recognized that the criteria for these evaluations, described below, cannot encompass all of the factors that may be relevant to an evaluation of carcinogenicity. In considering all of the relevant scientific data, the Working Group may assign the agent to a higher or lower category than a strict interpretation of these criteria would indicate.' (IARC 2006 preamble Section 6, Evaluation and rationale). This sentence emphasises that in certain circumstances expert judgement may overrule the strict interpretation of the IARC criteria for "sufficient" and "limited". These same limitations apply with the current criteria in that expert judgement is necessary and can override the strict interpretation of the definitions.

Annex I: 3.6.2.2.3. Strength of evidence involves the enumeration of tumours in human and animal studies and determination of their level of statistical significance. Sufficient human evidence demonstrates causality between human exposure and the development of cancer, whereas sufficient evidence in animals shows a causal relationship between the substance and an increased incidence of tumours. Limited evidence in humans is demonstrated by a positive association between exposure and cancer, but a causal relationship cannot be stated. Limited evidence in animals is provided when data suggest a carcinogenic effect, but are less than sufficient. The terms 'sufficient' and 'limited' have been used here as they have been defined by the International Agency for Research on Cancer (IARC) and read as follows:

(a) Carcinogenicity in humans

The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories:

- sufficient evidence of carcinogenicity: a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence;
- limited evidence of carcinogenicity: a positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered to be credible, but chance, bias or confounding could not be ruled out with reasonable

confidence.

(b) Carcinogenicity in experimental animals

Carcinogenicity in experimental animals can be evaluated using conventional bioassays, bioassays that employ genetically modified animals, and other in-vivo bioassays that focus on one or more of the critical stages of carcinogenesis. In the absence of data from conventional long-term bioassays or from assays with neoplasia as the end-point, consistently positive results in several models that address several stages in the multistage process of carcinogenesis should be considered in evaluating the degree of evidence of carcinogenicity in experimental animals. The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories:

- sufficient evidence of carcinogenicity: a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide sufficient evidence. A single study in one species and sex might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites;
- limited evidence of carcinogenicity: the data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs.

For human studies, the quality and power of the epidemiology studies require expert consideration and would normally lead to a Category 1A classification if data of adequate quality shows causality of exposure and cancer development. IR/CSA, Section R.7.7.10.2, further discusses the types of human epidemiology data available and the limitations of the data. Where there is sufficient doubt in the human data then classification in Category 1B may be more appropriate. On the other hand epidemiological studies may fail, because of uncertainties in the exposure assessment and/or limited sensitivity and statistical power, to confirm the carcinogenic properties of a substance as identified in animal studies (WHO Working group, 2000).

3.6.2.3.2 Additional considerations for classification

Annex I: 3.6.2.2.4. Additional considerations (as part of the weight of evidence approach (see 1.1.1)). Beyond the determination of the strength of evidence for carcinogenicity, a number of other factors need to be considered that influence the overall likelihood that a substance poses a carcinogenic hazard in humans. The full list of factors that influence this determination would be very lengthy, but some of the more important ones are considered here.

3.6.2.2.5. The factors can be viewed as either increasing or decreasing the level of concern for human carcinogenicity. The relative emphasis accorded to each factor depends upon the amount and coherence of evidence bearing on each. Generally there is a requirement for more complete information to decrease than to increase the level of concern. Additional considerations should be used in evaluating the tumour findings and the other factors in a case-by-case manner.

3.6.2.2.6. Some important factors which may be taken into consideration, when assessing the

overall level of concern are:

(a) tumour type and background incidence;

(b) multi-site responses;

(c) progression of lesions to malignancy;

(d) reduced tumour latency;

(e) whether responses are in single or both sexes;

(f) whether responses are in a single species or several species;

(g) structural similarity to a substance(s) for which there is good evidence of carcinogenicity;

(h) routes of exposure;

(i) comparison of absorption, distribution, metabolism and excretion between test animals and humans;

(j) the possibility of a confounding effect of excessive toxicity at test doses;

(k) mode of action and its relevance for humans, such as cytotoxicity with growth stimulation, mitogenesis, immunosuppression, mutagenicity.

As indicated above, the evaluation of animal carcinogenicity data requires consideration of a number of important additional factors which may increase or decrease the level of concern and the classification category. The list in Annex I, 3.6.2.6 is not exhaustive. Each of these factors is discussed individually below.

(a) Tumour type and background incidence

Knowledge about the tumour type including its tumour biology is indispensable to decide on the relevance of observed tumours for humans.

By default, carcinogenic effects in experimental animals are considered relevant to humans and are considered for classification as carcinogens. Only when there is sufficient evidence showing that a certain type of tumour is not relevant to humans should this tumour type be excluded for classification.

Certain tumour types observed in animal carcinogenicity studies are of questionable or no relevance to humans. In case of multiple tumours anticipated to have no relevance for humans justification should be given for each tumour type. The justification for dismissing any particular tumour should be presented as a scientifically robust and transparent argument.

There are several reasons why a tumour observed in animals may be judged to be not relevant for humans or may be judged to be of lower concern. In most of these cases the tumour arises via a mode of action which does not occur in humans (see this Section part k). In some cases the tumour may arise in a tissue known to be overly susceptible in the species tested to development of certain tumours and consequently may be judged to be less relevant for humans. In a few cases a tumour may occur in a tissue with no equivalent in humans.

Tumours occurring in tissues with no human equivalent

Some of the commonly used animal species have some tissues with no equivalent in humans. Tumours occurring in these tissues include the following

– Forestomach tumours in rodents following administration by gavage of irritating or corrosive, non mutagenic substances. In rodents, the stomach is divided into two parts by the muco-epidermoid junction separating squamous from glandular epithelium. The proximal part, or forestomach, is non-glandular, forms a continuum with the oesophagus, and is lined by keratinized, stratified squamous epithelium. While humans do not have a

forestomach, they do have comparable squamous epithelial tissues in the oral cavity and the upper two-thirds of the oesophagus. See also this Section (k), IARC (2003), and RIVM (2003).

- Tumours in the Zymbal's glands. Zymbal's glands are located beneath squamous epithelium at the anterior and posterior aspect of the ear canal. The external portion of the gland in rats is 3 to 5 millimetres in diameter.
- Tumours in the Harderian glands. Harderian glands are found in all vertebrates that possess a nictitating membrane, or third eyelid. They are located behind the eyeball in the orbit nictitating membrane, encircling the optic nerve. Humans have a rudimentary one.

Tumours occurring in such tissues indicate that the substance has the potential to induce carcinogenic effects in the species tested. It cannot automatically be ruled out that the substance could cause similar tumours of comparable cell/tissue origin (e.g. squamous cell tumours at other epithelial tissues) in humans. Careful consideration and expert judgement of these tumours in the context of the complete tumour response (i.e. if there are also tumours at other sites) and the assumed mode of action is required to decide if these findings would support a classification. However, tumours observed only in these tissues, with no other observed tumours are unlikely to lead to classification. However, such determinations must be evaluated carefully in justifying the carcinogenic potential for humans; any occurrence of other tumours at distant sites must also be considered.

Considering the background incidence and use of historical control data

Any statistically significant increase in tumour incidence, especially where there is a dose-response relationship, is generally taken as positive evidence of carcinogenic activity. However, in some cases the results involve an increase incidence of tumours in treated animals which lies at the borderline of biological and/or statistical significance or there is an increase in a spontaneous tumour type, then comparison of the tumour incidence with historical control tumour data is strongly encouraged.

Historical control data provide useful information on the normal pattern and range of tumour types and incidences for a particular strain/species, which may not be reflected by the tumour findings in the concurrent controls in any individual study. This can be particularly relevant for animal strains which have a propensity to develop a particular type of tumour spontaneously with variable and potentially high incidence. In such a case the tumour incidence in the treated group may be significantly above the concurrent control but could still be within the historical incidence range for that tumour type in that species and therefore may not be providing reliable evidence of treatment related carcinogenicity.

Some examples of animal tissues with a high spontaneous tumour incidence are:

- Adrenal pheochromocytoma in male F344 rats (NTP, 2007a), Sprague-Dawley rats (NTP, 2005; RIVM, 2001; Ozaki *et al*., 2002);
- Pituitary adenomas in F344 rats (NTP, 2007a), Sprague-Dawley rats (NTP 2005; RIVM 2005);
- Mammary gland tumours (adenomas and carcinomas) in female Sprague-Dawley rats (NTP, 2005);
- Mononuclear cell leukaemia in F344 rats (NTP, 2007a; RIVM, 2005);
- Liver tumours in B6C3F1 mice (NTP, 2007b; Haseman *et al*. 1998; Battershill, J.M. and Fielder, R.J., 1998);
- Leydig cell adenomas in male F344 rats (Cook *et al*., 1999; Mati *et al*., 2002; RIVM, 2004; EU Specialised Experts Report, 2004).

Historical control data can also be useful to judge the biological significance of marginal increases in uncommon tumours. If there is a small increase in a particular tumour type which historical data shows to be very uncommon and unlikely to have occurred by chance then this may support a conclusion of carcinogenicity without the requirement for a statistically significant increase.

Use of historical control data should be on a case by case basis with due consideration of the appropriateness and relevance of the historical control data for the study under evaluation. In a general sense, the historical control data set should be matched as closely as possible to the study being evaluated. The historical data must be from the same animal strain/species, and ideally, be from the same laboratory to minimise any potential confounding due to variations in laboratory conditions, study conditions, animal suppliers, husbandry etc. It is also known that tumour incidences in control animals can change over time, due to factors such as genetic drift, changes in diagnostic criteria for pathological changes/tumour types, and husbandry factors (including the standard diet used), so the historical data should be contemporary to the study being evaluated (e.g. within a period of up to around 5 years of the study). Historical data older than this should be used with caution and acknowledgement of its lower relevance and reliability. (RIVM, 2005; Fung *et al*, 1996; Greim *et al*, 2003).

Even when a particular tumour type may be discounted, expert judgment must be used in assessing the total tumour profile in any animal. However, appearance of only spontaneous tumours, especially if they appear only at high dose levels, may be sufficient to downgrade a classification from Category 1B to Category 2, or even no classification. Where the only available tumour data are liver tumours in certain sensitive strains of mice, without any other supplementary evidence, the substance may not be classified in any of the categories, (Battershill and Fielder, 1998). Expert judgment is required to evaluate the relevance of the results.

(b) Multi-site responses

In general, chemicals are evaluated for carcinogenic potential in two-year bioassays conducted in mice and rats. The chemicals produce a spectrum of responses ranging from no effects in either species to induction of malignant neoplasms in multiple tissues in both species. Between these two extremes, there are variable responses in tissues, sexes and species, which demonstrate that there are important differences among the carcinogens, as well as between the species in which they are tested. The tumour profile observed with a substance should be taken into account when considering the most appropriate classification.

Evidence shows that substances which cause tumours in either multiple sites and/or multiple species tend to be more potent carcinogens than those causing tumours at only one site in one species (Dybing *et al.*, 1997). This is often true for substances which are mutagenic. Also, where human carcinogens have been tested in two or more species, the majority have caused cancer in several species (Tennant, 1993). Thus, if a substance causes tumours at multiple sites and/or in more than one species then this usually provides strong evidence of carcinogenicity. Typically such a tumour profile would lead to a classification in category 1B.

(c) Progression of lesions to malignancy

In general, if a substance involves a treatment related increase in tumours then it will meet the criteria for classification as a carcinogen.

If the substance has been shown to cause malignant tumours this will usually constitute sufficient evidence of carcinogenicity supporting Category 1B (Annex I, Section 3.6.2.2.3)

The induction of only benign tumours usually provides a lower strength of evidence for carcinogenicity than the induction of malignant tumours and will usually support Category 2

(Annex I, Section 3.6.2.2.3). However, benign tumours may also be of significant concern and the strength of evidence for carcinogenicity that they provide should be considered using expert judgement. For instance, some benign tumours may have the potential to progress to malignant tumours and therefore any indication that the observed tumours have the potential to progress to malignancy may increase the level of concern. Also, some benign tumours, for example brain tumours, may be of concern in themselves.

(d) Reduced tumour latency

The latency of tumour development i.e. how quickly a substance induces tumours, often reflects the potency of a carcinogen. This is particularly true for mutagenic substances which often induce tumours with relatively short latency and usually more rapidly than non-genotoxic agents. Tumour latency is not generally investigated in detail in standard carcinogenicity studies, although some information may be provided if the study used serial sacrifices.

The latency of tumour formation does not materially affect the classification and hazard category. Any substance causing cancer will attract classification regardless of the latency for tumour development. This also includes tumour responses at late treatment/life periods if substance-related. However unusual tumour types or tumours occurring with reduced latency may add to the weight of evidence for the carcinogenic potential of a substance, even if the tumours are not statistically significant.

(e) Whether responses are in single or both sexes

In general, in standard carcinogenicity studies both male and female animals are tested. There may be cases where tumours are only observed in one sex.

Tumours in one sex only may arise for two broad reasons. The tumours may occur in a gender-specific tissue, for instance the uterus or testes (sex-specific tissue), or in a non sex-specific tissue, in one sex only. Tumours may also be induced by a mechanism that is gender (or sex) -specific, for instance a hormonally-mediated mechanism or one involving gender (or sex) -specific differences in toxicokinetics. As with all cases the strength of evidence of carcinogenicity should be assessed based on the totality of the information available using a weight of evidence type approach. A default position is that such tumours are still evidence of carcinogenicity and should be evaluated in light of the total tumorigenic response to the substance observed at other sites (multi-site responses or incidence above background) in determining the carcinogenic potential and the classification category.

If tumours are seen only in one sex of an animal species, the mode of action should be carefully evaluated to see if the response is consistent with the postulated mode of action. Effects seen only in one sex in a test species may be less convincing than effects seen in both sexes, unless there is a clear patho-physiological difference consistent with the mode of action to explain the single sex response. However, there is no requirement for a mechanistic understanding of tumour induction in order to use these findings to support classification. If there is clear evidence for induction of either a gender (or a sex)-specific tumour then classification in Cat 1B may be appropriate. However, it has to be taken into account that according to the criteria additional data are required to provide sufficient evidence for animal carcinogenicity (1B).

(f) Whether responses are in a single species or several species

The criteria indicate that carcinogenicity in a single animal study (both sexes, ideally in a GLP study) could be sufficient evidence and could therefore lead to a Category 1B classification in the absence of any other data. This represents a change compared to the

previous EU-system where such a study would rarely lead to the equivalent of a Category 1B classification. For classification as a Category 2 carcinogen under DSD either positive results in two animal species should be available or clear positive evidence in one species, together with supporting evidence such as genotoxicity data, metabolic or biochemical studies, induction of benign tumours, structural relationship with other known carcinogens, or data from epidemiological studies suggesting an association.

However, as defined under 'sufficient' evidence (Annex I, section 3.6.2.2.3 (b)), a single study in one species and sex might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites. Moreover a single study in one species and sex in combination with positive in-vivo mutagenicity data would be considered to provide sufficient evidence of carcinogenicity.

Positive responses in several species add to the weight of evidence, that a chemical is a carcinogen.

(g) Structural similarity or not to a chemical(s) for which there is good evidence of carcinogenicity

See Section 3.6.2.3.4.

(h) Routes of exposure;

> **Annex I: 3.6.2.2.8.** The classification shall take into consideration whether or not the substance is absorbed by a given route(s); or whether there are only local tumours at the site of administration for the tested route(s), and adequate testing by other major route(s) show lack of carcinogenicity.

The classification for carcinogenicity generally does not specify specific routes of exposure. If a chemical has been shown to cause tumours by any route of administration then it may require classification, unless there is a robust justification for dismissing the findings from a particular route. However, under the previous EU system (Annex VI to DSD), classification specifically via inhalation was accepted by application of the risk phrase R49; May cause cancer by inhalation and a specific hazard statement has been established in CLP, H350i; May cause cancer by inhalation (CLP, Annex VII, Table 1.1).

Most standard carcinogenicity studies use physiological routes of exposure for humans, namely inhalation, oral or dermal exposure. The findings from such routes are usually considered directly relevant for humans. Studies using these routes will generally take precedence over similar studies using other routes of exposure.

Sometimes other non-physiological routes are used, such as intra-muscular, sub-cutaneous, intra-peritoneal and intra-tracheal injections or instillations. Findings from studies using these routes may provide useful information but should be considered with caution. Usually dosing via these routes provides a high bolus dose which gives different toxicokinetics to normal routes and can lead to atypical indication of carcinogenicity. For instance, the high local concentration can lead to local tumours at the site of injection. These would not normally be considered reliable indications of carcinogenicity as they most likely arose from the abnormally high local concentration of the test substance and would lead to a lower category classification or no classification.

Where findings are available from studies using standard routes and non-physiological routes, the former will generally take precedence. Usually studies using non-standard routes provide supporting evidence only.

The hazard statement allows for identifying the route of exposure “if it is conclusively proven that no other routes of exposure cause the hazard” (Annex I, section 3.6.4.1). In this case the

hazard statement may be modified accordingly. Genotoxic carcinogens are generally suspected to be carcinogenic by any route.

(i) Comparison of absorption, distribution, metabolism and excretion between test animals and humans;

Annex I: 3.6.2.2.9. It is important that whatever is known of the physico-chemical, toxicokinetic and toxicodynamic properties of the substances, as well as any available relevant information on chemical analogues, i.e. structure activity relationship, is taken into consideration when undertaking classification.

Consideration of absorption, distribution, metabolism and excretion (toxicokinetics) of the substance in the test animal species and in humans is one important consideration, including where a substance is metabolised to an active carcinogenic metabolite. Toxicokinetic behaviour is normally assumed to be similar in animals and humans, at least from a qualitative perspective. On the other hand, certain tumour types in animals may be associated with toxicokinetics or toxicodynamics that are unique to the animal species tested and may not be predictive of carcinogenicity in humans. Where significant qualitative and quantitative differences in toxicokinetics exist between animals and humans this can impact on the relevance of the animal findings for humans and in certain instances may influence the category of classification. Where a carcinogenic metabolite identified in animals is demonstrated not to be produced in humans, no classification may be warranted where it can be shown that this is the only mechanism of action for carcinogenicity.

The use of physiologically-based pharmacokinetic (PB/PK) modelling requires more validation and while it may not lead directly to a modification of classification, however expert judgement in conjunction with PB/PK modelling may help to modify the concern for humans.

(j) The possibility of a confounding effect of excessive toxicity at test doses

In lifetime bioassays compounds are routinely tested using at least three dose levels to enable hazard identification and hazard characterisation as part of risk assessment. Of these doses, the highest dose needs to induce minimal toxicity, such as characterised by an approximately 10% reduction in body weight gain (maximal tolerated dose, MTD dose). The MTD is the highest dose of the test agent during the bioassay that can be predicted not to alter the animal's normal longevity from effects other than carcinogenicity. Data obtained from a sub-chronic or other repeated dose toxicity study are used as the basis for determining the MTD.

Excessive toxicity, for instance toxicity at doses exceeding the MTD, can affect the carcinogenic responses in bioassays. Such toxicity can cause effects such as cell death (necrosis) with associated regenerative hyperplasia, which can lead to tumour development as a secondary consequence unrelated to the intrinsic potential of the substance itself to cause tumours at lower less toxic doses.

Tumours occurring only at excessive doses associated with severe toxicity generally have a more doubtful potential for carcinogenicity in humans. In addition, tumours occurring only at sites of contact and/or only at excessive doses need to be carefully evaluated for human relevance for carcinogenic hazard. For example, as indicated in this Section (a) 'Tumour type and background incidence', forestomach tumours, following administration by gavage of an irritating or corrosive, non-mutagenic chemical, may be of questionable relevance, both due to the lack of a corresponding tissue in humans, but importantly, due to the high dose direct effect on the tissue. However, such determinations must be evaluated carefully in justifying the carcinogenic potential for humans; any occurrence of other tumours at distant sites must also be considered.

The proceedings of a WHO/IPCS workshop on the Harmonization of Risk Assessment for Carcinogenicity and Mutagenicity (Germ cells) - A Scoping Meeting (IPCS, 1995; Ashby *et al*, 1996), points to a number of scientific questions arising for classification of chemicals, e.g. mouse liver tumours, peroxisome proliferation, receptor-mediated reactions, chemicals which are carcinogenic only at toxic doses and which do not demonstrate mutagenicity.

If a test compound is only found to be carcinogenic at the highest dose(s) used in a lifetime bioassay, and the characteristics associated with doses exceeding the MTD as outlined above are present, this could be an indication of a confounding effect of excessive toxicity. This may support a classification of the test compound in Category 2 or no classification.

(k) Mode of action and its relevance for humans, such as mutagenicity, cytotoxicity with growth stimulation, mitogenesis, immunosuppression

Carcinogenic chemicals have conventionally been divided into two categories according to the presumed mode of action; genotoxic or non-genotoxic. Genotoxic modes of action involve genetic alterations caused by the chemical interacting directly with DNA to possibly result in a change in the primary sequence of DNA after cell division. A chemical can also cause genetic alterations indirectly following interaction with other cellular processes (e.g., secondary to the induction of oxidative stress). Non-genotoxic modes of action include epigenetic changes, i.e., effects that do not involve alterations in DNA but that may influence gene expression, altered cell-cell communication, or other factors involved in the carcinogenic process. For example, chronic cytotoxicity with subsequent regenerative cell proliferation is considered a mode of action by which tumour development can be enhanced: the induction of urinary bladder tumours in rats may, in certain cases, be due to persistent irritation/inflammation, tissue erosion and regenerative hyperplasia of the urothelium following the formation of bladder stones. Other modes of non-genotoxic action can involve specific receptors (e.g., peroxisome proliferator-activated receptor-alpha (PPARα) which is associated with liver tumours in rodents; or tumours induced by various hormonal mechanisms). More detail is given in IR/CIS Section R7.7.8.

Some modes of action of tumour formation are considered to be not relevant to humans. Where such a mechanism is identified then classification may not be appropriate Only if a mode of action of tumour development is conclusively determined not to be operative in humans may the carcinogenic evidence for that tumour be discounted. However, a weight of evidence evaluation for a substance calls for any other tumorigenic activity to be evaluated as well. In addition, the existence of a secondary mechanism of action with the implication of a practical threshold above a certain dose level (e.g., hormonal effects on target organs or on mechanisms of physiological regulation, chronic stimulation of cell proliferation) may lead to a downgrading of a Category 1 to Category 2 classification.

The various international documents on carcinogen assessment all note that mode of action in and of itself, or consideration of comparative metabolism, should be evaluated on a case-by-case basis and are part of an analytic evaluative approach. One must look closely at any mode of action in animal experiments taking into consideration comparative toxicokinetics/toxicodynamics between the animal test species and humans to determine the relevance of the results to humans. This may lead to the possibility of discounting very specific effects of certain types of chemicals. Life stage-dependent effects on cellular differentiation may also lead to qualitative differences between animals and humans.

To establish a mode of action will usually require specific investigative studies over and above the standard carcinogenicity study. All available data must be considered carefully to judge if it can be concluded with confidence that the tumours are being induced through that specific mechanism. The IPCS Framework for Analyzing the Relevance of a Cancer Mode of

Action for Humans (2007) can be a useful way to construct and present a robust and transparent assessment of such data.

Some mechanisms of tumour formation considered not relevant for humans:

- Kidney tumours in male rats associated with substances causing α2μ-globulin nephropathy (IARC, 1999)
- Pheochromocytomas in male rats exposed to particulates through inhalation secondary to hypoxemia (Ozaki *et al*, 2002)
- Leydig cell adenomas induced by dopamine antagonists or gonadotropin-releasing hormone (GnRH) (EU Specialised Experts, 2004; RIVM, 2004)
- Urinary bladder tumours due to crystals in the bladder (IARC, 1999)
- Forestomach tumours in rodents following administration by gavage of irritating or corrosive, non-genotoxic substances (RIVM, 2003; IARC 2003)
- Certain thyroid tumours in rodents mediated by UDP glucuronyltransferase (UGT) induction (IARC, 1999; EU Specialised Experts, 1999)
- Liver tumours in rodents conclusively linked to peroxisome proliferation (IARC, 1994)

3.6.2.3.3 Consideration of mutagenicity

Annex I: 3.6.2.2.6. Mutagenicity: It is recognised that genetic events are central in the overall process of cancer development. Therefore evidence of mutagenic activity in vivo may indicate that a substance has a potential for carcinogenic effects.

As indicated in Section 3.6.2.1 and above, carcinogenic chemicals have conventionally been divided according to the presumed mode of action; genotoxic or non-genotoxic. Evidence of genotoxic activity is gained from studies on mutagenic activity.

It should be noted that in general if a substance is mutagenic then it will be considered to be potentially carcinogenic in humans however mutagenicity data alone are insufficient information to justify a carcinogen classification. In some cases where only *in vitro* and *in vivo* mutagenicity are present without carcinogenicity data, a Category 2 classification can be considered when all factors have been considered such as type and quality of the mutagenicity data, structure activity relationships etc. A single positive carcinogenicity study in one species and sex in combination with positive *in-vivo* mutagenicity data would be considered to provide sufficient evidence of carcinogenicity.

Lack of genotoxicity is an indicator that other mechanisms are in operation as indicated in Section 3.6.2.3.2(k) above. Thus careful analysis based on all available information is required to identify the mechanism and derive a classification category taking into account the factors leading to the tumours observed, in the animals.

3.6.2.3.4 Non testing data

Annex I: 3.6.2.2.7. A substance that has not been tested for carcinogenicity may in certain instances be classified in Category 1A, Category 1B or Category 2 based on tumour data from a structural analogue together with substantial support from consideration of other important factors such as formation of common significant metabolites, e.g. for benzidine congener dyes.

A chemical that has not been tested for carcinogenicity may in certain instances be classified as a carcinogen based on tumour data from a structurally similar chemical with which it is predicted to have similar carcinogenic activity. Such an approach must always be based on a robust and transparent argument to support this supposition. There may also be evidence demonstrating similarity in terms of other important factors such as toxicokinetics or

mutagenic activity etc. (OECD 2004, 2005, 2007; IR/CSA, Section R.6, QSARs and grouping of chemicals).

In the absence of carcinogenicity data, read-across can be used to support a classification for carcinogenicity when the chemical in question is similar to a known or suspected carcinogen (Category 1A, 1B or 2). The similarity between chemicals is considered in terms of structural features, physico-chemical properties and overall toxicological profile.

In general the chemicals will share a common structural element or functional group (*i.e.*, a toxiphore) that has been shown to be integral to the underlying mechanism of carcinogenicity for chemicals with this toxiphore in well conducted studies. These toxiphores can be identified through expert judgement or through automated systems such as (Q)SARs. The read-across should also consider the physico-chemical properties of the chemical and data from other toxicity studies to judge the similarity between the chemicals in terms of bioavailability by relevant routes of exposure and toxicokinetics. The toxicity profile from other studies should also be compared (*e.g.,* acute and repeated-dose toxicity and mutagenicity) and should share similarities in nature and severity. Data from shorter term toxicity studies may be useful, particularly for non-genotoxic carcinogens, to indicate that the chemicals cause the same underlying pathological changes (*e.g.,* hyperplasia), and act via a common mode of action. Any predictions made on the basis of read-across should take into account the totality of data on the chemicals in question, including the physico-chemical properties, toxicological profile, toxicokinetics, structural analogy and the performance of any (Q)SAR models used, in a weight of evidence approach driven by expert judgement. The final decision must be clear, scientifically defensible and transparent.

The specific category depends on the category of the known carcinogen and the degree of confidence in the robustness of the read-across prediction. The category will not be higher than the chemical used to read-across from, but normally may be the same. However a lower category may be applied if the read-across highlights a possible carcinogenic hazard, and thus supports a classification, but there is uncertainty as to the robustness of the read-across prediction or there is evidence, for instance from mechanistic or other studies, that the chemical may be of lower concern for carcinogenicity.

If a chemical is similar to a substance known to be carcinogenic and shares the toxiphore that is considered to be causally related to carcinogenicity, then it is unlikely that there will be sufficient confidence in a prediction of no hazard (for instance based on arguments relating to differences in physico-chemical or steric properties), to justify no classification in the absence of supporting negative experimental data. However, the bioavailability of the toxiphore will need evaluation (IR/CSA R.6).

3.6.2.4 Decision on classification

As mentioned throughout, classification as a carcinogen is based on consideration of the strength of evidence with additional considerations (weight of evidence) being taken into account as appropriate. It is recognised that, in most cases, expert judgment is necessary to determine the classification category.

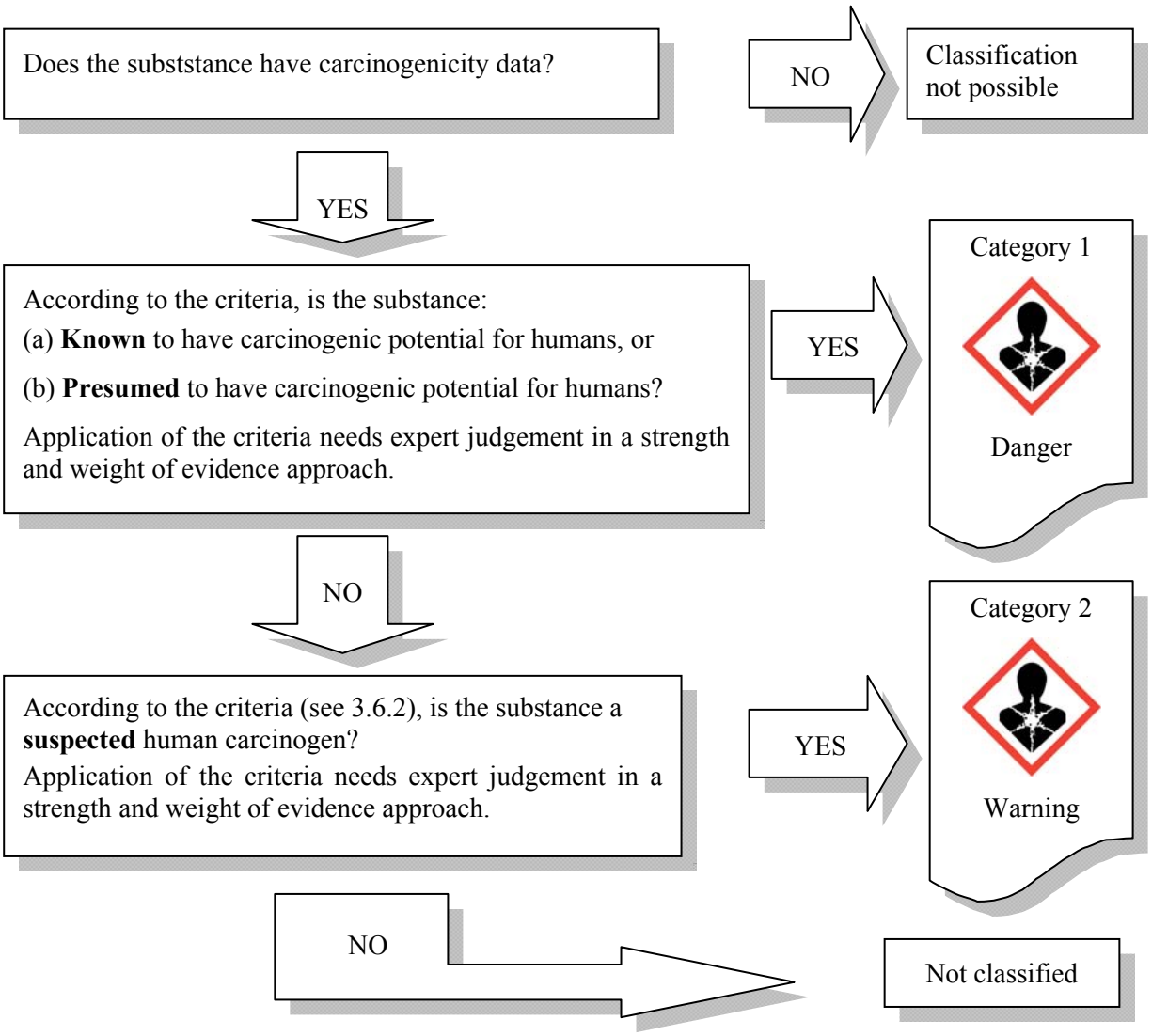
3.6.2.5 Setting of specific concentration limits

Experimental studies have revealed large variations in the doses of various carcinogenic substances needed to induce tumours in animals. Thus, the amounts of chemical carcinogens required to induce tumours vary with a factor of up to 10^8-10^9 for different compounds. It is reasonable to assume that there is similar variation in the potency of substances carcinogenic to humans (Sanner and Dybing, 2005).

The carcinogenic properties of mixtures are normally not tested. The classification and labelling of mixtures for carcinogenicity is therefore based on the classification of the ingredients and the percentage of each ingredient in the mixture. As indicated in Section 3.6.3, the criteria contain default percentages for classification of mixtures with carcinogenic properties but CLP, Article 10.1 allows the use of specific concentration limits (SCL) based on the potency of the carcinogen(s). The EU has adopted the T25 concept for carcinogenicity (Dybing *et al*., 1997) with additional considerations as a measure for intrinsic potency and a guidance document (EC, 1999) to assist in establishing SCLs for carcinogens. By using this approach the SCL may occasionally be reduced or raised from the default generic concentration limits.

3.6.2.6 Decision logic for classification of substances

The decision logic which follows is taken from the GHS Guidance. It is strongly recommended that the person responsible for classification, study the criteria for classification before and during use of the decision logic.



3.6.3 Classification of mixtures for carcinogenicity

3.6.3.1 Classification criteria for mixtures

Classification of mixtures will be based on the available test data for the **individual ingredients** of the mixture, using cut-off values/concentration limits for those ingredients and taking into account potency consideration. The classification may **a case-by-case basis** be based on the available test data for the mixture as a whole (see Section 3.6.3.1.2) or based on bridging principles (see Section 3.6.3.1.3).

3.6.3.1.1 When data are available for all ingredients or only for some ingredients

Annex I: 3.6.3.1.1. The mixture will be classified as a carcinogen when at least one ingredient has been classified as a Category 1A, Category 1B or Category 2 carcinogen and is present at or above the appropriate generic concentration limit as shown in Table 3.6.2 below for Category 1A, Category 1B and Category 2 respectively.

Table 3.6.2

Generic concentration limits of ingredients of a mixture classified as carcinogen that trigger classification of the mixture

Ingredient classified as:	Generic concentration limits triggering classification of a mixture as:		
	Category 1A carcinogen	Category 1B carcinogen	Category 2 carcinogen
Category 1A carcinogen	≥ 0,1 %	—	—
Category 1B carcinogen	—	≥ 0,1 %	—
Category 2 carcinogen	—	—	≥ 1,0 % [Note 1]

Note

The concentration limits in the table above apply to solids and liquids (w/w units) as well as gases (v/v units).

Note 1

If a Category 2 carcinogen is present in the mixture as an ingredient at a concentration ≥ 0,1% a SDS shall be available for the mixture upon request.

In case a SCL has been established for one or more ingredients these SCLs have precedence over the respective GCLs. See Section 3.6.2.5for the setting of SCLs for substances.

3.6.3.1.2 When data are available for the complete mixture

Annex I: 3.6.3.2.1. Classification of mixtures will be based on the available test data for the individual ingredients of the mixture using concentration limits for the ingredients classified as carcinogens. On a case-by-case basis, test data on mixtures may be used for classification when demonstrating effects that have not been established from the evaluation based on the individual ingredients. In such cases, the test results for the mixture as a whole must be shown to be conclusive taking into account dose and other factors such as duration, observations, sensitivity and statistical analysis of carcinogenicity test systems. Adequate documentation supporting the classification shall be retained and made available for review upon request.

3.6.3.1.3 When data are not available for the complete mixture: bridging principles

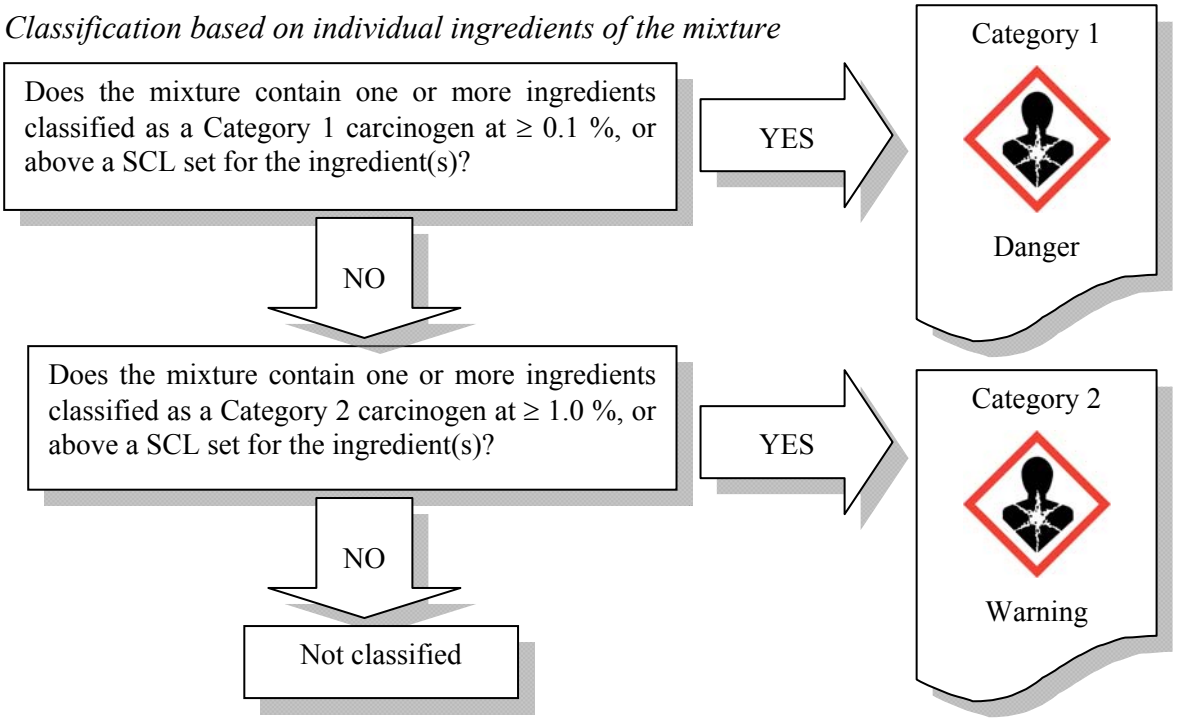
Annex I: 3.6.3.3.1. Where the mixture itself has not been tested to determine its carcinogenic hazard, but there are sufficient data on the individual ingredients and similar tested mixtures (subject to the provisions of paragraph 3.6.3.2.1) to adequately characterise the hazards of the mixture, these data shall be used in accordance with the applicable bridging rules set out in section 1.1.3.

Note that not all bridging principles in Annex I, section 1.1.3. are applicable when classifying for carcinogenicity.

3.6.3.2 Decision logic for classification of mixtures

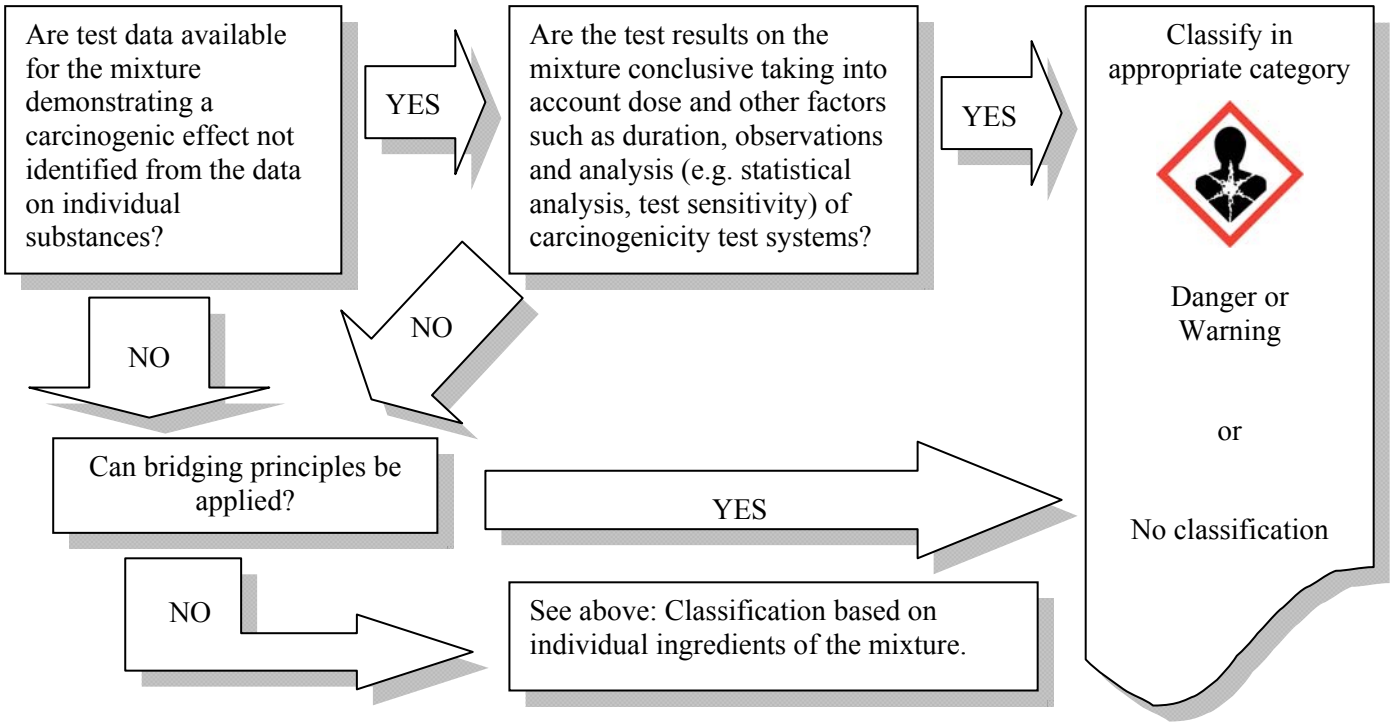
The decision logic which is based on the GHS Guidance is revised to meet CLP requirements. It is strongly recommended that the person responsible for classification, study the criteria for classification before and during use of the decision logic.

Classification based on individual ingredients of the mixture



Modified classification on a case-by-case basis

Test data on mixtures may be used for classification when demonstrating effects that have not been established from the evaluation based on the individual ingredients (CLP Section 3.6.3.1.1, see also CLP Article 6(3)).



3.6.4 Hazard communication in form of labelling for carcinogenicity

3.6.4.1 Pictograms, signal words, hazard statements and precautionary statements

Annex I; 3.6.4.1 Label elements shall be used in accordance with Table 3.6.3, for substances or mixtures meeting the criteria for classification in this hazard class.

Table3.6.3

Label elements for carcinogenicity

Classification	Category 1A or Category 1B	Category 2
GHS Pictograms		
Signal Word	Danger	Warning
Hazard Statement	H350: May cause cancer (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	H351: Suspected of causing cancer (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)
Precautionary Statement Prevention	P201 P202 P281	P201 P202 P281
Precautionary Statement Response	P308 + P313	P308 + P313
Precautionary Statement Storage	P405	P405
Precautionary Statement Disposal	P501	P501

The wording of the Precautionary Statements is found in CLP Annex IV, Part 2.

Where there is conclusive proof that cancer is caused only by certain route(s), then this route may be stated in the hazard statement. In case of Category 1 carcinogens where there is conclusive proof that cancer is caused only by inhalation, the hazard phrase “H350i: May cause cancer by inhalation” applies (CLP Annex VII Table 1.1).

3.6.4.2 Additional labelling provisions

There are no additional labelling provisions for carcinogenic substances and mixtures in CLP, however there are provisions laid out in Annex XVII to REACH. The packaging of substances with harmonised classification as carcinogenic Category 1A or Category 1B, or mixtures containing such substances, "must be marked visibly**,** legibly and indelibly as follows: ‘Restricted to professional users’." (REACH, Annex XVII, point 28).

3.6.5 Re-classification of substances and mixtures classified for carcinogenicity according to DSD and DPD

3.6.5.1 Is direct "translation" of classification and labelling possible?

A direct translation as indicated in the translation table in Annex VII to CLP is generally possible. Translation from classification according to DSD and DPD to the classification according to CLP is as follows:

Carc. Cat. 1 is translated into Carc. 1A;

Carc. Cat. 2 is translated into Carc. 1B, and

Carc. Cat. 3 is translated into Carc. 2, respectively.

3.6.5.2 Some additional considerations for re-classification

There are only few situations where the direct translation may lead to different results, however, these are likely to be very rare.

The first difference in applying the CLP criteria is that sufficient evidence (Carc. 1B) for carcinogenicity in animals can also be derived from two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. The second difference applying the CLP criteria is that sufficient evidence (Carc. 1B) for carcinogenicity in animals can be derived from an increased incidence of tumours in both sexes of a single species in a well-conducted study, ideally conducted under GLP. The criteria according to DSD allowed classification in Carc. Cat. 2 (analogous to CLP Carc. 1B) where there were positive results in two animal species or clear positive evidence in one species, together with supporting evidence such as genotoxicity data, metabolic or biochemical studies, induction of benign tumours, structural relationship with other known carcinogens, or data from epidemiological studies suggesting an association.

Another difference can be derived from the IARC classification as '*possibly carcinogenic to humans (IARC 2B)'*. This category is used for substances for which there is less than *sufficient evidence of carcinogenicity* in experimental animals. According to IARC, classification as '*possibly carcinogenic to humans'* may be derived from solely strong evidence from mechanistic and other relevant data. This means that no *in vivo* carcinogenicity nor (Q)SAR data need to be available to arrive at classification for limited evidence of carcinogenicity.

3.6.6 Examples of classification for carcinogenicity

Classification for carcinogenicity involves the consideration of many different factors, as outlined above, and is a complex task which needs expert judgement. Therefore no examples of classification for carcinogenicity are included in this guidance document.

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3.7 REPRODUCTIVE TOXICITY

3.7.1 Definitions and general considerations for reproductive toxicity

Annex I: 3.7.1.1. Reproductive toxicity includes adverse effects on sexual function and fertility in adult males and females, as well as developmental toxicity in the offspring. The definitions presented below are adapted from those agreed as working definitions in IPCS/EHC Document N°225, Principles for Evaluating Health Risks to Reproduction Associated with Exposure to Chemicals. For classification purposes, the known induction of genetically based heritable effects in the offspring is addressed in Germ Cell Mutagenicity (section 3.5), since in the present classification system it is considered more appropriate to address such effects under the separate hazard class of germ cell mutagenicity.

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

(a) Adverse effects on sexual function and fertility;

(b) Adverse effects on development of the offspring.

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

3.7.1.2. For the purpose of classification the hazard class Reproductive Toxicity is differentiated into:

- adverse effects
  - on sexual function and fertility, or
  - on development;
- effects on or via lactation

3.7.1.3. *Adverse effects on sexual function and fertility*

Any effect of substances that has the potential to interfere with sexual function and fertility. This includes, but is not limited to, alterations to the female and male reproductive system, adverse effects on onset of puberty, gamete production and transport, reproductive cycle normality, sexual behaviour, fertility, parturition, pregnancy outcomes, premature reproductive senescence, or modifications in other functions that are dependent on the integrity of the reproductive systems.

3.7.1.4. *Adverse effects on development of the offspring*

Developmental toxicity includes, in its widest sense, any effect which interferes with normal development of the conceptus, either before or after birth, and resulting from exposure of either parent prior to conception, or exposure of the developing offspring during prenatal development, or postnatally, to the time of sexual maturation. However, it is considered that classification under the heading of developmental toxicity is primarily intended to provide a hazard warning for pregnant women, and for men and women of reproductive capacity. Therefore, for pragmatic purposes of classification, developmental toxicity essentially means adverse effects induced during pregnancy, or as a result of parental exposure. These effects can be manifested at any point in the life span of the organism. The major manifestations of developmental toxicity include (1) death of the developing organism, (2) structural abnormality, (3) altered growth, and (4) functional deficiency.

3.7.1.1 Special considerations on effects on or via lactation

This classification is intended to indicate when a substance may cause harm due to its effects on or via lactation. This can be due to the substance being absorbed by women and adversely affecting milk production or quality, or due to the substance (or its metabolites) being present in breast milk in amounts sufficient to cause concern for the health of a breastfed child.

Annex I: 3.7.1.5. Adverse effects on or via lactation are included under reproductive toxicity, but for classification purposes such effects are treated separately. This is because it is desirable to be able to classify substances specifically for an adverse effect on lactation so that a specific hazard warning about this effect can be provided for lactating mothers.

Therefore, if the adverse effects that lead to impaired development in the offspring also occur after *in utero* exposure then the substance would also be classified for developmental toxicity. In other words, the classification for effects on or via lactation is independent of consideration of the reproductive toxicity of the substance, and a substance can be classified for effects on or via lactation whether or not the substance is also classified for reproductive toxicity.

Classification for effects on or via lactation alone is not sufficient for a substance to be subject to harmonised classification and labelling in accordance with CLP, Article 36.

3.7.2 Classification of substances for reproductive toxicity

3.7.2.1 Identification of hazard information

3.7.2.1.1 Identification of human data

Epidemiological studies as well as clinical data and case reports may be available as stated in CLP, Annex I, 3.7.2.2.3 and further under IR/CSA, Section R.7.6.3.2.

3.7.2.1.2 Identification of non human data

In-vitro, animal data and non-testing information used for classification is outlined in CLP Annex I, 3.7.2.5. and further specific references to different testing methods are listed in IR/CSA, Section R.7.6.3.1.

3.7.2.2 Classification criteria

Annex I: 3.7.2.1.1. For the purpose of classification for reproductive toxicity, substances are allocated to one of two categories. Within each category, effects on sexual function and fertility, and on development, are considered separately. In addition, effects on lactation are allocated to a separate hazard category.

Table 3.7.1 (a)

Hazard categories for reproductive toxicants

Categories	Criteria
CATEGORY 1	Known or presumed human reproductive toxicant Substances are classified in Category 1 for reproductive toxicity when they are known to have produced an adverse effect on sexual function and fertility, or on development in humans or when there is evidence from animal studies, possibly supplemented with other information, to provide a strong presumption that the substance has the capacity to interfere with reproduction in humans. The classification of a substance is further distinguished on the basis of whether the evidence for classification is primarily from human data (Category 1A) or from animal data (Category 1B).
Category 1A	Known human reproductive toxicant The classification of a substance in this Category 1A is largely based on evidence from humans.
Category 1B	Presumed human reproductive toxicant The classification of a substance in this Category 1B is largely based on data from animal studies. Such data shall provide clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate.
CATEGORY 2	Suspected human reproductive toxicant Substances are classified in Category 2 for reproductive toxicity when there is some evidence from humans or experimental animals, possibly

	supplemented with other information, of an adverse effect on sexual function and fertility, or on development, and where the evidence is not sufficiently convincing to place the substance in Category 1. If deficiencies in the study make the quality of evidence less convincing, Category 2 could be the more appropriate classification. Such effects shall have been observed in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects.

3.7.2.2.1 Classification in the presence of parental toxicity

3.7.2.2.1.1 Effects to be considered in the presence of marked systemic effects

In general all findings on reproductive toxicity should be considered for classification purposes irrespective of the level of parental toxicity. A comparison between the severity of the effects on fertility/development and the severity of other toxicological findings must be performed.

Fertility effects

Adverse effects on fertility and reproductive performance seen only at dose levels causing marked systemic toxicity (e.g. lethality, dramatic reduction in absolute body weight, coma) are not relevant for classification purposes.

There is no established relationship between fertility effects and less marked systemic toxicity. Therefore it should be assumed that effects on fertility seen at dose levels causing less marked systemic toxicity are not a secondary consequence of this toxicity. However, mating behaviour can be influenced by parental effects not directly related to reproduction (e.g. sedation, paralysis), and such effects on mating behaviour may not warrant classification.

Developmental effects:

Annex I: 3.7.2.4. *Maternal toxicity*

3.7.2.4.1. Development of the offspring throughout gestation and during the early postnatal stages can be influenced by toxic effects in the mother either through non-specific mechanisms related to stress and the disruption of maternal homeostasis, or by specific maternally-mediated mechanisms. In the interpretation of the developmental outcome to decide classification for developmental effects it is important to consider the possible influence of maternal toxicity. This is a complex issue because of uncertainties surrounding the relationship between maternal toxicity and developmental outcome. Expert judgement and a weight of evidence approach, using all available studies, shall be used to determine the degree of influence that shall be attributed to maternal toxicity when interpreting the criteria for classification for developmental effects. The adverse effects in the embryo/foetus shall be first considered, and then maternal toxicity, along with any other factors which are likely to have influenced these effects, as weight of evidence, to help reach a conclusion about classification.

3.7.2.4.2. Based on pragmatic observation, maternal toxicity may, depending on severity, influence development via non-specific secondary mechanisms, producing effects such as depressed foetal weight, retarded ossification, and possibly resorptions and certain malformations in some strains of certain species. However, the limited number of studies which have investigated the relationship between developmental effects and general maternal toxicity have failed to demonstrate a consistent, reproducible relationship across species. Developmental effects which occur even in the presence of maternal toxicity are considered to be evidence of developmental toxicity, unless it can be unequivocally demonstrated on a case-by-case basis that the developmental effects are secondary to maternal toxicity. Moreover, classification shall be considered where there is a

significant toxic effect in the offspring, e.g. irreversible effects such as structural malformations, embryo/foetal lethality, significant post-natal functional deficiencies.

3.7.2.4.3. Classification shall not automatically be discounted for substances that produce developmental toxicity only in association with maternal toxicity, even if a specific maternally-mediated mechanism has been demonstrated. In such a case, classification in Category 2 may be considered more appropriate than Category 1. However, when a substance is so toxic that maternal death or severe inanition results, or the dams are prostrate and incapable of nursing the pups, it is reasonable to assume that developmental toxicity is produced solely as a secondary consequence of maternal toxicity and discount the developmental effects. Classification is not necessarily the outcome in the case of minor developmental changes, when there is only a small reduction in foetal/pup body weight or retardation of ossification when seen in association with maternal toxicity.

Adverse effects on postnatal survival and growth seen only at dose levels causing maternal toxicity may be due to lack of maternal care or other causes such as adverse effects on or via lactation or developmental toxicity. In case post-natal effects are caused by lack of maternal care classification for developmental effects may not be warranted.

3.7.2.2.1.2 Relevance of specific effects in the parent

All types of reproductive toxic effects may be considered as secondary to parental toxicity. With current knowledge it is not possible to identify specific effects indicating toxicity in parental animals which do not have any relevance to reproductive toxicity (e.g. peroxisome proliferation). However parental toxicity that is less than marked should not influence the classification for reproductive toxicity independent of the specific parental effects observed.

In general it is very difficult to prove a causal relationship between a parentally mediated mechanism and adverse effects in the offspring. Usually data are insufficient to conclude if an effect on the offspring is a direct effect or secondary to parental toxicity. In order to determine whether a reproductive toxic effect is independent or secondary to a parental effect, it would be most appropriate to correlate individual data for offspring and their parents. Nevertheless, associations between parental and offspring effects do not by default prove a causal relationship.

In cases where a causal relationship is established between reproductive and parental toxicity and the effects on the offspring can be proved to be secondary to maternal toxicity, they may still be relevant for developmental classification, dependent on the severity of the effects.

A comparison between the severity of the maternal toxicity and the severity of the findings in the offspring must be performed. There are several examples showing that the developing organism can be more susceptible and the long-term consequences can be more severe than in the adult. The mother might recover while the offspring could be permanently affected.

Annex I: 3.7.2.4.4. Some of the end points used to assess maternal effects are provided below. Data on these end points, if available, need to be evaluated in light of their statistical or biological significance and dose response relationship.

Maternal mortality:

an increased incidence of mortality among the treated dams over the controls shall be considered evidence of maternal toxicity if the increase occurs in a dose-related manner and can be attributed to the systemic toxicity of the test material. Maternal mortality greater than 10 % is considered excessive and the data for that dose level shall not normally be considered for further evaluation.

Mating index

(no. animals with seminal plugs or sperm/no. mated x 100)([1])

Fertility index
(no. animals with implants/no. of matings x 100)

Gestation length
(if allowed to deliver)

Body weight and body weight change:
Consideration of the maternal body weight change and/or adjusted (corrected) maternal body weight shall be included in the evaluation of maternal toxicity whenever such data are available. The calculation of an adjusted (corrected) mean maternal body weight change, which is the difference between the initial and terminal body weight minus the gravid uterine weight (or alternatively, the sum of the weights of the foetuses), may indicate whether the effect is maternal or intrauterine. In rabbits, the body weight gain may not be useful indicators of maternal toxicity because of normal fluctuations in body weight during pregnancy.

Food and water consumption (if relevant):
The observation of a significant decrease in the average food or water consumption in treated dams compared to the control group is useful in evaluating maternal toxicity, particularly when the test material is administered in the diet or drinking water. Changes in food or water consumption need to be evaluated in conjunction with maternal body weights when determining if the effects noted are reflective of maternal toxicity or more simply, unpalatability of the test material in feed or water.

Clinical evaluations (including clinical signs, markers, haematology and clinical chemistry studies):
The observation of increased incidence of significant clinical signs of toxicity in treated dams relative to the control group is useful in evaluating maternal toxicity. If this is to be used as the basis for the assessment of maternal toxicity, the types, incidence, degree and duration of clinical signs shall be reported in the study. Clinical signs of maternal intoxication include: coma, prostration, hyperactivity, loss of righting reflex, ataxia, or laboured breathing.

Post-mortem data:
Increased incidence and/or severity of post-mortem findings may be indicative of maternal toxicity. This can include gross or microscopic pathological findings or organ weight data, including absolute organ weight, organ-to-body weight ratio, or organ-to-brain weight ratio. When supported by findings of adverse histopathological effects in the affected organ(s), the observation of a significant change in the average weight of suspected target organ(s) of treated dams, compared to those in the control group, may be considered evidence of maternal toxicity.

([1]) It is recognised that the Mating index and the Fertility index can also be affected by the male.

3.7.2.2.2 Substances causing effects on or via lactation

Annex I: *Table 3.7.1 (b)*

Hazard category for lactation effects

EFFECTS ON OR VIA LACTATION

Effects on or via lactation are allocated to a separate single category. It is recognised that for many substances there is no information on the potential to cause adverse effects on the offspring via lactation. However, substances which are absorbed by women and have been shown to interfere with lactation, or which may be present (including metabolites) in breast milk in amounts sufficient to cause concern for the health of a breastfed child, shall be classified and labelled to indicate this property hazardous to breastfed babies. This classification can be assigned on the:

(a) human evidence indicating a hazard to babies during the lactation period; and/or

(b) results of one or two generation studies in animals which provide clear evidence of adverse effect in the offspring due to transfer in the milk or adverse effect on the quality of the milk; and/or

(c) absorption, metabolism, distribution and excretion studies that indicate the likelihood that the substance is present in potentially toxic levels in breast milk.

There are the two general criteria for this classification.

(i) …are absorbed by women and have been shown to interfere with lactation.

This relates to effects in the mother that impact adversely on the breast milk, either in terms of the quantity produced or the quality of the milk produced (i.e. the composition). Any effect on the quantity or quality of the breast milk is likely to be due to systemic effects in the mother. However, overt maternal toxicity may not be seen (e.g. the substance may just affect the transfer of a nutrient into the milk with no consequence for the mother). The type and magnitude of the maternal effects and their potential influence on lactation/milk production need to be considered on a case-by-case basis to determine whether classification for effects on or via lactation is necessary.

If a substance causes marked overt systemic toxicity in the mother at the same dose level then it is possible that this may indirectly impair milk production or impair maternal care as a non-specific secondary effect. The type and magnitude of the maternal effects and their potential influence on lactation/milk production needs to be considered on a case-by-case basis using expert judgment. If there is robust evidence to indicate that the effects on lactation are not caused directly by the substance then it should not be classified as such.

A substance which does not cause overt toxicity in the mother but which interferes with milk production or quality will normally be classified for effects on or via lactation because in this case the effect on lactation is most likely a direct substance-related effect.

(ii) … may be present (including metabolites) in breast milk in amounts sufficient to cause concern for the health of a breastfed child.

This relates to the ability of the substance (including metabolites), to enter the breast milk in amounts sufficient to cause a concern. When the effect on the offspring is caused by the substance (or metabolite) after transport through the milk then the maternal toxicity has no relevance for classification. In general, positive data should usually be available to show that a substance leads to an adverse effect in offspring due to effects on lactation to support classification. However, in exceptional circumstances, if there are substantiated grounds for concern that the substance may have an adverse effect via lactation then it may be classified as such in the absence of direct evidence. This should be based on a quantitative comparison of the estimated transfer via the milk and the threshold for toxicity in the pups. This might apply in cases where the substance has the capacity to bioaccumulate which would lead to a potentially higher burden in the offspring, or where there is evidence that the offspring may be more sensitive to the substance's toxicity than adult.

The mere presence of the substance in the milk alone, without a strong justification for a concern to offspring, would normally not support classification for effects on or via lactation.

3.7.2.3 Evaluation of hazard information

Appropriate classification will always depend on an integrated assessment of all available data and their interrelationship using a weight of evidence approach. Individual datasets should be analysed case by case using expert judgment.

3.7.2.3.1 Use of data from standard repeat dose tests

Fertility effects:

Toxicological effects, including marked effects, observed in a standard repeat dose study could be considered valid for the pre-mating phase for adult females and the pre- and post-mating phase for adult males. However in case of contradictions between the standard repeat dose studies and reproductive studies, the result from the latter should be considered more relevant.

For pregnant and lactating females and juveniles data from standard repeat dose studies cannot easily be extrapolated.

Developmental effects:

A detailed assessment of toxicity in pregnant animals cannot be extrapolated from studies with non-pregnant animals. However information from general toxicity studies might give an indication of the maternal toxicity that could be anticipated in a subsequent developmental toxicity study.

3.7.2.3.2 Study design

Assessment of the dose-response relationships of parental and reproductive toxicity end points and their possible interrelationship require study designs where the dose intervals are not too far apart. This will improve dose-response assessment and will also reduce the chance of masking malformations by severe toxicity (e.g. resorptions, lethality) at high dose levels. This may lead to experimental designs in which more than the standard three dose groups and a control are tested. Endpoints from repeat dose toxicity studies may be considered useful for inclusion in subsequent reproductive toxicity studies. These endpoints should be evaluated both in parental animals and in offspring.

3.7.2.3.3 Evaluation of evidence relating to effects on or via lactation

(a) Human evidence indicating a hazard to babies during the lactation period;

This criterion acknowledges that human data, e.g. from epidemiological studies or case reports, indicating a hazard to babies during the lactation period can also be used to support classification for effects on or via lactation. The use of human data is self-explanatory and any study should be assessed on its merits for which expert judgment may be required. Observations in humans that give evidence of adverse effects in breastfed babies of mothers exposed to the chemical in question should be taken to provide clear evidence supporting classification. Such studies which do not show an adverse effect need to be considered carefully. Human studies investigate the risk under the specific conditions of exposure, and a negative finding may just reflect inadequate methods to detect effects or insufficient exposures rather than prove the absence of a hazard.

In practice, useful human data are likely to be rare due to the nature of the endpoint. More likely are survey type studies which measure the levels of the chemical in breast milk. Such studies may provide useful information on the potential for maternal exposure to lead to the presence of the chemical in the breast milk and so they may be of use in assessing the need for classification for effects on or via lactation.

(b) Results of one or two generation studies in animals which provide clear evidence of adverse effect in the offspring due to transfer in the milk or adverse effect on the quality of the milk;

Ideally, studies will be available which inform directly on whether the substance causes adverse effects in the offspring due to an adverse effect on lactation. One generation or multi-

generation reproductive toxicity studies, which involve direct exposure or exposure via the milk of the offspring postnatally, usually provide information on this. The most common study performed today is the two-generation study, but one-generation studies with new study designs, like the screening study OECD TG421/422 or the developmental neurotoxicity study OECD TG426, also exist. The value of these studies is that they directly observe the pups during lactation and any adverse effects, such as deaths, decreased viability, clinical signs such as reduced bodyweight gain etc, can be directly observed and quantified. However, expert judgement is required to decide whether these effects in pups are due to a direct adverse effect on lactation, or are due to impaired nursing behaviour which is a non specific secondary consequence of maternal toxicity. If the impaired nursing behaviour is proven to be a substance related specific effect on behaviour, then classification for effects on or via lactation may be appropriate. It should also be noted that some developmental effects resulting from exposure in utero would only manifest post-natally and those should not be used for classification for effects on or via lactation. Cross-fostering studies, where available, may help establish whether effects are due to in utero or lactational exposure. If there is sufficient data that animal results are not relevant to humans, they should not be taken into account.

(c) Absorption, metabolism, distribution and excretion studies that indicate the likelihood that the substance is present in potentially toxic levels in breast milk;

The criterion indicates that toxicokinetic studies showing that the substance can be present at potentially toxic levels in breast milk can support classification. The implicit assumption behind this clause is that the pups may receive a body burden of the toxic entity through suckling that is sufficient to cause toxicity when the level of the toxic entity in the milk is above a certain threshold level ("a level to cause concern"). There is no robust way to estimate what this threshold is, although the likely body burden expected in the breastfed child may be compared to the toxicity data in adults (e.g. an appropriate NOAEL or BMD) to indicate whether toxicity is likely. The mere presence of a substance in the milk, without a robust argument that these levels may be potentially toxic to offspring would not normally support classification.

The toxicokinetics of a substance and the likelihood that it will enter the breast milk may be predicted on the basis of the physico-chemical properties of the chemical (e.g. using pKa, logP, water solubility, and molecular weight etc) and this information could be used as part of the argumentation outlined above. The potential of a substance to bioaccumulate following repeated exposure may also be an important factor to consider as this may contribute to the body burden reaching a potentially toxic level in the offspring. Studies where the offspring/neonates have extended exposure, such as multi-generation studies, implicitly allow for bioaccumulation and so findings from these studies can, in themselves, be taken to provide information on the potential effects of bioaccumulation. Where these types of studies are not available, potential bioaccumulation can be taken into consideration as part of the toxicokinetic assessment using expert judgement.

There may be toxicokinetic and toxicodynamic reasons why neonates may potentially be more or less vulnerable to a particular adverse effect than adults due to the fact that certain systems (e.g. the immune and metabolic systems) and tissues/organs are immature and are still developing. Whether the neonate is more or less vulnerable than adults will depend on the specific chemical and will be determined by factors such as the hazardous properties of the chemical, its' physico-chemical properties and how it is metabolised. Therefore, the relative sensitivity of neonates and adults to a substance must be judged on a case by case basis using expert judgement. In the absence of any reliable and robust information to inform on this, it

should be assumed that neonates and adults are equivalent in terms of sensitivity to the substance.

Overall, classification for effects on or via lactation can be assigned on the basis of toxicokinetic data or a well substantiated estimate of the exposure through the milk alone provided that it is supported by an argument clearly justifying that the level present in the breast milk would be likely to harm developing offspring.

3.7.2.4 Decision on classification

According to CLP Annex I, Section 3.7.2.1.1, reproductive toxic substances are allocated to either Category 1A, 1B or 2. Effects on lactation are allocated to a separate hazard category and should be ascribed to a substance irrespective if it classified in any other category for reproductive toxicity or not.

3.7.2.5 Setting of 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.

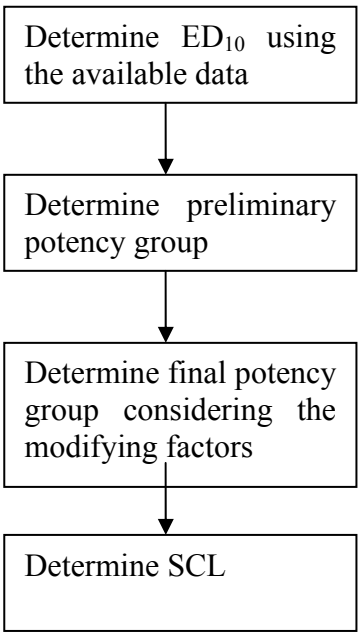
In exceptional circumstances specific concentration limits may be set by the manufacturer, importer or downstream user where he has adequate, reliable and conclusive scientific information that a hazard of a substance classified as hazardous is not evident at a level above the concentrations set for 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.

3.7.2.5.1 Procedure

The available data from animal and human studies are evaluated to establish the reproductive toxicity dose descriptor, ED_{10} (effective dose with a 10% effect level above the background), as described below. A preliminary conclusion as to whether the substance shows high, medium or low potency is taken based on the ED_{10} data. The preliminary potency evaluation may be modified after due consideration of a number of modifying factors as described in chapter 3.7.2.5.5. This results in the final potency group. Each final potency group is connected with a generic concentration limit (GCL) or a specific concentration limit (SCL). In this way SCLs are then set taking into account all relevant considerations. See figure 3.7.2.5.1. A background document containing the justification of the boundaries of the potency groups and the SCLs is available in Annex VI to this document.

It is noted that there may be alternative approaches to assess potency, such as basing it on the BMD Methodology (Bench Mark Dose). However such alternative methods are not elaborated in this current guidance, although this does not exclude their use. If alternative approaches are used, they have to be clearly justified from a scientific and regulatory point of view (see Article 10, CLP) and they must be able to provide robust scientific proposals and justifications.

Figure 3.7.2.5.1 Procedure for setting SCL for reproductive toxicity



3.7.2.5.2 Cases where potency evaluation is difficult or unfeasible

The process for evaluating potency assumes the availability of certain types of data. However, these data may not always be available. Also, the classification of substances as reproductive toxicants may be based on information such as grouping, read-across and the use of QSARs (Guidance IR/CSA, sections R.6 and R.7.2.3.1). In such cases, no direct estimate of the reproductive toxicity potency based on an ED_{10} value is possible. While there are often good reasons for extrapolation of the hazardous properties from one or more substances to another, the expected potency of the individual substances within the group may vary. In these cases a potency evaluation may be difficult or impossible. However, determination of the classification and the potency using non-testing methods is possible in some cases. These cases could include interpolation of an ED_{10} within a group of substances with comparable structures and effects or correction for molecular weight in case of extrapolation between different salts with comparable availability. If the classification of a substance in Category 2 is done on the basis of "limited evidence", the quality of the available data will in such cases determine whether a potency assessment is possible. In cases where no further evaluation is possible, the generic concentration limits of CLP apply. In general, more conclusive evidence is required when moving a substance to a lower potency group than to a higher potency group.

3.7.2.5.3 Determination of the ED_{10} value

The ED_{10} value (as used for reprotoxicity SCLs) is the lowest dose which induces reproductive toxic effects which fulfil the criteria for classification for reproductive toxicity with an incidence or magnitude of 10% after correction for the spontaneous incidence (see in 3.7.2.5.3.2).

Determining exactly which effect or combination of effects is the one that fulfils the classification criteria may seem difficult. However, for the majority of substances in the database, the developmental effect(s) observed at the lowest dose level was(/were) an increase in malformations and/or lethalities of the offspring. The ED_{10} for effects on sexual function and fertility is mainly based on effects on fertility and histopathological changes of the

reproductive organs. These effects clearly fulfil the classification requirements. Also, allocation to the final SCLs is based on a limited number of potency groups and not on the exact ED_{10} value. Therefore, in practice, it is likely that the ED_{10} values for several different effects fall into the same potency grouping, resulting in the same SCL.

The ED_{10} may be obtained either directly or by linear interpolation from experimental data or estimated using Bench Mark Dose (BMD) software. The use of BMD software will result in a more precise estimate of the ED_{10} because all data from the dose-response curve are used. The use of BMD software is needed when an ED_{10} cannot be determined using linear interpolation due to the absence of a NOAEL when the LOAEL has an effect size above 10%. In general, however, the use of BMD software is not required because of the wide potency groups used for setting the SCLs. However, it could be important for substances which are close to the boundary of a potency group. When an ED_{10} cannot be calculated by direct or linear interpolation from experimental data or by the use of BMD software, interpolation between the control group and the LOAEL should be used to determine the ED_{10}. In such cases, only SCLs below the GCL can be determined and not those above the GCL, if no other reliable information is available, because it may be difficult in these cases to prove the absence of effects at lower dose levels.

3.7.2.5.3.1 Determination in practice

In practice, often several effects on reproduction are observed in various studies, and the classification is based on the weight of evidence of all results. As a first step, it should be determined whether the classification is for effects on development, for effects on sexual function and fertility or both. The effects used for classification for developmental toxicity should be used to determine the potency for developmental toxicity only. The same applies to effects on sexual function and fertility. This means that for substances fulfilling the criteria for classification for both developmental effects and effects on sexual function and fertility, two ED_{10} values are derived which may differ and lead eventually to different SCLs. For both developmental effects and effects on sexual function and fertility, the lowest ED_{10} for the effect(s) that fulfil the criteria for classification in the different studies, is then used as the ED_{10} that determines the potency of that substance. Where there are doubts as to whether a specific effect fulfils the classification criteria, ED_{10} values for different effects could be taken forward to the next step, when modifing factors are considered, to determine the impact.

The calculation of the ED_{10} by linear interpolation requires a different approach depending on whether the effect is measured as an incidence (quantal data, non-parametric data), a magnitude (continuous data, parametric data) or both.

3.7.2.5.3.2 Quantal or non-parametric data

For effects that are measured as changes in incidence, such as an increase in the number of malformations or resorptions, the ED_{10} is defined as the dose level at which 10% of the test population above the incidence in the concurrent control shows the effect. There may be occasions where the historical control data have to be taken into account (for example when the concurrent control data are atypical and close to the extremes of the historical data). In the example in Table 3.7.2.5.1, the ED_{10} is 90 mg/kg bw/day because at this dose level 12% - 2% (control) = 10% of the test population shows the effect above the incidence in the control group.

Table 3.7.2.5.1 Example of the calculation of the ED_{10}

Dose	0 mg/kg	10 mg/kg	30 mg/kg	90 mg/kg
Malformations	2%	3%	7%	12%

For some effects the results of the calculation of the ED_{10} based on the incidence in pups may be different from that based on the incidence in litters. Scientific evidence may indicate which parameter is more appropriate, but in the absence of such information it is not possible to estimate which ED_{10} is more appropriate for a specific effect. In such cases, both the incidence in offspring and the incidence in litters should be calculated, and the lower ED_{10} value should be used.

3.7.2.5.3.3 Continuous or parametric data

For effects that are measured as changes in magnitude such as mean pup weight or testis weight, the ED_{10} is defined as the dose at which a change of 10%, compared to the concurrent control group, is observed. In the example in Table 3.7.2.5.2, the ED_{10} is 19.3 mg/kg bw/day because at this dose level the mean foetal bodyweight is calculated to be 90% of the control value. A 10% reduction of the control value of 6.2 g gives 5.58 g. Interpolation between 10 and 30 mg/kg bw/day to a dose level which would be expected to result in a foetal bodyweight of 5.58 g gives a value of 19.3 mg/kg bw/day.

Calculations: (30 – 10)/ (6 - 5.1) = 22.2 ; 6.0 – 5.58 = 0.42 ; 0.42 x 22,2 = 9.3 ; 10 + 9.3 = 19.3 mg/kg bw/day.

Table 3.7.2.5.2 Example on the calculation of the ED_{10}

dose	0 mg/kg	10 mg/kg	30 mg/kg	90 mg/kg
Mean foetal bodyweight (g)	6.2	6.0	5.1	4.5
		NOAEL	LOAEL	

3.7.2.5.3.4 Data combining incidence and magnitude

Some effects such as histopathological changes in the testis are a combination of effects on incidence and magnitude (grading of the effect by a pathologist). However, calculation of an ED_{10} taking both the incidence and the magnitude into account is not possible or at least more complex. The ED_{10} should therefore be based on the incidence of the effect below or above a certain magnitude. The magnitude of the effects that will be selected as a starting point has to be chosen carefully. Normally the particular effect size would be the lowest relevant for the respective classification. The ED_{10} is then determined as the dose level at which the incidence, of effects with a magnitude above that of the starting point, is 10% above the incidence in the control group. In practice this means that the grading system is converted into a simplified system where only percentages of animals in each dose group with an effect with a magnitude above the starting point are regarded as positive. However, it is recognised that this approach uses only a part of the actual data and is imprecise, and it may be appropriate that other effects also be considered in determining the ED_{10}.

Table 3.7.2.5.3 Example on the calculation of the ED_{10} for testicular effects (N=10)

	Dose (mg/kg)	**Testicular degeneration (n)**				
		none	slight	moderate	marked	severe
	0	4	5	1	0	0
	10	5	5	0	0	0
NOAEL	30	5	4	1	0	0
LOAEL	90	0	0	4	2	4

For the example in Table 3.7.2.5.3, the effects observed in the 10 mg/kg and 30 mg/kg dose groups have to be considered as equivalent to the effects of the control group so the NOAEL is 30 mg/kg. The magnitude of the testicular effect in the control group and the 10 and 30 mg/kg bw/day groups is slight or less. Because of the incidence observed in these three groups, the level of damage estimated as the starting point magnitude is 'slight'. The ED_{10} is then defined as a 10% increase of moderate effects or more above the control. In this example the incidences for moderate testicular degeneration or more are 10%, 0%, 10% and 100% at respectively 0, 10, 30 and 90 mg/kg bw/day. The ED_{10} is then defined as the dose level with 20% (control plus 10%) of moderate testicular effects. The ED_{10} would be 36.6 mg/kg bw/day based on interpolation between 30 and 90 mg/kg bw/day to a dose with 20% animals with moderate testicular degeneration or higher.

3.7.2.5.3.5 Specific data types

Non-oral studies

In most cases only oral studies will be available and used for determination of the potency. However, if the classification is based on the effects seen in non-oral studies or only non-oral studies are available, then these data should also be used to determine the potency. This requires route-to-route extrapolation of the external dermal or inhalatory dose to a corresponding oral dose. This should be done as described in the ECHA guidance on information requirements and chemical safety assessment in REACH (IR/CSA, section R.8).

Extrapolation from dermal exposure to oral exposure should only be done when there are sufficient kinetic data on dermal availability because assuming a high dermal availability is not a worst case assumption. In cases where such data are not available a direct comparison of the dermal dose with the oral potency ranges could be performed in exceptional cases.

However, such comparison should not result in moving the substance to a lower potency group (higher ED_{10}) – only moving the substance to a higher potency group (lower ED_{10}) should be considered.

Extrapolation from inhalatory exposure to oral exposure can only be done when there are sufficient kinetic data on inhaled availability because assuming a high inhaled availability is not a worst case assumption. If no inhalatory information on availability is available then it should be assumed that the inhalation and oral availability are comparable. However, such comparison should not result in moving the substance to a lower potency group (higher ED_{10}) – only moving the substance to a higher potency group (lower ED_{10}) should be considered.

Human data

The use of human data for ED_{10} calculation has several drawbacks including limited data on exposure, limited data on the size of the exposed population and limited information on whether the exposure included the window of sensitivity. For all these reasons, it is difficult to determine an ED_{10} based on human data. Therefore, and because in most instances animal data are also available for determining an ED_{10}, these data are evaluated together on a case by case basis. Guidance on the use of human data for the derivation of DNELs and DMELs has been developed by ECHA and is available at the ECHA website, see http://guidance.echa.europa.eu/guidance4_en.htm

3.7.2.5.4 Provisional evaluation of the potency classification

A preliminary potency evaluation applying the ED_{10} value is made at this stage.

ED_{10} values can be used to place substances classified as a reproductive toxicant into selected ranges that define potency groups. In this way, it is possible to identify reproductive toxicants of high, medium and low potency. For the purpose of determining the preliminary potency group, the boundaries in Table 3.7.2.5.4 are used.

Table 3.7.2.5.4 Boundaries of the potency groups[48].

Potency group	**Boundaries**
High potency group	ED_{10} value $\leq$ 4 mg/kg bw/day
Medium potency group	4 mg/kg bw/day < ED_{10} value < 400 mg/kg bw/day
Low potency group	ED_{10} value $\geq$ 400 mg/kg bw/day.

3.7.2.5.5 Modifying factors

Modifying factors are a means to account for case-specific data situations which indicate that the potency group for a substance as obtained by the preliminary assessment, should be changed. While most modifying factors would result in a higher potency group than the preliminary one, also the opposite could occur: If substance-specific knowledge is available (such as e.g. toxicokinetic information on a higher bioavailability in test animals vs. humans), also a lower potency class might be assigned.

While some modifying factors should always be taken into account, other modifying factors could be more relevant when the potency is close to the boundary between two groups (see Table 3.7.2.5.4 above).

[48] see Annex VI of this guidance document for more details

Some modifying factors are of a more qualitative nature. When applied, they will simply point to a potency group different from the one resulting from the preliminary assessment. Other modifying factors might be quantifiable, at least on a semi-quantitative scale. In such cases, a potency group higher (or lower) than the preliminary one should be chosen if the estimated size of the modifying factor exceeds the distance of the preliminary ED10 to the border of the relevant (higher or lower) adjacent potency group.

Furthermore, for some substances more than one modifying factor will apply. It will then take expert judgement to decide on how to reasonably combine all of these individual factors into one overall modifying factor. In exceptional cases, such a combination of individual factors might even result in a change of two potency classes (e.g. assignment of the high potency class, where the preliminary assessment had resulted in the low potency class).

In this context, it should be noted that several of the modifying factors may be interrelated. Moreover, some factors may have already been taken into account in deciding on the classification as a reproductive toxicant. Where such considerations have been made, care should be taken not to use that information again when determining the potency. For example, when the effects determining the ED_{10} were observed at dose levels also causing maternal toxicity, this should already have been taken into consideration during the classification and should not be used again to set a higher SCL.

3.7.2.5.5.1 Type of effect / severity

The type of effect(s) resulting in the same classification as reproductive toxicant differs between substances. Some effects could be considered as more severe than others, however, ranking different effects based on their severity is controversial and difficult to establish criteria. Further, the effects of a developmental toxicant can differ between dose levels from variations via malformations to death of the foetuses. The adverse effects on fertility and sexual function of a substance can differ between dose levels from small changes in testes histopathology through effects on fertility to an irreversible and complete absence of fertility. As the difference between the dose levels is often smaller than the proposed potency groups (factor 10-100) this will make no difference in most cases. Also classification is in most cases based on severe effects like malformations or death of the foetuses for developmental toxicants and effects on fertility or histopathological changes of the reproductive organs for fertility toxicants. For most classified substances such severe effects were already observed at the lowest dose with reproductive effects [(Muller et al, 2012)]. Therefore, differentiation between types of effect is considered to have limited added value. Exceptions can be dealt with on a case by case basis.

For example, if the ED_{10} results in a preliminary conclusion for the medium potency group but is close to the border for the high potency group and the ED_{10} is based on a severe effect like malformations or irreversible effects on sexual function and fertility then using the higher potency group (lower ED_{10}) for that substance should be considered. To determine what is "close to the border" is to compare the distance to the next category border with the significance of modifying factors.

3.7.2.5.5.2 Data availability

There are several aspects to this modifying factor, some of which are:

- limited data availability where certain test protocols are lacking and therefore certain parameters have not been evaluated,
- limited data availability where the spectrum of evaluated parameters is sufficient, but only studies with limited duration are available, and

- limited data availability where only a LOAEL, but no NOAEL could be identified.

Where only limited data are available, such as a screening study (OECD 421 and 422), a 28-day repeated dose toxicity study or non-OECD studies which do not exclude the presence of reproductive effects at lower dose levels, the calculated ED_{10} should not be used to set a SCL above the GCL.

Furthermore it should be considered to assign a modifying factor accounting for the limitations in the database in a similar approach to the one used in deriving DNELs under REACH. Guidance regarding the potential size of such a factor can be obtained from ECHA's Guidance on IR/CSA R.8 ('Characterisation of dose [concentration]-response for human health'). Section R.8.4.3.1 'Assessment of factors relating to extrapolation', gives recommendations on how to set factors for extrapolating to longer study durations as well as for compensation of the lack of a NOAEL or of the generally poor quality of a database.

If there are only limited data which result in an ED_{10} in the medium potency group which is close to the border for the high potency group, then using the higher potency group should be considered. For example an ED_{10} of 8 mg/kg bw/day might have been estimated based on a LOAEL for malformations in the absence of a NOAEL, This ED_{10} is only higher by a factor of 2 (i.e 2 times the border of the high potency group of 4 mg/kg bw/d : see. Table 3.7.2.5.4 above), and assigning the high potency group should be considered until additional data at lower dose levels are available. Thus, there is uncertainty, if the ED_{10} based on extrapolation from and below the LOAEL in the absence of a NOAEL and a correction may be justified. The size of this uncertainty could be determined by the BMDL (Benchmark dose lower 95%-confidence bound). In such cases, the BMDL could be used as a potency estimate instead of the ED_{10}.

3.7.2.5.5.3 Dose-response relationship

The ED_{10} will in most cases probably be in the same range as the NOAEL and LOAEL. However, in cases of a shallow dose effect relationship curve, the LOAEL may sometimes be clearly below the ED_{10}. In such situations, if a substance would fall into a lower potency group based on the ED_{10} but into a higher potency group based on the LOAEL then the higher potency group should be used for that substance.

3.7.2.5.5.4 Mode or mechanism of action

It is assumed that effects observed in animal studies are relevant to humans. Where it is known that the mode or mechanism of action is not relevant for humans or is of doubtful relevance to humans, this should have been taken into account in the classification and should not be used again as a modifying factor for potency. However, quantitative differences in toxicodynamics can be taken into account when not already taken into account in the classification. In cases where mechanistic information shows a lower sensitivity in humans than in experimental animals, this may move substances which are close to the potency boundaries to a lower potency group. In cases where mechanistic information indicates a higher sensitivity in humans than in experimental animals, this may move substances near the potency boundaries to a higher potency group. In general, more conclusive evidence is required when moving a substance to a lower potency group than to a higher potency group.

3.7.2.5.5.5 Toxicokinetics

The toxicokinetics of a substance can differ between the tested animal species and humans. Where a difference is known this should be taken into account when determining the potency group of a substance. This should be based on a comprehensive knowledge of all involved toxicokinetic factors and not only on a single parameter. Also differences in kinetics between

pregnant and non-pregnant animals and transport to the foetus should be taken into account. Based on the available data, quantification of this modifying factor has to be performed on a case by case basis. This modifying factor can work in both directions, as e.g. bioavailability in humans might be known to be lower or higher than in the animal species tested.. In general, more conclusive evidence is required when moving a substance to a lower potency group than to a higher potency group.

3.7.2.5.5.6 Bio-accumulation of substances

The study design of, for example, developmental studies is aimed at exposure only during development. For substances which bio-accumulate, the actual exposure in the time window of sensitivity for some developmental effects may therefore be much lower than when exposure at the same external dose level would have started long before the sensitivity window. Furthermore, human exposure may occur for a long period before the sensitive window. This should be taken into account when determining the potency group. For substances for which no experimental data are available with respect to their potential for accumulation, section R.7.12 of ECHA's IR/CSA Guidance R.7c ('Endpoint specific guidance') provides some hints on how to make an informed estimate about a respective concern.

"Suspected" bio-accumulating substances should be considered as to whether they should be moved into the next higher potency group (lower ED_{10}). However this should be considered on a case by case basis and the "suspected" bio-accumulation ability should be justifed. In the case that the following evidence should be available, the higher potency group would not be necessary:

- the relevant studies used for the ED_{10} were performed in a way that internal doses could have been expected to have reached a steady state during a sufficiently long part of the study time, and in particular with developmental studies during critical time windows of development, or
- the increase in the internal dose caused by the accumulation versus that following a single administration, is smaller than the distance between the ED_{10} and the border to the next higher potency group.

For example, if a substance preliminarily assigned to the medium potency group is known or suspected to be bio-accumulative and the ED_{10} for development has been obtained from a pre-natal developmental study in rats without any significant pre-treatment of the dams before mating, assignment to the high potency category should be considered. Conversely, if reliable toxicokinetic data demonstrate that steady state plasma levels after prolonged repeated administration do not exceed those after single exposure by more than a factor of 2, while the preliminary ED_{10} is 20 mg/kg bw/d (i.e. factor 5 from the border to the high potency category) changing the potency class might not appear necessary.

3.7.2.5.6 Assigning specific concentration limits (SCLs)

Based upon the preliminary potency evaluation using only the ED_{10} and applying the modifying factors, a substance can be placed in the final potency group using the table below. The GCL or SCL of that substance can then be found in the same table.

Table 3.7.2.5.5 SCLs for substances in each potency group and classification category

	Category 1		Category 2	
	Dose	SCL	Dose	SCL
Group 1 high potency	ED_{10} below 4 mg/kg bw/day	0.03% (factors of 10 lower for extremely potent substances [B])	ED_{10} below 4 mg/kg bw/day	0.3% (factors of 10 lower for extremely potent substances)
Group 2 medium potency	$ED_{10} \geq 4$ mg/kg bw/day, and $\leq$ 400 mg/kg bw/day	0.3% (GCL)	$ED_{10} \geq 4$ mg/kg bw/day, and $\leq$ 400 mg/kg bw/day	3% (GCL)
Group 3 low potency	ED_{10} above 400 mg/kg bw/day	3%	ED_{10} above 400 mg/kg bw/day	3-10% [A]

[A] The limit of 10% may be considered in certain cases, such as for substances with a ED_{10} value above 1000 mg/kg bw/day and a NOAEL below 1000 mg/kg bw/day.

[B] For substances with an ED10 more than 10 fold below 4 mg/kg bw/day, meaning an ED10 below 0.4 mg/kg bw/day, a 10-fold lower SCL should be used. For even more potent substance the SCL should be lowered with a factor of 10 for every factor of 10 the ED10 is below 4 mg/kg bw/day.

3.7.2.5.6.1 Assigning two SCLs to a substance

A substance toxic to reproduction is classified in one category for both effects on development and on sexual function and fertility. Within each category effects on development and on sexual function & fertility are considered separately. The potency and resulting concentration limits have to be determined separately for the two main types of reproductive toxic effects. In case the potency and resulting specific concentration limits are different for sexual function/fertility and development for a substance, the substance needs to be assigned one SCL for developmental toxicity and another SCL for effects on sexual function and fertility. These concentration limits will in all cases trigger different specifications of the hazard statements for the two main types of effects, to be applied to mixtures containing the substance (see also 3.7.4.1, Annex I, CLP)

3.7.6 Examples

3.7.6.1 Examples of the determination of SCLs

Four examples are given below:

3.7.6.1.1 Example 1

1.Identification

Substance Name:	XXXXXX

2. EU CLP classification

Repro	1B
H	360D

3. ED_{10} in animals

Brief summary

OECD 414, Wistar rats, GD 6-19, 0, 20, 60, 180 mg/kg bw. The number of live foetuses per litter was significantly reduced and the postimplantation loss was 43 % at the high dose compared to only 8 % in the control being statistically significant.
The mean foetal body weight was reduced by 14 %. Further, the incidence of external malformations (anasarca and/or cleft palate) was significantly increased. About 10 % of the high dose foetuses were affected (13/132 foetuses; in 7/22 litters) while no such changes were observed in the control.
Skeletal malformations were also statistically significantly increased: 7.8 % affected foetuses per litter (7/73 foetuses in 5/21 litters) were noted in the high dose group compared to 1.1 % in the control. The incidences of shortened scapula (4/73 foetuses), bent radius/ulna (2/73 foetuses), malpositioned and bipartite sternebrae (2/73 foetuses) were statistically significantly increased. Soft tissue variations (dilated renal pelvis and ureter) were significantly increased in foetuses from high dose dams compared to controls (27.1 % vs. 6.4 %).
At 0, 20, 60, 180 mg/kg 7.9, 14.8, 9.6, 43 % postimplantation loss was found, respectively.

Remarks on the study used for the determination of the ED_{10}

Species, strain, sex:	Female Wistar rat
Study type:	OECD 414
Route of administration:	Oral gavage
Effect descriptor for LOAEL:	Post-implantation loss, anasarca, cleft palate
Mode of action:	Not known
Genotoxicity classification:	None
Potential to accumulate:	No data. not known

Determination of the ED_{10} value

Control resorption rate (= postimplantation loss) is 7.9%. ED_{10} rate would be 17.9%. Interpolation between NOAEL (classification) (9.6% at 60 mg/kg) and LOAEL (classification) (43% at 180 mg/kg) leads to an ED_{10} of 89.8 mg/kg bw/d. Calculation: (180 – 60) / (43 – 9.6) = 3.593 mg/kg per % (steepness). Going from 9.6% to 17.9% requires addition of 8.3%. This equals 8.3% * 3.593 mg/kg per % = 29.8 plus 60 as the starting point = 89.8 mg/kg bw/day. The ED_{10} for other relevant effects was above 89.8 mg/kg bw/day.

Preliminary potency group

medium

4. Elements that may modify the preliminary potency evaluation

4.1. Dose-response relationship

Not relevant as ED_{10} not borderline.

4.2. Type of effect / severity

Not relevant as ED_{10} not borderline.

4.3. Data availability

Not relevant. Only one valid study available.

4.4. Mode of action

No data.

4.5. Toxicokinetics

No data.

4.6. Bio-accumulation

Little information, only environmental. Accumulation in organisms is not to be expeceted due to the calculated BCF at 3.16. The substance tends not to accumulate in biota due to the low calculated BCF (<<500) and low measured log Kow (<<4).

5. Allocation of potency group and SCL

medium potency, GCL

6.References

Confidential

3.7.6.1.2 Example 2 (developmental part only)

1. Identification

Substance Name :	XXXXXX

2. EU CLP classification

Repro	1B
H	360 FD

3. ED_{10} in animals

Brief summary

Study used for the determination of the ED_{10}:

Pregnant females received daily gavage doses of 0, 25, 50, 100 or 175 mg/kg during the gestation period (GD 6-19).

LOAEL effect	0 mg/kg	25 mg/kg	50 mg/kg	100 mg/kg	175 mg/kg
Skeletal malformations	2/22 (9 %)	2/17 (12 %)	5/15 (33%)	10/19 (53%)	6/12 (50%)

Clear maternal toxicity was evident only at the highest dose level.

Remarks on the study used for the determination of the ED_{10}

Species, strain, sex:	Rabbit, New Zealand White, female
Study type:	Developmental 6-19
Route of administration:	Gavage
Effect descriptor for LOAEL:	Skeletal malformations (axial skeleton, ribs)
Mode of action:	Substance is metabolised to a substance which causes the developmental effect
Genotoxicity classification:	None
Potential to accumulate:	Unknown

Determination of the ED_{10} value

ED_{10} was determined as 33 mg/kg.

Control skeletal malformations is 9%. ED_{10} rate would be 19%. Interpolation between NOAEL (classification) (12% at 25 mg/kg) and LOAEL (classification) (33% at 50 mg/kg) leads to an ED_{10} of 33.3 mg/kg bw/day.

Calculation:

(50– 25) / (33 – 12) = 1.19 mg/kg per % (steepness). Going from 12% to 19% requires addition of 7%. This equals 7% * 1.19 mg/kg per % = 8.3 plus 25 as the starting point = 33.3 mg/kg bw/day.

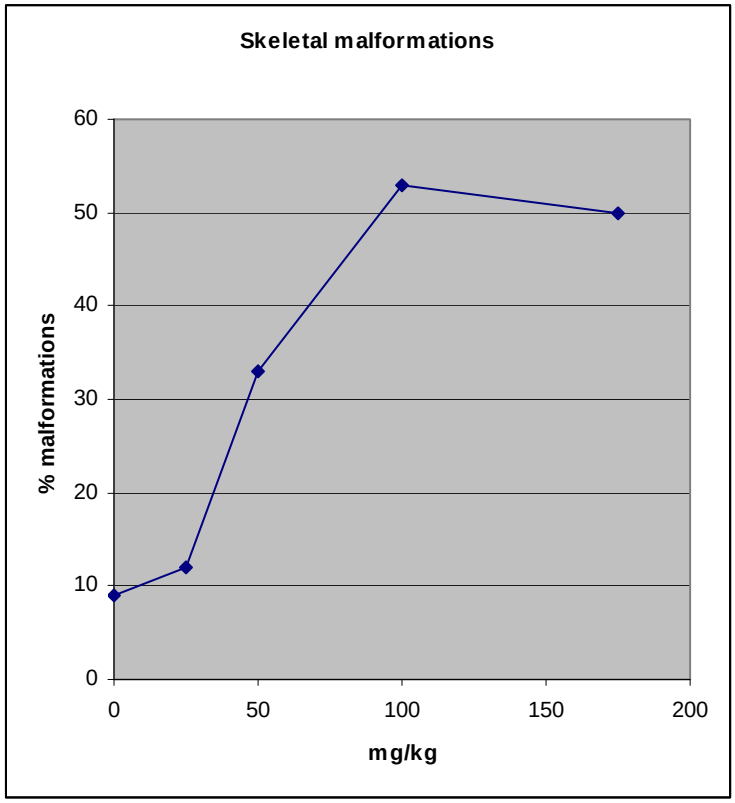
Preliminary potency group

Medium potency group.

4. Elements that may modify the preliminary potency evaluation:

4.1 Dose-response relationship

The effect on which the classification is based is the occurrence of malformations. As the lowest ED_{10} was the ED_{10} for skeletal malformations, this ED_{10} was chosen as the basis for the SCL. The dose effect relationship is clear. The ED_{10} (33 mg/kg) is not borderline with the LOAEL. There is no reason to consider the dose-response relationship to modify the potency of the substance.



4.2 Type of effect / severity

The effect on which the classification is based is the occurrence of malformations, which is a severe effect. Moving the substance to a higher potency group should be considered.

4.3 Data availability

Not relevant. Different studies are available showing a developmental effect on different species (rat, mouse, rabbit).

4.4 Mode of action

The toxic metabolite has been extensively investigated and established as a strong embryotoxicant and teratogen. There is no mechanistic information showing a higher or a lesser sensitivity in humans than in experimental animals.

4.5 Toxicokinetics

Human and rat liver microsomal preparations (mixtures) have been shown to produce qualitatively and quantitively similar oxidative metabolic products suggesting that the human pathways for this substance may be similar to those observed in experimental animals.

4.6 Bio-accumulation

Unknown

5. Allocation of potency group and SCL

The effect on which the classification is based is the occurrence of malformations. This is a severe effect.

Due to the fact that the ED_{10} (33 mg/kg) is not a borderline case, it is not justified to move the substance to the highest potency group although the ED_{10} is based on a severe effect like malformations.

Medium potency, GCL.

6. References

Confidential

3.7.6.1.3 Example 3 (limited to developmental toxicity)

1. Identification

Substance Name :	XXXXXX

2. EU CLP classification

Repro	1B
H	360 fD

3. ED_{10} in animals

Brief summary

Remarks on	Several studies in rats were available for the evaluation of the developmental effect of this substance. These included 2-generation studies, developmental toxicity studies, and studies with exposure in sensitive periods during gestation. The most relevant study for the evaluation of potency was considered to be a two-generation study performed according to the revised OECD Test Guideline 416. In this study the substance was administered in the diet. Developmental toxicity was evident as reduced absolute and adjusted AGD in F1 and F2 offspring as well as and reduced foetal and testicular weight in offspring. The NOAEL was 50 mg/kg bw/day based on reduced AGD from 250 mg/kg bw/day. These effects were reported in the absence of marked maternal toxicity. Effects on the reproductive organs were also reported in male offspring in the developmental toxicity studies at higher doses.

the study used for the determination of the ED_{10}

Species, strain, sex: Study type:	CD(Sprague-Dawley) rats male and female: 2-generation according to OECD 416
Route of administration:	Oral in feed
Effect descriptor for LOAEL:	Overall: reduced anogenital distance Classification: increase in areolae in males
Mode of action:	Antiandrogenic effect, mechanism relevant for humans
Genotoxicity classification:	Not classified for germ cell mutagenicity
Potential to accumulate:	No

Determination of the ED_{10} value

Calculation of the ED_{10} value: 416 mg/kg bw/day

Dose (mg/kg bw/day)	% male F1 with areola
0	2.63
50	0.0
250 (NOAEL)	0.76
750 (LOAEL)	32.3

The ED_{10} is calculated by interpolation between 250 and 750 mg/kg bw/day to a dose level with 10% above control level. Roughly, an increase of 30% above control was found at 750 mg/kg bw/day. Interpolation between 250 and 750 mg/kg bw/day results in a dose of 16.67 mg/kg bw/day for each % of increase in areola ((750-250)/30). A 10% increase (ED_{10}) is expected at 250 + 10 * 16.67 = 416 mg/kg bw/day.

Preliminary potency group

Low potency

4. Elements that may modify the preliminary potency evaluation

4.1 Dose-response relationship

A dose-response relationship on decreased AGD was evident for decrease in AGD in the two-generation study. (AGD was decreased in male offspring in a dose-related pattern from 250 mg/kg bw/day (1. 89 mm at 250 mg/kg bw/day and 1.70 mm at 750 mg/kg bw/day (control: 2.06 mm)).

4.2 Type of effect / severity

Development: reduced anogenital distance (absolute and adjusted) from 250 mg/kg bw/day in F1 and F2 offspring. Weight changes in the reproductive organs in F1 and F2 male offspring, and macroscopic and microscopic lesions in the reproductive organs in male offspring at 750 mg/kg bw/day.

Maternal toxicity: organ weight changes, and histopahological lesions in the liver graded as minimal in females at 750 mg/kg bw/day.

NOAEL for developmental effects: 50 mg/kg bw/day based on reduced anogenital distance from 250 mg/kg bw/day in F1 and F2 offspring.

NOAEL for maternal toxicity: 250 mg/kg bw/day.

4.3 Data availability

A two-generation study is considered relevant for the assessment of development toxicity.

4.3 Mode of action

The mechanism (antiandrogen activity) is considered relevant for humans.

4.5 Toxicokinetics

When metabolites are measured in urine, they are related to the day before exposure. The metabolites of the substance in rats differ quantitatively from those in humans. In several studies the pattern of malformations induced by some of the metabolites were similar to that produced by the substance, suggesting that the metabolic products may be responsible for the developmental toxicity.

Although there is a difference in toxicokinetics between rats and humans, this difference is not expected to result in a difference in potency between rats and humans as the available data indicate comparable effects and potency of the metabolites.

4.6 Bio-accumulation

Low to medium bioaccumulation

5. Allocation of potency group and SCL

The ED_{10} was 416 mg/kg bw/day. The elements that may modify the potency evaluation were considered to not modify the potency. This substance is shown to have a low potency. Therefore an SCL of 3 % should be applied.

6. References

Confidential.

3.7.6.1.4 Example 4

1 Identification

Substance Name :	XXXXXX

2 EU CLP classification

Repro	2
H	361f

3 ED_{10} in animals

Brief summary:

Only two repeated dose studies are available for this substance and no fertility studies. In the inhalatory repeated dose study testicular lesions were observed after exposure to 2.87 mg/l for 4 exposures of 16 to 20 hours per week during 11 weeks. Other dose levels were not tested. In the oral 90 day study, effects on the testes were observed after exposure to 660 mg/kg bw/day. Other dose levels were not tested.

Remarks on the study used for the determination of the ED_{10}

Species, strain, sex:	Rats, CD(SD)BR males
Study type:	90 days, 5 days per week, 120 day observation period
Route of administration:	gavage
Effect descriptor for LOAEL:	testicular atrophy in 50% of the animals
Mode of action:	A metabolite is assumed to be causing the testicular effects. A direct effect of this metabolite on the Sertoli cells is postulated.
Genotoxicity classification:	none
Potential to accumulate:	unknown

Determination of the ED_{10} value

The dose level of 660 mg/kg bw/day is considered as the LOAEL but in the absence of a NOAEL an ED_{10} cannot be determined by interpolation or the BMD approach because only one dose level was tested. An ED_{10} can be estimated based on interpolation between 660 mg/kg bw/day (50% of the animals affected) and the control (0 % of the animals affected). This results in an ED_{10} of 132 mg/kg bw/day by interpolation.

Preliminary potency group

Medium potency group

4 Elements that may modify the preliminary potency evaluation

4.1 Dose-response relationship

There is no data available on the dose response relationship.

4.2 Type of effect / severity

There are clear testicular effects. It is unknown whether these effects will result in functional effects on fertility as this has not been tested.

4.3 Data availability

There is only limited data available at one exposure level.. A LOAEL can be determined but it in the absence of a NOAEL it cannot be excluded that effects on sexual organs occur at levels below the LOAEL. The available data are considered as limited.

4.4 Mode of action

A metabolite is assumed to be the cause of the testicular effects. A direct effect of this metabolite on the Sertoli cells is postulated.

4.5 Toxicokinetics

Unknown

4.6 Bio-accumulation

Unknown

5 Allocation of potency group and SCL

An ED_{10} can only be estimated using interpolation between the only dose tested and the controls.. The resulting ED10 indicates medium potency. However, there is only very limited data. As there is only an LOAEL and no NOAEL, it cannot be excluded that testicular effects can be induced at lower levels. However, there is no evidence that this substance can induce testicular effects at dose levels below 4 mg/kg bw/day. Therefore, a medium potency is considered the best estimate based on the available data.

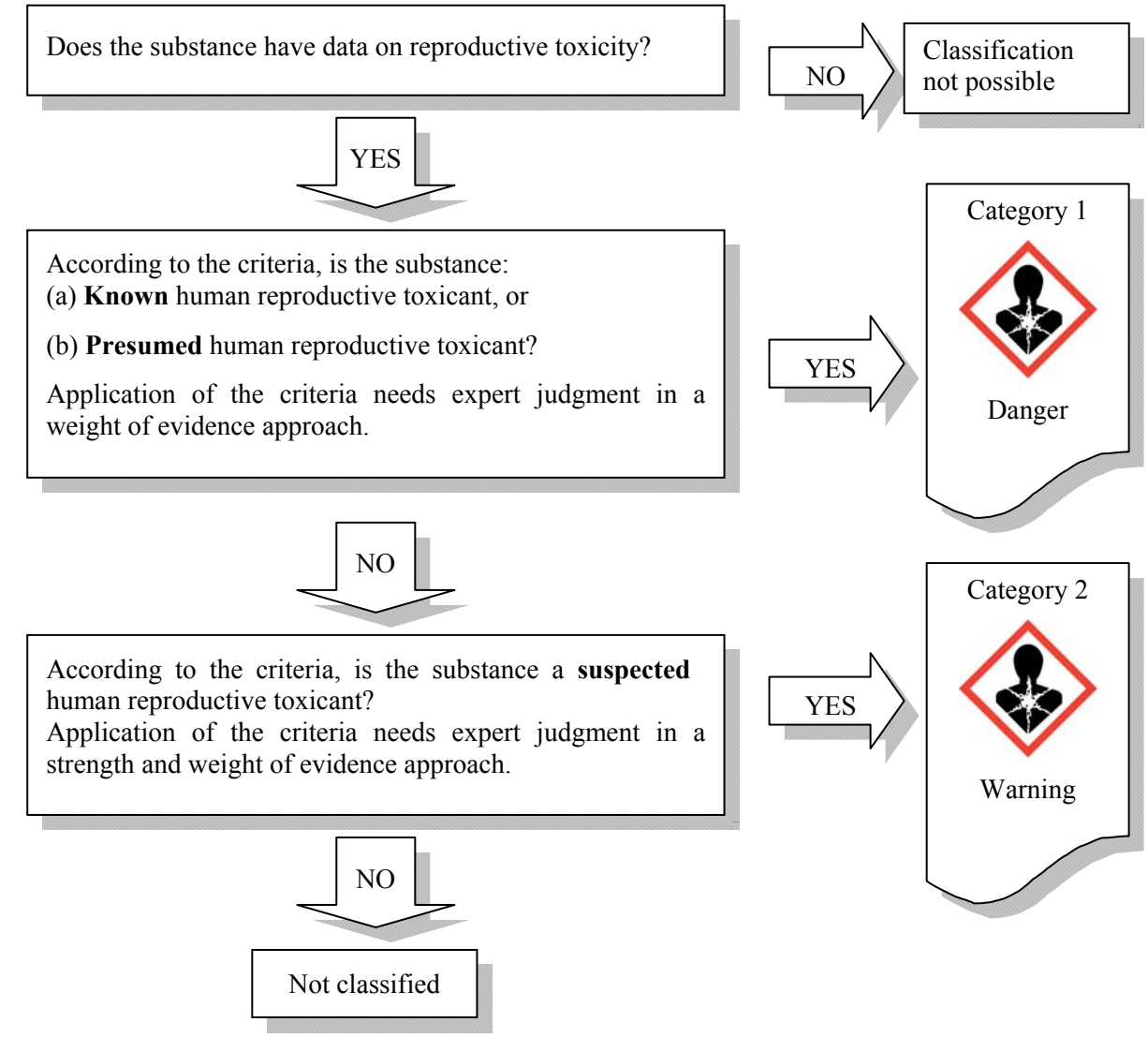
6 References

Confidential

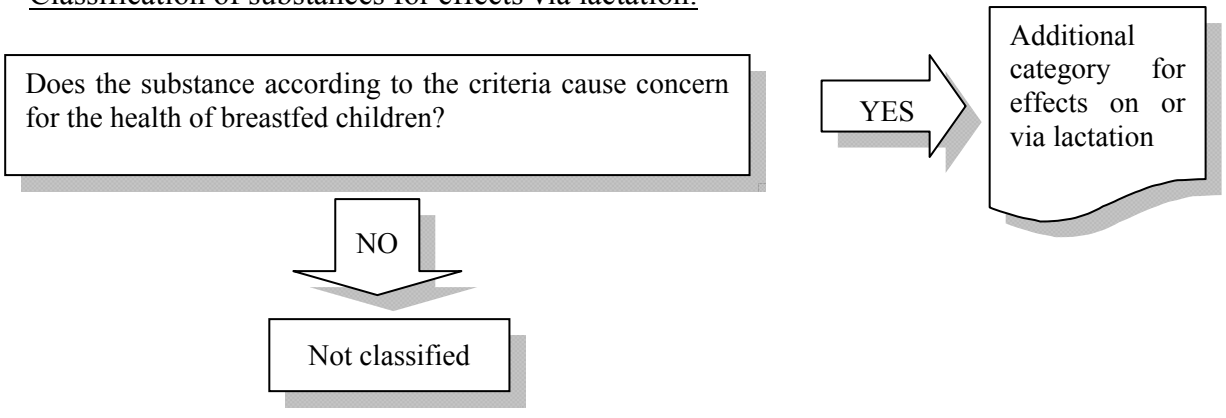
3.7.2.6 Decision logic

The decision logic which follows is provided here as additional guidance. It is strongly recommended that the person responsible for classification study the criteria before and during use of the decision logic.

Classification of substances for fertility or developmental effects:



Classification of substances for effects via lactation:



3.7.3 Classification of mixtures for reproductive toxicity

3.7.3.1 Classification criteria

Reproductive toxicity classification of mixtures is based on the presence of an ingredient classified for reproductive toxicity (see CLP Article 6(3) and Annex I, 3.7.3). Only in case there is data available for the mixture itself which demonstrate effects not retrieved from the ingredients, this data might be used for classification. If such data is not available for the mixture itself, data on a similar mixture can be used in accordance to the bridging principle (see CLP Annex I, 1.1.3).

Annex I: *Table 3.7.2*

Generic concentration limits of ingredients of a mixture classified as reproduction toxicants or for effects on or via lactation that trigger classification of the mixture

Ingredient classified as:	Generic concentration limits triggering classification of a mixture as:			
	Category 1A reproductive toxicant	Category 1B reproductive toxicant	Category 2 reproductive toxicant	Additional category for effects on or via lactation
Category 1A reproductive toxicant	≥ 0,3 % [Note 1]			
Category 1B reproductive toxicant		≥ 0,3 % [Note 1]		
Category 2 reproductive toxicant			≥ 3,0 % [Note 1]	
Additional category for effects on or via lactation				≥ 0,3 % [Note 1]

Note

The concentration limits in the table above apply to solids and liquids (w/w units) as well as gases (v/v units).

Note 1

If a Category 1 or Category 2 reproductive toxicant or a substance classified for effects on or via lactation is present in the mixture as an ingredient at a concentration above 0,1 %, a SDS shall be available for the mixture upon request.

3.7.3.1.1 When data are available for the individual ingredients

Annex I: 3.7.3.1.1. The mixture shall be classified as a reproductive toxicant when at least one ingredient has been classified as a Category 1A, Category 1B or Category 2 reproductive toxicant and is present at or above the appropriate generic concentration limit as shown in Table 3.7.2 below for Category 1A, Category 1B and Category 2 respectively.

3.7.3.1.2. The mixture shall be classified for effects on or via lactation when at least one ingredient has been classified for effects on or via lactation and is present at or above the appropriate generic

concentration limit as shown in Table 3.7.2 for the additional category for effects on or via lactation.

3.7.3.1.2 When data are available for the complete mixture

Annex I: 3.7.3.2.1 Classification of mixtures will be based on the available test data for the individual ingredients of the mixture using concentration limits for the ingredients of the mixture. On a case-by-case basis, test data on mixtures may be used for classification when demonstrating effects that have not been established from the evaluation based on the individual components. In such cases, the test results for the mixture as a whole must be shown to be conclusive taking into account dose and other factors such as duration, observations, sensitivity and statistical analysis of reproduction test systems. Adequate documentation supporting the classification shall be retained and made available for review upon request.

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

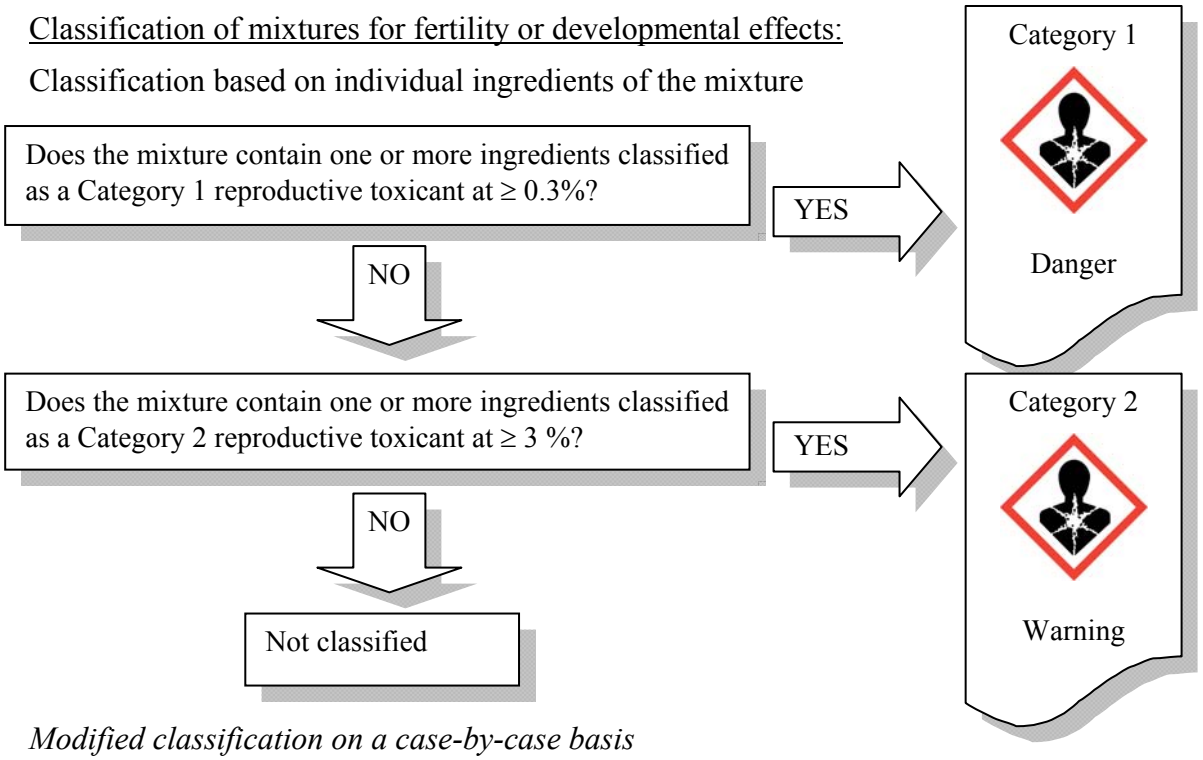
Annex I: 3.7.3.3.1 Subject to the provisions of paragraph 3.7.3.2.1, where the mixture itself has not been tested to determine its reproductive toxicity, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterise the hazards of the mixture, these data shall be used in accordance with the applicable bridging rules set out in section 1.1.3.

3.7.3.2 Decision logic

The decision logic which follows is provided here as additional guidance. It is strongly recommended that the person responsible for classification study the criteria before and during use of the decision logic.

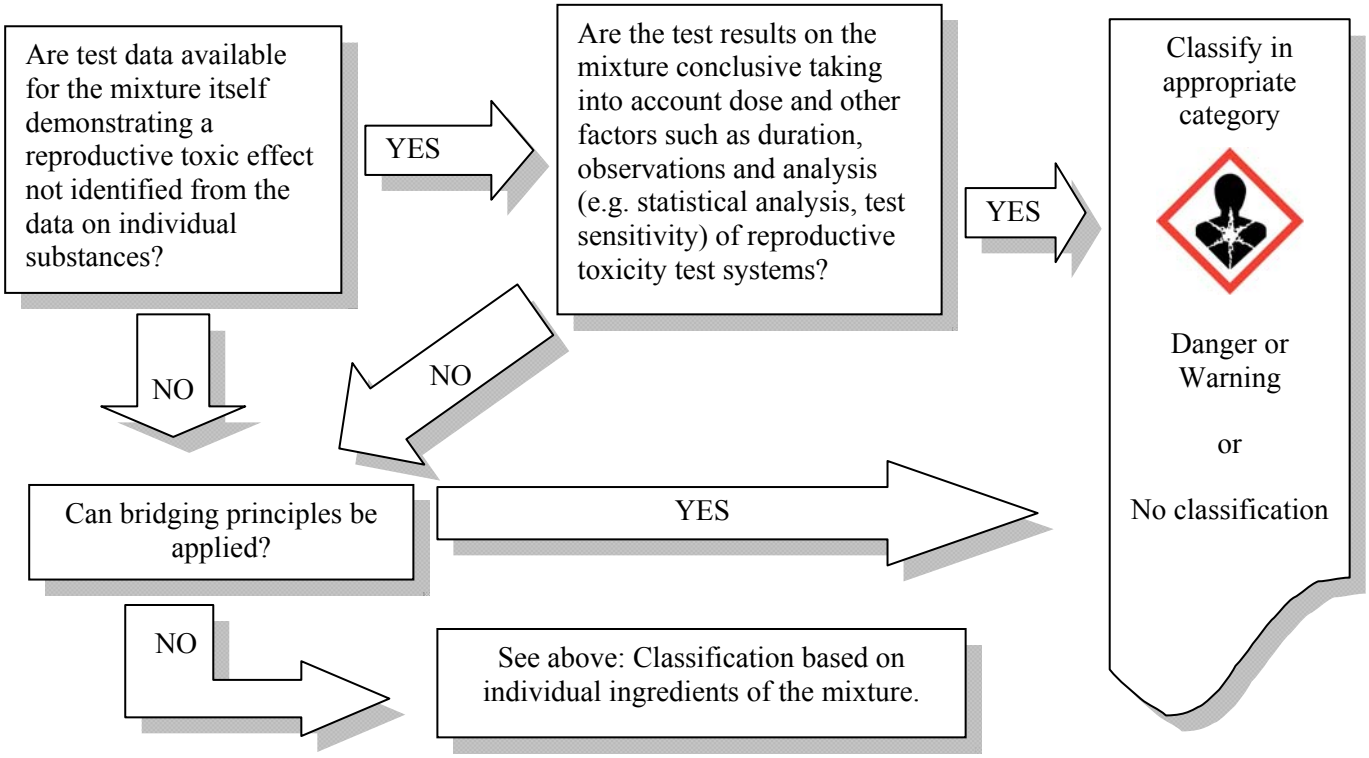
<u>Classification of mixtures for fertility or developmental effects:</u>

Classification based on individual ingredients of the mixture



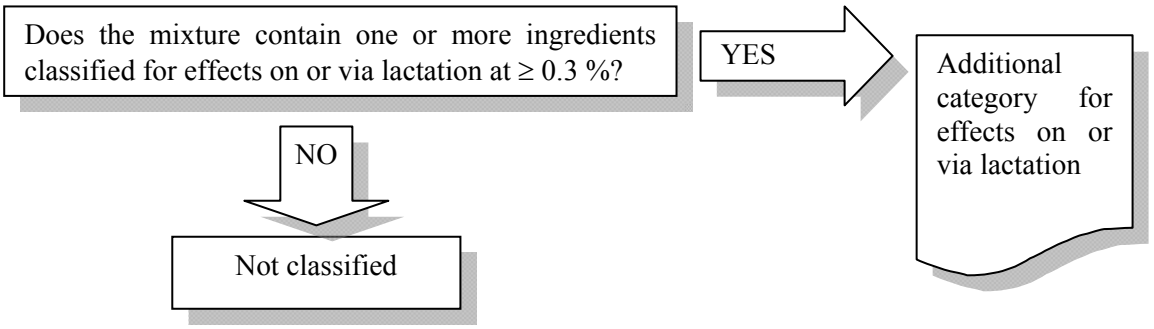
Modified classification on a case-by-case basis

Test data on mixtures may be used for classification when demonstrating effects that have not been established from the evaluation based on the individual ingredients (CLP Annex I, 3.7.3.1.1, see also CLP Article 6(3)).



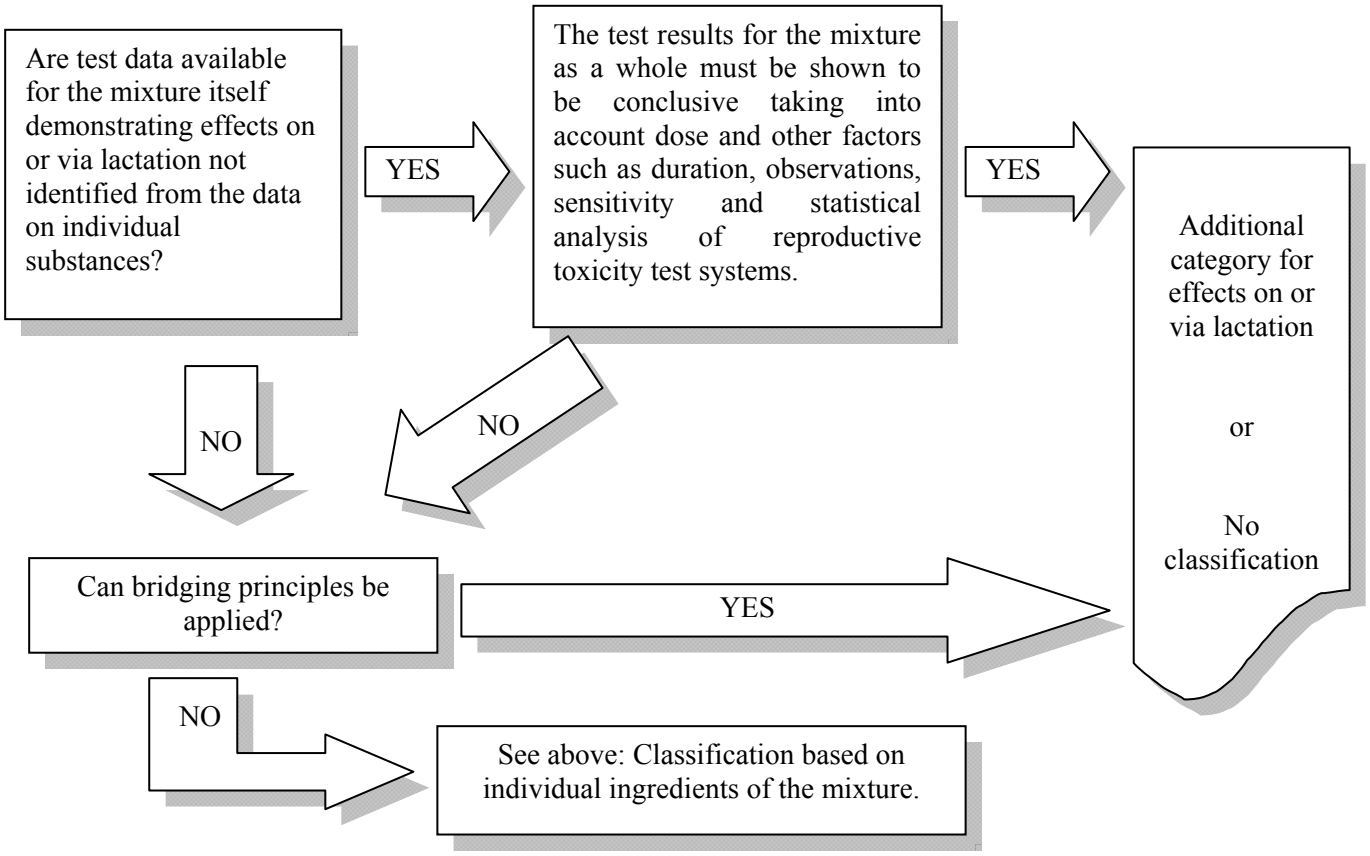
Classification of mixtures for effects via lactation:

Classification based on individual ingredients of the mixture



Modified classification on a case-by-case basis

Test data on mixtures may be used for classification when demonstrating effects that have not been established from the evaluation based on the individual ingredients (CLP Annex I, 3.7.3.1.1, see also CLP Article 6(3)).



3.7.4 Hazard communication in form of labelling for reproductive toxicity

3.7.4.1 Pictograms, signal words, hazard statements and precautionary statements

Annex I: 3.7.4.1. Label elements shall be used for substances or mixtures meeting the criteria for classification in this hazard class in accordance with Table 3.7.3.

Table 3.7.3

Label elements for reproductive toxicity

Classification	Category 1A or Category 1B	Category 2	Additional category for effects on or via lactation
GHS Pictograms			No pictogram
Signal Word	Danger	Warning	No signal word
Hazard Statement	H360: May damagefertility or the unborn child (state specific effect if known)(state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	H361: Suspected of damaging fertility or the unborn child (state specific effect if known) (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	H362: May cause harm to breast-fed children.
Precautionary Statement Prevention	P201 P202 P281	P201 P202 P281	P201 P260 P263 P264 P270
Precautionary Statement Response	P308 + P313	P308 + P313	P308 + P313
Precautionary Statement Storage	P405	P405	

As shown in CLP Annex I, Table 3.7.3, a substance classified as reproductive toxicant in Category 1A or 1B shall be assigned the hazard statements H360 and a substance classified in Category 2 shall be assigned H361. Each of these two hazard statements includes the mentioning of the adverse effects on sexual function and fertility or adverse effects on development of the offspring.

Depending on the data available, the hazard statement H360 or H361 shall e.g. be assigned a reproductive toxic substance: in the case the criteria for Category 1A/1B or 2 are fulfilled, for *either* sexual function or fertility *or* developmental toxicity and when the other reproductive effect cannot be excluded.

In case reliable and adequate data are available on reproductive toxicity, (so that it is possible to ascribe one category for the fertility effects and one category for developmental toxic effects); it is possible to specify the hazard in the hazard statement. The resulting different variants of H360 and H361 are shown in the table below, which also provides some examples when they should be assigned a substance.

Table 3.7.4.1: *Hazard statements for reproductive toxicity: H360 and H361, and their specifications*

H360	"May damage fertility or the unborn child" *Examples:* *1) a substance classified in Repr Cat 1A/B because of adverse effects on fertility and for which developmental toxic effects cannot be excluded* *2) a substance classified in Repr Cat 1 A/B but the effects cannot be specified with respect to fertility or developmental toxicity*
H361	"Suspected of damaging fertility or the unborn child" *Example:* *1) a substance classified in Repr. Cat 2 on the basis of effects on developmental toxicity and for which fertility effects cannot be excluded* 2) *a substance classified in Repr. Cat 2 but the effects cannot be specified with respect to fertility or developmental toxicity*
H360F	"May damage fertility." *Example: a substance classified in Repr Cat 1A/B on the basis of fertility effects and effects on developmental toxicity can be excluded according to reliable and adequate data*
H360D	"May damage the unborn child." *Example: a substance classified in Repr Cat 1A/B on the basis of developmental toxicity and effects on fertility can be excluded according to reliable and adequate data*
H361f	"Suspected of damaging fertility". *Example: a substance classified in Repr Cat 2 on the basis of fertility effects and effects on developmental toxicity can be excluded according to reliable and adequate data*
H361d	Suspected of damaging the unborn child. *Example: a substance classified in Repr Cat 2 on the basis of fertility effects and effects on developmental toxicity can be excluded according to reliable and adequate data*
H360FD	May damage fertility. May damage the unborn child. *Example: a substance classified in Repr Cat 1A/B on the basis of fertility effects and developmental toxicity.*
H361fd	Suspected of damaging fertility. Suspected of damaging the unborn child. *Example: a substance classified in Repr Cat 2 on the basis of fertility effects and developmental toxicity.*
H360Fd	May damage fertility. Suspected of damaging the unborn child. *Example: a substance classified in Repr Cat 1A/B on the basis of fertility effects and in Repr Cat 2 on the basis of developmental toxicity.*

H360Df	May damage the unborn child. Suspected of damaging fertility. *Example: a substance classified in Repr Cat 1A/B on the basis of developmental toxicity and classified in Repr Cat 2 on the basis of fertility effects.*

According to CLP Annex I, Section 3.7.4.1, the hazard statements shall be amended by specifying the route of exposure if it is conclusively proven that no other routes of exposure will lead to an adverse effect on sexual function or fertility or development of the offspring. When conclusively proven, it is meant that valid *in vivo* test data need to be available for all three exposure routes clearly indicating that only one exposure route has caused positive results i.e. adverse effects on the reproduction. Moreover, such a finding should be considered plausible with respect to the mechanism or mode of action. It is estimated that such a situation would rarely occur. Thus, amendment of the hazard statement with the route of exposure generally does not have to be considered.

3.7.4.2 Additional labelling provisions

There are no additional labelling provisions for reproductive toxic substances and mixtures in CLP, however there are provisions laid out in Annex XVII to REACH. The packaging of substances harmonised classified for reproductive toxicity Category 1A or Category 1B, and mixtures containing such substances, "must be marked visibly**,** legibly and indelibly as follows: 'Restricted to professional users'." (REACH, Annex XVII, point 30).

3.7.5 Re-classification of substances and mixtures classified for reproductive toxicity according to DSD and DPD

3.7.5.1 Is direct "translation" of classification and labelling possible?

Generally yes. In case there is no re-evaluation of the data, the hazard statement specifying both 'damage to fertility' and 'damage to the unborn child' should be assigned. It is possible to omit the hazard statement specifying fertility or developmental effects; in case there are clearly negative results (see Section 3.7.4.1).

However, in some very rare situations, a reproductive toxicant classified with Repr. Cat. 3; R62 may need classification with Repr. Cat. 1B H360 under CLP. According to Annex VI to DSD, for the classification of a substance into Category 2 for impaired fertility, there should normally be clear evidence in one animal species, with supporting evidence on mechanism of action or site of action, or chemical relationship to other known anti-fertility agents or other information from humans which would lead to the conclusion that effects would be likely to be seen in humans. According to CLP, such supporting evidence is not needed.

Classification for effects on or via lactation according to CLP is directly equivalent to assignment of R64 according to DSD as the criteria are essentially the same. Therefore, direct translation of R64 to H362 is possible.

3.8 SPECIFIC TARGET ORGAN TOXICITY – SINGLE EXPOSURE (STOT-SE)

3.8.1 Definitions and general considerations for STOT-SE

Annex 1: 3.8.1.1. Specific target organ toxicity (single exposure) is defined as specific, non lethal target organ toxicity arising from a single exposure to a substance or mixture. All significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed and not specifically addressed in Chapters 3.1 to 3.7 and 3.10 are included (see also 3.8.1.6).

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

Acute toxicity classification is generally assigned on the basis of evident lethality (e.g.an LD_{50}/LC_{50} value) or where the potential to cause lethality can be concluded from evident toxicity (e.g. from fixed dose procedure). STOT-SE should be considered where there is clear evidence of toxicity to a specific organ especially when it is observed in the absence of lethality.

Furthermore, specific toxic effects covered by other hazard classes are not included in STOT-SE. STOT-SE should only be assigned where the observed toxicity is not covered more appropriately by another hazard class. For example, specific effects caused after a single exposure like corrosion of skin or effects on the reproductive organs should be used for classification for skin corrosion or reproductive toxicity, respectively, but not for STOT-SE.

Annex 1: 3.8.1.4. Assessment shall take into consideration not only significant changes in a single organ or biological system but also generalised changes of a less severe nature involving several organs.

3.8.1.5. Specific target organ toxicity can occur by any route that is relevant for humans, i.e. principally oral, dermal or inhalation.

3.8.1.7. The hazard class Specific Target Organ Toxicity – Single Exposure is differentiated into:

Specific target organ toxicity – single exposure, Category 1 and 2;

Specific target organ toxicity – single exposure, Category 3.

The hazard class STOT-SE has 3 categories, with Categories 1 and 2 being distinct from Category 3 in terms of the toxicity they cover and the criteria. Categories 1 and 2 for non lethal "significant and/or severe toxic effects" are the basis for classification with the category reflecting the dose level required to cause the effect. Category 3 covers "transient effects" occurring after single exposure, specifically respiratory tract irritation (RTI) and narcotic effects (NE). The relationship between Categories 1/2 vs. Category 3 is discussed in Section 3.8.2.43.

3.8.2 Classification of substances for STOT-SE

3.8.2.1 Identification of hazard information

Annex 1: 3.8.2.1.5. The information required to evaluate specific target organ toxicity comes either from single exposure in humans, such as: exposure at home, in the workplace or environmentally, or from studies conducted in experimental animals.

CLP does not require testing of substances or mixtures for classification purposes. The assessment is based on the respective criteria together with available adequate and robust test data/information. Generally, information relevant to STOT-SE can be obtained from human experience or acute toxicity studies in animals.

3.8.2.1.1 Identification of human data

Relevant information with respect to toxicity after single exposure may be available from case reports, epidemiological studies, medical surveillance and reporting schemes and national poisons centres.

Data on sensory irritation of the airways may be available from volunteer studies including objective measurements of RTI such as electrophysiological responses, data from lateralization threshold testing, biomarkers of inflammation in nasal or bronchoalveolar lavage fluids (IR/CSA, Section 7.2.3.2). For more details see IR/CSA, Section 7.4.3.2 and R.7.2.

3.8.2.1.2 Identification of non human data

Annex 1: 3.8.2.1.5 The standard animal studies in rats or mice that provide this information are acute toxicity studies which can include clinical observations and detailed macroscopic and microscopic examination to enable the toxic effects on target tissues/organs to be identified. Results of acute toxicity studies conducted in other species may also provide relevant information.

Annex 1: 3.8.2.1.7.3. Evidence from appropriate studies in experimental animals can furnish much more detail, in the form of clinical observations, and macroscopic and microscopic pathological examination, and this can often reveal hazards that may not be life-threatening but could indicate functional impairment. Consequently all available evidence, and relevance to human health, must be taken into consideration in the classification process, …

<u>Non-testing data</u>

Physicochemical data

Physicochemical properties, such as pH, physical form, solubility, vapour pressure, particle size, can be important parameters in evaluating toxicity studies and in determining the most appropriate classification especially with respect to inhalation where physical form and particle size can have a significant impact on toxicity.

(Q)SAR models, Read across

"Non-testing" data (i.e. data not obtained from experimental methods) can be provided by the use of techniques such as grouping/category formation, Quantitative and qualitative Structure Activity Relationship (Q)SAR models and expert systems, which generally relate physico-chemical properties and chemical structure to toxicity. The use of these methods is described in more detail in Section 2.3.2 and IR/CSA, Section R.7.4.4.1.

The potential use of (Q)SAR models for predicting effects relevant to STOT-SE Categories 1/2 is currently quite limited and may only be applicable in specific cases. However, they may be somewhat more useful for STOT-SE Category 3 where there are some well established relationships between physicochemical properties or chemical structure and effects such as narcosis and respiratory tract irritation. For instance substances such as aldehydes, unsaturated carbonic esters and reactive inorganic compounds are generally found to be respiratory tract irritants.

In addition, there are systems which can predict the metabolism of substances. These can be useful in providing information on the potential for the substance to be metabolised to substances with known toxicity. An example is certain esters, which after enzymatic cleavage to carbonic acids and alcohols in the nasal region, cause respiratory irritation.

For more details see IR/CSA, Section 7.4.3.1.

Testing data

Animal data

The standard tests on acute toxicity are listed in IR/CSA, Section R.7.4.3.1.

For **Category 1 and 2**, in general terms, most studies involving single exposure via any relevant route of exposure, such as acute toxicity studies, can be used for classification purposes. Older acute toxicity studies which tended to only measure lethality as an observational endpoint (e.g. to determine LD_{50}/LC_{50}) will generally not provide useful information for STOT-SE. However, newer acute toxicity test protocols, such as the fixed-dose and up-down procedures, have a wider range of observations on signs of toxicity and therefore may provide information relevant for STOT-SE. Other standard studies, e.g. neurotoxicity tests, or ad-hoc studies designed to investigate acute toxicity, can also provide valuable information for STOT-SE.

Care must be taken not to classify for STOT-SE for effects which are not yet lethal at a certain dose, but would lead to lethality within the numeric classification criteria. In other words, if lethality would occur at relevant doses then a classification for acute toxicity would take precedence and STOT-SE would not be assigned.

Although classification in **Category 3** is primarily based on human data, if available, animal data can be included in the evaluation. These animal data on RTI and NE will generally come from standard acute inhalation studies, although it is possible that narcosis could be observed in studies using other routes. Standard acute toxicity tests are often more useful for Category 3 than for STOT-SE Categories 1/2 because overt findings of narcosis and RTI are more often reported in clinical observations.

The Alarie test gives specific information on the potential for sensory irritation. Further, information on this test and its limitations can be found in IR/CSA, Section R.7.2.

Furthermore the Inhalation Hazard Test (Annex to OECD TG 403) might give information on the potential for RTI of volatile substances. Though the focus of STOT-SE is on effects caused by single exposure, data from studies with repeated exposure might give additional valuable information, especially with respect to the underlying mode of action of RTI.

In vitro data

Since there are currently no *in vitro* tests that have been officially adopted by the EU or OECD for assessment of acute toxicity, there are also no useful test systems for STOT-SE (see IR/CSA, Section R.7.4.3.1). Any available studies should be assessed using expert judgement.

3.8.2.2 Classification criteria for Categories 1 and 2

Annex I: 3.8.2.1.1. Substances are classified for immediate or delayed effects separately, by the use of expert judgement (see 1.1.1) on the basis of the weight of all evidence available, including the use of recommended guidance values (see 3.8.2.1.9). Substances are then placed in Category 1 or 2, depending upon the nature and severity of the effect(s) observed (Table 3.8.1).

Table 3.8.1

Categories for specific target organ toxicity-single exposure

Categories	Criteria
Category 1	Substances that have produced significant toxicity in humans or that, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to produce significant toxicity in humans following single exposure Substances are classified in Category 1 for specific target organ toxicity (single exposure) on the basis of: (a) reliable and good quality evidence from human cases or epidemiological studies; or (b) observations from appropriate studies in experimental animals in which significant and/or severe toxic effects of relevance to human health were produced at generally low exposure concentrations. Guidance dose/concentration values are provided below (see 3.8.2.1.9) to be used as part of weight-of-evidence evaluation.
Category 2	Substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following single exposure Substances are classified in Category 2 for specific target organ toxicity (single exposure) on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations. Guidance dose/concentration values are provided below (see 3.8.2.1.9) in order to help in classification. In exceptional cases, human evidence can also be used to place a substance in Category 2 (see 3.8.2.1.6).

Note: Attempts shall be made to determine the primary target organ of toxicity and to classify for that purpose, such as hepatotoxicants, neurotoxicants. The data shall be carefully evaluated and, where possible, secondary effects should not be included (e.g. a hepatotoxicant can produce secondary effects in the nervous or gastro-intestinal systems).

3.8.2.1.2. The relevant route or routes of exposure by which the classified substance produces damage shall be identified (see 3.8.1.5).

STOT-SE Category 1 and 2 is assigned on the basis of findings of “significant” or “severe” toxicity. In this context “significant” means changes which clearly indicate functional disturbance or morphological changes which are toxicologically relevant. “Severe” effects are generally more profound or serious than “significant” effects and are of a considerably adverse nature with significant impact on health. Both factors have to be evaluated by weight of evidence and expert judgement.

3.8.2.2.1 Guidance values

Annex 1: 3.8.2.1.9.1 In order to help reach a decision about whether a substance shall be classified or not, and to what degree it shall be classified (Category 1 or Category 2), dose/concentration 'guidance values' are provided for consideration of the dose/concentration which has been shown to produce significant health effects.

Annex 1: 3.8.2.1.9.3. The guidance value (C) ranges for single-dose exposure which has produced a significant non-lethal toxic effect are those applicable to acute toxicity testing, as indicated in Table 3.8.2.

Table 3.8.2

Guidance value ranges for single-dose exposures [a]

		Guidance value ranges for:*		
Route of exposure	Units	Category 1	Category 2	Category 3
Oral (rat)	mg/kg body weight	C ≤ 300	2000 ≥ C > 300	Guidance values do not apply [b]
Dermal (rat or rabbit)	mg/kg body weight	C ≤ 1000	2000 ≥ C > 1000	
Inhalation (rat) gas	ppmV/4h	C ≤ 2500	20000 ≥ C > 2500	
Inhalation (rat) vapour	mg/l/4h	C ≤ 10	20 ≥ C > 10	
Inhalation (rat) dust/mist/fume	mg/l/4h	C ≤ 1.0	5,0 ≥ C >1,0	

Note

(a) The guidance values and ranges mentioned in Table 3.8.2 above are intended only for guidance purposes, i.e. to be used as part of the weight of evidence approach, and to assist with decision about classification. They are not intended as strict demarcation values.

(b) Guidance values are not provided for Category 3 substances since this classification is primarily based on human data. Animal data, if available, shall be included in the weight of evidence evaluation.

* Note: There is a misprint inAnnex I, Table 3.8.2; the heading 'Guidance value ranges for:' should also belong to the column 'Category 1'.

Where significant or severe toxicity has been observed in animal studies, the dose/exposure level causing these effects is compared to the guidance values provided to determine if classification in Category 1 or 2 is most appropriate.

In cases of inhalation studies with exposure times different to 4 hours an extrapolation can be performed similar to the one described in the Chapter 3.1 for Acute Toxicity.

3.8.2.3 Classification criteria for Category 3: Transient target organ effects

Currently, the criteria for classification in Category 3 only cover the transient effects of "respiratory tract irritation" and "narcotic effects".

Annex I: *Table 3.8.1 (continued)* **Categories for specific target organ toxicity-single exposure**	
Categories	Criteria
Category 3	Transient target organ effects This category only includes narcotic effects and respiratory tract irritation. These are target organ effects for which a substance does not meet the criteria to be classified in Categories 1 or 2 indicated above. These are effects which adversely alter human function for a short duration after exposure and from which humans may recover in a reasonable period without leaving significant alteration of structure or function. Substances are classified specifically for these effects as laid down in 3.8.2.2

Annex 1: 3.8.2.2.1 Criteria for respiratory tract irritation

The criteria for classifying substances as Category 3 for respiratory tract irritation are:

(a) respiratory irritant effects (characterized by localized redness, oedema, pruritis and/or pain) that impair function with symptoms such as cough, pain, choking, and breathing difficulties are included. This evaluation will be based primarily on human data.

(b) subjective human observations could be supported by objective measurements of clear respiratory tract irritation (RTI) (such as electrophysiological responses, biomarkers of inflammation in nasal or bronchoalveolar lavage fluids).

(c) he symptoms observed in humans shall also be typical of those that would be produced in the exposed population rather than being an isolated idiosyncratic reaction or response triggered only in individuals with hypersensitive airways. Ambiguous reports simply of "irritation" shall be excluded as this term is commonly used to describe a wide range of sensations including those such as smell, unpleasant taste, a tickling sensation, and dryness, which are outside the scope of classification for respiratory irritation.

(d) there are currently no validated animal tests that deal specifically with RTI, however, useful information may be obtained from the single and repeated inhalation toxicity tests. For example, animal studies may provide useful information in terms of clinical signs of toxicity (dyspnoea, rhinitis etc) and histopathology (e.g. hyperemia, edema, minimal inflammation, thickened mucous layer) which are reversible and may be reflective of the characteristic clinical symptoms described above. Such animal studies can be used as part of weight of evidence evaluation.

(e) this special classification would occur only when more severe organ effects including in the respiratory system are not observed.

It is clearly indicated in the CLP that there are currently no validated animal tests that deal specifically with RTI, but that animal studies can be used as a part of weight of evidence evaluation (3.8.2.2.1.2(d)). However when there are no data in human and animal data suggesting RTI effects, expert judgement is needed to estimate the severity of the effects observed in animals, the conditions of the test, the physical-chemical properties of the substance and whether those considerations alone might be sufficient for a classification in Category 3 for RTI.

The generic term RTI covers two different effects: "sensory irritation" and "local cytotoxic effects". Classification in STOT-SE Category 3 for respiratory tract irritation is generally limited to local cytotoxic effects.

Sensory irritation refers to the local and central reflex interaction of a substance with the autonomic nerve receptors, which are widely distributed in the mucosal tissues of the eyes and upper respiratory tract. It helps to minimize exposure by decreasing the respiration-time-volume and inducing the exposed to leave the areas of irritant concentrations, if possible. Sensory irritation-related effects are fully reversible given that its biological function is to serve as a warning against substances that could damage the airways.

Local cytotoxic irritant effects induce tissue changes at the site of contact which can be detected by clinico-pathological or pathological methods. Such effects may induce long lasting functional impairment of the respiratory system.

The basic mechanisms underlying morphological changes comprise cytotoxicity and induction of inflammation. Based on the quality and severity of morphological changes, the function of the respiratory system will be impaired, which may lead to the development of consequential systemic effects, i.e. there might be consequences on distal organs by a diminution of the oxygen supply. As the functional impairment is seldom evaluated by experimental inhalation studies in animals, data on functional changes will mainly be available from experience in humans.

Further see IR/CSA, Section R.7.2.

Annex 1: 3.8.2.2.2. Criteria for narcotic effects

The criteria for classifying substances as Category 3 for narcotic effects are:

(a) central nervous system depression including narcotic effects in humans such as drowsiness, narcosis, reduced alertness, loss of reflexes, lack of coordination, and vertigo are included. These effects can also be manifested as severe headache or nausea, and can lead to reduced judgment, dizziness, irritability, fatigue, impaired memory function, deficits in perception and coordination, reaction time, or sleepiness.

(b) narcotic effects observed in animal studies may include lethargy, lack of coordination, loss of righting reflex, and ataxia. If these effects are not transient in nature, then they shall be considered to support classification for Category 1 or 2 specific target organ toxicity single exposure.

3.8.2.4 Evaluation of hazard information on STOT-SE for substances

3.8.2.4.1 Evaluation of human data

Annex I: 3.8.2.1.6. In exceptional cases, based on expert judgement, it is appropriate to place certain substances with human evidence of target organ toxicity in Category 2:

(a) when the weight of human evidence is not sufficiently convincing to warrant Category 1 classification, and/or

(b) based on the nature and severity of effects.

Dose/concentration levels in humans shall not be considered in the classification and any available evidence from animal studies shall be consistent with the Category 2 classification. In other words, if there are also animal data available on the substance that warrant Category 1 classification, the substance shall be classified as Category 1.

Annex 1: 3.8.2.1.7.2. Evidence from human experience/incidents is usually restricted to reports of adverse health consequence, often with uncertainty about exposure conditions, and may not provide the scientific detail that can be obtained from well-conducted studies in experimental animals.

Annex 1: 3.8.2.1.10.2. When well-substantiated human data are available showing a specific target organ toxic effect that can be reliably attributed to single exposure to a substance, the substance shall normally be classified. Positive human data, regardless of probable dose, predominates over animal data. Thus, if a substance is unclassified because specific target organ toxicity observed was considered not relevant or significant to humans, if subsequent human incident data become available showing a specific target organ toxic effect, the substance shall be classified.

Human data are potentially very valuable for determining an appropriate classification as they provide direct evidence on the effects of a substance in humans. However, the evaluation of human data is often made difficult by various limitations frequently found with the types of studies and data highlighted in Section 3.8.2.4.1. These include uncertainties relating to exposure assessment (i.e. unreliable information on the amount of a substance the subjects were exposed to or ingested) and confounding exposures to other substances. As a result it should be acknowledged that human data often do not provide sufficiently robust evidence on their own to support classification but may contribute to a weight of evidence assessment with other available information such as animal studies.

Categories 1 and 2

In general, where reliable and robust human data are available showing that the substance causes significant target organ toxicity these take precedence over other data, and directly support classification in Category 1. Available animal data may support this conclusion but do not detract from it (e.g. if the same effect is not observed in animals).

In exceptional cases, where target organ toxicity is observed in humans but the data reported are not sufficiently convincing to support Category 1 because of the lack of details in the observations or in the exposure conditions, and/or with regard to the nature and the severity of the effects observed, then classification in Category 2 could be justified (CLP Annex I, 3.8.2.1.6). In this case, any animal data must also be consistent with Category 2 and not support Category 1 (see below). In this case, if the animal data support Category 1, they will take precedence over the human data. This is because the reliability of the human data in this case is probably lower than the reliability of data from standard well conducted animal studies and should accordingly have less weight in the assessment.

When using human data, there is no consideration of the human dose/exposure level that caused those effects.

Category 3

Respiratory Tract Irritation

Human evidence for RTI often comes from occupational case reports where exposure is associated with signs of RTI. Such reports should be interpreted carefully using expert judgement to ensure that they provide reliable information. For instance, there should be a clear relationship between exposure and the development of signs of RTI, with RTI appearing relatively soon after the start of exposure. A solid substance which causes RTI due to physical/mechanical irritation when inhaled as a dust should not be classified. For more details on RTI, see R7a.7.2.1, and example n° 3 for sulfur dioxide.

Narcotic Effects

Narcotic effects may range from slight dizziness to deep unconsciousness and may be caused by several mechanisms:

- pharmaceutical drugs (designed effect; often receptor-mediated; effective dose usually low; patient under professional observation; limited importance for industrial chemicals and their safety assessment.)

- unspecific effects of many organic industrial chemicals on CNS-membranes at high dose levels (often solvent vapours, ≥ 6000 ppm in respired air volume). Such effects can be expected at high exposure levels due to otherwise low toxicity.
- organic chemicals with similarities to and interference with CNS-transmitters; often metabolic transformation necessary; certain solvents, e.g. butandiol, butyrolactone, methoxyethanol; medium levels of effective dose. Children may be considerably more susceptible than adults.
- chemicals with high specific CNS toxicity; narcotic effects usually close to near-lethal doses (example: H_2S).

Narcotic effects are usually readily reversible on cessation of exposure with no permanent damage or changes.

Human evidence relating to narcosis should be evaluated carefully. Often the reporting of clinical signs is relatively subjective and reports of effects such as severe headache and dizziness should be interpreted carefully to judge if they provide robust evidence of narcosis. Where relevant human data do not mirror realistic exposure conditions, for instance in case reports from accidental over-exposure situations, supportive information may be needed to corroborate the observed effects. A single case report from accidental or deliberate exposure (i.e. abuse) is unlikely to provide sufficiently robust evidence to support classification without other evidence. For more details on evaluation of available human information see also Section 3.1.2.3.1 and IR/CSA, Section R.7.4 (especially R.7.4.4.2). Example n° 4 for toluene illustrates the procedure.

3.8.2.4.2 Evaluation of non human data

Annex 1: 3.8.2.1.5. The standard animal studies in rats or mice that provide information are acute toxicity studies which can include clinical observations and detailed macroscopic and microscopic examination to enable the toxic effects on target tissues/ organs to be identified. Results of acute toxicity studies conducted in other species may also provide relevant information.

Annex 1: 3.8.2.1.10.1. When a substance is characterised only by use of animal data (typical of new substances, but also true for many existing substances), the classification process includes reference to dose/concentration guidance values as one of the elements that contribute to the weight of evidence approach.

Annex 1: 3.8.2.1.10.3. A substance that has not been tested for specific target organ toxicity may, where appropriate, be classified on the basis of data from a validated structure activity relationship and expert judgement-based extrapolation from a structural analogue that has previously been classified together with substantial support from consideration of other important factors such as formation of common significant metabolites.

The type of evidence mentioned in CLP Annex I, 3.8.2.1.7 and 3.8.2.1.8 to support or not to support classification (e.g. clinical biochemistry, changes in organ weights with no evidence of organ dysfunction) is rarely obtained from animal tests designed to measure acute lethality/toxicity (See section 3.8.2.1.2).

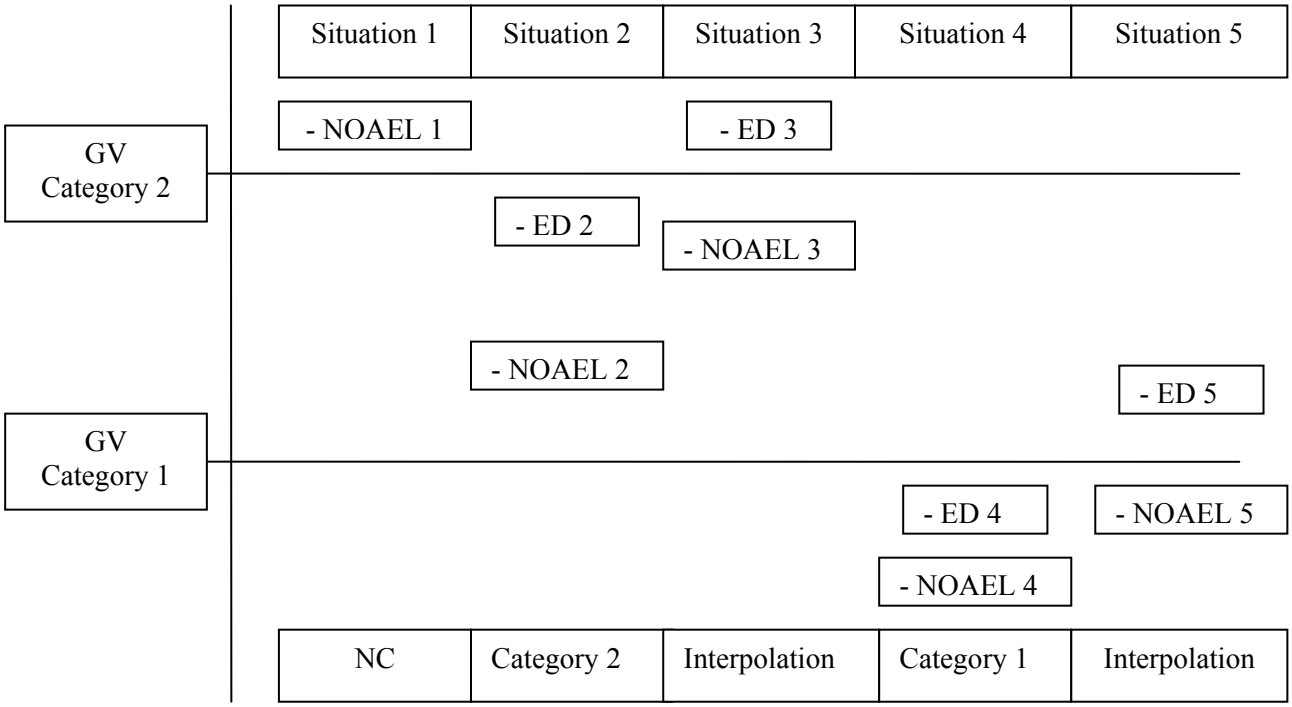
Categories 1 and 2

Generic guidance on data evaluation is presented in IR/CSA, Section R.7.4 and R.7.4.4.2. All available animal data which are of acceptable quality should be used in a weight of evidence approach based on a comparison with the classification criteria described above. The assessment should be done for each route of exposure.

For each study the effects seen in each sex at or around the guidance values (GV) for Category 1 and Category 2 should be compared with the effects warranting classification in Category 1 and 2. In general findings in the most sensitive sex would be used to determine the classification. If the NOAEL from the study is above the GV, the results of that study do not indicate classification for that category (situations 1 and 2 in Figure 1). If the NOAEL is below the GV then the effective dose (ED) level, the lowest dose inducing significant/severe target organ toxicity as defined in Section 3.8.2.2.1 should be determined based on the criteria described above. If the ED is below the GV then this study indicates that classification is warranted (situations 2 and 4 in Figure 1).

In a case where the ED is above a GV but the NOAEL is below the GV (situations 3 and 5) then interpolation between the ED and the NOAEL is required to determine whether the effects expected at or below the GV would warrant classification .

Figure 3.8.2.4.2 *Comparison between the NOAEL and the ED versus the guidance values*



Where a number of studies are available these should be assessed using a weight of evidence approach to determine the most appropriate classification. Where the findings from individual studies would lead to a different classification then the studies should be assessed in terms of their quality, species and strain used, nature of the tested substance (including the impurity profile and physical form) etc to choose the most appropriate study to support classification. In general, the study giving the most severe classification will be used unless there are good reasons that it is not the most appropriate. If the effects observed in animals are not considered relevant for humans then these should not be used to support classification. Similarly, if there is robust evidence that humans differ in sensitivity or susceptibility to the effect observed in the study then this should be taken into account, possibly leading to an increase or decrease in the classification assigned. The final classification based on non human data will be the most severe classification of the three exposure routes.

Category 3

There are no similar guidance values for Category 3. Therefore, if the study shows clear evidence for narcotic effects or respiratory tract irritation at any dose level then this could support classification with Category 3.

In evaluating inhalation studies a differentiation of respiratory tract effects and systemic effects should always be attempted. In addition, the region in the respiratory tract and the qualitative nature of observed effects is pivotal. Often, the lesions observed are representing stages of a reaction pattern leading to severe and irreversible functional and structural alterations. Therefore reversibility of effects is a significant discriminator. For further details see also Section 3.8.2.3.

3.8.2.4.3 Evaluation of non-testing and *in vitro* data

Non-testing and *in vitro* data can contribute to the weight of evidence supporting a classification. As described in Annex XI of REACH approaches such as (Q)SAR, grouping and read-across can provide information on the hazardous properties of substances in place of testing and can be used for classification purposes. Also see R7.4.4.1.

3.8.2.4.4 Conversions

The guidance values are given in mg/kg bodyweight. Where the doses in a study are given in different units they will need to be converted as appropriate. For instance the dosages in feeding and drinking water studies are often expressed in ppm, mg test substance/ kg (feed) or mg (test substance)/l (drinking water).

The conversion from mg/l to ppm assuming an ambient pressure of 1 at 101.3 kPa and 25°C is ppm = 0.0245 mg/l × 1/MW.

3.8.2.4.5 Weight of evidence

Annex 1: 3.8.2.1.6. In exceptional cases, based on expert judgement, it is appropriate to place certain substances with human evidence of target organ toxicity in Category 2:

1) when the weight of evidence is not sufficiently convincing to warrant Category 1 classification, and/or

2) based on the nature and severity of effects.

Dose/concentration levels in humans shall not be considered in the classification and any available evidence from animal studies shall be consistent with the Category 2 classification. In other words, if there are also animal data available on the substance that warrant Category 1 classification, the substance shall be classified as Category 1.

The available information should be considered using expert judgement and a weight of evidence assessment, as described in CLP Annex I, 1.1.1 and Module 1.

Valid human data generally take precedence over animal and other non-test data. If there are human data indicating no classification but there are also non-human data indicating classification then the classification is based on the non-human data unless it is shown that the human data cover the exposure range of the non-human data or that the non-human data are not relevant for humans. If the human and non-human data both indicate no classification then classification is not required.

If there are no human data then the classification is based on the non-human data.

3.8.2.5 Decision on classification of substances

Decision on classification for STOT-SE is based on the results of weight of evidence approach described in 2.3.

STOT-SE and acute toxicity are independent of each other and both may be assigned to a substance if the respective criteria are met. However, care should be taken not to assign each class for the same effect, in other words a double classification for the same effect has to be avoided. STOT-SE will be considered where there is clear evidence for a specific organ toxicity especially in absence of lethality, see examples no 1 and no 3 (methanol and tricresylphosphate).

If no classification has been warranted for acute toxicity despite significant toxic effect, the substance should be considered for classification as STOT-SE.

Normally, the assignment of STOT-SE Category 1 or 2 is independent to the assignment of Category 3. Therefore, a substance may be classified in both Category 1/2 and Category 3 if the respective criteria are met, for instance, in the case of a neurotoxic substance that also causes transient narcotic effects. If Category 1/2 is assigned on the basis of effects in the respiratory tract then Category 3 should not be assigned as this would provide no additional information.

Classification as acutely toxic and/or corrosive is considered to cover and communicate the specific toxicological effect(s) adequately. An additional classification as specific target organ toxicant (single exposure, Category 1 or 2) is not indicated if the severe toxicological effect is the consequence of the local (i.e. corrosive) mode of action.

It is a reasonable assumption that corrosive substances may also cause respiratory tract irritation when inhaled at exposure concentrations below those causing frank respiratory tract corrosion. If there is evidence from animal studies or from human experience to support this then Category 3 may be appropriate. In general, a classification for corrosivity is considered to implicitly cover the potential to cause RTI and so the additional Category 3 is considered to be superfluous, although it can be assigned at the discretion of the classifier. The Category 3 classification would occur only when more severe effects in the respiratory system are not observed.

Category 3 effects should be confined to changes, whether functional or morphological, occurring in the upper respiratory tract (nasal passages, pharynx and larynx). Localized irritation with associated adaptive responses (e.g., inflammation, epithelial metaplasia, goblet cell hyperplasia, proliferative effects) may occur and are consistent with Category 3 responses. Injury of the olfactory epithelium should be distinguished in terms of irritation-related (non-specific) and metabolic/ non-irritant (specific).

3.8.2.6 Setting of specific concentration limits for STOT-SE

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.

Specific concentration limits (SCLs) for STOT-SE may be set by the supplier in some situations according to Article 10 of CLP. For STOT-SE, this may only be done for substances inducing STOT-SE Category 1 at a dose level or concentration clearly (more than one magnitude) below the guidance values according to Table 3.8.2, e.g. below 30 mg/kg bodyweight from the oral single exposure study. This will be mainly based on data in experimental animals but can also be based on human data if reliable exposure data are available. The SCL (SCL Cat. 1) for a Category 1 substance triggering classification of a mixture in Category 1 can be determined using the following formula:

$$SCLCat.1 = \frac{ED}{GV1} \times 100\% \qquad \text{Equation 3.8.2.6(a)}$$

SCL Cat 1: 0.7 mg/kgbw/300 mg/kgbw x 100%=0.22% --> 0.2%

In this formula the ED is the dose of the Category 1 substance inducing significant specific target organ toxicity and GV1 is the guidance value for Category 1 according to Table 3.8.2 of Annex I. The resulting SCL is rounded down to the nearest preferred value[49] (1, 2 or 5).

Example of determining STOT-SE SCL for a Category 1 substance:

$$= \frac{0.7 mg/kgbw}{300 mg/kgbw} \times 100\% \qquad = 0.22\% \text{ --> } 0.2\%$$

Though classification of a mixture in Category 1 is not triggered if a Category 1 constituent is present in lower concentrations than the established SCL, a classification in Category 2 should be considered.

The SCL (SCL Cat. 2)for a Category 1 substance triggering classification of a mixture in Category 2 can be determined using the following formula:

$$SCLCat.2 = \frac{ED}{GV2} \times 100\% \qquad \text{Equation 3.8.2.6(b)}$$

In this formula the ED is the dose of the Category 1 substance inducing specific target organ toxicity and GV2 is the upper guidance value for Category 2 according to Table 3.8.2 of Annex I. The resulting SCL is rounded down to the nearest preferred values (1, 2 or 5). However, if the calculated SCL for classification in Category 2 is above 1%, which is the Generic Concentration Limit, then no SCL should be set.

Example for a substance in SCL Category 2:

$$= \frac{0.7 mg/kgbw}{2000 mg/kgbw} \times 100\% \qquad = 0.035 \text{ --> } 0.02\% \text{ (rounded down)}$$

[49] This is the "preferred value approach" as used in EU and are values to be established preferentially as the numerical values 1.2 or 5 or multiples by powers of ten.

For example, a Category 1substance inducing specific target organ toxicity at 0.7 mg/kg bw/day in an acute oral study would generate an SCL for classification of mixtures in Category 1 at 0.2% and in Category 2 at 0.02% (Cat1: $C \geq 0.2\%$; Cat 2: $0.02\% \leq C < 0.2\%$).

It is not appropriate to determine SCLs for substances classified in Category 2 since ingredients with a higher potency (i.e. lower effect doses than the lower guidance values of Category 2) will be classified in Category 1; substances with higher effect doses than the upper guidance value of Cat2 will generally not be classified.

Classification in STOT-SE Category 3 for RTI and narcotic effects does not take potency into account and consequently does not have any guidance values. A pragmatic default GCL of 20% is suggested, although a lower or higher SCL may be used where it can be justified. Therefore, an SCL can be determined on a case-by-case basis for substances classified as STOT-SE Category 3 and expert judgement shall be exercised.

Specific concentration limits for each of the hazard classes skin and eye irritation, and STOT-SE Category 3 for respiratory tract irritation need to be addressed separately, while unjustified read-across of SCLs from one hazard class to another is not acceptable.

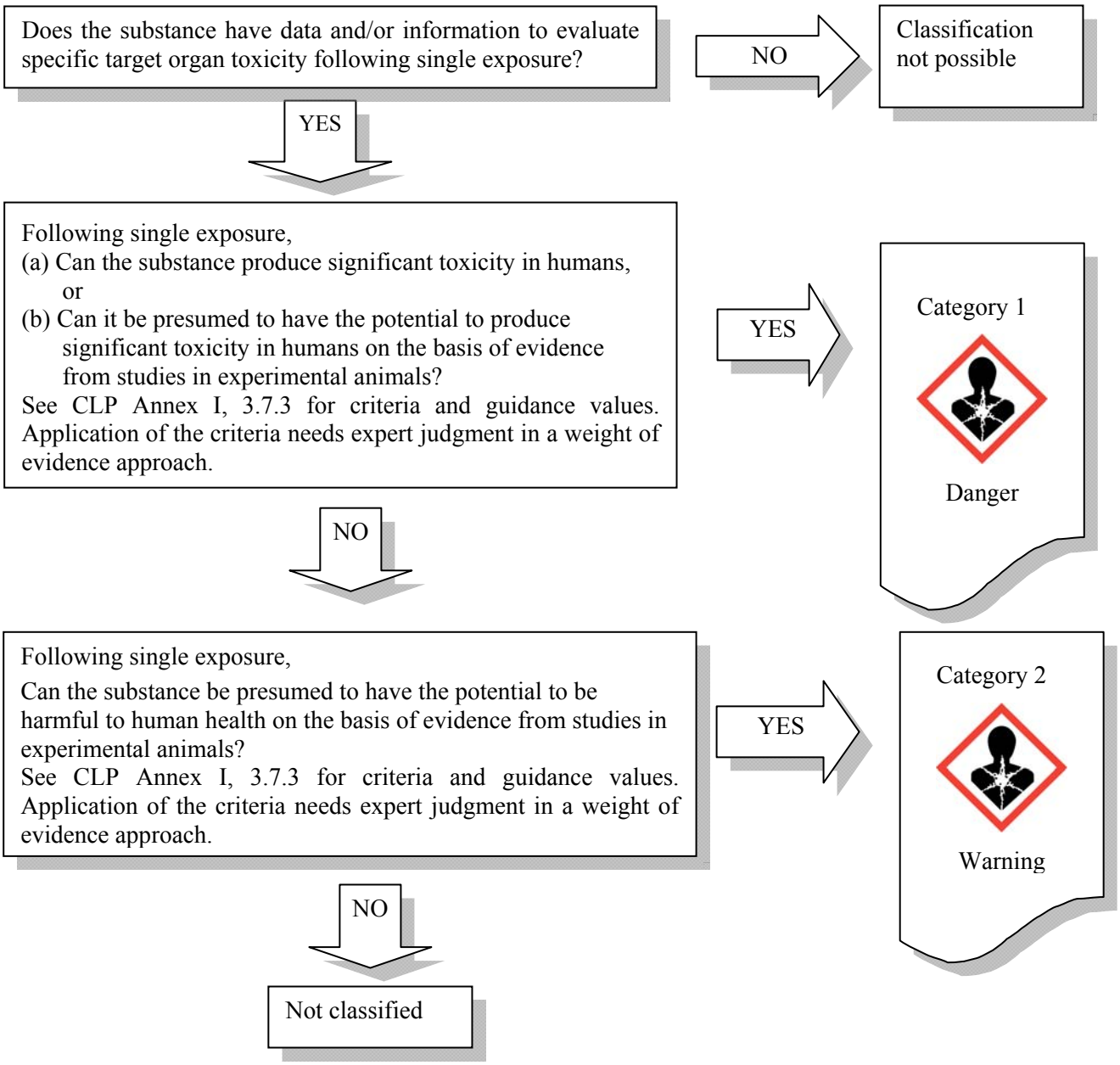
For narcotic effects, the factors to be taken into consideration in order to set lower or higher SCLs are the effective dose/concentration, and in addition for liquids, the volatility (saturated vapour concentration) of the substance.

3.8.2.7 Decision logic

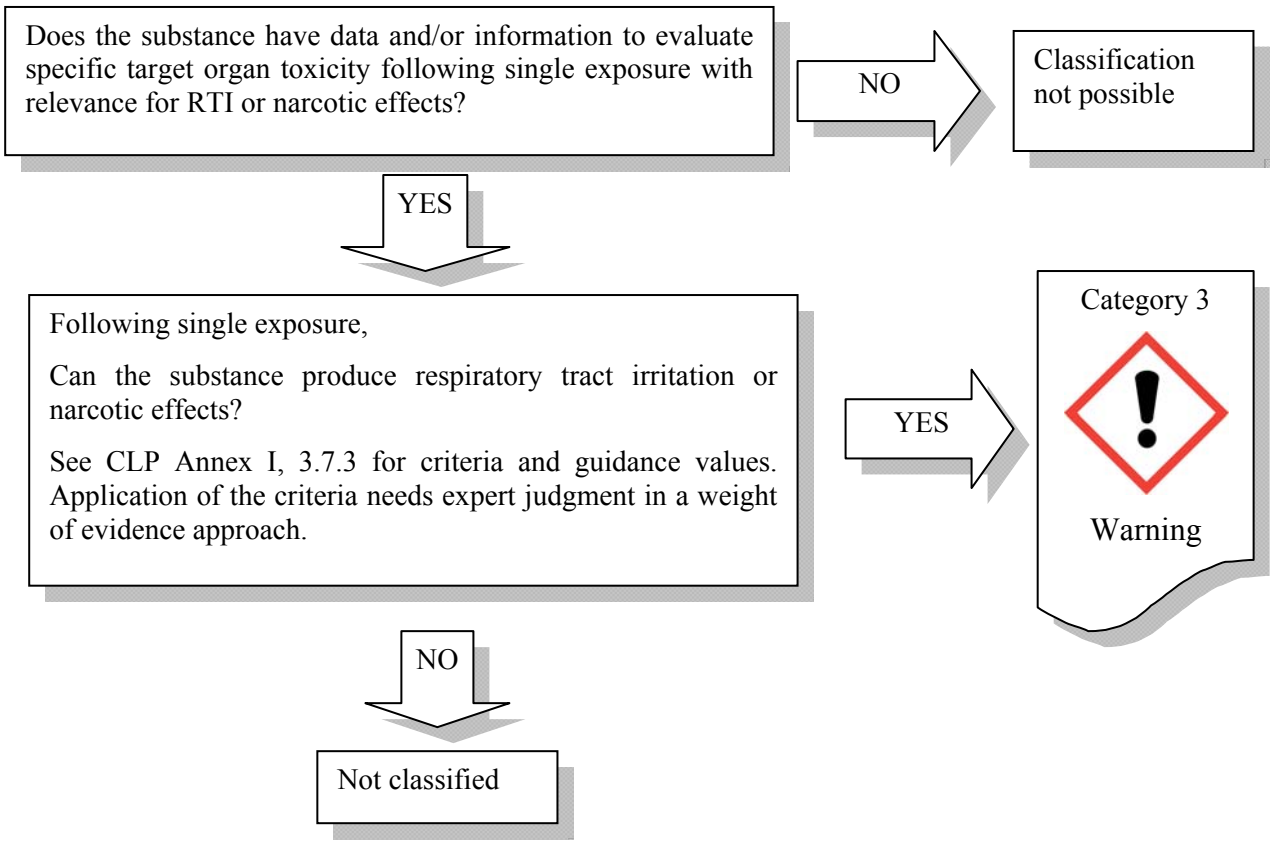
The decision logic is provided as additional guidance. It is strongly recommended that the person responsible for classification study the criteria for classification before and during use of the decision logic.

This decision logic deviates slightly from the original UNGHS in separating the connection between Category 2 and Category 3, since, different from the procedure in other hazard classes, they have to be regarded as independent.

Classification in Category 1 and Category 2



Classification in Category 3



3.8.3 Classification of mixtures for STOT-SE

3.8.3.1 Identification of hazard information

Where toxicological information is available on a mixture this should be used to derive the appropriate classification. Such information may be available from the mixture manufacturer. Where such information on the mixture itself is not available information on similar mixtures and/or the component substances in the mixture must be used, as described below.

3.8.3.2 Classification criteria for mixtures

Annex 1: 3.8.3.1. Mixtures are classified using the same criteria as for substances, or alternatively as described below.

3.8.3.2.1 When data are available for the complete mixture

Annex 1: 3.8.3.2.1. When reliable and good quality evidence from human experience or appropriate studies in experimental animals, as described in the criteria for substances, is available for the mixture, then the mixture shall be classified by weight of evidence evaluation of these data (see 1.1.1.3). Care shall be exercised in evaluating data on mixtures, that the dose, duration, observation or analysis, do not render the results inconclusive

In cases where test data for mixtures are available, the classification process is exactly the same as for substances.

3.8.3.2.2 When data are not available for the complete mixture: bridging principles

Annex 1: 3.8.3.3.1. Where the mixture itself has not been tested to determine its specific target organ toxicity, but there are sufficient data on the individual ingredients and similar tested mixtures toadequately characterise the hazards of the mixture, these data shall be used in accordance with the bridging principles set out in section 1.1.3.

When there are no test data on the mixture as a whole, so called “Bridging principles” may be applied where there are data available on similar tested mixtures and on the individual hazardous ingredient substances within the mixture that are sufficient to adequately assess the hazards of the mixture.

3.8.3.2.3 When data are available for all components or only for some components of the mixture

Annex 1: 3.8.3.4.1. Where there is no reliable evidence or test data for the specific mixture itself, and the bridging principles cannot be used to enable classification, then classification of the mixture is based on the classification of the ingredient substances. In this case, the mixture shall be classified as a specific target organ toxicant (specific organ specified), following single exposure, when at least one ingredient has been classified as a Category 1 or Category 2 specific target organ toxicant and is present at or above the appropriate generic concentration limit as mentioned in Table 3.8.3 below for Category 1 and 2 respectively.

A mixture not classified as corrosive but containing a corrosive ingredient should be considered for classification in Category 3 RTI on a case-by-case basis following the approach explained above (see Section 3.8.2.3). More information on classification of mixtures into Category 3 is provided below (Section 3.8.3.3**)**

3.8.3.2.4 Components of a mixture that should be taken into account for the purpose of classification

Components with a concentration equal to or greater than the generic concentration limits (1% for Category 1 components and 10% for Category 2. See Table 3.8.3) or with a Specific Concentration Limit (see Section 3.8.2.6) will be taken into account for classification purposes. For Category 3, the GCL is 20%. Specific concentration limits have preference over the generic ones.

3.8.3.3 Generic concentration limits for substances triggering classification of mixtures for STOT-SE

The STOT-SE hazard class does not foresee summation of Category 1 or 2 substances in the classification process of a mixture. Furthermore, as Category 1 and 2 depict different hazards than Category 3 the assessment must be done independently from each other.

Annex 1: *Table 3.8.3*

Generic concentration limits of ingredients of a mixture classified as a specific target organ toxicant that trigger classification of the mixture as Category 1 or 2

Ingredient classified as:	Generic concentration limits triggering classification of the mixture as :	
	Category 1	Category 2
Category 1 Specific Target Organ Toxicant	Concentration ≥ 10%	1.0% ≤ concentration < 10%
Category 2 Specific Target Organ Toxicant		Concentration ≥ 10% [(Note 1)]

Note 1:

If a Category 2 specific target organ toxicant is present in the mixture as an ingredient at a concentration ≥ 1.0% a SDS shall be available for the mixture upon request.

3.8.3.4.4. Care shall be exercised when toxicants affecting more than one organ system are combined that the potentiation or synergistic interactions are considered, because certain substances can cause target organ toxicity at < 1% concentration when other ingredients in the mixture are known to potentiate its toxic effect.

3.8.3.4.5. Care shall be exercised when extrapolating toxicity of a mixture that contains Category 3 ingredient(s). A generic concentration limit of 20% is appropriate; however, it shall be recognised that this concentration limit may be higher or lower depending on the Category 3 ingredient(s) and that some effects such as respiratory tract irritation may not occur below a certain concentration while other effects such as narcotic effects may occur below this 20% value. Expert judgement shall be exercised.

Categories 1 and 2

Each single classified component in a concentration range given in Table 3.8.3 triggers the classification of the mixture, i.e. additivity of the concentrations of the components is not applicable.

Category 3

When a mixture contains a number of substances classified with Category 3 and present at a concentration below the GCL (i.e. 20%), an additive approach to determine the classification of the mixture as a whole may be appropriate. In the additive approach the concentrations of the individual substances with the same hazard (i.e. RTI or narcotic effects) are totalled separately. If each individual total is greater than the GCL then the mixture should be classified as Category 3 for that hazard. A mixture may be classified either as STOT SE 3 (RTI) or STOT SE 3 (narcotic effects) or both.

Example

The following example shows whether or not additivity should be considered for Specific Target Organ Toxicity – Single Exposure (STOT-SE) Category 3 transient effects.

Ingredient information:

Ingredient	Wt%	Classification
Ingredient 1	0.5	-
Ingredient 2	3.5	Category 3 – Respiratory Tract Irritation
Ingredient 3	15	Category 3 - Narcotic effects
Ingredient 4	15	Category 3 - Narcotic effects
Ingredient 5	66	-

Answer**:**

Mixture is Category 3 – Narcotic effects

∑%Category 3 – Narcotic effects = 15% + 15% = 30% which is > 20%%, therefore classify as Category 3 – Narcotic Effects

∑%Category 3 – Respiratory Irritation = 3.5%, which is < 20%, not classified for Respiratory Irritation

Rationale:

(a) Classification via application of substance criteria is not possible since test data was not provided for the mixture (paragraph 3.8.3.2);

(b) Classification via the application of bridging principles is not possible since data on a similar mixture was not provided (paragraph 3.8.3.3.1);

(c) Application of paragraph 3.8.3.4.5 is used for classification. Expert judgement is necessary when applying this paragraph. Paragraph 3.8.3.4.5 notes that a cut-off value/concentration limit of 20% has been suggested, but that the cut-off value/concentration limit at which effects occur may be higher or less depending on the Category 3 ingredient(s). In this case, the classifiers judged that 30% is sufficient to classify.

SCLs

In the case where a specific concentration limit has been established for one or more ingredients these SCLs have precedence over the generic concentration limit.

3.8.3.4 Decision logic for mixtures

A mixture should be classified either in Category 1 or in Category 2, according to the criteria described above. The corresponding hazard statement (H370 for Category 1 or H371 for

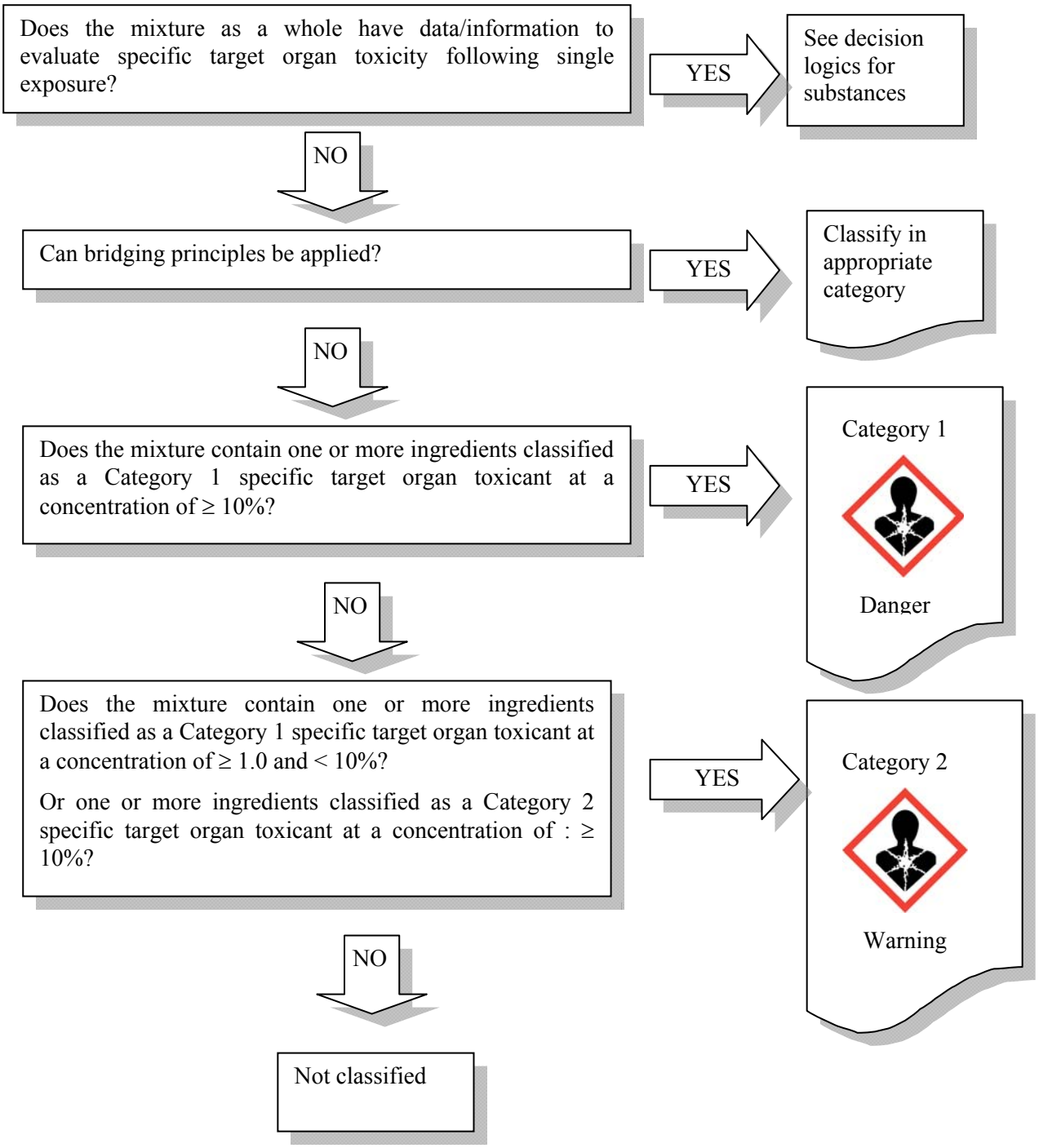
Category 2) should be used without specifying the target organs, except if the classification of the mixture is based on data available for the complete mixture, in which case the target organs may be given. In the same way, the route of exposure should not be specified, except if data are available for the complete mixture and it is conclusively demonstrated that no other routes of exposure cause the hazard.

If the criteria are fulfilled to classify also the mixture in Category 3 for respiratory irritation or narcotic effects, only the corresponding hazard statement (H335 and/or H336) will be added in hazard communication.

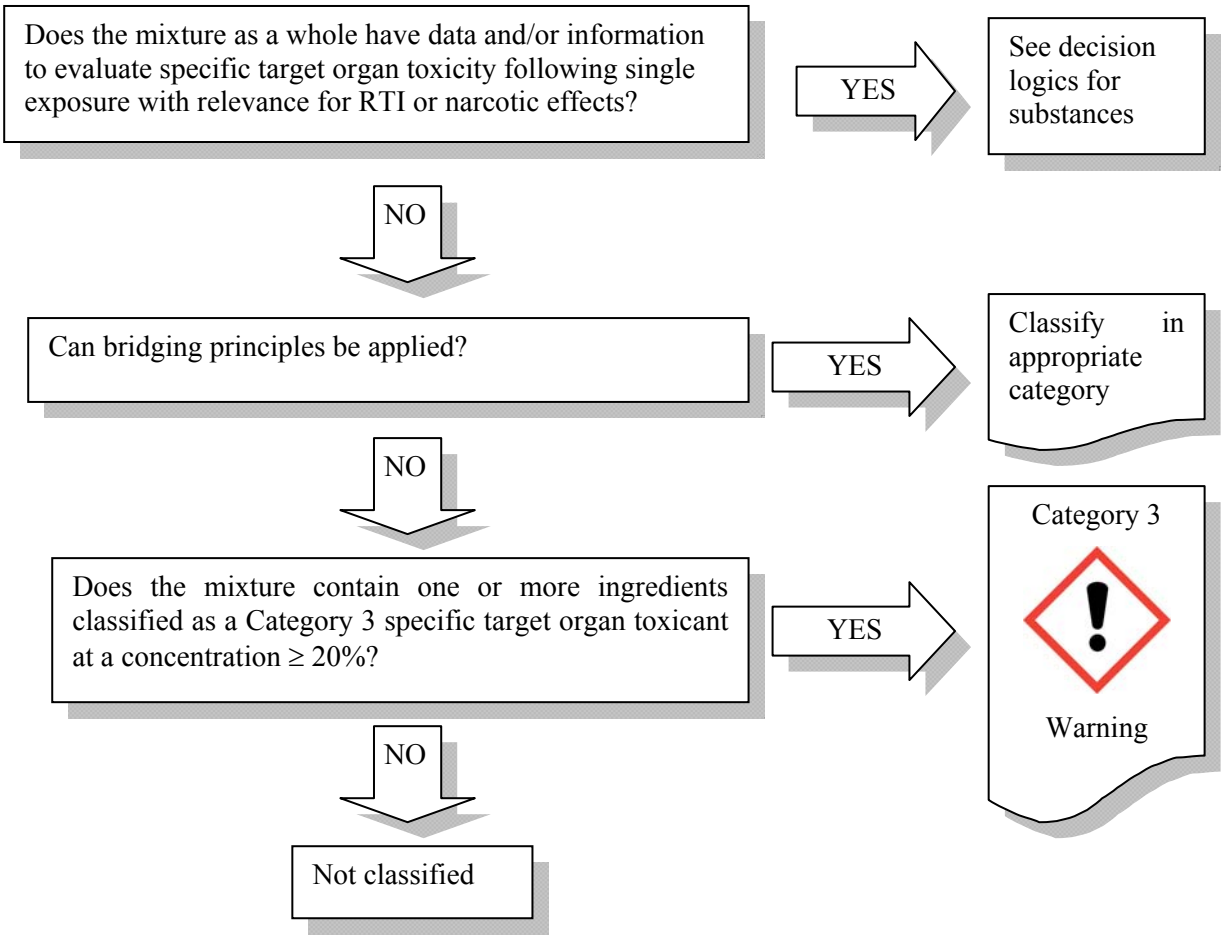
The decision logic is provided as additional guidance. It is strongly recommended that the person responsible for classification study the criteria for classification before and during use of the decision logic.

This decision logic deviates slightly from the original UNGHS in separating the connection between Category 2 and Category 3, since different from the procedure in other hazard classes they have to be regarded as independent.

Classification in Category 1 or 2



Classification in Category 3



3.8.4 Hazard communication in form of labelling for STOT-SE

3.8.4.1 Pictograms, signal words, hazard statements and precautionary statements

Annex I: 3.8.4.1. Label elements shall be used in accordance with Table 3.8.4., for substances or mixtures meeting the criteria for classification in this hazard class.

Table 3.8.4

Label elements for specific target organ toxicity after single exposure

Classification	Category 1	Category 2	Category 3
GHS Pictograms			
Signal word	Danger	Warning	Warning
Hazard statement	H370: Causes damage to organs (or state all organs affected, if known) (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	H371: May cause damage to organs (or state all organs affected, if known) (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	H335: May cause respiratory irritation; or H336: May cause drowsiness and dizziness
Precautionary statement Prevention	P260 P264 P270	P260 P264 P270	P261 P271
Precautionary Statement Response	P307 + P311 P321	P309 + P311	P304 + P340 P312
Precautionary Statement Storage	P405	P405	P403 + P233 P405
Precautionary Statement Disposal	P501	P501	P501

The hazard statement should include the primary target organ(s) of toxicity. Organs in which secondary effects were observed should not be included. The route of exposure should not be specified, except if it is conclusively demonstrated that no other routes of exposure cause the hazard. When a mixture is classified for STOT-SE on basis of test data, the hazard statement will specify the target organs, in the same way as for a substance. If a mixture is classified on basis of the ingredients, the hazard statement (H370 for Category 1 or H371 for Category 2) may be used without specifying the target organs, as appropriate.

In the same way, the route of exposure should not be specified, except if data are available for the complete mixture and if it is conclusively demonstrated that no other routes of exposure cause the hazard. It is recommended to include no more than three primary target organs for practical reasons and because the classification is for specific target organ toxicity. If more

target organs are effected it is recommended that the overall systemic damage should be reflected by using the phrase "damage to organs".

3.8.4.2 Additional labelling provisions

AnnexI: 3.8.2.1.10.4

Saturated vapour concentration shall be considered, where appropriate, as an additional element to provide for specific health and safety protection.

According to CLP Annex I, 3.8.2.1.10.4 the saturated vapour concentration shall be considered as an additional element for providing specific health and safety protection. Thus if a classified substance is highly volatile a supplementary precautionary advice (e.g. "Special/additional care should be taken due to the high saturated vapour pressure") might be given in order to emphasize the hazard in case it is not already covered by the general **Precuationary** statements. (As a rule substances for which the ratio of the effect concentration at <= 4h to the SVC at 20° C is<= 1/10).

Diluted corrosive substances (may) exhibit an irritation potential with respect to the respiratory tract if they have a sufficient saturated vapour concentration. Expert judgement is needed for a decision with respect to a classification in STOT-SE Category 3. In these cases a switch from one hazard class (skin corrosion/irritation) to another (STOT-SE) would be justified.

3.8.5 Re-classification of substances and mixtures classified for STOT-SE according to DSD and DPD

Classification with STOT–SE 1 and 2 according to CLP is comparable to the classification with R39/X and R68/X according to DSD. Classification with R39 – 41 has been used occasionally for substances inducing mortality in eye irritation studies. This classification should not be translated to STOT SE but will result in additional labelling with EUH070. Classification with STOT–SE 3 according to CLP is comparable to the classification with R37 and R67 according to DSD.

3.8.5.1 Is direct "translation" of Classification and Labelling possible for STOT-SE substances?

Direct translation of substances or mixtures classified with R39/X is possible but the category may change. All substances or mixtures classified with R39/24, R39/25, R39/27, R38/28 and/or vapours and dusts/mists/fumes classified with R39/26 or R39/23 shall be classified as STOT SE 1 because less adverse effects and higher guidance values are required for classification according to CLP compared to DSD. Setting of SCLs may be considered for substances showing STOT SE at levels clearly below the guidance values (See section 3.8.2.6).

All substances or mixtures classified with R68/22, R68/21 and/or R68/20 (for vapours) shall be classified at least as STOT SE 2. However, due to the higher guidance values, the requirement for less severe effects, and because STOT SE in humans always leads to classification in Category 1, this is a minimal classification and may not adequately convey the seriousness of the toxicity. Therefore, classification in Category 1 should be considered. Dusts/mists/fumes classified with R68/20 can be directly translated into STOT SE 2 because the guidance values are the same. Gasses classified with R68/20 should be re-evaluated because of the change from guidance values in mg/L into ppm.

If translation results in a classification in STOT SE 1 for one route and in STOT SE 2 for another route only classification in Category 1 is required (for both routes).

Classification as STOT SE is not route specific as it was for classification with R39/X and R68/X. The route specificity of STOT SE is included in the hazard statement and includes route-to-route extrapolation by default unless conclusively shown otherwise. Therefore, the route specific data on STOT SE should be re-evaluated. A re-evaluation is also necessary because the primary target organs for STOT SE should be stated in the hazard statement.

All substances or mixtures classified with R67 shall be classified as STOT SE Category 3 H336.

All substances or mixtures classified with R37 shall be classified as STOT SE Category 3 H335. Also additional labelling with EUH071 (Corrosive to the respiratory tract) shall be considered.

3.8.5.2 Re-evaluation of the STOT-SE data

Gasses classified with R39/23 or R39/26 should be re-evaluated because of the change from guidance values in mg/L into ppm.

Substances or mixtures not classified for STOT-SE, should be considered for re-evaluation because less adverse effects and higher guidance values are required for classification according to CLP compared to DSD. Also, effects in humans are now considered for classification without restrictions to the exposure level.

3.8.6 Examples of classification for STOT-SE

3.8.6.1 Examples of substances fulfilling the criteria for classification

3.8.6.1.1 Example 1: Methanol

Application	Use of adequate and reliable human data, where animal data are not appropriate. Independent classification for STOT-SE and Acute toxicity due to different effects		
	Test Data	**Classification**	**Rationale**
Available information	*Animal data:* LD_{50} rat > 5,000 (mg/kg) No specific target organ toxicity (impairment of seeing ability) observed in rats, even in high doses.	Classification not possible	The rat is known to be insensitive to the toxicity of methanol and is thus not considered to be a good model for human effects (different effect/mode of action)
	Human experience: Broad human experience from many case reports about blindness following oral intake. Methanol is known to cause lethal intoxications in humans (mostly via ingestion) in relatively low doses: " …minimal lethal dose in the absence of medical treatment is between 300 and 1000 mg/kg" (IPCS)	STOT-SE Category 1	The classification criteria for Category 1 are fulfilled: clear human evidence of a specific target organ toxicity effect which is not covered by Acute toxicity.
Remarks	**The standard animal species for single exposure (acute) tests, the rat, is not sensitive, i.e. no appropriate species for this specific target organ effect. Methanol is classified independently for acute toxicity, since the impairment of vision is not causal for the lethality, i. e. there are different effects.** **Labelling:** **Pictogram GHS 08; Signal word: Danger; Hazard statement: H370 Causes damage to the eye.**		

3.8.6.1.2 Example 2: Tricresyl phosphate

Application	Use of valid human evidence supported by animal data		
	Test Data	**Classification**	**Rationale**
Available information	**Human experience:** There are well documented case reports about severe neurotoxic effects **Animal experiments:** Severe neurotoxic effects (Paralysis) were observed after single exposure of doses < 200 mg/kg LD_{50} rat oral 3000 - 3900 mg/kg	STOT-SE Category 1	The classification criteria are clearly fulfilled based on human experience as well as on results of animal studies
Remarks	**Labelling:** Pictogram GHS 08; Signal word: Danger; Hazard Statement: H370 Causes damage to the central nervous system.		

3.8.6.1.3 Example 3: Sulfur dioxide

Application	Use of valid human evidence		
	Test Data	**Classification**	**Rationale**
Available information	**Human experience:** Broad, well documented human experience on irritating effect to respiratory system.	STOT-SE Category 3	The classification criteria for Category 3 (Respiratory Tract Irritation) are fulfilled based on well documented experience in humans
Remarks	Labelling: Pictogram GHS 07; Signal word: Warning; Hazard statement: H335 May cause respiratory irritation		

3.8.6.1.4 Example 4: Toluene

Application			
	Test Data	**Classification**	**Rationale**
Available information	**Animal data:** In valid animal experiments narcotic effects (transient effect on nervous system) at >= 8 mg/l were observed.	STOT-SE Category 3	The classification criteria for Category 3 (Narcotic Effects) are fulfilled based on well documented result s in animal experiments
Remarks	Labelling: Pictogram GHS 07; Signal word: Warning; Hazard statement: H336 May cause drowsiness and dizziness		

3.8.6.2 Examples of substances not fulfilling the criteria for classification

3.8.6.2.1 Example 5: ABC

Application	SE in case same effect leading to Acute toxicity classification		
	Test Data	**Classification**	**Rationale**
Available information	**Animal data:** In a study in rats after single exposure at 2,000mg/kg severe damage in liver (macroscopic examination) and mortality in 6/10 animals were observed	No classification in STOT- SE	Though a specific organ is damaged, the substance will be classified in Acute Toxicity (Category 4), since lethality was observed which was due to the liver impairment. It is assumed that the LD_{50}=ATE is ≤ 2,000 mg/kg. There should be no double classification for the same effect/mechanism causing lethality by impairment of a specific organ, thus no classification for STOT-SE

3.8.6.2.2 Example 6: N,N-Dimethylaniline

Application	No classification for STOT-SE in case same effect leading to Acute toxicity classification		
	Test Data	**Classification**	**Rationale**
Available information	**Animal data:** Acute oral toxicity: LD_{50} values > 1,120-1,300 oral rat and 1,690 mg/kg bw dermal rabbit; ca. 50 mg/kg are lethal in cats due to high Met HB formation ; no specific target organ toxicity (blood toxicity) observed in rats.	No classification in STOT-SE	The criteria for STOT-SE classification are not fulfilled despite a clear specific target organ effect in humans and in a relevant animal species. The substance is classified in Category 3 Acute Toxicity since the Met HB formation is causative for the lethality in humans and in animals (cats) in low doses.
	Human experience: Broad human experience from many case reports about lethal intoxications caused by methemoglobinemia following oral/dermal/inhalation exposure to aromatic amines	No classification in STOT-SE	
Remarks	The standard animal species for single exposure (acute) tests, the rat, is not sensitive, i.e. no appropriate species for this specific effect.		

3.9 SPECIFIC TARGET ORGAN TOXICITY – REPEATED EXPOSURE (STOT-RE)

3.9.1 Definitions and general considerations for STOT-RE

Annex I: 3.9.1.1. Specific target organ toxicity (repeated exposure) means specific, target organ toxicity arising from a repeated exposure to a substance or mixture. All significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed are included. However, other specific toxic effects that are specifically addressed in Chapters 3.1 to 3.8 and Chapter 3.10 are not included here.

According to CLP Annex I, 3.9.1.1, specific toxic effects covered by other hazard classes are not included in STOT-RE. STOT-RE should only be assigned where the observed toxicity is not covered more appropriately by another hazard class. For example specific effects like tumours or effects on the reproductive organs should be used for classification for carcinogenicity or reproductive toxicity, respectively, but not for STOT-RE.

Annex I: 3.9.1.3. These adverse health effects include consistent and identifiable toxic effects in humans, or, in experimental animals, toxicologically significant changes which have affected the function or morphology of a tissue/organ, or have produced serious changes to the biochemistry or haematology of the organism and these changes are relevant for human health.

3.9.1.4. Assessment shall take into consideration not only significant changes in a single organ or biological system but also generalised changes of a less severe nature involving several organs.

3.9.1.5. Specific target organ toxicity can occur by any route that is relevant for humans, i.e. principally oral, dermal or inhalation.

Annex I: 3.9.2.2. The relevant route or routes of exposure by which the classified substance produces damage shall be identified.

The purpose of STOT-RE is to identify the primary target organ(s) of toxicity (CLP Annex I, 3.9.1.4) for inclusion in the hazard statement. Where possible secondary effects are observed in other organs, they should be carefully considered for the classification. The STOT-RE classification should identify those routes by which the substance causes the target organ toxicity (CLP Annex I, 3.9.1.5 and 3.9.2.2). This is usually based on the available evidence for each route. There are no compelling reasons to do route to route extrapolation to attempt to assess the toxicity by other routes of exposure for which there are no data.

Annex I: 3.9.1.6. Non-lethal toxic effects observed after a single-event exposure are classified as described in Specific target organ toxicity — Single exposure (section 3.8) and are therefore excluded from section 3.9.

Where the same target organ toxicity of similar severity is observed after single and repeated exposure to a similar dose, it may be concluded that the toxicity is essentially an acute (i.e. single exposure) effect with no accumulation or exacerbation of the toxicity with repeated exposure. In such a case classification with STOT-SE only would be appropriate.

3.9.2 Classification of substances for STOT-RE

3.9.2.1 Identification of hazard information

Annex 1: 3.9.2.5. The information required to evaluate specific target organ toxicity comes either from repeated exposure in humans, such as exposure at home, in the workplace or environmentally, or from studies conducted in experimental animals.

CLP does not require testing of substances and mixtures for classification purposes. The assessment is based on the respective criteria and consideration of all available adequate and reliable information, primarily such relating to repeated-dose exposures but also taking into account the general physico-chemical nature of the substance. The most useful information is generally from human epidemiology, case studies and animal studies, but information obtained using read-across from similar substances and from appropriate *in vitro* models can also be used, where appropriate.

3.9.2.1.1 Identification of human data

Relevant information with respect to repeated dose toxicity may be available from case reports, epidemiological studies, medical surveillance and reporting schemes, and national poisons centres.

Details are given in IR/CSA, Section 7.5.3.2.

3.9.2.1.2 Identification of non human data

Annex 1: 3.9.2.5. …. The standard animal studies in rats or mice that provide this information are 28 day, 90 day or lifetime studies (up to 2 years) that include haematological, clinicochemical and detailed macroscopic and microscopic examination to enable the toxic effects on target tissues/organs to be identified. Data from repeat dose studies performed in other species shall also be used, if available. Other long-term exposure studies, such as on carcinogenicity, neurotoxicity or reproductive toxicity, may also provide evidence of specific target organ toxicity that could be used in the assessment of classification.

Non-testing data

Physico-chemical data

Physicochemical properties, such as pH, physical form, solubility, vapour pressure, and particle size, can be important parameters in evaluating toxicity studies and in determining the most appropriate classification especially with respect to inhalation where physical form and particle size can have a significant impact on toxicity.

(Q)SAR models

Structurally or mechanistically related substance(s), read-across/grouping/chemical category and metabolic pathway approach: A (Q)SAR analysis for a substance may give indications for a specific mechanism of action and identify possible organ or systemic toxicity upon repeated exposure. Overall, (Q)SAR approaches are currently not well validated for repeated dose toxicity. (IR/CSA, Section R7.5.4.1). Data on structurally analogous substances may be available and add to the toxicity profile of the substance under investigation. The concept of grouping, including both read-across and the related chemical category concept have been developed under the OECD HPV program. 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. (For more details see IR/CSA,

Sections R.6.1 and R.6.2.5.2 and OECD (2004)). OECD Principles for the Validation, for Regulatory Purposes, of (Quantitative) Structure-Activity Relationship Models)

Testing data

Animal data

"The most appropriate data on repeated dose toxicity for use in hazard characterisation and risk assessment are primarily obtained from studies in experimental animals conforming to internationally agreed test guidelines. In some circumstances repeated dose toxicity studies not conforming to conventional test guidelines may also provide relevant information for this endpoint" (IR/CSA, Section R.7.5.3.1). Studies not performed according to Standard Test Guidelines and/or GLP have to be evaluated on case by case basis by expert judgement and in the context of a total weight of evidence assessment if there are more data (for more information see Section 3.9.2.3.4 and IR/CSA, Section R.7.5.4.1.

The standard test guidelines are described in IR/CSA, Section R.7.5.4.1. There may also be studies employing different species and routes of exposure. In addition, special toxicity studies investigating further the nature, mechanism and/or dose relationship of a critical effect in a target organ or tissue may also have been performed for some substances. Other studies providing information on repeated dose toxicity: although not aiming at investigating repeated dose toxicity per se and other available EU/OECD test guideline studies involving repeated exposure of experimental animals may provide useful information on repeated dose toxicity, e.g reproduction toxicity or carcinogenicity studies. For more details see IR/CSA, Section R .7.5.4.1 (ECHA, 2008).

In vitro data

At present available *in vitro* data is not useful on its own for regulatory decisions such as classification and labelling. However, such data may be helpful in the assessment of repeated dose toxicity, for instance to detect local target organ effects and/or to clarify the mechanisms of action. Since, at present, there are no validated and regulatory accepted *in vitro* methods, the quality of each of these studies and the adequacy of the data provided should be carefully evaluated" (IR/CSA, Section R.7.5.4.1).

3.9.2.2 Classification criteria for substances

Annex 1: 3.9.2.1. Substances are classified as specific target organ toxicants following repeated exposure by the use of expert judgement (see 1.1.1), on the basis of the weight of all evidence available, including the use of recommended guidance values which take into account the duration of exposure and the dose/concentration which produced the effect(s), (see 3.9.2.9), and are placed in one of two categories, depending upon the nature and severity of the effect(s) observed (Table 3.9.1).

Table 3.9.1

Categories for specific target organ toxicity-repeated exposure

Categories	Criteria
Category 1	Substances that have produced significant toxicity in humans or that, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to produce significant toxicity in humans following repeated exposure. Substances are classified in Category 1 for target organ toxicity (repeat exposure) on the basis of: reliable and good quality evidence from human cases or epidemiological studies; or observations from appropriate studies in experimental animals in which significant

	and/or severe toxic effects, of relevance to human health, were produced at generally low exposure concentrations. Guidance dose/concentration values are provided below (see 3.9.2.9), to be used as part of a weight-of- evidence evaluation.
Category 2	Substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following repeated exposure. Substances are classified in category 2 for target organ toxicity (repeat exposure) on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations. Guidance dose/concentration values are provided below (see 3.9.2.9) in order to help in classification. In exceptional cases human evidence can also be used to place a substance in Category 2 (see 3.9.2.6).
Note Attempts shall be made to determine the primary target organ of toxicity and classify for that purpose, such as hepatotoxicants, neurotoxicants. One shall carefully evaluate the data and, where possible, not include secondary effects (a hepatotoxicant can produce secondary effects in the nervous or gastro-intestinal systems).	

In the Note above "classify" would mean to identify the primary target organ.

STOT-RE is assigned on the basis of findings of “significant” or “severe” toxicity. In this context “significant” means changes which clearly indicate functional disturbance or morphological changes which are toxicologically relevant. “Severe” effects are generally more profound or serious than “significant” effects and are of a considerably adverse nature which significantly impact on health. Both factors have to be evaluated by weight of evidence and expert judgement.

Annex 1: 3.9.2.9.4. The decision to classify at all can be influenced by reference to the dose/concentration guidance values at or below which a significant toxic effect has been observed.

Annex 1: 3.9.2.9.6. Thus classification in Category 1 is applicable, when significant toxic effects observed in a 90-day repeated-dose study conducted in experimental animals are seen to occur at or below the guidance values (C) as indicated in Table 3.9.2 below:

Table 3.9.2

Guidance values to assist in Category 1 classification

Route of exposure	Units	Guidance values (dose/concentration)
Oral (rat)	mg/kg body weight/day	C ≤ 10
Dermal (rat or rabbit)	mg/kg body weight/day	C ≤ 20
Inhalation (rat) gas	ppmV/6h/day	C ≤ 50
Inhalation (rat) vapour	mg/litre/6h/day	C ≤ 0,2
Inhalation (rat) dust/mist/fume	mg/litre/6h/day	C ≤ 0,02

Annex 3.9.2.9.7. Classification in Category 2 is applicable, when significant toxic effects observed in a 90-day repeated-dose study conducted in experimental animals are seen to occur within the guidance value ranges as indicated in Table 3.9.3 below:

Table 3.9.3

Guidance values to assist in Category 2 classification

Route of Exposure	Units Guidance	Value Ranges: (dose/concentration)
Oral (rat)	mg/kg body weight/day	$10 < C \leq 100$
Dermal (rat or rabbit)	mg/kg body weight/day	$20 < C \leq 200$
Inhalation (rat) gas	ppmV/6h/day	$50 < C \leq 250$
Inhalation (rat) vapour	mg/litre/6h/day	$0,2 < C \leq 1,0$
Inhalation (rat) dust/mist/fume	mg/litre/6h/day	$0,02 < C \leq 0,2$

Annex 1 3.9.2.9.8. The guidance values and ranges mentioned in paragraphs 3.9.2.9.6 and 3.9.2.9.7 are intended only for guidance purposes, i.e., to be used as part of the weight of evidence approach, and to assist with decisions about classification. They are not intended as strict demarcation values.

Annex 1 3.9.2.9.5. The guidance values refer to effects seen in a standard 90-day toxicity study conducted in rats. They can be used as a basis to extrapolate equivalent guidance values for toxicity studies of greater or lesser duration, using dose/exposure time extrapolation similar to Haber's rule for inhalation, which states essentially that the effective dose is directly proportional to the exposure concentration and the duration of exposure. The assessment shall be done on a case-by-case basis; for a 28-day study the guidance values below is increased by a factor of three.

Haber's rule is used to adjust the standard guidance values, which are for studies of 90-day duration, for studies of longer or shorter durations. It should be used cautiously with due consideration of the nature of the substance in question and the resulting value produced.

In particular, care should be taken when using Haber's rule to assess inhalation data on substances which are corrosive or local active or have the potential to accumulate with repeated exposure.

One particular problem to note is that when adjusting the guidance value for very short study durations this can lead to very high guidance values which are not appropriate. For instance, for a 4 day exposure a guidance value of 2250 mg/kg bw/day for classification as STOT RE category 2 could potentially be produced. This is above the limit for acute toxicity of 2000 mg/kg bw and it does not make sense to have a guidance value for repeated dose toxicity that is above the guidance value for mortality after acute exposure. To address this problem a pragmatic approach is proposed. For studies with exposure durations shorter than 9 days (i.e 10% of the 90 days to which the default general guidance value applies) the guidance value used should be no greater than 10 times the default guidance value. For example, the effects in an oral range-finding study of 9 days or less should be compared with a guidance value of 1000 mg/kg bw/day for STOT-RE Category 2.

Expert judgement is needed for the establishment of equivalent guidance values because one needs to know about the limitations of the applicability of the proportionality. In the following table the equivalents for 28-day and 90-day studies according to Haber's rule are given:

Table 3.9.2.2 *Equivalent guidance values for 28-day and 90-day studies*

Study type	Species	Unit	Category 1 90-day	Category 1 28-day	Category 2 90-day	Category 2 28-day
Oral	Rat	mg/kg bw/d	≤ 10	≤ 30	≤ 100	≤ 300
Dermal	Rat	mg/kg bw/d	≤ 20	≤ 60	≤ 200	≤ 600
Inhalation, gas	Rat	ppmV/6 h/d	≤ 50	≤ 150	≤ 250	≤ 750
Inhalation, vapor	Rat	mg/l/6 h/d	≤ 0.2	≤ 0.6	≤ 1	≤ 3
Inhalation, dust/mist/fume	Rat	mg/l/6 h/d	≤ 0.02	≤ 0.06	≤ 0.2	≤ 0.6

Annex 1: 3.9.2.9.9. Thus it is feasible that a specific profile of toxicity occurs in repeat-dose animal studies at a dose/concentration below the guidance value, such as < 100 mg/kg bw/day by the oral route, however the nature of the effect, such as nephrotoxicity seen only in male rats of a particular strain known to be susceptible to this effect may result in the decision not to classify. Conversely, a specific profile of toxicity may be seen in animal studies occurring at above a guidance value, such as ≥ 100 mg/kg bw/day by the oral route, and in addition there is supplementary information from other sources, such as other long-term administration studies, or human case experience, which supports a conclusion that, in view of the weight of evidence, classification is the prudent action to take.

3.9.2.3 Evaluation of hazard information

Annex 1: 3.9.2.4. …….Evaluation shall be based on all existing data, including peer-reviewed published studies and additional acceptable data.

3.9.2.3.1 Evaluation of human data

Annex 1: 1.1.1.4. For the purpose of classification for health hazards (Part 3) established hazardous effects seen in appropriate animal studies or from human experience that are consistent with the criteria for classification shall normally justify classification. Where evidence is available from both humans and animals and there is a conflict between the findings, the quality and reliability of the evidence from both sources shall be evaluated in order to resolve the question of classification. Generally, adequate, reliable and representative data on humans (including epidemiological studies, scientifically valid case studies as specified in this Annex or statistically backed experience) shall have precedence over other data. However, even well-designed and conducted epidemiological studies may lack a sufficient number of subjects to detect relatively rare but still significant effects, to assess potentially confounding factors. Therefore, positive results from well-conducted animal studies are not necessarily negated by the lack of positive human experience but require an assessment of the robustness, quality and statistical power of both the human and animal data.

Annex 1 3.9.2.7.2. Evidence from human experience/incidents is usually restricted to reports of adverse health consequence, often with uncertainty about exposure conditions, and may not provide the scientific detail that can be obtained from well-conducted studies in experimental animals.

Where relevant human data do not mirror realistic exposure conditions, supportive information may be needed to corroborate the observed effects. A single case report from

deliberate exposure (i.e. abuse) is unlikely to provide sufficiently robust evidence to support classification without other evidence.

IR/CSA, Section R.7.5.4.2 gives a detailed description on the use of human hazard information

3.9.2.3.2 Evaluation of non human data

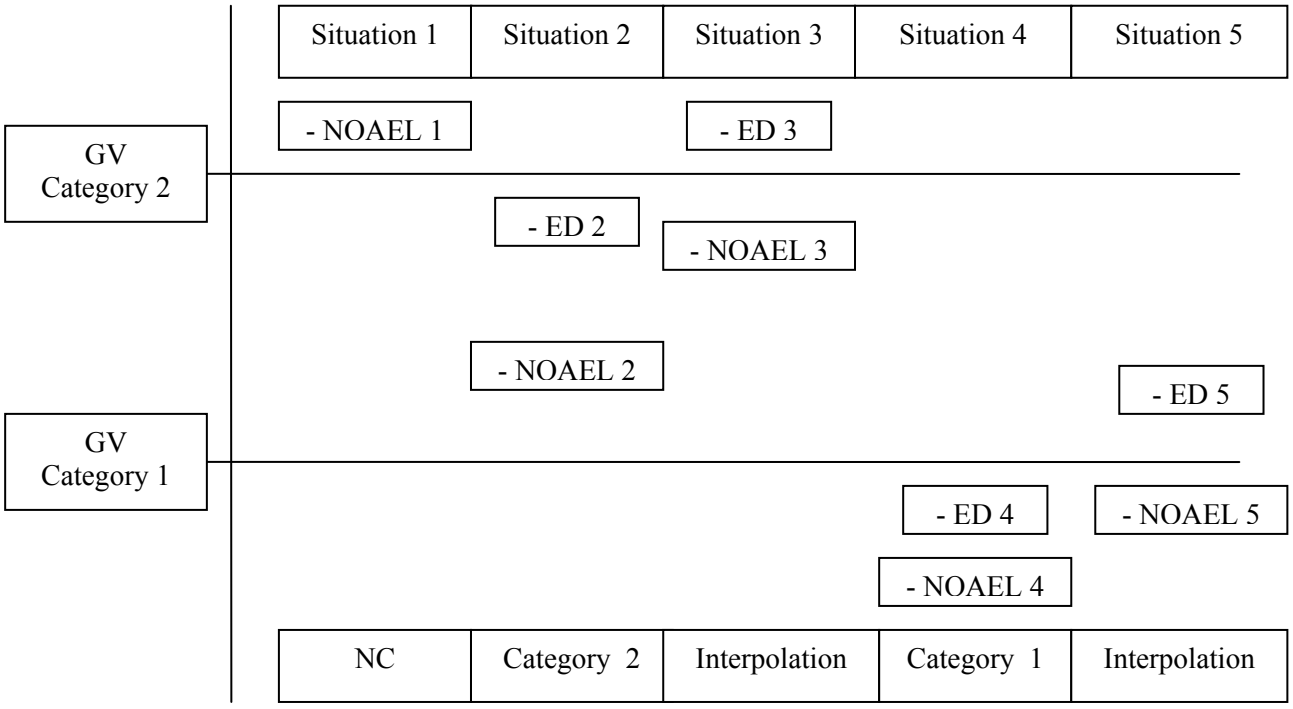
Annex 1 3.9.2.7.3. Evidence from appropriate studies in experimental animals can furnish much more detail, in the form of clinical observations, haematology, clinical chemistry, and macroscopic and microscopic pathological examination, and this can often reveal hazards that may not be life-threatening but could indicate functional impairment.

All available animal data which are of acceptable quality should be used in a weight of evidence approach based on a comparison with the classification criteria described above. This should be done separately for each route for which data are available.

For each study the effects seen in each sex at or around the guidance values for Category 1 and Category 2 should be compared with the effects warranting classification in Category 1 and 2. In general findings in the most sensitive sex would be used to determine the classification. If the NOAEL from the study is above the guidance value (GV), the results of that study do not indicate classification for that category (situations 1 and 2 in Figure 3.9.2.3.2). If the NOAEL is below the GV then the effective dose level (ED), i.e. the lowest dose inducing significant/severe target organ toxicity as defined in Section 3.9.2.2, should be determined based on the criteria described above. If the ED is below the GV then this study indicates that classification is warranted (situations 2 and 4 in Figure 1).

In a case where the ED is above a GV but the NOAEL is below the GV (situations 3 and 5) then interpolation between the ED and the NOAEL is required to determine whether the effects expected at or below the GV would warrant classification .

Figure 3.9.2.3.2 *Comparison between the NOAEL and the ED versus the guidance values*



Where a number of studies are available these should be assessed using a weight of evidence approach to determine the most appropriate classification. Where the findings from individual studies would lead to a different classification then the studies should be assessed in terms of their quality, species and strain used, nature of the tested substance (including the impurity profile and physical form) etc to choose the most appropriate study to support classification. In general, the study giving the most severe classification will be used unless there are good reasons that it is not the most appropriate. If the effects observed in animals are not considered relevant for humans then these should not be used to support classification. Similarly, if there is robust evidence that humans differ in sensitivity or susceptibility to the effect observed in the study then this should be taken into account, possibly leading to an increase or decrease in the classification assigned.

If there are differences in effects at the GV between studies with different duration then more weight is usually given to studies of a longer duration (28 days or more). This is because animals may not have fully adapted to the exposure in studies of shorter durations and also because longer duration studies tend to include more thorough and extensive investigations (e.g. in terms of detailed pathology and haematological effects etc) which can generally give more substantial information compared to shorter duration studies. If a 90-day as well as a 28-day study are available expert judgement has to be used and not just Haber's rule.

If there are differences in effects between good quality data in the same sex, species and strain then other variables such as particle size, vehicle, substance purity and impurities and concentration should be considered. If the results are considered to be depending on a specific impurity then different classifications depending on the concentration of the impurity could be considered.

Any information pertaining to the relevance of findings in animals to humans must be taken into account and may be used to modify the classification from how it would be if based on the available animal data. For instance, it may be shown that the findings in animals are not relevant for humans, for example if the toxicity in animals is mediated by a mode of action that does not occur in humans. This would potentially provide a supporting case for no classification. Similarly, evidence may suggest that the potency of the substance may be higher or lower in humans than in animals, for example because of differences in toxicokinetics/toxicodynamics between the species. Such evidence could be used to increase or decrease the severity of the classification as appropriate. It should be noted that such arguments for modifying the classification must be robust and transparent (see 3.9.2.3.4).

The final classification based on non human data will be the most severe classification of the three routes. If it is shown that classification for this endpoint is not required for a specific route then this can be included in the hazard statement. Evaluation of non human data can result in no classification, STOT RE 1 or STOT RE 2. The results of the evaluation in non human data should be used in combination with the results of the evaluation of human data.

If it is shown that classification for this endpoint is not required for a specific route then this can be included in the hazard statement according to the table below.

Table 3.9.2.4.1 *Inclusion of route of exposure in Hazard statement*

Route 1	Route 2	Route 3	H-statement
Category 1	Category 2	unknown	Causes damage to organs through prolonged or repeated exposure
Category 1	Category 2	NC	Causes damage to organs via route 1 and 2
Category 1	NC	unknown	Causes damage to organs through prolonged or repeated exposure
Category 1	unknown	unknown	Causes damage to organs through prolonged or repeated exposure
Category 1	NC	NC	Causes damage to organs via route 1

3.9.2.3.3 Conversions

The guidance values are giving in mg/kg bodyweight. Where the doses in a study are given in different units they will need to be converted as appropriate. For instance the dosages in feeding and drinking water studies are often expressed in ppm, mg test substance/ kg (feed) or mg (test substance)/l (drinking water).

Where insufficient information is reported in the study to perform the conversion, Table 3.9.2.3.3.1 and Table 3.9.2.3.3.2 can be used as "Approximate relations". These tables are derived from the following documents: IR/CSA, Chapter 8, Table 17; and OECD ENV/JM/MONO (2002)19, 04-Sep-2002, Table 1; L.R. Arrington (Introductory Laboratory Animal Science, 1978).

Table 3.9.2.4.2(a) *Food conversion*

Animal	Weight (kg)	Food consumed per day (g)	Factor 1mg/kgbw/d equivalent to ppm in diet
Rat, young	0.10	10	10
Rat ,older	0.40	20	20
Mouse	0.02	3	7
Dog	10	250	40

Table 3.9.2.4.2(b) *Conversion drinking water*

Animal	Weight (kg)	Drinkingwater consumed per day(g)	Factor 1mg/kgbw/d equivalent to ppm in drinking water
Rat, young	0.25	28 (25-30)	9
Rat ,older	0.40	28 (25-30)	14
Mouse	0.025	5 (4-7)	8
Dog	13	350	37

The conversion is performed according to the following simple equation:

$$\text{mg/kgbw} = \text{ppm/factor}$$

Example: In a 4 week study rats received the 1000 ppm test substance in feed

Dosage (mg/kg bw): 1000:10= 100 mg/kgbw.

In any case a calculation of the average substance intake based on measured bodyweight and consumption data is preferable and should be performed where possible.

Gases: mg/l into ppm:

Effect doses from gases given in the unit mg/l have to be converted into the unit ppm as used by the CLP via the following simplified formula assuming values for ambient pressure of 1 atm = 101.3 kPa and 25 ° c:

$$mg/l = ppm \times MW/0.02445$$

3.9.2.3.4 Weight of evidence

Annex 1: 3.9.2.3. Classification is determined by expert judgment (see section 1.1.1), on the basis of the weight of all evidence available including the guidance presented below.

3.9.2.4. Weight of evidence of all data (see section 1.1.1), including human incidents, epidemiology, and studies conducted in experimental animals, is used to substantiate specific target organ toxic effects that merit classification. This taps the considerable body of industrial toxicology data collected over the years. Evaluation shall be based on all existing data, including peer-reviewed published studies and additional acceptable data.

Annex 1: 3.9.2.10.2. When well-substantiated human data are available showing a specific target organ toxic effect that can be reliably attributed to repeated or prolonged exposure to a substance, the substance shall normally be classified. Positive human data, regardless of probable dose, predominates over animal data. Thus, if a substance is unclassified because no specific target organ toxicity was seen at or below the dose/concentration guidance value for animal testing, if subsequent human incident data become available showing a specific target organ toxic effect, the substance shall be classified.

3.9.2.10.3. A substance that has not been tested for specific target organ toxicity may, where appropriate, be classified on the basis of data from a validated structure activity relationship and expert judgment-based extrapolation from a structural analogue that has previously been classified together with substantial support from consideration of other important factors such as formation of common significant metabolites.

In cases where there is sufficient human evidence that meets the criteria given in CLP Annex I, Table 3.9.1 to support classification then this will normally lead to classification in Category 1, irrespective of other information available.

Where human evidence does not meet this criterion, for example when the weight of evidence is not sufficiently convincing (limited number of cases or doubt on causal relationship) or because of the nature and severity of the effects (CLP Annex I, 3.9.2.7.3 and 3.9.2.8.1), then classification is based primarily on the non-human data

If there are no human data then the classification is based on the non-human data. If there is human data indicating no classification but there is also non-human data indicating classification then the classification is based on the non-human data unless it is shown that the human data cover the exposure range of the non-human data and that the non-human data are not relevant for humans. If the human and non-human data both indicate no classification then classification is not required.

3.9.2.4 Decision on classification

Annex 1: 3.9.2.7.1. Reliable evidence associating repeated exposure to the substance with a consistent and identifiable toxic effect demonstrates support for the classification.

Annex 1: 3.9.2.7.3. Evidence from appropriate studies in experimental animals can furnish much more detail, in the form of clinical observations, haematology, clinical chemistry, and macroscopic and microscopic pathological examination, and this can often reveal hazards that may not be life-threatening but could indicate functional impairment. Consequently all available evidence, and relevance to human health, shall be taken into consideration in the classification process, including but not limited to the following toxic effects in humans and/or animals:

(a) morbidity or death resulting from repeated or long-term exposure. Morbidity or death may result from repeated exposure, even to relatively low doses/concentrations, due to bioaccumulation of the substance or its metabolites, and/or due to the overwhelming of the de-toxification process by repeated exposure to the substance or its metabolites.

(b) significant functional changes in the central or peripheral nervous systems or other organ systems, including signs of central nervous system depression and effects on special senses (e.g., sight, hearing and sense of smell).

(c) any consistent and significant adverse change in clinical biochemistry, haematology, or urinalysis parameters.

(d) significant organ damage noted at necropsy and/or subsequently seen or confirmed at microscopic examination.

(e) multi-focal or diffuse necrosis, fibrosis or granuloma formation in vital organs with regenerative capacity.

(f) morphological changes that are potentially reversible but provide clear evidence of marked organ dysfunction (e.g., severe fatty change in the liver).

(g) evidence of appreciable cell death (including cell degeneration and reduced cell number) in vital organs incapable of regeneration.

Annex 1: 3.9.2.8. Effects considered not to support classification for specific target organ toxicity following repeated exposure

3.9.2.8.1. It is recognised that effects may be seen in humans and/or animals that do not justify classification. Such effects include, but are not limited to:

(a) Clinical observations or small changes in bodyweight gain, food consumption or water intake that have toxicological importance but that do not, by themselves, indicate “significant" toxicity.

(b) Small changes in clinical biochemistry, haematology or urinalysis parameters and/or transient effects, when such changes or effects are of doubtful or minimal toxicological importance

(c) Changes in organ weights with no evidence of organ dysfunction.

(d) Adaptive responses that are not considered toxicologically relevant.

(e) Substance-induced species-specific mechanisms of toxicity, i.e. demonstrated with reasonable certainty to be not relevant for human health, shall not justify classification.

If the evaluation of available data on a substance shows that the criteria for classification in a category are fulfilled than the substance shall be classified in that category for STOT-RE. If the data show that classification is warranted in Category 1 for one route and in Category 2 for another route then the substance shall only be classified in Category 1. The corresponding hazard statements are provided in Section 3.9.4.1.

If only data is available for one route showing that classification is warranted than no route should be stated in the hazard statement. If the data conclusively show that no classification for STOT-RE is warranted for a specific route then the remaining routes should be stated. If the data show that classification is warranted in Category 1 for one route and in Category 2 for another route then the hazard statement for Category 1 should include both routes because substances are placed in one of two categories.

3.9.2.5 Additional considerations

In the following sections some special aspects in the decision process on classification are described in more detail.

3.9.2.5.1 Irritating/corrosive substances

Substances (or mixtures) classified as corrosive may cause severe toxicological effects following repeated exposure, especially in the lungs following inhalation exposure. In such cases, it has to be evaluated whether the severe effect is a reflection of true repeated exposure toxicity or whether it is in fact just acute toxicity (i.e. corrosivity). One way to distinguish between these possibilities is to consider the dose level which causes the toxicity. If the dose is more than half an order of magnitude lower than that mediating the evident acute toxicity (corrosivity) then it could be considered to be a repeated-dose effect distinct from the acute toxicity. In this case, classification as specific target organ toxicant (repeated exposure) would be warranted even if the substance (or mixture) is also classified as acutely toxic and/or corrosive.

In assessing non systemic effects caused by irritating/corrosive substances it should be kept in mind, that the guidance values /criteria for R48 in the DSD and later on those for STOT-RE of the CLP were derived from acute toxicity criteria (lethality based) assuming that systemic effects show a time dependent increase of severity due to accumulation of toxicity and taking also adaptive and detoxification processes into account. The effect considered in this context was lethality. This indicates that classification was intended for the presence of severe health damage, only. (see ECBI/67/00)

3.9.2.5.2 Hematotoxicity

Methaemoglobin generating agents

Methaemoglobinemia has often been regarded as an acute clinical symptom resulting from the action of methemoglobin-generating agents. If lethality is observed in humans or in animals[50] or can be predicted (QSAR), methemoglobin generating substances should be classified in the Acute Toxicity Hazard Class. Since this effect is difficult to detect in rodents, expert judgement should be used (cf. Guidance on Acute toxicity, Example2). If methemoglobinemia does not result in lethality but exposure to methaemoglobin generating agents results in signs of damage to the erythrocytes and haemolysis, anaemia or hypoxemia, the formation of methaemoglobin shall be classified accordingly either in STOT-SE or STOT-RE. (Muller A. *et al*., 2006).

Haemolytic anaemia

The guidance developed for classification of substances inducing haemolytic anaemia according to 67/548/EEC (Muller A. et al., 2006) cannot directly be used under CLP because

[50] Observation of lethality following methemoglobin formation is not usual, as several animals are more tolerant to it. Extrapolation to the human situation must be the critical decision key.

of the changes in criteria (see CLP Annex I, 3.9.2.7.3 c and 3.9.2.8.b, d). The major criterion for haemolytic anaemia changed:

- From "Any consistent changes in haematology which indicate severe organ dysfunction."
- To "Any consistent and significant adverse changes in haematology."

This indicates that less adverse effects are considered for classification according to CLP. This is consistent with the changes in the other criteria for classification for repeated exposure.

Adaptation towards the criteria according to CLP results in the following guidance:

It is evident that anaemia describes a continuum of effects, from sub-clinical to potentially lethal in severity. Overall, the interpretation of study findings requires an assessment of the totality of findings, to judge whether they constitute an adaptive response or an adverse toxicologically significant effect. If a haemolytic substance induces one or more of the serious health effects listed as examples below within the critical range of doses, classification is warranted. It is sufficient for classification that only one of these criteria is fulfilled.

Annex I: 2.9.2.7.3.

(a) morbidity or death resulting from repeated or long-term exposure. Morbidity or death may result from repeated exposure, even to relatively low doses/concentrations, due to bioaccumulation of the substance or its metabolites, and/or due to the overwhelming of the de-toxification process by repeated exposure to the substance or its metabolites;

Example:

- Premature deaths in anaemic animals that are not limited to the first three days of treatment in the repeated dose study. (Mortality during days 0–3 may be relevant for acute toxicity.)
- Clinical signs of hypoxia, e.g. cyanosis, dyspnoea, pallor, in anaemic animals that are not limited to the first three days of treatment in the repeated dose study.

(b) significant functional changes in the central or peripheral nervous systems or other organ systems, including signs of central nervous system depression and effects on special senses (e.g. sight, hearing and sense of smell);

(c) any consistent and significant adverse effect in clinical biochemistry, haematology or urinalysis parameters;

Examples:

- Reduction in Hb at ≥20%.
- Reduction in functional Hb at ≥20% due to a combination of Hb reduction and MetHb increase.
- Haemoglobinuria that is not limited to the first three days of treatment in the repeated dose study in combination with other changes indicating significant haemolytic anaemia (e.g. a reduction in Hb at ≥10%).
- Haemosiderinuria supported by relevant histopathological findings in the kidney in combination with other changes indicating significant haemolytic anaemia (e.g. a reduction in Hb at ≥10%).

(d) significant organ damage noted at necropsy and/or subsequently seen or confirmed at microscopic examination;

(e) multifocal or diffuse necrosis, fibrosis or granuloma formation in vital organs with regenerative

capacity;

Example:

– Multifocal or diffuse fibrosis in the spleen, liver or kidney.

(f) morphological changes that are potentially reversible but are clear evidence of marked organ dysfunction (e.g. severe fatty change in the liver)

Example:

– Tubular nephrosis

(g) evidence of appreciable cell death (including cell degeneration and reduced cell number) in vital organs incapable of regeneration.

In the case where multiple less severe effects with regenerative capacity were observed, the classification should apply as

"Assessment shall take into consideration not only significant changes in a single organ or biological system but also generalised changes of a less severe nature involving several organs."

Example:

– Marked increase of haemosiderosis in the spleen, liver or kidney in combination with other changes indicating significant haemolytic anaemia (e.g. a reduction in Hb at ≥10%) in a 28 day study.

– Significant increase in haemosiderosis in the spleen, liver or kidney in combination with microscopic effects like necrosis, fibrosis or cirrhosis.

Annex I: 3.9.2.8.1. It is recognised that effects may be seen in humans and/or animals that do not justify classification. Such effects include, but are not limited to:

(a) clinical observations or small changes in bodyweight gain, food consumption or water intake that have toxicological importance but that do not, by themselves, indicate 'significant' toxicity;

(b) small changes in clinical biochemistry, haematology or urinalysis parameters and/or transient effects, when such changes or effects are of doubtful or minimal toxicological importance;

Example:

– Significant decrease in Hb without any other significant indicators of haemolytic anaemia.

– Minimal to slight increase in MetHb formation without any other indications of significant haemolytic anaemia.

(c) changes in organ weights with no evidence of organ dysfunction;

(d) adaptive responses that are not considered toxicologically relevant.

Example:

– Only adaptive or compensating effects without significant signs of haemolytic anaemia.

(e) substance-induced species-specific mechanisms of toxicity, i.e. demonstrated with reasonable certainty to be not relevant for human health, shall not justify classification.

3.9.2.5.3 Mechanisms not relevant to humans (CLP Annex I, 3.9.2.8.1. (e))

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

α-2-μ globulin nephropathy in male rats

The protein α-2-μ globulin, which is primarily synthesized in male rats, has the capability to bind to certain chemicals. The resultant adducts accumulate as droplets in the kidneys and causes progressive renal toxicity within a few weeks which can ultimately lead to kidney tumours. This specific mechanism is unique to male rats and has no relevance for humans. Examples of chemicals causing α-2-μ globulin nephropathy are: unleaded gasoline, chlorinated paraffins, isophorone, d-limonene.

Specific thyroid toxicity via liver enzyme induction

Certain chemicals cause induction of liver enzymes and are interfering with the regulation of thyroid hormones. An increase in the activity of hepatic UDPG-transferase results in increased glucuronidation of thyroid hormones and increased excretion. It is known that rodents are highly sensitive to a reduction in thyroid hormone levels (T4), resulting in thyroid toxicity (e.g. hypertrophy, hyperplasia) after repeated stimulation / exposure of this organ. This in turn is related to an increase in the activity of hepatic UDPG-transferase. Humans, unlike rodents, possess a T_4 binding protein that greatly reduces susceptibility to plasma T_4 depletion and thyroid stimulation. Thus, such a mechanism/effect cannot be directly extrapolated to humans, i.e. these thyroid effects observed in rodents caused by an increase in hepatic UDPG-transferase are therefore considered of insufficient concern for classification (see ECBI/22/98-Add1).

Peroxisome induction/proliferation

Peroxisomes are cell-organelles which can be induced to a specifically high level in rats and mice under certain conditions, e.g. by repeated exposure to long chain and branched fatty acids. Peroxisome proliferation which is especially occurring in the liver causes liver toxicity (e.g. hyperplasia, oxidative stress) and can ultimately after longterm exposure also may lead to tumours.There is no evidence of e.g. hepatomegaly from clinical studies in humans treated with peroxisome proliferators (I.H.F.Purchase, Human & Experimental Toxicology (1994), 13, Suppl.2 S47-S48). Examples are Clofibrat and Diethylhexylphthalate (DEHP).

Lung Overload

The relevance of lung overload in animals to humans is currently not clear and is subject to continued scientific debate.

3.9.2.5.4 Adaptive responses (CLP Annex I, 3.9.2.8.1. (d))

Adaptive (compensatory) changes generally constitute a normal biochemical or physiological response to a substance or to the effect of the substance (e.g. in response to methaemoglobin formation), usually manifested as an increase in background processes such as metabolism or erythropoiesis etc, which are generally reversible with no adverse consequences on cessation of exposure. In some cases the adaptive response may also be associated with pathological changes which reflect the normal response of the target tissue to substances. For example, liver hypertrophy in response to enzyme induction, the increase in alveolar macrophages following inhalation of insoluble particles that must be cleared from the lungs, and the

development of epithelial hyperplasia and metaplasia in the rat larynx in response to inhalation of irritants.

Determination of whether adaptive changes support a classification requires a holistic assessment of the nature and severity of the observations and their dose-response relationship using expert judgement. Exposure to a substance can lead to a spectrum of effects which vary in incidence and severity with dose. At lower doses there may be adaptive changes which are not considered to be toxicologically significant or adverse, whereas at higher doses these changes may become more severe and/or other effects may occur which together constitute frank toxicity. Also, sometimes the adaptive effect is observed but the primary effect is not because the relevant parameter is not determined or not determined at the right time. For example, irritation of the larynx after inhalation of irritants is not observed at the end of a repeated dose study because of the quick response. The adaptive effect can then be used as an indication of the primary effect. It is often difficult to clearly distinguish between changes which are adaptive in nature and those which represent clear overt toxicity and this assessment requires expert judgement. Where the response to a substance is considered to be purely adaptive at dose levels relevant for classification then no classification would be appropriate.

3.9.2.5.5 Post-observation periods in 28 day and 90 day studies

For subacute/subchronic testing protocols, the usual guideline procedure is to sacrifice the exposed animals immediately after the end of the exposure period (d 29 or 91).

Japanese agencies often require a 14 days postobservation period for 28 day studies (OECD 407). This means that 10 more animals in the top dose and 10 more animals as an additional control group are then necessary.

The reversibility of organotoxic effects can in most cases be estimated by the pathologist from histologic findings without a post-observation period.

- Certain effects are entirely reversible such as simple irritation or many forms of liver, testicular and hematotoxicity.
- Other effects may be reversible in morphological terms but the reserve capacity of the organism may be irreversibly compromised (such as in the case of kidney toxicity with a persistent loss in kidney nephrons).
- Some forms of tissue toxicity may be fundamentally irreversible, such as CNS- and neuro-toxicity with specific histological findings, cardiac toxicity and lung toxicity. Often, such effects do not return to normal morphology and may deteriorate even after the end of exposure.

3.9.2.6 Setting of specific concentration limits

Specific concentration limits (SCLs) for STOT-RE may be set by the supplier in some situations according to Article 10 of CLP. For STOT-RE, this may only be done for substances inducing target organ toxicity at a dose level or concentration clearly (more than one magnitude) below the guidance values according to CLP Annex I, Table 3.9.2, that corresponds to ED below 1 mg/kg bodyweight from the 90-day oral study. Where the exposure duration is not 90 days the ED has to be adjusted to an equivalent for 90 days using Haber's law and expert judgement (as described above). This will be mainly based on data in experimental animals but can also be used for human data if reliable exposure data are available. Setting of SCLs above the GCL is not applicable for STOT RE because classification for STOT RE is based on potency. Substances with a low potency do not require classification for this hazard class and substances with a medium or high potency are classified in a category defined by the GV.

The SCL for a Category 1 substance (*SCLCat.1*) can be determined using the following formula:

$$SCLCat.1 = \frac{ED}{GV1} \times 100\% \qquad \text{Equation 3.9.2.6(a)}$$

SCL Cat 1: 0.12 mg/kgbw/10 mg/kgbw x 100%= 1.2% --> 1%

ED (effective dose) is the dose inducing specific target organ toxicity and GV1 is the guidance value for Category 1 according to CLP Annex I, Table 3.9.2 of Annex I corrected for the exposure duration. The resulting SCL is rounded down to the nearest preferred value (1, 2 or 5).

Though classification of a mixture in Category 1 is not triggered if a Category 1 constituent is present in lower concentrations than the established SCL, a classification in Category 2 should be considered. The SCL for classification of a mixture in Category 2 (*SCLCat. 2*) based on substances classified in Category 1can be determined using the following formula:

$$SCLCat.2 = \frac{ED}{GV2} \times 100\% \qquad \text{Equation 3.9.2.6(b)}$$

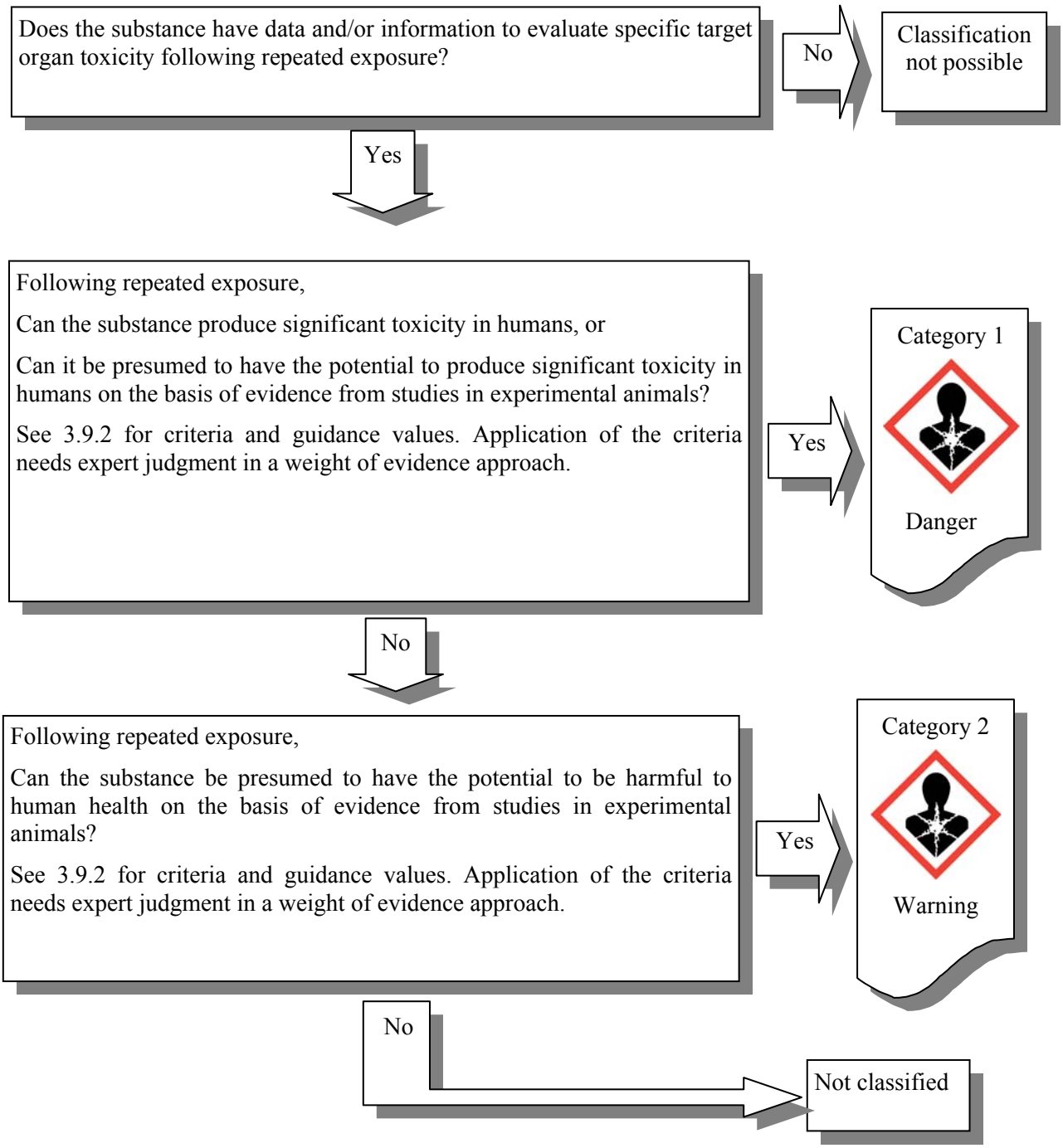
SCL Cat 2: 0.12 mg/kgbw/100 mg/kgbw x 100%=0.12% --> 0.1%

In this formula the ED (effective dose) is the dose inducing specific target organ toxicity and GV2 is the upper guidance value for Category 2 according to CLP Annex I, Table 3.9.3 corrected for the exposure duration. The resulting SCL is rounded down to the nearest preferred values (1, 2 or 5).

It is not appropriate to determine SCLs for substances classified in Category 2 since ingredients with a higher potency (i.e. lower effect doses than the guidance values of Category 2) will be classified in Category 1 and substances with respective higher effect doses will generally not be classified. For example, a substance inducing significant specific target organ toxicity at 0.12 mg/kg bw/day in a 90-day oral study would require a SCL for Category 1 of 1% and for Category 2 of 0.1%.

3.9.2.7 Decision logic for classification of substances

The decision logic which follows is provided as additional guidance to the criteria. It is strongly recommended that the person responsible for classification, study the criteria for classification before and during use of the decision logic.



3.9.3 Classification of mixtures for STOT-RE

3.9.3.1 Identification of hazard information

Where toxicological information is available on a mixture this should be used to derive the appropriate classification. Such information may be available from the mixture manufacturer. Where such information on the mixture itself is not available information on similar mixtures and/or the component substances in the mixture must be used, as described below.

Further, the hazard information on all individual components in the mixture could be identified as described in Section 3.9.3.3.2.

3.9.3.2 Classification criteria for mixtures

Annex 1: 3.9.3.1. Mixtures are classified using the same criteria as for substances, or alternatively as described below. As with substances, mixtures shall be classified for specific target organ toxicity following repeated exposure.

3.9.3.3 When data are available for the complete mixture

Annex 1: 3.9.3.2.1. When reliable and good quality evidence from human experience or appropriate studies in experimental animals, as described in the criteria for substances, is available for the mixture (see 1.1.1.3), then the mixture shall be classified by weight of evidence evaluation of these data. Care shall be exercised in evaluating data on mixtures, that the dose, duration, observation or analysis, do not render the results inconclusive.

In cases where test data for mixtures are available, the classification process is exactly the same as for substances.

3.9.3.3.1 When data are not available for the complete mixture: bridging principles

Annex 1: 3.9.3.3.1. Where the mixture itself has not been tested to determine its specific target organ toxicity, but there are sufficient data on the individual ingredients *and* similar tested mixtures to adequately characterise the hazards of the mixture, these data shall be used in accordance with the bridging principles set out in section 1.1.3.

When there are no test data on the mixture as a whole, so called “Bridging principles” may be applied where there are data available on similar tested mixtures and on the individual hazardous ingredient substances within the mixture that are sufficient to adequately assess the hazards of the mixture.

3.9.3.3.2 When data are available for all components or only for some components of the mixture

Annex 1: 3.9.3.4.1. Where there is no reliable evidence or test data for the specific mixture itself, and the bridging principles cannot be used to enable classification, then classification of the mixture is based on the classification of the ingredient substances. In this case, the mixture shall be classified as a specific target organ toxicant (specific organ specified), when at least one ingredient has been classified as a Category 1 or Category 2 specific target organ toxicant and is present at or above the appropriate generic concentration limit as laid out in Table 3.9.4 below for Category 1 and 2 respectively.

3.9.3.3.3 Components of a mixture that should be taken into account for the purpose of classification

Components with a concentration equal to or greater than the generic concentration limits (1% for Category 1 components and 10 % for Category 2; see CLP Annex I, Table 3.9.4) or with a specific concentration limit (see also 3.9.3.5) will be taken into account for classification purposes. Specific concentration limits have preference over the generic concentration limits.

3.9.3.4 Generic concentration limits for substances triggering classification of mixtures

Annex 1: *Table 3.9.4*

Generic concentration limits of ingredients of a mixture classified as a specific target organ toxicant that trigger classification of the mixture.

Ingredient classified as:	Generic concentration limits triggering classification of the mixture as:	
	Category 1	Category 2
Category 1 Specific Target Organ Toxicant	Concentration ≥ 10%	1.0% ≤ concentration < 10%
Category 2 Specific Target Organ Toxicant		Concentration ≥ 10% (Note 1)

Note 1
If a Category 2 specific target organ toxicant is present in the mixture as an ingredient at a concentration ≥ 1,0 % a SDS shall be available for the mixture upon request.

Annex 1: 3.9.3.4.4. Care shall be exercised when toxicants affecting more than one organ system are combined that the potentiation or synergistic interactions are considered, because certain substances can cause target organ toxicity at < 1% concentration when other ingredients in the mixture are known to potentiate its toxic effect.

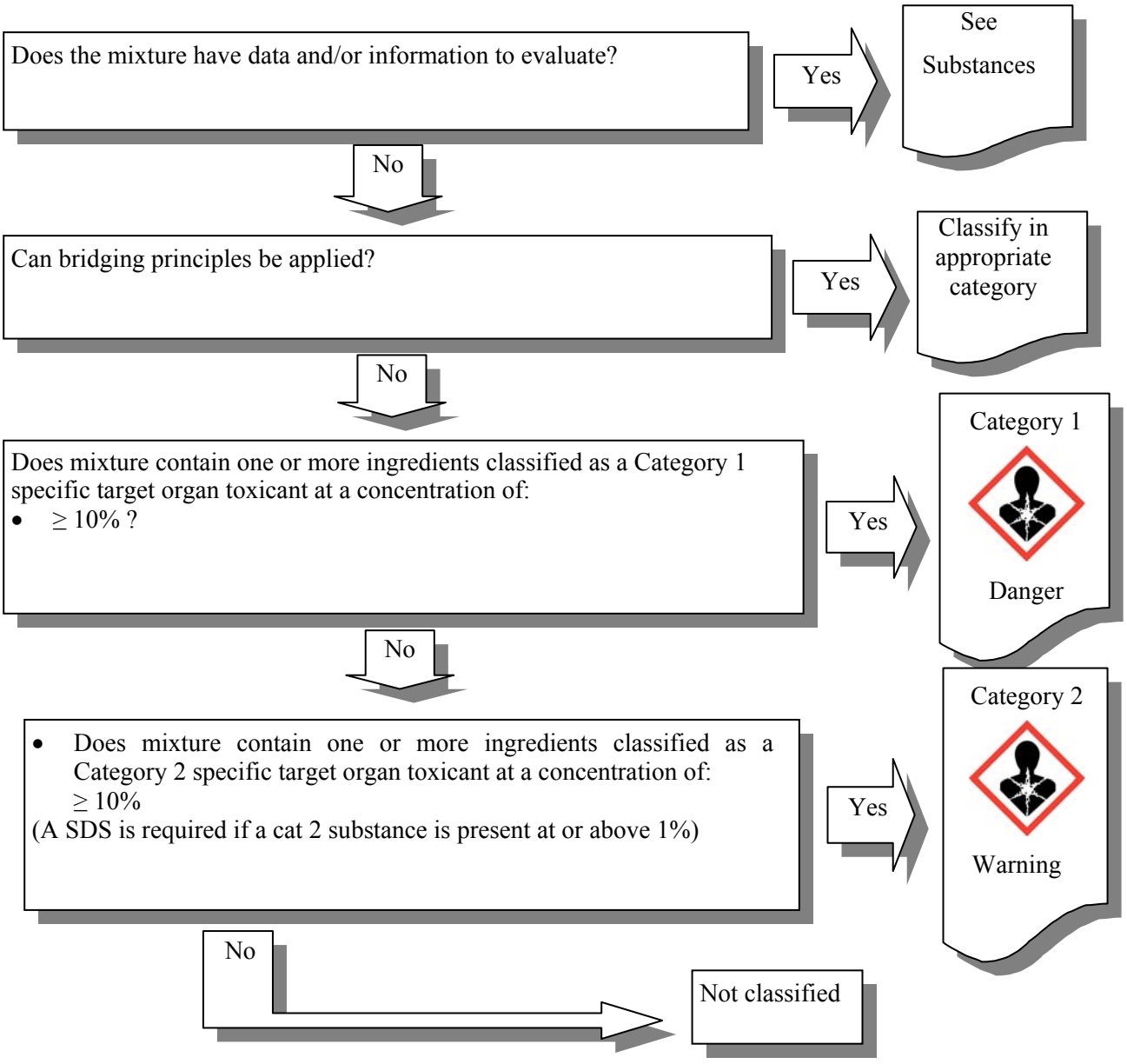
In the case a specific concentration limit has been established for one or more ingredients these SCLs have precedence over the respective generic concentration limit.

When classifying a mixture for STOT-RE the additive approach, where the concentrations of individual components with the same hazards are summed, is not used. If any individual component is present at a concentration higher than the relevant generic or specific concentration limit then the mixture will be classified.

3.9.3.5 Decision logic for mixtures

A mixture should be classified either in Category 1 or in Category 2, according to the criteria described above. When a mixture is classified for STOT-SE on basis of test data, the hazard statement will specify the target organs, in the same way as for a substance. If a mixture is classified on basis of the ingredients, the hazard statement (H372 for Category 1 or H373 for Category 2) may be used without specifying the target organs, as appropriate. In the same way, the route of exposure should not be specified, except if data are available for the complete mixture and if it is conclusively demonstrated that no other routes of exposure cause the hazard.

The decision logic which follows is provided as additional guidance to the criteria**.** It is strongly recommended that the person responsible for classification study the criteria for classification before and during use of the decision logic.



3.9.4 Hazard communication in form of labelling for STOT RE

3.9.4.1 Pictograms, signal words, hazard statements and precautionary statements

Annex I: 3.9.4.1. Label elements shall be used in accordance with Table 3.9.5 for substances or mixtures meeting the criteria for classification in this hazard class.

Table 3.9.5

Label elements for specific target organ toxicity after repeated exposure

Classification	Category 1	Category 2
GHS Pictograms		
Signal word	Danger	Warning
Hazard statement	H372: Causes damage to organs (state all organs affected, if known) through prolonged or repeated exposure (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	H373: May cause damage to organs (state all organs affected, if known) through prolonged or repeated exposure (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)
Precautionary statement prevention	P260 P264 P270	P260
Precautionary statement response	P314	P314
Precautionary statement storage		
Precautionary statement disposal	P501	P501

The hazard statement should include the primary target organ(s) of toxicity. Organs in which secondary effects were observed should not be included. The route of exposure should not be specified, except if it is conclusively demonstrated that no other routes of exposure cause the hazard.

When a mixture is classified for STOT-RE on basis of test data, the hazard statement will specify the target organs, in the same way as for a substance. If a mixture is classified on basis of the ingredients, the hazard statement (H372 for Category 1 or H373 for Category 2) may be used without specifying the target organs, as appropriate.

In the same way, the route of exposure should not be specified, except if data are available for the complete mixture and if it is conclusively demonstrated that no other routes of exposure cause the hazard.

It is recommended to include no more then three primary target organs for practical reasons and because the classification is for specific target organ toxicity. If more target organs are affected it is recommended that the overall systemic damage should be reflected by using the more general term “damage of organs”.

3.9.4.2 Additional labelling provisions

Annex 1: 3.9.2.10.4 Saturated vapour concentration shall be considered, where appropriate, as an additional element to provide for specific health and safety protection

According to CLP Annex I, 3.9.2.10.4 the saturated vapour concentration shall be considered as an additional element for providing specific health and safety protection. Thus if a classified substance is highly volatile a supplementary precautionary advice (e.g. "Special/additional care should be taken due to the high saturated vapour pressure") might be given in order to emphasize the hazard in case it is not already covered by the general **P** statements. (As a rule substances for which the ratio of the effect concentration at ≤ 4h to the SVC at 20° C is ≤ 1/10).

Although not according to the criteria of STOT-RE, the following EU-special hazard statement "Repeated exposure" may be used when appropriate:

EUH066- "Repeated exposure may cause skin dryness or cracking" (see Chapter 3.2 Skin/Corrosion/Irritation).

3.9.5 Re-classification of substances and mixtures classified for STOT-RE according to DSD and DPD

Classification with STOT–RE according to CLP is comparable to the classification with R48/X according to DSD. Also substances and mixtures currently classified with R33 should be considered because there is no corresponding classification in CLP. However, differences are present regarding the approach to route-to-route extrapolation.

3.9.5.1 Is direct "translation" of classification and labelling possible for STOT-RE substances?

Direct translation of substances or mixtures classified with R48/X is possible because classification criteria are based on the dose and the severity of a toxic effect and are comparable in both, CLP and DSD. However, in some cases a change in the Category may result by reviewing the data.

Substances or mixtures classified with R48/23, R48/20 (for vapour), R48/24 and/or R48/25 shall be classified as STOT-RE Category 1 because less adverse effects and higher guidance values are required for classification according to CLP compared to DSD. Notable, there is one exception: dust/mist/fume with an ED > 0.02 and ≤ 0.025 mg/l/6h which are classified according to DSD with R48/23 might not be classified in Category 1 according to CLP. Setting of SCL may be considered for substances showing STOT-RE at levels clearly below the guidance values (see 3.9.2.6).

All substances or mixtures classified with R48/20 (for dust/mist/fume), R48/21 and/or R48/22 shall be classified generally at least as STOT-RE Cat 2. Again, dust/mist/fume with an ED > 0.2 and ≤ 0.25 mg/l/6h which are classified according to DSD with R48/20 might not be classified according to CLP. However, due to the general increase in guidance values, the requirement for less severe effects classification in Category 2 should also be considered but.

If translation results in a classification in STOT-RE Category 1 for one route and in STOT-RE Category 2 for another route only classification in Category 1 is required (for both routes). In contrast to DSD where the route of exposure is included in the classification and correlates with the routes tested (or extrapolated), according to CLP the exposure route should be specified only when it is conclusively proven that no other routes of exposure cause the hazard. Therefore, the route specific data on STOT-RE should be re-evaluated. A re-

evaluation is also necessary because the primary target organs for STOT-RE should be stated in the hazard statement.

3.9.5.2 Re-evaluation of the STOT-RE data

Gasses classified with R48/20 or R48/23 should be re-evaluated because the guidance values changed from general guidance values in mg/L for aerosols, vapours and gasses to a specific guidance value for gasses in ppm.

Substances or mixtures not classified for, STOT-RE including substances or mixtures classified with R33, should be re-evaluated because less adverse effects and higher guidance values are required for classification according to CLP compared to DSD. Also, effects in humans are now considered for classification generally without restrictions to the exposure level.

3.9.6 Examples of classification for STOT-RE

Remarks:

The classification proposals for the examples refer only to STOT-RE.

Labelling is done only with respect to hazard statements (statement with respect of organs affected = target organs).

3.9.6.1 Examples of substances fulfilling the criteria for classification

3.9.6.1.1 Example 1: Hydroxylamine / Hydroxylamonium salts (CAS no. 7803-49-8)

Application of criteria for evaluation/classification and decision on classification: Use of studies with different duration; Haber's rule; Expert judgement

Available information:

1) Human experience: No information available

2) Animal data:

Background:

Hydroxylamine and its salts are direct MetHb producers in contrast to aromatic amines, which require metabolic activation (XI/484/92).

Several studies are available for the assessment of the toxicity after repeated administration:

- 4-week drinking water study (BASF, 1989)
- 3-month drinking water study (BASF, 1989)
- Combined chronic/carcinogenicity study in drinking water in rats (BASF, 2001)

Though not explicitly stated in the criteria the "... study with the longest duration should normally be used".

- In the 3-month-study at the dose level of 21 mg/kg bw only "slight to moderate hematotoxic effects" were observed. Thus this dose would not be a sufficient ED causing "significant/severe" effects, but it can be concluded that via interpolation an ED would result within the Guidance Value Range for Cat 2 (10-100 mg/kg bw).
- A classification in Category 2 would be warranted based on the 3-month-study.

In the combined chronic/carcinogenicity study (BASF, 2001), the effects observed after 12 and 24 months are to be considered separately:

12 month study:

- 0 ppm (control): hemosiderin storage of low degree in males and females (spleen)
- 5 ppm (males 0.3 mg and females 0.4 mg/kg bw/day): No substance-induced effects; hemosiderin storage of low degree in males and females, comparable to controls.
- 20 ppm (males 1.1 mg and females 1.6 mg/kg b.w./day): Here, hemosiderin deposits with the gradation of moderate was observed in the spleens of the males; hemosiderin storage of low degree in females comparable to controls. This effect is not to be regarded as serious since hematology did not reveal any findings whatsoever with regard to anemia. This is supported by the fact that no substantial (1/10 moderate, but 1/10 severe in the male control group) extramedullary hematopoiesis was observed in this group. In the histopathological examination, the spleen was not found to be impaired morphologically. Thus, this dose is to be regarded as the NOAEL for males whereas it is the NOEL for females.
- 80 ppm (males 4.5 mg and females 6.2 mg/kg b.w./day): The clinicochemical findings are assessed as mild anemia in the males (e.g. decrease of RBC, HB and HT (< 10%); MCV increased at the beginning and compensatory normalization later) and, also as mild anemia in the females (decrease in RBC $\leq$ 12%, HB < 10% and HT < 10%). The increase of MCV, PLT and RET and of Howell-Jolly bodies is regarded as a compensatory effect, and the bone marrow still reacts, i.e. it does not demonstrate "... decreased bone marrow production of red blood cells" within the meaning of the criteria. The only slight increase of the Heinz bodies is considered to be a sign of a weak hematotoxic effect. From the point of view of histopathology, the effects (hemosiderin storage, extramedullary hematopoesis) can be regarded as signs of anemia, but not within the meaning of "serious" (the effect was more pronounced in the females than in the males). The extramedullary hematopoiesis observed is thus again compensatory in the sense of a functional counterreaction.

Assessment:

For a 12-month study, cut-off values of 25 and 2.5 mg/kg bw/day (100 mg/kg/day : 4) have to be regarded for STOT-RE Category 1 vs. Category 2 respectively. At the dose level of 1.1 (m) or 1.6 mg/kg bw/day (f), no hematotoxic effects whatsoever or extramedullary hematopoiesis were observed, nor substantial hemosiderin deposits. The effects at 4.5 (f) and 6.2 (m) mg/kg bw/day are regarded as mild anemia; however, more distinct effects may be expected to occur up to the cut-off value (25 mg/kg/day). Therefore, a classification in Category 2 seems justified.

24-month study:

In contrast to the 12-month study, no complete hematological examination was carried out, i.e. only morphological parameters were evaluated, yet full histopathology. The following findings relevant to classification – with the exception of the neoplasias – were obtained:

- 5 ppm (males 0.2 mg and females 0.4 mg/kg b.w./day): No nonneoplastic effects
- 20 ppm (males 1 mg and females 1.6 mg/kg b.w./day): Increased proportion of hemosiderin deposits in the spleens of the females, but no extramedullary hematopoiesis, which demonstrates that there was no clear anemia before.

  Remark:
  The fact that, at this dose level, hemosiderin was detected only in the males in the 12-

month study and an increased proportion of it only in the females in the 24-month study shows that this effect was only borderline.

– 80 ppm (males 3.7 mg and females 6.2 mg/kg b.w./day): Again hemosiderin storage and extramedullary hematopoesis were observed, yet no serious effects in hematology nor histopathology.Furthermore, the results of the study do not indicate that any animal died prematurely on account of the anemia.

Remark:
No effects at all were observed in kidneys nor in liver in the 12-month study. In the 3 month study only in the highest dose the relative liver weights were increased in the males; in the 3 month as well as in the 24-month study only marginal effects (diffuse hemosiderin storage in the liver) in both sexes was observed in the highest dose.

Assessment:

The results of the 24 month study show that effects as seen after 12 month exposure are not substantially increased.

Classification:

Based on the evaluation of the 3-month-study and the more relevant 12-month-study by expert judgement a classification in Category 2 is warranted.

Labelling:

Hazard statement: H373 May cause damage to blood system through prolonged or repeated exposure

(See also ECBI/ 14/3/ Add 3 (2003) and ECBI/56/04 Rev 1)

3.9.6.1.2 Example 2: But-2-yn-1,4-diol (EC No 203-788-6; CAS No 110-65-6)

Current classification according to DSD: Xn; R48/22

Application of criteria for evaluation/classification and allocation of hazard statements with respect to specific target organs and route of exposure

Available information:

1) Human experience: no information available
2) Animal data:
   - 28 d oral study
   - 28 d inhalation study
   - Acute oral toxicity: LD50 rat 132 (males) and 176 (females) mg/kg -> Category 3
   - Acute dermal toxicity: LD50 424 (males) and 983 (female) mg/kg -> Category3
   - Acute inhalation toxicity: LC50 rat 0.69 mg/l -> Category 2
   - Corrosivity in animal experiments (Category 1)

STOT-RE oral:

28 d rat oral (gavage): doses 0; 1; 10; 50 mg/kgbw/d

- 1 mg/kg: NOEL
- 10-mg/kg: LOEL
- Increased liver weight (not statistically significant)
- Hepatic and spleenic changes.(no clear desription of severity given)
- Diminished RBC counts in females, yet no other changes in blood chemisry

- Histopathology: in 2/10 males and 3/10 females swelling of parenchymal cells and increased polymorphism of the hepatocyte nuclei and the nuclear cells. These effects are regarded as not "significant/severe toxic effects "
- 50 mg/kg: mortality (3/8 males; 3/8 females); hepato-and nephrotoxicity responsible for mortality; no distinct hepato-and nephrotoxicity described for survivors
- Hematology: Decrease in RBC count ca. 20% and 21% in HB both in females; decrease in Hematocrite 11%. These effects are regarded as " moderate hematotoxicity".

Conclusion for the highest dose group: severe effects.

Assessment:

The substance has a high acute toxicity (s. a.). Since the factor between the acute LD50 and the subacute lethal dose (20 applications) is only 2-3, it can be assumed that the substance has a low cumulative potential. On the other hand there is a steep dose response in the 4 week study, thus it can be concluded by interpolation that at 30 mg/kg moderate but no "significant/severe" toxicity could be expected; 30 mg/kg is the guidance value for Category 1 in a 4 week study according to Habers rule: 10 mg/kg x 3)

STOT-RE inhalation

In a valid 4 week inhalation study (vapour) rats were exposed to 0.5; 5; and 25 mg/m3/6h/d.

- 0.5 mg/m3: NOAEC for local effects in therespiratory tract
- 5 mg/ m3: minimal –slight focal squamous metaplasia and inflammation in the larynx
- 25 mg m3: minimal –slight focal squamous metaplasia and inflammation in the larynx
- 25 mg/ m3: NOAEC for systemic effects including hematology, clinical chemistry, histopathology and neuropathology examinations

Assessment:

Up to the highest concentration tested there were no systemic effects. Since the substance is classified as corrosive an irritation of the respiratory tract by the vapour could be expected and has been observed in minimal-slight degree at 5-25 mg/m3. It is assumed that the irritation would increase with higher concentrations.The corrosive/irritation potential is covered by the classification as "corrosive" Category1, thus no classification as STOT-RE with respect to the inhalation route would result.

Classification:

Category 2 for the oral route is proposed since within the guidance values of 30-300 mg/kg in a 4 week study serious effect occurred. According to a total weight of evidence approach it is concluded that these significant effects would not be observed below 30 mg/kg, the concentration limit for Category 1.

Classification via the inhalation route is not warranted, since at the highest concentration tested only local effects, but no systemic effects were observed. The local effects (corrosivity/irritancy) are covered by the respective classification.

Labelling:

HAZARD STATEMENT: H373 MAY CAUSE DAMAGE TO LIVER AND KIDNEY THROUGH PROLONGED OR REPEATED EXPOSURE

Remark. Since the substance is classified as STOT-RE via the oral route and specific toxicity has not been conclusively excluded for the dermal route (rather it can be expected due to high dermal absorbtion in acute toxicity, Category 3) the Hazard statement for STOT-RE in total without specifying a route has to be applied based on the classification via the oral route.

(See also Risk assessment report BUT-2YNE-1,4-DIOL; EC 2005)

3.9.6.1.3 Example 3: XYZ

Application of criteria for evaluation/classification and allocation of hazard statements with respect to specific target organs and route of exposure

Available information:

1) Human experience: No information available
2) Animal data:

Key chronic toxicity data (underlined for EU classification)			CLP Repeated Exposure (STOT) classification
Type of study - Effects	NOAEL ppm (mg/kg/d)	LOAEL ppm (mg/kg/d)	
mouse, oral 28 days 0, 300, 600, 1200 ppm (M: 0, 51-58, 101-115, 177-226 mg/kg/d, F: 0, 59-66, 111-127, 221-281 mg/kg/d) hematological changes in M (↓ RBC count, Hb, Ht)	M: no NOAEL F: 300 (59-66)	M: 300 (51-58) F: 600 (111-127)	Category 2 based on the effects on blood
rat, oral 13 weeks 0, 50, 500, 1000 ppm (M: 0, 3.5, 38, 67 mg/kg/d, F: 0, 4, 38, 80 mg/kg/d) hematological changes in F (↓ RBC count, Hb, Ht)	50 (M: 3.5, F: 4)	500 (M: 38, F: 38)	Category 2 based on the effects on blood
male rat, oral 30, 60, 90 days 0, 5, 10, 25 mg/kg/d (by gavage) (open literature) mortality at 5 (5/25), 10 (7/25) & 25 (8/25) mg/kg			No classification is proposed on basis of this study because the death observed in the 3 groups are in contradiction with the other relevant experiments in this species. (death no dose related, some animals (2/6) are already dead after 30 days at 5 mg/kg)
rat, oral 2-years 0, 30, 150, 300 ppm (M : 0, 1.46, 7.31, 14.66 mg/kg/d, F : 0, 1.8, 8.86, 18.57 mg/kg/d)	30 (M: 1.46, F: 1.8)	150 (M: 7.31, F: 8.86)	Category.2based on the effects on blood (haemolytic anaemia accompanied by

eyelid masses: 1 F/50 at 150 ppm, 5 M/50 & 3 F/49 at 300 ppm changes in erythroid parameters (↓ RBC count, ↑ MC Hb, ↑ MCV in F at 300 ppm) extramedullary hemopoiesis in liver (M : 150 & 300 ppm, F : 300 ppm), spleens ↑ myeloid hyperplasia in BM in femur & sternum ofF at 300 ppm ↑ i. hemorrhages w/i mesenteric lymph nodes at 150 & 300 ppm			compensatory mechanisms)
rat, oral 80 weeks M: 0, 5, 20, 52 mg/kg/d F: 0, 6, 26, 67 mg/kg/d (open literature) ataxic syndrom in F at 67 mg/kg/d (unusual gait). The condition of these rats worsened, leading to paralysis posterior to the lumbar region atrophy of the hing legs. No specific hystopathological lesion of CNS or PNS.			No classification (effects above the cut-off values)
rat, oral, 104 weeks 0, 3, 30, 300 ppm (M: 0, 0.1, 1.2, 11.6 mg/kg/d, F: 0, 0.1, 1.4, 13.8 mg/kg/d) (open literature) anemia in 300 ppm (F) (not in 30 ppm) regressive changes of sciatic nerve (degeneration) + atrophy of calf muscle in F at 300 ppm, but no neurologcal signs progression of myocardial lesions at 300 ppm			Category 2 based on the effects on blood and nervous system
mouse, oral, 97/98 weeks M : 0, 15, 150, 300 ppm (0, 3, 24, 50 mg/kg/d) F : 0, 15, 300, 600 ppm (0, 3, 57, 112 mg/kg/d) retinal atrophy at ≥ 150 ppm (↓ or absence of outer nuclear cell layer of retina) ↑ turnover of erythrocytes	15 (M: 5.2, F: 3.1)		Category 2 based on the effects on blood. Category 2 based on the effects on the retina

Classification for XYZ : STOT-RE Category 2

Labelling :

Symbol: GHS08

Signal word: Warning

Hazard statement: H373 May cause damage to the blood and nervous systems through prolonged or repeated exposure.

Justification :

The effects on blood are reported in the 2 species (mouse, rat), at doses low enough to justify Category 2. The effects on NS are reported in the rat at doses low enough to justify Category 2.

3.9.6.2 Examples of substances not fulfilling the criteria for classification

3.9.6.2.1 Example 4: MCCPs (Medium Chain Chlorinated Paraffins) = Alkanes, C_{14-17}, Chloro- (EC No 287-477-0; CAS No 85535-85-9)

Application of criteria for evaluation/classification with regard to mechanisms not relevant to humans (see Section 3.9.2.5.3)

Available information:

1) Human experience: No information available

2) Animal data: see summary

Key chronic toxicity data: *Summary of data for repeated exposure*
The only available data relate to a number of oral dosing studies (up to 90 days duration) that have investigated the repeated dose toxicity of MCCPs (C_{14-17}, 40% or 52% chlorinated paraffins) in rodents. However, only two studies emerge as providing helpful dose-response information in respect of classification and labelling (IRDC 1984, Poon *et al* 1995). The others, all presented in more detail in the ESR RAR, were generally mechanistic studies on the interplay between liver and thyroid and the relevance of effects on these organs to human health, conducted at relatively high exposure levels. In rats, the liver, thyroid and kidney are the target organs for repeated dose toxicity of MCCPs. For the liver, increases in weight and changes in enzyme activity are seen in rats at exposure levels of 36 mg/kg/day or more (Poon *et al* 1995). These effects are considered part of an adaptive response to an increase in metabolic demand. There is also the possibility that peroxisome proliferation plays a role. These findings were not considered to justify classification. At higher exposure levels (around 360 mg/kg/day), single cell necrosis was observed in rats (Poon *et al* 1995), but this is above the cut-off level for classification. Increased thyroid weight was observed in a 90-day study only at the highest exposure level tested, 625 mg/kg/day (IRDC 1984). Histopathologically, lesions such as hyperplasia have been observed down to the lowest exposure levels tested (eg. 0.4 mg/kg/day by Poon *et al* 1995) with an exposure-related increase in severity. However, the severity only ranged from "mild" to "moderate" even with an increase in exposure of 3 orders of magnitude. The thyroid changes (increased weight and follicular hypertrophy and hyperplasia) are considered to occur as a result of repeated stimulation of this organ caused by the well-characterised negative feedback control effect arising from plasma T_4 depletion. This in turn is related to an increase in the activity of hepatic UDPG-transferase. Humans, unlike rodents, possess a T_4 binding protein that greatly reduces susceptibility to plasma T_4 depletion and thyroid stimulation. The thyroid effects observed in rats are therefore considered

of insufficient concern for classification.

No adverse renal effects were seen in males and female rats at 0.4 mg/kg/day in a 90-day study (Poon *et al*, 1995). Inner medullary tubular dilatation was seen at 4 mg/kg/day in the kidneys of females only. These lesions were slight, with changes increasing only marginally in severity and incidence at higher levels (up to 420 mg/kg/day for females). An exposure-related increase in the incidence and severity of a mixed population of interstitial inflammatory cells, tubular regeneration and minimal degenerative changes in the tubular epithelium was seen in treated males and females at 10 mg/kg/day or more. At 10 mg/kg/day the severity of these changes was graded as 'trace', and even at the highest exposure level, 625 mg/kg/day it was only 'mild'. As the effects observed in the highest dose group do not seem to be severe, no classification is proposed for repeated-exposure effects.

Mechanistic studies conducted using short-chain chlorinated paraffins (SCCPs, C_{10-13}) indicate deposition of β2μ globulin in proximal convoluted tubules and this may be the primary mechanism for renal toxicity in male rats.

Classification for MCCP's: No classification for STOT-RE

Justification:

Effects on the liver: the effects justifying the classification (necrosis) are above the cut-off limit values.

Effects on the thyroid: the effects observed are specific for the rat and do not justify classification.

Effects on the kidneys: the data are not detailed enough to have an idea what are effectively the effects around the cut-off values (10-100 mg/kg) instead of 50 mg/kg (DSD cut-off value) but probably we could come to the same conclusion, i.e. the effect is not enough to justify the classification in any category.

3.9.6.3 Examples of mixtures fulfilling the criteria for classification

3.9.6.3.1 Example 5:

Application of criteria for mixture classification: 'When data are available for the complete mixture' (see Section 3.9.3.3).

Available information:

A mixture with a suspect ingredient (8%) has been tested in a valid 90-day oral study according to TG OECD 408 and GLP. At the dose of 90 mg/kg bw/day severe liver damage (necrosis) has been observed, at 30 mg/kg bw/day slight-moderate liver impairment. The NOAEL was 9 mg/kg bw/day.

Classification: STOT-RE Category 2

Justification:

The classification is based on data of a valid, appropriate animal study for the complete mixture. Therefore the criteria for substances (CLP Annex I, Table 3.9.3) are applied.

3.9.6.3.2 Example 6

Application of criteria for mixture classification: 'When data are available for all components' (Section 3.9.3.3). Components of a mixture that should be taken into account are listed below together with their concentrations. Generic concentration limits should be used, non-additivity is applied.

Available information:

Ingredient	% w/w	Classification
1	39	NC
2	5.5	STOT-RE Category1
3	54	NC
4	1.5	STOT-RE Category 2

Classification of the mixture: STOT-RE Category 2

Justification:

No test data with respect to STOT-RE are available for the complete mixture. Bridging principles can not be applied since no respective test data on a similar mixture are available. The classification of the mixture will be based on the classified ingredients (CLP Annex I, Table 3.9.4).

There is one Category 1 ingredient in a concentration of <10 %. Therefore the mixture is not classified in Category 1. There is one Category 1 ingredient in a concentration of ≥ 1% and <10 %, therefore Category2 is warranted. The Category 2 ingredient with 1.5 % is not taken into account at all, since the concentration is < 10%.

3.9.6.3.3 Example 7

Application of criteria for mixture classification 'When data are available for all components' (Section 3.9.3.3). Components of a mixture that should be taken into account are listed below together with their concentrations. Generic concentration limits should be used besides when specific concentration limits are indicated, non-additivity applies.

Available information:

Ingredient	Classification	Concentration (% w/w)	Mixture Classification	Remarks
A	Category 1	0.1		SCL 0.2%
B	Category 1	9		

Classification of the mixture: Category 2 based on 9% of B, which is ≥ 1% and < 10%; A does not contribute to the classification of the mixture, as the concentration of A is < 0.2% (the SCL) and additivity of the two ingredients is not foreseen.

3.9.6.3.4 Example 8

Application of criteria for mixture classification 'When data are available for all components' (Section 3.9.3.3). Components of a mixture that should be taken into account are listed below together with their concentrations. Generic concentration limits should be used besides when specific concentration limits are indicated, non-additivity applies.

Available information:

Ingredient	Classification	Concentration (% w/w)	Remarks

A	Cat 1	0.3	SCL 0.2%
C	Cat 2	9	

Classification of the mixture: Category 1 since the concentration of A, even if being lower than the generic concentration limit, is higher than the SCL; C does not contribute to the classification.

3.9.6.4 Example of mixtures not fulfilling the criteria for classification

3.9.6.4.1 Example 9

Application of criteria for mixture classification: 'When data are available for all components' (Section 3.9.3.3); components of a mixture that should be taken into account are listed below together with their concentrations. Generic concentration limits should be used, non-additivity is applied:

Available information:

Ingredient	Concentration (% w/w)	Classification
1	39	NC
2	9	STOT-RE Category2
3	49.5	NC
4	2.5	STOT-RE Category 2

Classification of the mixture: NC (no classification).

Justification:

No test data with respect to STOT-RE are available for the mixture as a whole. Bridging principles can not be applied, since no respective test data on a similar mixture are available (CLP Annex I, Table 3.9.4).

The classification of the mixture is based on the classified ingredients. No ingredient is classified in Category 1. Therefore the mixture cannot be classified in Category 1. Though the sum of the Category 2 ingredients (11.5 %) is above the generic concentration limit of 10%, the mixture is not classified. This is because for STOT-RE the no additivity approach applies and no individual ingredient ≥ 10% is present in the mixture.

3.9.7 References

Muller, A. et al (2006) Regulatory Toxicology and Pharmacology 45, 229-241

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[51], 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.

[51] 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[52]), 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° 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.

[52] 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://echa.europa.eu/web/guest/support/guidance-on-reach-and-clp-implementation).

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

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

(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[54] substances: such substances, for example, complex hydrocarbons , or other UVCB[55] 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[56]. 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;

(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

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

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

[56] 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).

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 assess the sameness of two substances containing the same impurity in different amount see 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 are equivalent in terms of species relevance, testing conditions 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° 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

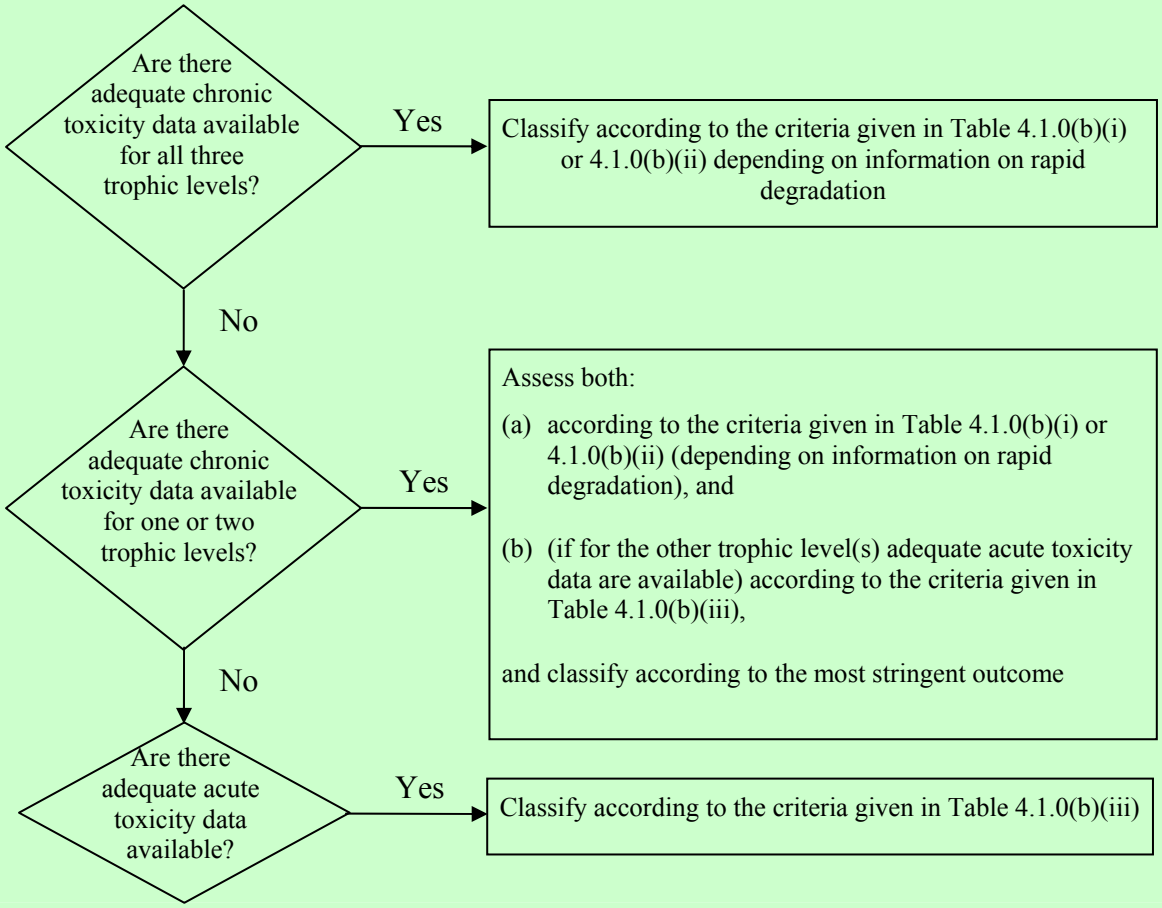
4.1.3.3.1 Outline of the core classification system

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 normalenvironmental conditions (for detailed information please check also the Annexes to this guidance).

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} ≤ 1	1	0,01 < NOEC ≤ 0,1	1	-
0,01 < L(E)C_{50} ≤ 0,1	10	0,001 < NOEC ≤ 0,01	10	1
0,001 < L(E)C_{50} ≤ 0,01	100	0,0001 < NOEC ≤ 0,001	100	10
0,0001 < L(E)C_{50} ≤ 0,001	1000	0,00001 < NOEC ≤ 0,0001	1000	100
0,00001 < L(E)C_{50} ≤ 0,0001	10000	0,000001 < NOEC ≤ 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 4.1.0 (a)(b, point iii) is used for defining long-term aquatic hazard, the resulting M-factor derived for acute aquatic hazard classification is also applied to the long-term aquatic hazard 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).

Labelling elements based on the classification:

Element	Code
GHS Pictogram	GHS09
Signal Word	WARNING
Hazard Statement	H410[57]
Precautionary statement(s)	P273, P391, P501

[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 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.

Labelling elements based on the classification:

Element	Code
GHS Pictogram	GHS09
Signal Word	WARNING
Hazard Statement	H410[58]
Precautionary statement(s)	P273, P391, P501

[58] 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*:	12.3 mg/l (96 h LC_{50})	C.1. / static, non-GLP
	Lepomis macrochirus:	22.5 mg/l (96 h LC_{50})	C.1. / static, GLP
Crustacea	*Daphnia magna*:	0.79 mg/l (48 h EC_{50})	C.2. / static, non-GLP
	Daphnia magna:	1.06 mg/l (48 h EC_{50})	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} ≤ 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[59]
Precautionary statement(s)	P273, P391, P501

[59] 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.

4.1.3.4.4 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[60]:	*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	

[60] 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[61]
Precautionary statement(s)	P273, P391, P501

[61] 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: Abiotic degradation, hydrolysis: (half-life (d)):		No data < 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.

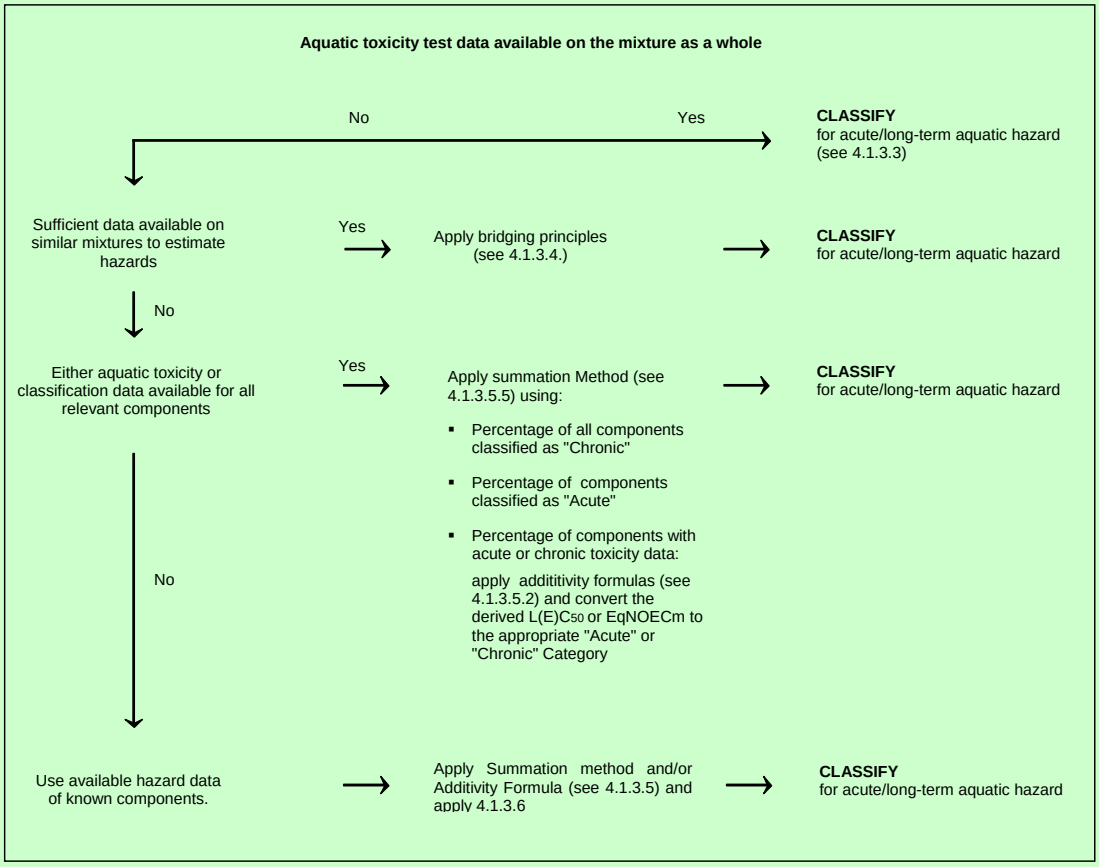
Elements of the tiered approach include:

– 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.[62]
- 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".

[62] 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 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.

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 generic concentration limits (GCLs) 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 is available for all three trophic levels: classification based on test data for 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 is available and toxicity data on the mixture as a whole is available for some, but not all three trophic levels: use of the summation method

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[63]
Precautionary statement(s)	P273, P391, P501

[63] 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

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*	0.37 mg/l	1.37 mg/l	

subspicatus	(72 hr E_rC_{50})	(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*[64]:
$L(E)C_{50m} = 60 / (50/0.37 \text{ mg/L} + 10/0.3\text{mg/L}) = 0.36 \text{ mg/L}$
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 1	50 %
Component 2	0.53 mg/L (72 hr NOEC Algae); No information on degradation	Assign Chronic 2	10%
Component 3	No data	-	10%
Component 4	Not classified	Chronic 1	30 %

[64] 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.

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*[65] 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[66]
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”.

[65] See also section 4.1.4.6 of this guidance.
[66] 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[67]	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:

– 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

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

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

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[68] should be classified as hazardous to the ozone layer (category 1).

[68] 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 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 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 shall also be considered if the test methodology is suitable. 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). The final classification shall be made according to the most stringent outcome.

(c) In order to remove or lower a long-term aquatic classification, using chronic toxicity data, it must be demonstrated that the NOEC(s) (or equivalent ECx) used would be suitable to remove or lower the concern for all taxa which resulted in classification based on acute data in combination with degradability, and/or bioaccumulation. This can often be achieved by using a long-term NOEC for the most sensitive species identified by the acute toxicity. Thus, if a classification has been based on a fish acute LC50, it would generally not be possible to remove or lower this classification using a long-term NOEC from an invertebrate toxicity test. In this case, the NOEC would normally need to be derived from a long-term fish test of the same species or one of equivalent or greater sensitivity. Equally, if classification has resulted from the acute toxicity of more than one taxonomic group, it is likely that NOECs from each taxonomic group will be needed. In case of classification of a substance as Chronic 4, sufficient evidence should be provided that the NOEC or equivalent ECx for each taxonomic group is greater than 1 mg/l or greater than the water solubility of the substances under consideration.

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. In addition, caution is also needed when deriving appropriate M-factors, in particular when the nominal effect concentrations are close to the thresholds for diverging M-factors. 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 measuring the 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

US EPA 1996. Ecological Effects Test Guidelines - OPPTS Harmonized Test Guidelines Series 850.1000 -- Public Drafts, EPA 712-C-96-113. http://www.epa.gov/opptsfrs/publications/OPPTS_Harmonized/850_Ecological_Effects_Test_Guidelines/Drafts/

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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:

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 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

b) 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

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:

a) 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

b) 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

c) 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.

OECD (1992), OECD Test Guidelines No. 301 methods A-F

Pedersen, F., H. Tyle, J. R. Niemeldi, B. Guttmann, L. Lander, and A. Wedebrand 1995. Environmental Hazard Classification – data collection and interpretation guide. TemaNord 1995:581

Langenberg J.H., W.J.G.M. Peijnenburg & E. Rorije (1996). On the usefulness and reliability of existing QSBRs for risk assessment and priority setting. SAR and QSAR in Environmental Research 5, 1-16

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 [69] (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 or 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 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.

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

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 $\geq$ 1000, the identification and quantification of degradation products documented to be $\geq$ 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 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 (e.g. 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[70]). 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).

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:

[70] 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.

- *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 (e.g. 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, depletion 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[71] 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[72] should be 0.01 mg/l, 0.1 mg/l or 1 mg/l depending on the transformation rate and the duration of the test being extended to 28 days (long-term test).

IV.2.3 Comparison of aquatic toxicity data and solubility data

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[71] 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.

[72] 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.

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 and continuing discussions on the interpretation of rapid removal from the water column in the context of classification, it has been decided to remove certain parts from the Annex IV for the time being until agreement on the validity of use of the concept of rapid removal for classification purposes has been reached.

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 hazards* 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 hazards are assessed individually.

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.

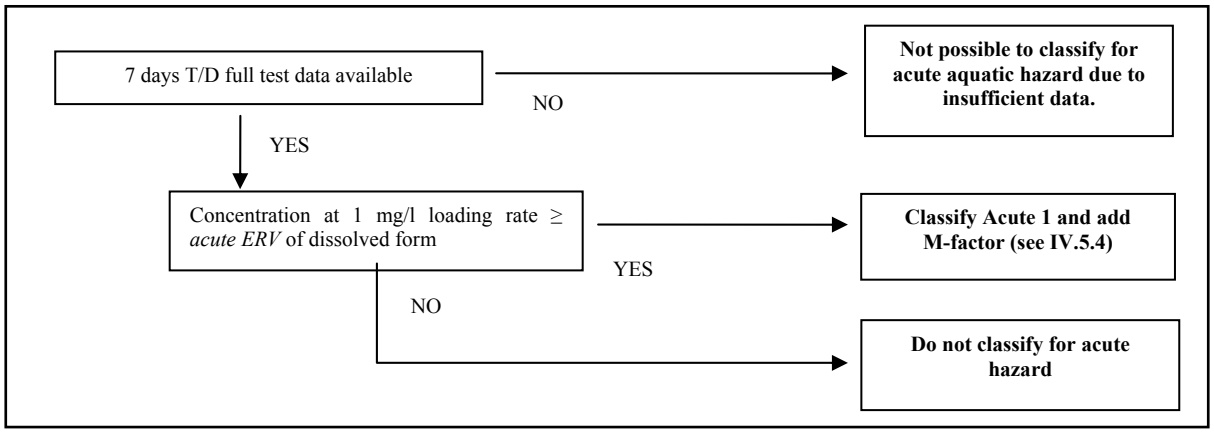
Where *the acute ERV* for the metal ions of concern is greater than 1 mg/l the metals need not be considered further in the classification scheme for acute hazard.

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 5.4).

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.5.4); 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 environmental transformation:

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 5.4); 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.5.4);

(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.

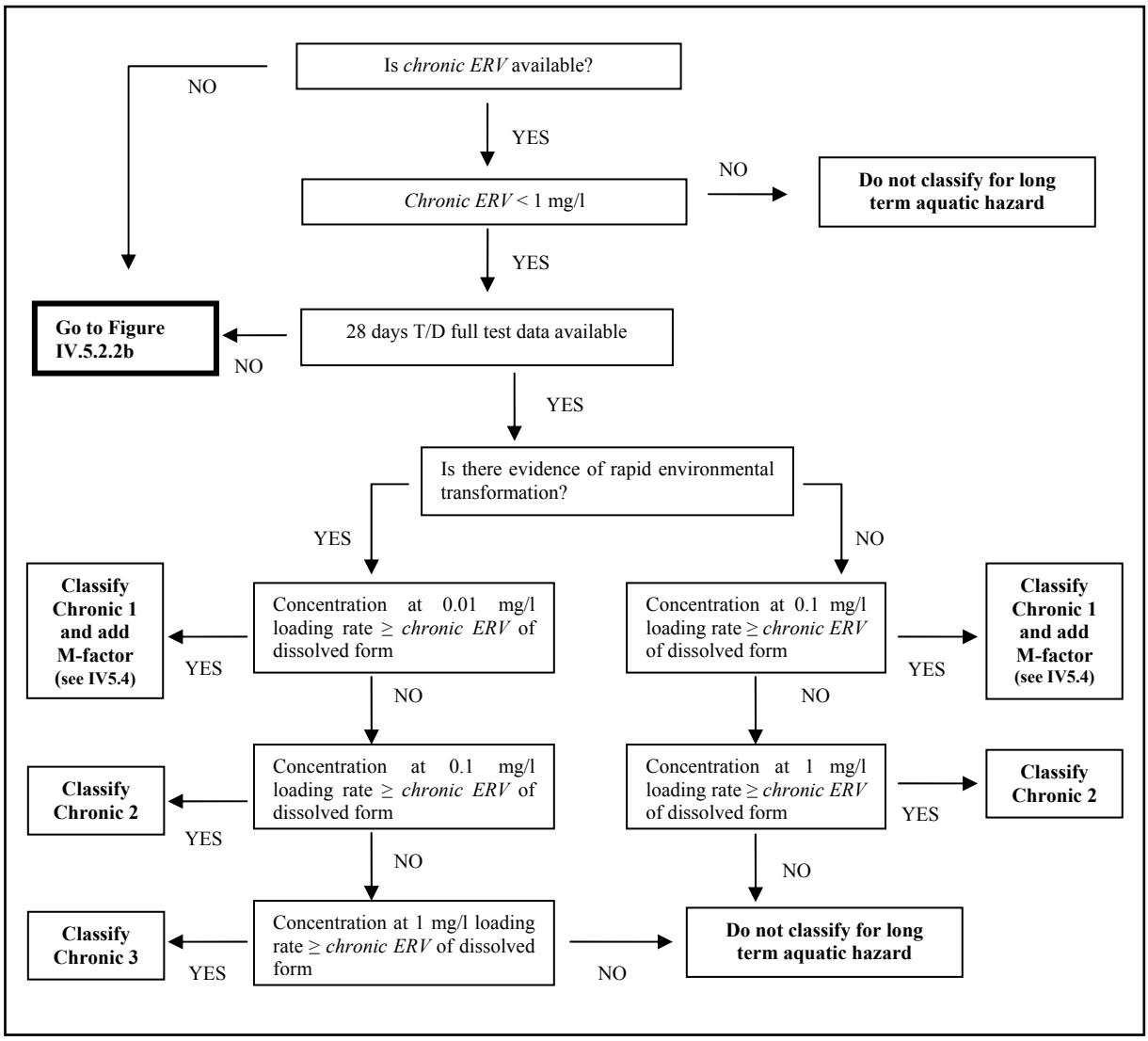
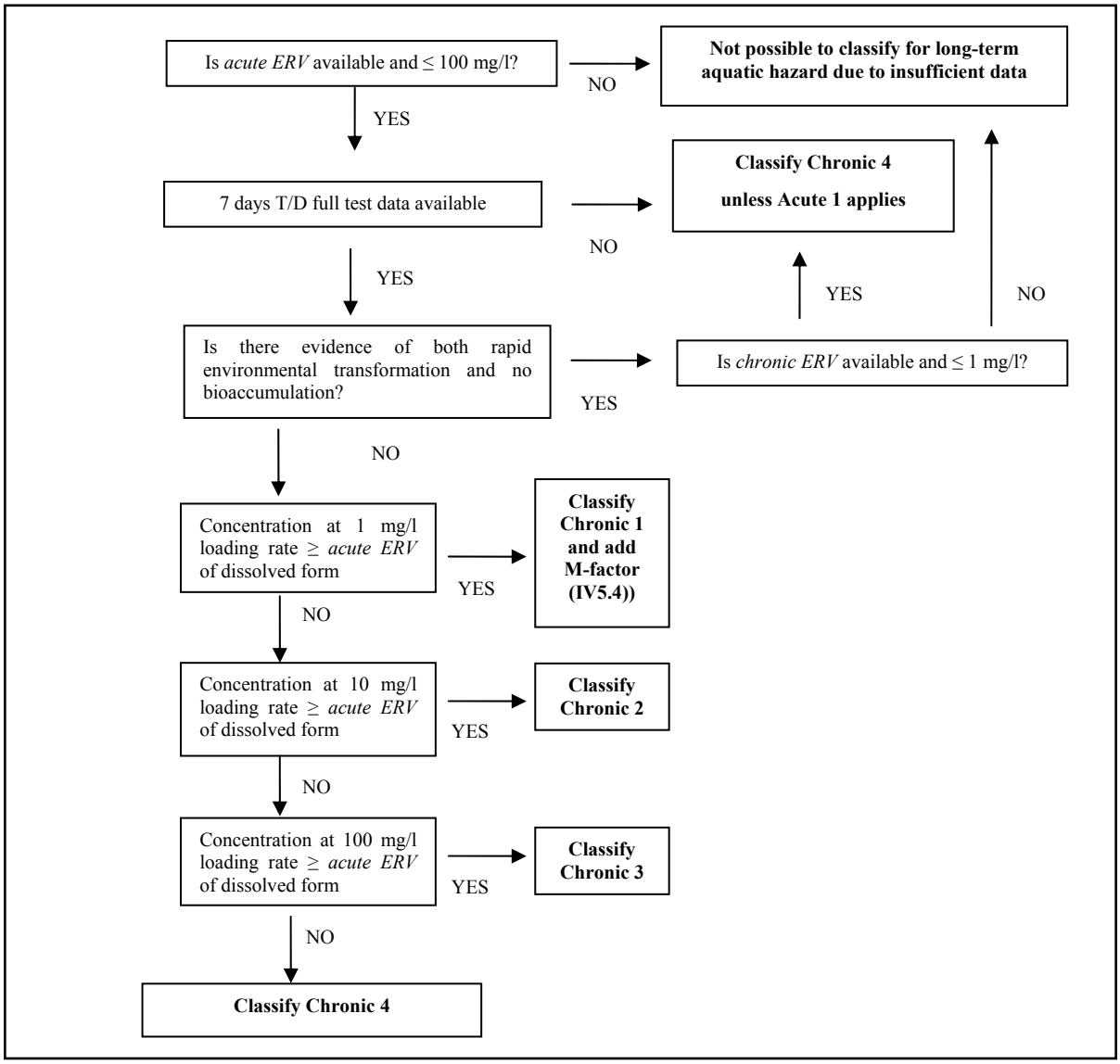


Figure IV.5.2.2b Classification strategy for determining long-term aquatic hazard for metals in absence of appropriate chronic toxicity reference and/or T/Dp data.



IV.5.3 Classification strategies for metal compounds

Notice! Acute and long-term hazards are assessed individually.

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

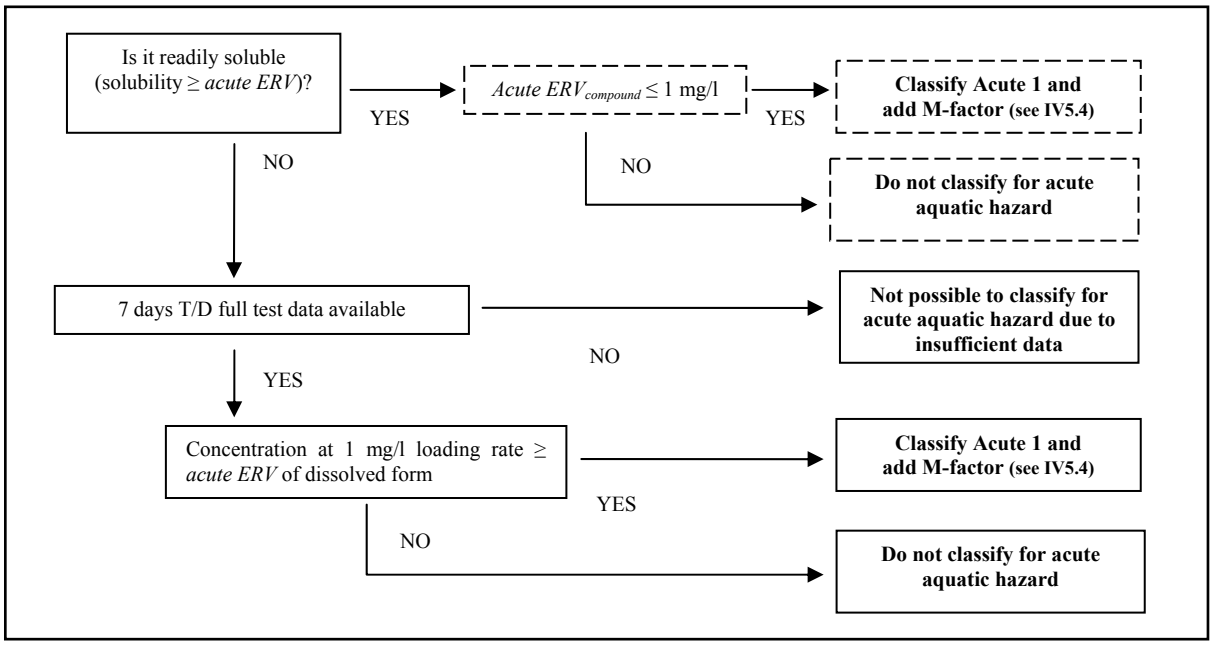
Classify the metal compound as ***Category Acute 1*** if the acute $ERV_{compound} \leq 1$ mg/l, an M-factor must also be established as part of this classification (see IV.5.4).

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.5.4).

Figure IV.5.3.1 Classification strategy for determining acute aquatic hazard for metal compounds.



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 environmental transformation:

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.5.4); or

b) Classify the metal compound as Category Chronic 2 if the chronic $ERV_{compound} > 0.1$mg/l and ≤ 1 mg/l.

If there is *evidence* of rapid environmental transformation:

c) **Classify** the metal compound as ***Category Chronic 1*** if the chronic ERVcompound ≤ 0.01 mg/l,an M-factor must also be established as part of this classification (see IV.5.4); or

d) **Classify** the metal compound as ***Category Chronic 2*** if the chronic $ERV_{compound} > 0.01$mg/l and ≤ 0.1 mg/l; or

e) **Classify** the metal compound as ***Category Chronic 3*** if the chronic $ERV_{compound} > 0.1$mg/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 $ERV_{\mathbf{compound}}$ 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.5.4); 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 environmental transformation:

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.5.4); 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 environmental transformation 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.5.4); 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 environmental transformation and no bioaccumulation, an M-factor must also be established as part of this classification(see IV.5.4);

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 environmental transformation 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 environmental transformation 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 environmental transformation and no bioaccumulation.

Figure IV.5.3.2a Classification strategy for determining long-term aquatic hazard for metal compounds.

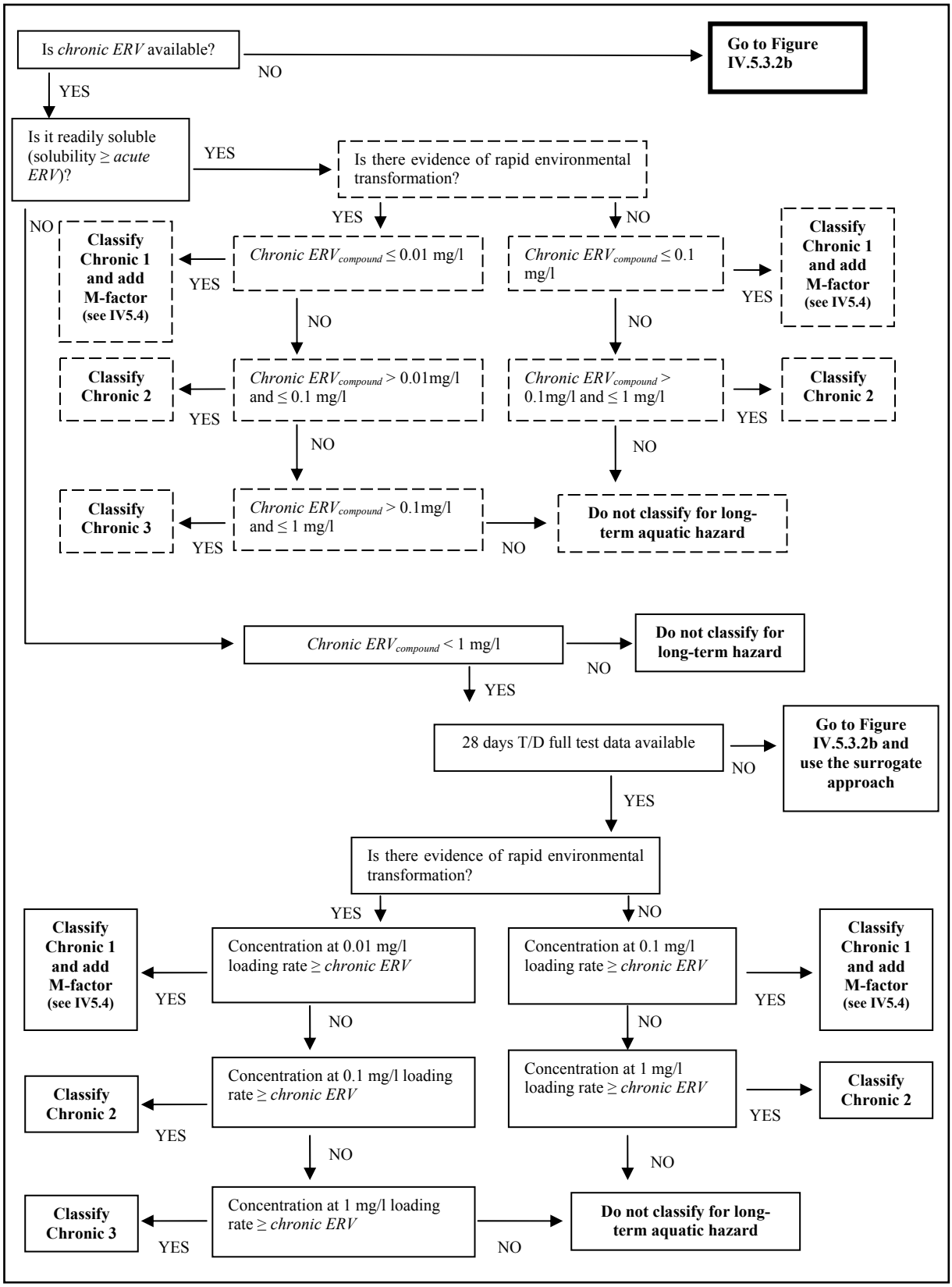
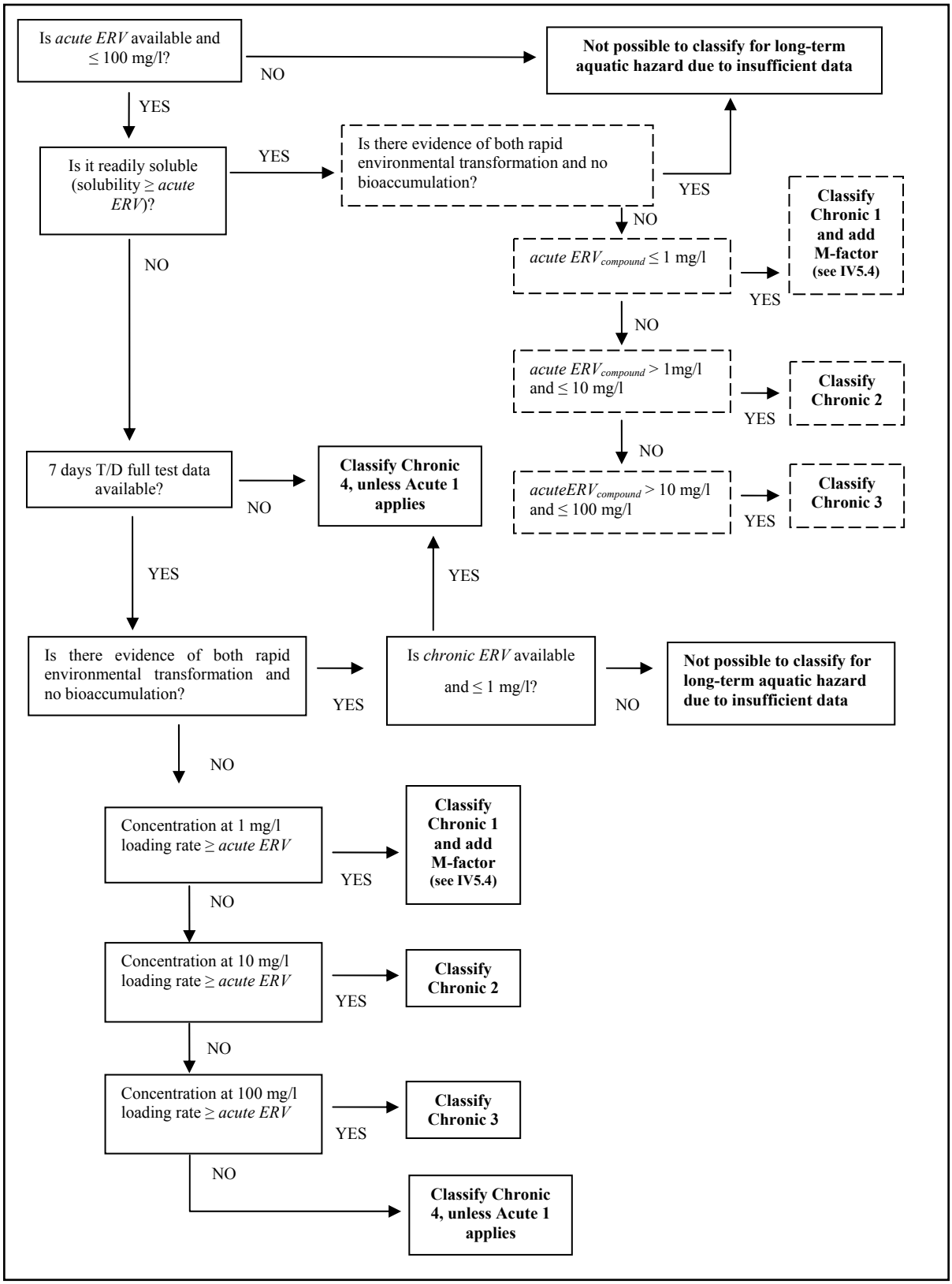


Figure IV.5.3.2b Classification strategy for determining long-term aquatic hazard for metal compounds in absence of appropriate chronic toxicity reference and/or T/Dp data.



IV.5.4 Setting M-factors for metals and inorganic metal compounds

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.

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).

For *soluble metal compounds* M-factors are applied as for organic substances (see table IV.5.4.1).

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.5.4.1: 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 environmental transformation	Rapid environmental transformation
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.5.5 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:

$$\log (C_{Me(aq)}, \text{mg/l}) = a + b \log(A_{meas})$$

$C_{Me(aq)}$ = 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.5.6 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.5.6.1 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.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 no evidence of rapid environmental transformation (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 at 28 days (only low and medium loading rates) and no evidence of rapid environmental transformation.
- Example C: 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 no evidence of rapid environmental transformation.

- *Explanatory note to Example D* - Critical Surface Area (CSA) Approach.

- Example D: Hazard classification of a soluble metal salt: the case of rapid environmental transformation through speciation in the water column.

Example A: Soluble metal compound with acute and chronic toxicity data and no evidence of rapid environmental transformation ($Me_2 (SO4)_2$).

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[73]		
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[74]		
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
Algae/aquatic plants: *Scenedesmus subspicatus*:	21.6 µg/l (72 h NOEC) at pH 8	C.3. / static, GLP

[73] Tests performed with readily soluble salts such as metal sulphates and metal chlorides.
[74] Tests performed with readily soluble salts such as metal sulphates and metal chlorides.

	8.7 µg/l (72 h NOEC) at pH 6.2	C.3. / static, non-GLP
Degradation (evidence of rapid degradation)		
Rapid environmental transformation	No evidence.	
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**.

Evidence of rapid environmental transformation:

No information available, so substance considered as not rapidly transformed by normal environmental processes.

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
- 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). [75]
- 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 environmental transformation cannot be demonstrated given the lack of sufficient information.
- 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 environmental transformation.

Labelling elements based on the classification:

Element	Code
GHS Pictogram	GHS09
Signal Word	WARNING
Hazard Statement	H400, H410 → H410[76]
Precautionary statement(s)	P273, P391, P501

[75] 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.

[76] 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 at 28 days (only low and medium loading rates) and no evidence of rapid environmental transformation

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 0.1 mg/l loading	pH 6: no data available pH 8: no data available	Metals TDp, non-GLP Metals TDp, non-GLP
	at 0.01 mg/l loading	pH 6: 9 µg/l pH 8: <1 (DL)	Metals TDp, non-GLP Metals TDp, non-GLP
MWT of the metal ion versus compound		60 / 91	
Acute aquatic toxicity of metal ion[77]			
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 four values : 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 8 106 µg/l (48 h EC_{50}) at pH 8	C.2. / static, non-GLP
Algae/aquatic plants	*Scenedesmus subspicatus*:	154 µg/l (72 h ErC_{50}) at pH 8 78 µg/l (72 h ErC_{50}) at pH 6	C.3. / static, GLP
	Lemna gibba:	670 µg/l (7 d ErC_{50}) at pH 8	C.26. / semi-static, GLP

[77] Tests performed with readily soluble salts such as metal sulphates and metal chlorides.

Chronic aquatic toxicity[78]			
Fish:	*Danio rerio*:	24 µg/l (28 d NOEC) at pH 6 87 µg/l (28 d NOEC) at pH 8	OECD 210 / 28 d flow-through, non-GLP OECD 210 /28 d flow through, GLP)
Crustacea:	*Daphnia magna*	37 µg/l (21 d EC_{10}) at pH 7.8 8.6 µgl (21 d NOEC) at pH 6.4	C.20. / semi-static, GLP C.20. / semi-static, non-GLP
Algae/aquatic plants:	*Scenedesmus subspicatus*:	21.6 µg/l (96 h NOEC) at pH 8 8.7 µg/l (72 h EC_{10}) at pH 6.2	C.3. / static, GLP C.3. / static, non-GLP
Degradation (evidence of rapid degradation)			
Rapid environmental transformation		No data available therefore considered as not rapidly transformed.	
Bioaccumulation			
Bioconcentration factor in fish		+/- 200 at NOEC level	

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:

- 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

[78] Tests performed with readily soluble salts such as metal sulphates and metal chlorides.

Evidence of rapid environmental transformation:

- No information available and therefore substance considered as not rapidly transformed by normal environmental processes.

Chronic aquatic toxicity for a substance not rapidly transformed:

- 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 not rapidly transformed:

- The release after 28 d at pH 6 at a loading of 0.1 mg/l is not 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:

- 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 soluble metal compound is consequently not required given this factor has already been included for the loading rate of the TDp test.
- 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).
- No valid info is available on rapid transformation by normal environmental processes so the poorly soluble metal compound is considered to be not rapidly transformed.
- 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 C: 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 no evidence of rapid environmental transformation

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[79]		
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

[79] Tests performed with readily soluble salts such as metal sulphates and metal chlorides.

Chronic aquatic toxicity[80]		
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 21d): 20 µg/l - At high pH: (EC10 21d): 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 environmental transformation	No information.	.
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 6. 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
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

[80] Tests performed with readily soluble salts such as metal sulphates and metal chlorides.

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[81] 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 to reach the acute ERV for the most critical pH (6) is $\boldsymbol{SA_{crit}}$ **0.101 m^2/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.

Evidence of rapid environmental transformation:

- No information available and therefore substance considered as not rapidly transformed by normal environmental processes.

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 not rapidly transformed:

- 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)

  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], where *SA* was measured with the BET nitrogen adsorption-desorption technique.

  An equal approach can be followed for the lower pH level.

[81] The finest representative metal powder should be used for TDp testing.

- 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 2
- 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. (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 does not fulfil the criterion for rapid environmental transformation.
- 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. Therefore, ***chronic 2 hazard classification for the metal in the powder form is warranted.***.
- 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	H411
Precautionary statement(s)	P273, P391, 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

Explanatory note to Example C - 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 D: Hazard classification of a soluble metal salt: the case of rapid environmental transformation through speciation in the water column

General approach

This example was selected to:

(i) illustrate the use of information on the metal oxidation and resulting transformation of metal ions in the water column for classification decisions;

(ii) provide 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 environmental transformation.

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

Assessment of the rapid environmental transformation:

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 species are less than 16 days this can be considered as rapidly transformed in 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**
$MeSO_47H_2O$	278.0	4.978
$MeSO_4H_2O$	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
$MeCl_3.6H_2O$	*Daphnia pulex*	48h	Immobility	12.9
$Me_2(SO_4)_3$	*Daphnia longispina*	48h	Immobility	11.5

Test substance	Test organism	Duration	Endpoints	L(E)C_{50} (mg Me L^{-1})
$MeCl_3.6H_2O$	*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.

Since all chronic aquatic toxicity values are higher than 1 mg/l and rapid transformation to a metal hydroxide takes place by normal environmental processes, no classification is warranted.

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/web/guest
UN GHS	UN	http://www.unece.org/trans/danger/publi/ghs/ghs_welcome_e.html
eChemPortal	OECD	http://www.echemportal.org/
REACH guidance	ECHA	http://echa.europa.eu/web/guest/support/guidance-on-reach-and-clp-implementation
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	http://www.echa.europa.eu/web/guest/information-on-chemicals/cl-inventory-database

VI ANNEX VI: BACKGROUND DOCUMENT TO THE GUIDANCE FOR SETTING SPECIFIC CONCENTRATION LIMITS FOR SUBSTANCES CLASSIFIED FOR REPRODUCTIVE TOXICITY ACCORDING TO REGULATION (EC) NO 1272/2008

1 Executive summary

Regulation (EC) No 1272/2008 on the classification, labelling and packaging of substances and mixtures (CLP Regulation or CLP) contains rules including criteria for the classification of substances and mixtures. While the classification of substances for human health hazards is based on specific criteria for each hazard class, the classification of mixtures is mainly based on the concentration and the classification of the substances contained in the mixture. CLP includes generic concentration limits (GCLs) which are specific for a hazard class and category and which indicate a threshold above which the presence of a substance in a mixture leads to classification of the mixture. However, under certain conditions specific concentration limits (SCLs) must or may be used . As the Regulation itself does not provide any further guidance on when and how to set SCLs, guidance has been developed for certain hazard classes (see the respective chapters on setting SCLs in Part 3 of the Guidance on the Application of the CLP Criteria).

This Annex provides a background to the method for the determination of SCLs for substances classified as reproductive toxicants as outlined in the guidance in Part 3.

The potency, expressed as the dose for the induction of reproductive effects was identified as the best determinant for setting SCLs. The ED_{10} for effects warranting classification was selected as the most appropriate parameter for estimating the potency. The ED_{10} is the dose level which induces reproductive effects in 10% of the animals above the control group or a change of 10% in the effect compared to the control group. Based on the ED_{10} the substance is placed in a potency group. However, modifying factors can alter the potency group, especially when the potency estimate is close to the boundary between two groups.

The distribution of the potency of a large number of substances classified in Annex VI to CLP as developmental toxicants and/or substances affecting sexual function and fertility was determined by means of establishing two databases. In line with other methods for setting SCLs for other hazard classes, it is proposed to define three potency groups. The boundaries for the potency groups were determined in line with the provisions outlined in Article 10(1) of CLP, the results of the database analyses and policy considerations. Most substances are foreseen to fall into the medium potency group which is linked to the GCL. For substances in the high and low potency group, the SCLs included in the table below are proposed.

	Category 1		Category 2	
	Dose	SCL	Dose	SCL
High potency group	ED_{10} below 4 mg/kg bw/day	0.03% (factors of 10 lower for extremely potent substances[B])	ED_{10} below 4 mg/kg bw/day	0.3% (factors of 10 lower for extremely potent substances)

Medium potency group	$ED_{10} \geq 4$ mg/kg bw/day, and $\leq$ 400 mg/kg bw/day	0.3% (GCL)	$ED_{10} \geq 4$ mg/kg bw/day, and $\leq$ 400 mg/kg bw/day	3% (GCL)
Low potency group	ED_{10} above 400 mg/kg bw/day	3%	ED_{10} above 400 mg/kg bw/day	3-10% [A]

[A]The limit of 10% may be considered in certain cases, such as for substances with a ED_{10} value above 1000 mg/kg bw/day and a NOAEL below 1000 mg/kg bw/day

[B] For substances with an ED_{10} more than 10 fold below 4 mg/kg bw/day, meaning an ED_{10} below 0.4 mg/kg bw/day, a 10-fold lower SCL should be used. For even more potent substance the SCL should be lowered with a factor of 10 for every factor of 10 the ED_{10} is below 4 mg/kg bw/day.

2 Introduction

2.1 General description of the classification system for reprotoxic substances and mixtures

Regulation (EC) No 1272/2008 (CLP) contains rules for the classification of substances and mixtures. In chapter 3.7 of Annex I to this Regulation, criteria are given for the classification of substances as reprotoxicants in one of the following categories:

Category 1: Known or presumed human reproductive toxicant

Substances are classified in Category 1 for reproductive toxicity when they are known to have produced an adverse effect on sexual function and fertility, or on development in humans or when there is evidence from animal studies, possibly supplemented with other information, to provide a strong presumption that the substance has the capacity to interfere with reproduction in humans. The classification of a substance is further distinguished on the basis of whether the evidence for classification is primarily from human data (Category 1A) or from animal data (Category 1B).

Category 1A: Known human reproductive toxicant

The classification of a substance in Category 1A is largely based on evidence from humans.

Category 1B: Presumed human reproductive toxicant

The classification of a substance in Category 1B is largely based on data from animal studies. Such data must provide clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate.

Category 2: Suspected human reproductive toxicant

Substances are classified in Category 2 for reproductive toxicity when there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development, and where the evidence is not sufficiently convincing to place the substance in Category 1. If deficiencies in the study make the quality of

evidence less convincing, Category 2 could be the more appropriate classification. Such effects shall have been observed in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects.

Effects on or via lactation are also part of the hazard class reproductive toxicity. Classification for these effects is independent of the classification in the classes 1A, 1B or 2 as described above. Development of a method for the determination of SCLs for substances with effects on or via lactation is outside the scope of this document. Therefore, these effects and this classification are not further considered in this document.

The classification of mixtures containing substances classified for reproductive toxicity and of substances containing impurities, additives or constituents classified for reproductive toxicity is based on the concentration of the reproductive toxic component(s). Table 3.7.2 of Annex I to CLP contains GCLs above which classification for reproductive toxicity is required. The GCL is 0.3% for reprotoxicants Category 1A and 1B and 3.0% for Category 2. However, a GCL for all substances may not be protective for high potency substances and may be overprotective for substances with a low potency. Therefore, SCLs may be needed for such substances.

According to CLP Article 10, SCLs shall be set where adequate and reliable scientific information shows that the hazard of a substance is evident at a level below the GCL. This results in SCLs below the GCLs. SCLs above the GCLs may be set in exceptional circumstances where adequate, reliable and conclusive scientific information shows that a hazard of a substance is not evident at a concentration above the GCL. Normally, substances that fulfil the criteria for reproductive toxicity are subject to a harmonised classification and labelling and included in Annex VI to CLP. In such cases, SCLs are set via the procedure for harmonisation of classification and labelling of substances in line with CLP Article 37. When there is no such harmonised entry in Annex VI to CLP, a manufacturer, importer or downstream user must self-classify reproductive toxic substances and must set lower or may set higher SCLs than the GCLs if justified according to CLP Article 10(1). He may also provide a proposal for a harmonised classification (CLP Article 37(2)), including an SCL where appropriate.

2.2 Description of the process for the development of a method to set SCLs for reproductive toxic substances

There are no hazard specific criteria for the setting of SCLs in CLP . According to CLP Article 10 (7), the European Chemicals Agency (ECHA) is required to provide further guidance on the setting of SCLs. A working group was established to develop such guidance for the hazard class reproductive toxicity, with the exception of the effects on or via lactation.

The work on the proposal for guidance on the determination of SCLs for reproductive toxicants was initiated by an EU working group of the TC C&L (Technical Committee on Classification and Labelling of Dangerous Substances), continued under the REACH Implementation Project (RIP) 3.6 and subsequently under the auspices of ECHA.

To get an impression of the possible parameters for potency and their distribution, two databases were compiled, containing several parameters for a large number of substances classified for developmental toxicity and impaired fertility. Based on the compiled data choices were made for the most appropriate parameter, the boundaries of the potency groups and the associated SCLs.

In the course of the guidance development, three documents have been produced. The first document is the actual guidance chapter included in the Guidance on the Application of the

CLP Criteria. The second document is this annexed background document, describing the process and considerations and providing the rationale for the proposed guidance. The third document is a publication of the databases of parameters for developmental toxicants and substances with an effect on sexual function or fertility and the analyses of the databases [(Muller et al., 2012)]

Chapter 2 of this document describes potency parameters and contains a number of theoretical considerations on the determination of the most appropriate parameter and the SCLs. A description of the databases and the analyses is also provided in this chapter. Chapter 4 is dedicated to the non-modifying factors. Chapter 5 describes and justifies the potency boundaries and corresponding SCLs.

2.3 Considering potency in setting specific concentration limits for various health hazards

The criteria for classification for reproductive toxicity are based on the strength of scientific evidence that the substance can cause reproductive toxicity. In general, no specific considerations are given to the potency of the substance to induce reproductive toxicity.

On the other hand, classification for several other health hazard classes is based on potency. Substances with different potency are classified in different categories within the hazard class. The classification of mixtures for that hazard class is then based on the concentration of the substance in the mixture and the hazard category or the potency (for acute toxicity) of the substance.

For acute toxicity, the potency is based on the acute toxicity estimate (ATE). The ATE is the dose level which induces 50% mortality in a acute toxicity study (LD_{50} or LC_{50}) or the estimated LD_{50} or LC_{50} using fixed dose procedure or the acute toxic class method. This value is used to classify a substance into one of several categories. For mixtures, the ATE value is used to estimate the potency of a mixture by calculation. The estimated potency is then used to classify the mixture into a hazard category.

For specific target organ toxicity (STOT) after single and repeated exposure, the potency is defined as the dose at which the substance shows significant toxic effects in a study. Based on the potency, a substance is either classified for STOT into one of two hazard categories or not classified. The classification of a mixture containing a substance classified for STOT depends on the percentage of the substance in the mixture and the hazard category of the substance. A minimal percentage is included in the criteria. SCLs have to be determined for substances with a very high potency.

Classification for carcinogenicity is, as for reproductive toxicity, based on the strength of scientific evidence and again no specific consideration is given to the potency. The classification of mixtures containing a carcinogenic substance is based on the GCL unless a SCL has been allocated for that substance as provided in Annex VI to CLP. SCLs for carcinogenic substances are determined based on the potency for carcinogenic effects based on the T25. The T25 is defined as the daily dose (in mg/kg bw) inducing a tumour incidence of 25% upon lifetime exposure after correction for the spontaneous incidence. This is mainly based on animal studies. Substances are divided into 3 groups based on the T25. High potency substances have a T25 $\leq$ 1mg/kg bw/ day, medium potency substances have a T25 between 1 -100 mg/kg bw/day, and T25> 100 mg/kg bw/day for low potency substances. Besides the T25, other elements were included that modify the potency evaluation (Commission Working Group, date unknown). This method has been included in the Guidance on the Application of the CLP Criteria.

The use of potency for the classification into different categories for several other hazard classes and the use of the potency to set SCLs for carcinogenic substances, justifies the use of

potency as a first approach also for setting SCLs for reproductive toxic substances. As no definition of potency for reproductive toxicants was available, the following definition is used as a working definition:

Reproductive toxicity potency is defined as the dose which induces reproductive toxic effects with a specific type, incidence and magnitude, considering the study design in terms of species and strain, exposure route, exposure duration, exposure window in the life cycle, and possible concomitant parental toxicity.

According to this definition 'Potency' is primarily based on applied *dose* and can be modified by consideration of 'severity'. Within this definition the dose is defined as the amount of substance to which the animals or humans that showed the effect (meaning type, incidence and magnitude) were exposed on an mg/kg bw/day basis. The incidence is the proportion of animals or humans that showed the effect. The type of effect describes which property of an organ or system of the animal or human is affected and the magnitude describes the level of change compared to the control. Together, the incidence, type and magnitude describe the 'severity' of the effect, meaning how adverse the effect or combination of effects is. With specific incidence, type and magnitude (together specific severity) a comparable level of severity is indicated for different effects.

The working definition above allows potency to be defined at different levels of specific severity, for example at the ED_{10} and the LOAEL (Lowest Observed Adverse Effect Level), and for different type of effects. Therefore, several possible estimates for potency were investigated.

2.4 Parameters for potency for reproductive toxicity

A consistent database to derive potency estimates for reproductive toxicity was lacking. Therefore, data on substances classified for effects on reproduction were collected and analysed. This was done separately for substances with an effect on development and substances with an effect on sexual function and fertility because the types of effects clearly differ between these two main types of reproductive effects. Therefore, this chapter falls into two parts, namely one for parameters for potency of substances with developmental effects (chapter 2.3.1) and one for parameters for potency of substances with effects on sexual function and fertility (chapter 2.3.2). As potency is primarily based on the dose in mg/kg bw/day at which different adverse effects are observed, a number of parameters/dose descriptors (e.g. NOAEL[82], LOAEL[83], ED_{10} etc.) exist for each type of adverse effect. The collected data included the NOAEL, LOAEL and ED_{10} (effective dose with a 10% incidence or effect level above the background) as parameters for the effect on reproduction of each substance. They were further divided into effects fulfilling the criteria for classification (named "LOAEL (classification)" for example) and any effects on reproduction (named "NOAEL (overall)" for example). Together, this sub-division results in 6 different potency parameters, see Table 1. Other data, e.g. a mutagenicity classification of a substance, the type of effect at the LOAEL and species used in the test, were also collected. These parameters were analysed and the results tabulated and plotted graphically. The results are published by Muller et al., 2012. As the data for these two main types of reproductive toxicity were analysed separately, the results are provided separately.

2.4.1 Potency parameters for developmental toxicants (Muller et al, 2012)

Data for one or more of the parameters for development were available for 99 substances classified for developmental toxicity when the work on this guidance development started.

[82] NOAEL means No Observed Adverse Effect Level
[83] LOAEL means Lowest Observed Adverse Effect Level

For almost all substances a LOAEL is available but a NOAEL and ED_{10} were sometimes missing. The absence of a NOAEL is mostly caused by the absence of a dose level without an effect in the study or database of a substance. The absence of an ED_{10} value is mainly caused by the absence of a NOAEL and in most of those cases an ED_{10} could only be derived by a benchmark dose (BMD) approach to avoid interpolation between the LOAEL and the vehicle control. Another cause for the absence of ED_{10} values is the limited reporting of effect levels in the consulted study summaries or study reports.

The difference in the average value between the highest and lowest of the 6 parameters for potency is a factor of 4 or less. This is very small compared to the difference in potency between substances for each parameter of up to 1,000,000 fold (Table 1). The potency difference is more pronounced for a NOAEL or LOAEL compared to an ED_{10} mainly because for most potent substances only a NOAEL and/or a LOAEL was available but not an ED_{10}. The available data indicate that there is a close relation between the NOAEL, LOAEL and ED_{10} for most substances. The average LOAEL is between a factor of 2 and 3 above the average NOAEL. The fact that it is not closer to the factor of 3 to 4 that is normally used between dose levels is probably due to the absence of a NOAEL for a number of substances. The average ED_{10} (classification), is slightly higher than the average LOAEL (classification). The difference is more pronounced for the "overall" values, namely approximately a factor of 2. These findings are caused by both the dose spacing in the studies and the limited discriminative power of the NOAEL approach.

Table 1. Average values (assuming log/normal distribution) (in mg/kg bw/day) and potency differences for parameters for all developmental toxicants of the database (Muller et al, 2012)

Parameter	N	Average	Standard deviation	Lowest value	Highest value	Potency difference
NOAEL (overall)	68	12	10	0.002	684	342000
LOAEL (overall)	98	25	13	0.002	2281	1140500
ED_{10} (overall)	59	43	6	0.3	785	2617
NOAEL (classification)	76	18	11	0.002	1100	550000
LOAEL (classification)	97	40	13	0.002	2281	1140500
ED_{10} (classification)	63	48	6	0.3	933	3110

A part of the differences in average values and potency between the different parameters in Table 1 is probably caused by the difference in the number of substances for which a particular variable is present. When only substances are used for which all 6 parameters were present, this reduces the database to 44 substances (Table 2). A part of the difference between the parameters in potency difference can be explained by the unusual dose levels (NOAEL 0.026 mg/kg bw/day and LOAEL 0.26 mg/kg bw/day) used in the study for the substance that had the lowest values for all parameters (cadmium oxide).

Table 2. Average values (assuming log/normal distribution) (in mg/kg bw/day) and potency differences for parameters for developmental toxicants (N=44) with all 6 parameters (Muller et al, 2012)

Parameter	Average	Standard	Lowest	Highest	Potency

		deviation	value	value	difference
NOAEL (overall)	19	7	0.026	684	26308
LOAEL (overall)	58	7	0.260	2281	8773
ED_{10} (overall)	44	5	0.300	570	1900
NOAEL (classification)	25	7	0.026	684	26308
LOAEL (classification)	71	6	0.260	2281	8773
ED_{10} (classification)	49	6	0.300	933	3110

Comparing Tables 1 and 2 indicates no major changes in average, standard deviation and highest value for each parameter. However, the lowest value changes for several parameters. The resulting potency difference becomes much more comparable between the parameters. This indicates that the difference between the parameters in potency difference in Table 1 is mainly due to the absence of an ED_{10} for some very potent substances.

2.4.2 Potency parameters for substances with an adverse effect on sexual function and fertility (Muller et al, 2012)

Data for one or more of the potency parameters were available for 93 substances classified for adverse effects on sexual function and fertility (hereafter called fertility toxicants) when the work with the guidance development started. For all substances, an LOAEL was available but a NOAEL and an ED_{10} were sometimes missing. The absence of a NOAEL is mostly caused by the absence of a dose level without an effect in the study or database of a substance. The absence of an ED_{10} value is mainly caused by the absence of a NOAEL and in most of those cases an ED_{10} could only be derived by a Benchmark Dose (BMD) approach to avoid interpolation between the LOAEL and the vehicle control. Another cause for the absence of an ED_{10} values is the limited reporting of effect levels in the consulted study summaries or study reports.

The difference in the average values between the highest and lowest of the 6 parameters for potency is less than a factor of 4. This is small compared to the difference in potency between substances for each parameter of up to 30,000 (Table 3). The difference in potency within the parameters is more pronounced for the NOAEL values than for the values of LOAEL and ED_{10}, which is mainly due to one substance with a NOAEL of 0.032 mg/kg bw/day but an LOAEL of 10 mg/kg bw/day. The available data indicate that there is a close relation between the NOAEL, LOAEL and ED_{10} for most substances. The average LOAEL is between a factor 2 and 3 above the average NOAEL. The fact that it is not closer to the factor of 3 to 4 that is normally used between dose levels is probably due to the absence of an NOAEL for a number of substances. The average ED_{10} is between the average NOAEL and LOAEL.

Table 3. Average values (assuming log/normal distribution) (in mg/kg bw/day) and potency differences for parameters for all fertility toxicants of the database

Parameter	N	Average	Standard deviation	Lowest value	Highest value	Potency difference
NOAEL (overall)	68	20	7	0.032	635	19844
LOAEL (overall)	93	54	7	0.25	2060	8240
ED_{10} (overall)	37	31	5	0.6	1065	1775
NOAEL	70	24	7	0.032	940	29375

(classification)						
LOAEL (classification)	93	62	7	0.33	2060	6242
ED_{10} (classification)	37	33	6	0.6	1065	1775

A part of the differences in the average values and in potency between the different parameters in Table 3 is probably caused by the difference in the number of substances for which a particular parameter is present. When only substances are used for which all 6 parameters were present, this reduces the database to 34 substances (Table 4).

Table 4. Average values (assuming log/normal distribution) (in mg/kg bw/day) and potency differences for parameters for fertility toxicants (N=34) with all 6 parameters

Parameter	Average	Standard deviation	Lowest value	Highest value	Potency difference
NOAEL (overall)	19	6	0.3	250	833
LOAEL (overall)	72	6	0.7	1000	1429
ED_{10} (overall)	35	5	1.3	1065	819
NOAEL(classification)	24	6	0.3	940	3133
LOAEL(classification)	89	6	0.7	1580	2257
ED_{10} (classification)	39	5	1.3	1065	819

Comparing Tables 3 and 4 indicates no major changes in average, standard deviation and highest value for each parameter. However, the lowest value changes for some parameters. The resulting potency difference becomes much more comparable between the parameters. This indicates that part of the differences between the parameters in potency difference in Table 3 is due to the absence of an ED_{10} for some very potent substances.

2.4.3 Conclusions on the most appropriate parameter for potency

As LOAELs are available for almost all substances, this could be considered the most useful informed parameter on which to base potency. However, in the absence of a NOAEL, a LOAEL is not a suitable parameter for potency because there is no indication to what extent the real LOAEL could be lower than the LOAEL observed. The lower number of substances for which an ED_{10} is available is probably due to the limitations of the available study summaries for several substances. Use of the ED_{10} requires access to a detailed summary of the study or the study report itself which was not available for several substances in the database.

However, this guidance will be applied by both industry and Member State Competent Authorities when preparing proposals for harmonised classification and labelling, and by industry in case of self-classification of a reproductive toxic substance for which there is no entry in Annex VI to CLP.

Companies have access to their own studies. It is expected that by the completion of the REACH registration deadlines, more detailed information including ED_{10} will be available for more substances than in this database used to develop this guidance.

Member States will have access to the study summaries in the registrations. The full studies could be requested by ECHA or by a Member State Competent Authority, according to CLP Article 49(3).

It should be noted that in the absence of a NOAEL, an ED_{10} cannot be determined by interpolation, in case the size of the effect at the LOAEL is more than 10%. However, an ED_{10} can be estimated using bench mark dose (BMD) software when sufficient data are available. A NOAEL and LOAEL cannot be estimated using the BMD approach. In addition, a fixed level of effect of e.g. 10% (ED_{10}) is considered to be more representative for the potency and facilitates comparisons of relative potency between substances to a greater extent, than a LOAEL which is a chosen dose level.

For most other hazard classes, the SCLs are based on effect levels. For carcinogenicity the T25 is used, and for skin sensitisation the EC_3 value or the dose level with a certain level of responders is used. Therefore, the LOAEL or ED_{10} is considered a more appropriate parameter for determination of an SCL than the NOAEL.

For substances where there is a difference in the LOAEL overall (lowest dose with any effect on reproduction) versus the LOAEL classification (lowest dose with an effect on reproduction fulfilling the classification criteria), this is in most cases due to non-significant increases in lethalities or malformations or decreases in foetal body weight at the LOAEL overall versus significant increases in lethalities or malformations at the LOAEL classification. The difference between significant and non-significant effects will disappear if the ED_{10} is used as parameter for potency.

The difference in parameters between “overall” and “classification” was sometimes due to limited effects that normally do not warrant classification such as a small increase in variations at the LOAEL and to more severe effects warranting classification at a higher dose level. To have a more consistent parameter for potency, it was preferred to use the parameters for effects warranting classification.

Overall, the use of the ED_{10} for effects warranting classification is proposed as the most appropriate estimate for the potency. The advantage of this parameter is that it is a dose level with a specified level of effects of at least a certain severity. This is in line with most classification criteria and with other methods for the determination of SCLs.

Furthermore, not all aspects included in the working definition of reproductive potency are fully taken into account in the ED_{10}. Therefore, certain additional parameters should be considered which can change the potency group as determined by using the ED_{10}, resulting in the setting of lower or higher concentration limits. See chapter 4 for such modifying factors.

3 Modifying factors

Several possible elements of reproductive toxicity were considered as elements which should also be taken into account when determining the potency group for reproductive toxicity of a substance (modifying factors). Modifying factors may change the potency group for a substance. While some modifying factors should always be taken into account, other modifying factors could be more relevant when the potency is close to the boundary between two groups (see Table 8 above). It should be noted that several of the elements may be interrelated.

Some factors may have already been taken into account in deciding on the classification as a reproductive toxicant. Where such considerations have been made, care should be taken not to use that information again when determining the potency. For example, when the effects determining the ED_{10} were observed at dose levels also causing maternal toxicity, this should

already have been taken into consideration during the classification and should not be used again to set a higher SCL. Factors considered not to be used as modifying factors are included in section 4.7 of this Annex. The following factors are used as modifying factors:

- Type of effect / severity
- Data availability
- Dose-response relationship
- Mode or mechanism of action
- Toxicokinetics
- Bio-accumulation of substances

The justification of the use of these modifying factors is provided in the guidance (see section 3.7.2.5.5).

4 Non-modifying factors

A wide range of parameters were considered as possible modifying factors for the determination of reproductive potency. Parameters selected as modifying factors are included above. Parameters or factors considered but not included as modifying factors are listed below:

4. 1 Species and strains

The species used to determine the ED_{10} could be considered as a modifying factor if it is shown that a certain species is generally more sensitive to reproductive toxicants, meaning showing effects at a lower exposure level, and this can be considered relevant to humans. However, comparison of the different parameters between the two most used species for developmental effects, rats and rabbits, did not indicate a difference in average NOAEL, LOAEL or ED_{10} in this analysis. Furthermore, almost all studies that were determinative for the classification for fertility were studies in rats. Therefore, species is not regarded as a modifying factor. The most sensitive species for each substance has to be used to determine the potency parameter unless there is clear evidence that the observed effects are not relevant to humans or when there is good evidence for a difference in sensitivity between humans and the test species. This also applies to different strains.

4. 2 Systemic or maternal toxicity

Adverse effects on fertility and sexual function may be caused as a secondary effect of systemic toxicity to other organs. Developmental effects may be caused as a secondary effect of maternal toxicity. However, this should have already been taken into account for classifying a substance in a specific category. Therefore, this should not also be used for modifying the concentration limit.

4. 3 Mutagenicity

Analyses of the databases [(Muller et al., 2012)] indicate that substances classified both for reproductive toxicity and mutagenicity have a higher potency (lower ED_{10}) than substances classified for reproductive toxicity only. However, as this higher potency is already included in the lower ED_{10}, there is no need to use mutagenicity as a modifying factor.

4.4 Volatility

Volatility is a physical property related to exposure rather than to the intrinsic hazardous potency of a substance. However, the exposure level to a substance in a mixture is not only influenced by the concentration but also by the volatility of the substance. The higher the volatility of a substance the higher the inhalation exposure may be when handling such a substance in a mixture. Inhalation exposure to vapours are not covered by the experimental

oral testing limit of 1000 mg/kg bw/day as the exposure at workplaces can be more than one order of magnitude above the extrapolated exposure level covered by the limit dose (Schneider et al., 2007). This is probably the reason why no limit dose for classification is included in the classification criteria (see appendix I, 3.7.2.5.4). Therefore, volatility could be considered as a modifying factor.

However this argument is not specific for reproductive toxicity and should then apply to all relevant hazard classes. In methods for setting SCLs for other hazard classes such as carcinogenicity, the volatility is not used as a modifying factor, although it is suggested to be a factor to take into consideration when setting SCLs for narcotic effects (STOT-SE 3). Further, volatility is not specifically mentioned in the criteria for classification for any other hazard class other than STOT-SE and -RE (3.8.2.1.10.4 and 3.9.2.10.4) for which the guidance recommends a specific precautionary statement on the label for highly volatile substances.

However for some hazard classes, volatility is taken into account in the classification of substances and mixtures by using different numeric criteria (acute toxicity, table 3.1.1) or guidance values (STOT-SE table 3.8.2 and STOT-RE, table 3.9.2 and 3.9.3) for vapours than for dusts and mists. For STOT-SE and STOT-RE, the method for setting SCLs is directly depending on these guidance values.

It was decided not to include volatility as a modifying factor because it is a physical property that depends also on other factors (e.g. temperature and composition of the mixture) and is therefore more related to exposure rather that to the intrinsic hazardous potency of the substance.

5 Potency groups and specific concentration limits

5.1 Justification of the proposed potency boundaries and specific concentration limits

In the following some general considerations on potency groups are first provided, followed by justifications for the approach taken and for the suggested boundaries of the potency groups and the corresponding concentration limits.

5.1.1 General considerations on potency groups

5.1.1.1 Legal requirements

According to the second subparagraph of CLP Article 10(1)

"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."

According to the third subparagraph of CLP Article 10(1)

"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.".

5.1.1.2 Scientific results of the database analysis

The databases with ED_{10} values for substances (Category 1 and 2) with an effect on development and with an effect on sexual function and fertility were compared to determine

whether there is a difference in potency between Category 1 and Category 2 substances [(Muller et al, 2012)]. The results should be carefully interpreted because of the limitations of the database: the database is based on a limited number of substances and the available data per substance is reduced to a single number (ED_{10}) and some modifying factors. Reducing the data in the database would have included removal of differences in effects and doubts between Category 1 and Category 2. In any case, the comparisons indicate that the average potency of substances with an effect on development and with an effect on sexual function and fertility are comparable and that also the average potencies of Category 1 and 2 substances are comparable and certainly do not differ by a factor of 10.

5.1.1.3 Policy related considerations and proposed method

Data derived from an insensitive test method could in some cases not be regarded as adequate, reliable and conclusive evidence, as mentioned in Article 10 (1) (3rd para). For example, a screening assay which only uses a limited number of animals and studied endpoints, cannot be used to set higher SCLs (but can be used to set lower SCLs). Also a study resulting in an LOAEL without an NOAEL cannot be used to set higher SCLs.

Determination of the boundaries of the potency groups (see Table 8) and the SCL or GCL for each group is a policy related issue. CLP Article 10, the criteria in Annex I to CLP and the available data do not give a clear direction. Therefore, a simple system was developed. Furthermore, the approach taken is similar to the one developed for other hazard classes such as skin sensitization and carcinogenicity, which should be an appropriate justification for the current method.

Determination of the potency for reproductive toxicity will in most cases be based on limited data from one or a few studies. It was recognised that an exact SCL for each substance that also differs for each substance would indicate a precision that is not realistic or scientifically justified. Also, Janer (2007) has shown that the variation in the NOAELs of 2-generation studies for one substance is considerable. Therefore, it is proposed to divide the substances into large potency groups with associated SCLs as it is done for other hazard classes. Three potency groups are proposed. As shown in Table 10 below, substances with the lowest potency (highest ED_{10}) fall in a group with an SCL above the GCL. Most substances should fall in the group with the GCL. Only substances with a very high potency (low ED_{10}) should fall in the group with a SCL below the GCL. It is proposed to include approximately 70 – 80% in the GCL potency group and 5 to 15% in the low and high potency groups. Further, as the average potency of developmental toxicants and substances affecting sexual function and fertility are comparable, it is proposed to use the same boundaries for both types of effect. Also, the database shows there is no difference in potency between substances in Category 1 and Category 2. Therefore it is proposed to use the same boundaries for Category 1 and 2 substances.

5.1.1.4. Other methods considered

Several other options for a method for determining SCLs were discussed including a method that was used by the TC C&L in a limited number of cases in the past. This method is based on the limit dose of 1000 mg/kg bw/day, as described in the test guideline OECD 414 and 416.

The concentration limit expressed as a % in mixtures is derived by dividing the NOAEL by the limit dose followed by multiplication by 100 (see ECBI/47/02 Add.7). This method would result in an individual SCL for each substance. This would indicate a precision that cannot be expected from standard reproduction studies. Also this would result in an SCL for most substances and in a GCL for only some substances. Therefore, this method was not

considered. Potency groups are used in the proposed method because this does not give the impression of a high precision and allow the placing of many substances in the medium potency group with the connected GCL.

5.1.2 Justification of the boundaries between the three potency groups.

The estimated percentages of already classified substances in each group for both Category 1 and 2 substances with an effect on development or an adverse effect on fertility and sexual function are provided in the tables below. They are based on the distribution of potencies of known developmental toxicants and of known fertility toxicants [(Muller et al., 2012)]. Several possible values of the boundaries between the three groups are tested. The estimations are based on counting the number of substances above or below a number of possible boundaries and applying some of the modifying factors such as the presence of a NOAEL and considering also the saturated vapour concentration for substances in the low potency group. However, the saturated vapour concentration, reflecting volatility, is not proposed as a modifying factor in the guidance.

Taking into account all modifying factors for all substances would imply a full assessment of the potency for all substances. This was not possible within the available resources. As most modifying factors result in a shift from the low potency group into the medium potency group and from the medium potency group into the high potency group, it is likely that the percentages in the low potency group may decrease and the percentages in the high potency group may increase. (Thus, the effect of volatility on the frequencies in Table 9 should be marginal.)

Based on the ED_{10} distribution a rough estimate was made by the Working group of the optimal boundaries using a range of a factor of 100 for the medium potency group. Then the number of substances falling into several combinations of boundaries was estimated.

Table 9. Percentages of substances in the three potency groups using the ED_{10} and some of the modifying factors for different boundaries of the potency groups and considering the saturated vapour concentration of low potency substances.

			Boundaries of the high and low potency groups					
			<2 mg/kg	**<3 mg/kg**	**<4 mg/kg**	**<5 mg/kg**	**<6 mg/kg**	**<7 mg/kg**
Type of effect	**Classification**	**Potency group**	**>200 mg/kg**	**>300 mg/kg**	**>400 mg/kg**	**>500 mg/kg**	**>600 mg/kg**	**>700 mg/kg**
Development	Cat 1A/1B	High potency	12,1	13,8	17,2	20,7	20,7	20,7
	H360D	Medium potency	75,9	77,6	79,3	77,6	79,3	79,3
		Low potency	12,1	8,6	3,4	1,7	0,0	0,0
		% with SCL	24,1	22,4	20,7	22,4	20,7	20,7
	Cat 2	High potency	10,3	13,8	13,8	17,2	17,2	20,7
	H361d	Medium potency	72,4	72,4	79,3	75,9	82,8	79,3
		Low potency	17,2	13,8	6,9	6,9	0,0	0,0
		% with SCL	27,6	27,6	20,7	24,1	17,2	20,7
Fertility	Cat 1A/1B	High potency	3,4	3,4	3,4	6,9	10,3	13,8
	H360F	Medium potency	89,7	93,1	96,6	93,1	89,7	86,2
		Low potency	6,9	3,4	0,0	0,0	0,0	0,0
		% with SCL	10,3	6,9	3,4	6,9	10,3	13,8

			Boundaries of the high and low potency groups					
			<2 mg/kg	<3 mg/kg	<4 mg/kg	<5 mg/kg	<6 mg/kg	<7 mg/kg
Type of effect	**Classification**	**Potency group**	**>200 mg/kg**	**>300 mg/kg**	**>400 mg/kg**	**>500 mg/kg**	**>600 mg/kg**	**>700 mg/kg**
	Cat 2	High potency	6,3	9,4	10,9	15,6	15,6	17,2
	H361f	Medium potency	71,9	76,6	81,3	78,1	79,7	79,7
		Low potency	21,9	14,1	7,8	6,3	4,7	3,1
		% with SCL	28,1	23,4	18,8	21,9	20,3	20,3
All		avg high potency	8.0	10.1	11.3	15.1	16.0	18.1
		avg medium potency	77.5	79.9	84.1	81.2	82.9	81.1
		avg low potency	14.5	10.0	4.5	3.7	1.2	0.8
		avg % with SCL	22,5	20,1	15,9	18,8	17,1	18,9

As shown in Table 9 boundaries of 4 to 400 mg/kg bw/day would result in the maximum number of substances being included in the medium potency range for most types of effects and classifications and for both type of effects and classifications combined. For developmental effects Category 1 and 2 the percentage of substances in the medium potency group is within the target of ca. 70-80%. For effects on sexual function and fertility Category 2 this is almost the case. Only for Category 1 is this not the case. The percentage of substances in the medium potency group could be reduced by reducing the factor of 100 between the boundaries. However, because of the large difference in potency of the substances classified for reproductive toxicity of up to a million, this was not considered necessary. The percentage of substances in the high potency group is higher than the percentage in the lower potency group for the boundaries of 4 to 400 mg/kg bw/day. However, the percentage of substances in the high potency group was above 15% for substances classified for an effect on development in Category 1.

Following the PEG consultation, it was agred that volatility was not considered a modifying factor and thus, the ED_{10} distribution changes as shown in table 10. Borders of 4 to 400 mg/kg bw/day would result in the maximum number of substances being included in the medium potency range for most type of effects and classifications and for both type of effects and classifications combined. However, the same value also applies to some of the other borders. For developmental effects Category 1 and 2 the percentage of substances in the medium potency group is within the target of ca. 70-80%. For effects on sexual function and fertility Category 2 this is not the case. The percentage of substances in the medium potency group could be reduced by reducing the factor of 100 between the borders. However, because of the large difference in potency of the substances classified for reproductive toxicity of up to a million, this was not considered necessary. The percentage of substances in the high potency group is approximately the same as the percentage in the lower potency group for the borders of 4 to 400 mg/kg bw/day.

Table 10. Percentages of substances in the three potency groups using the ED_{10} and some of the modifying factors but not volatility for different borders of the potency groups.

			Borders of the high and low potency groups					
			≤2 mg/kg	**≤3 mg/kg**	**≤4 mg/kg**	**≤5 mg/kg**	**≤6 mg/kg**	**≤7 mg/kg**
Type of effect	**Classification**	**Potency group**	**≥200 mg/kg**	**≥300 mg/kg**	**≥400 mg/kg**	**≥500 mg/kg**	**≥600 mg/kg**	**≥700 mg/kg**
Development	Cat 1A/1B	High potency	12.1	13.8	17.2	20.7	20.7	20.7
	H360D	Medium potency	67.2	74.1	77.6	75.9	79.3	79.3
		Low potency	20.7	12.1	5.2	3.4	0	0
		% with SCL	32.8	25.9	22.4	24.1	20.7	20.7
	Cat 2	High potency	7.3	9.8	9.8	12.2	12.2	14.6
	H361d	Medium potency	68.2	65.8	70.7	70.7	75.6	78.1
		Low potency	24.4	24.4	19.5	17.1	12.2	7.3
		% with SCL	31.7	34.2	29.3	29.3	24.4	21.9
Fertility	Cat 1A/1B	High potency	3.4	3.4	3.4	6.9	10.3	13.8
	H360F	Medium potency	86.3	89.7	93.2	89.7	86.3	86.2
		Low potency	10.3	6.9	3.4	3.4	3.4	0
		% with SCL	13.7	10.3	6.8	10.3	13.7	13.8
	Cat 2	High potency	6.3	9.4	10.9	15.6	15.6	17.2
	H361f	Medium potency	68.7	73.4	78.2	75.0	76.6	76.5
		Low potency	25.0	17.2	10.9	9.4	7.8	6.3
		% with SCL	31.3	26.6	21.8	25.0	23.4	23.5
All		avg high potency	7.3	9.1	10.3	13.9	14.7	16.6
		avg medium potency	72.6	75.7	79.9	77.8	79.4	80.0
		avg low potency	20.1	15.2	9.8	8.3	5.9	3.4
		avg % with SCL	27.4	24.3	20.1	22.2	20.6	20.0

On average, combining both effect types and both classification categories, the goal of 70-80% of the substances in the medium potency group and 5 -15% of the substances in the low and high potency group was fulfilled with boundaries of 4 and 400 mg/kg bw/day. However, other combinations of boundaries such as 3 and 300 and 5 to 500 mg/kg bw/day also fulfill these requirements. Using these boundaries would result in a change of potency group for 10 to 14 substances (5 – 7%). Further it could be considered to lower the factor of 100 between the borders to increase the number of substances. For example, using boundaries of 5 to 300 mg/kg bw/day would result in 13.9% high potency substances, 15.2% low potency substances and 71% substances in the medium potency group. Also, the percentages provided in the tables 9 and 10 are calculated not using every modifying factor. Therefore, it can be stated that the choice of the boundaries is arbitrary. However, based on the available information, the boundaries of 4 to 400 mg/kg bw/day seem to be reasonable.

5.1.3 Concentration limits for Category 1 and Category 2 substances

The generic concentration limit (GCL) from the respective categories will be used for medium potency substances (group 2). As mentioned earlier the GCL is 0.3% for reproductive toxicants Category 1A and 1B and 3.0% for Category 2.

Category 1A and 1B

Different concentration limits have to be used for the different potency groups. Substances classified in Category 1 in the low potency group (group 3) can have a SCL above the GCL of 0.3%. We propose to use an SCL of 3% which is tenfold of the GCL. A factor of 10 is used often in CLP as difference in GCL between hazard categories. This factor is also used in the guidance for setting SCLs for carcinogens. For substances in group 1 (high potency), it is proposed to use a SCL of 0.03%. For extremely potent reproductive toxicants with an ED_{10} (classification) of more than 10 fold below the boundary limit of 4 mg/kg bw/day it is proposed to use even lower SCLs. For every factor of 10 below the upper limit the SCL is reduced with a factor of 10.

Category 2

Substances classified in Category 2 in the low potency group (group 3) can have a SCL above the GCL of 3%. We propose to use an SCL of 3-10% which is one to 3-fold of the GCL. An SCL above 10% was considered too high. The upper SCL of 10% can only be used in exceptional cases (NOAEL below 1000 mg/kg bw/day but ED_{10} above 1000 mg/kg bw/day). This would account for none of the substances in the database. For high potency substances (group 1), it is proposed to use an SCL of 0.3%. For extremely potent reproductive toxicants with an ED_{10} (classification) of more than 10-fold below the boundary limit of 4 mg/kg bw/day it is proposed to use even lower SCLs. For every factor of 10 below the upper limit, the SCL is reduced by a factor of 10.

The resulting SCLs for each potency group are presented in Table 11.

Table 11. SCLs for substances in each potency group and classification category

	Category 1		Category 2	
	Dose	SCL	Dose	SCL
Group 1 high potency	ED_{10} (classification) below 4 mg/kg bw/day	0.03% (factors of 10 lower for extremely potent substances[B])	ED_{10} (classification) below 4 mg/kg bw/day	0.3% (factors of 10 lower for extremely potent substances)
Group 2 medium potency	$ED_{10} \geq 4$ mg/kg bw/day, and $\leq$ 400 mg/kg bw/day	0.3% (GCL)	$ED_{10} \geq 4$ mg/kg bw/day, and $\leq$ 400 mg/kg bw/day	3% (GCL)
Group 3 low potency	ED_{10} (classification) above 400 mg/kg bw/day	3%	ED_{10} (classification) above 400 mg/kg bw/day	3-10% [A]

[A] The limit of 10% may be considered in certain cases, such as for substances with an ED_{10} value above 1000 mg/kg bw/day and a NOAEL below 1000 mg/kg bw/day.

[B] For substances with an ED_{10} more than 10 fold below 4 mg/kg bw/day, meaning an ED_{10} below 0.4 mg/kg bw/day, a 10-fold lower SCL should be used. For even more potent substance the SCL should be lowered with a factor of 10 for every factor of 10 the ED_{10} is below 4 mg/kg bw/day.

Assigning two SCLs to a substance

A reproductive toxic substance is classified in one category for both effects on development and on sexual function and fertility. Within each category effects on development and on sexual function & fertility are considered separately. The potency and resulting concentration limits have to be determined separately for the two main types of reproductive toxic effects. In case the potency and resulting specific concentration limits are different for sexual function/fertility and development for a substance, the substance needs to be assigned one SCL for developmental toxicity and another SCL for effects on sexual function and fertility. These concentration limits will in all cases trigger different specifications of the hazard statements for the two main types of effects, to be applied to mixtures containing the substance (see also 3.7.4.1, Annex I, CLP).

5.2 Assigning SCLs

The SCL or GCL for each substance can be determined using the final potency group of the substance using Table 9.

6 References

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