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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 6.0
Jan 2024

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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 2.0	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 The update includes the following: • Revision of Part 1, by eliminating and amending out of date information and restructuring the text in order to reflect the Guidance update.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.	April 2012

	• 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.	
Version 3.0	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
Version 4.0	(i) Revision of the CLP Guidance addressing content in relation to the Part 2: Physical hazards, Part 3: Health hazards and Annex VI following the 2nd and the 4th Adaptation to Technical Progress to the CLP Regulation (Commission Regulation (EU) No 286/2011 of 10 March 2011 and Commission Regulation (EU) No 487/2013 of 8 May 2013). The revision includes: • Numbering of chapters within CLP Guidance, Parts 2 & 3 were synchronised with corresponding chapter numbering of CLP, Annex I. • Changes in the legal text due the 2nd and 4th ATPs. • Changes in the legal text due to the 4th ATP were highlighted in orange within all relevant green boxes. All changes are preceded by a note highlighting the changes. (To note: a corrigendum will change the colour of relative legal text boxes from orange to green when the 4th ATP applies). In addition, the revisions to Part 2: Physical hazards include the following: • Chapters 'Pyrophoric liquids and solids' and 'Oxidising liquids and solids' were divided into four chapters: 'Pyrophoric liquids', 'Pyrophoric solids', 'Oxidising liquids' and 'Oxidising solids' respectively. • Based on the 4th ATP the CLP Guidance Chapter 2.2 Flammable gases was extended to take into account the scope of CLP, Annex I, section 2.2 to include chemically unstable gases. • Further, the 4th ATP amended the criteria in CLP Annex I, Section 2.3 Flammable aerosols and renamed it into	November 2013

2.3 Aerosols. Hence, the CLP Guidance was amended accordingly.

- All chapters were rechecked and redundant and/or outdated information were deleted, reorganised and/or revised. For example, 'Introduction' chapters were significantly shortened, however several "examples" sections (i.e. 'Example for classification…') were further elaborated.
- Where missing, a new sub-chapter 'Relation to other physical hazards' was added.
- Sub-chapter 2.0.4 'Physical state' was extended with additional information about substance/mixture form and some examples.
- In sub-chapter 2.1.5.2 'Additional labelling provisions' within chapter 2.1 'Explosives' further guidance about hazard communication was provided.
- In sub-chapter 2.5.6.1 a new recommendation for shot hazard codes to identify the classification of gasses under pressure was added.
- Footnotes with references to endorsed or on-going revisions of the GHS which have not yet been implemented into the CLP via a respective ATP were included in relevant sub-chapters of this guidance for information only.

In addition, the major revisions to Part 3: Health hazards include the following:

- All sections: revisions to legal text for the 4th ATP, including revisions to Precautionary Statements in the Tables with labelling information.
- Section 3.1: the introduction of new guidance for the 4th ATP in section 3.1.4.1.
- Sections 3.2.2.5 and 3.3.2.5: clarification to the recently published text (Version 3.0) for the setting of SCLs.
- Section 3.4 (sensitisation) has been significantly re-organised to present all the information on respiratory sensitisation together, followed by the information on skin sensitisation. This is in line with how the sections are presented in the CLP Regulation and in GHS documents.
- Section 3.4: integration of subcategories for respiratory and skin sensitisation based on potency of a substance; clarification of semi-quantitative terms like 'low to moderate sensitisation rate' and 'high or low exposure'; elaboration of evaluation of human data for skin sensitisation and the addition of new examples.
- Section 3.7: the introduction of new guidance for the 4th ATP in section3.7.4.1 and section 3.7.5.1.

	(ii) Corrigendum of Part 1: General principles for classification and labelling and Part 4: Environmental hazards and its related Annexes I-V. The corrigendum includes the following: • The list of abbreviations was updated. • Update or deletion of outdated references to Guidance on information requirements and chemical safety assessment, Endpoint specific guidance (Chapter R.7a) within Annexes I-V. • A footnote informing the reader that with effect from 1 September 2013, Directive 98/8/EC had been repealed by Biocidal Products Regulation (EU) No 528/2012 was added. • In Part 1, Part 4 and Annexes modal verbs 'shall' were replaced with 'must' where appropriate. • A footnote related to respiratory sensitisation and skin sensitisation in Table 1.1 was removed. • A correction to Example D, sub-chapter 4.1.4.7.5 was applied, namely a reference to CLP, Annex I, point (b) (ii) of Table 4.1.0 was introduced. In addition, the result of a summation method calculation was corrected.	
Version 4.1	Corrigendum to take account of the end of the transition period of the 4th ATP (as foreseen in version 4.0 above): • change the colour of relative legal text boxes from orange to green; • in Part 2, to delete section 2.2.1 Flammable gases and section 2.3.1 Flammable Aerosols (outdated text) and renumber sections 2.2.2 Flammable gases (including chemically unstable gases) and 2.3.2 Aerosols accordingly; • in Part 3, to delete the "outdated text" in sections 3.7.4.1 and 3.7.5.1 in Reproductive Toxicity. In addition, minor editorial errors were corrected and minor reformatting was made.	June 2015
Version 5.0	Partial revision of the Guidance to update the content mainly following the 8th Adaptation to Technical Progress to the CLP Regulation (Commission Regulation (EU) No 286/2011). Revision of few specific additional topics. The update includes the following: (i) Throughout the document: • Revision of legal references and legal text quotations. • Renumbering of some sections. • Deletion of sections regarding the reclassification of substances and mixtures previously classified in accordance with the DSD or DPD.	July 2017

(ii) Revision of Part 1:

- Deletion of reference to pre-CLP legislation and transitional period.
- Addition of reference to read-across and grouping in the context of bioavailability.
- Removal of quotation of Article 31(3) of REACH.
- Clarification about applicability of additivity principle.
- Clarification about the application of mixture rules to substances with CMR constituents.
- Reduction of section 1.2.3.1 on physical hazards to avoid redundancy with section 2.0.4.
- Revision of section 1.7 and removal of unnecessary information. Table on additional information using transport classification moved to a new Annex VII.

(iii) Revision of the following sections of Part 2:

- 2.1 (Explosives): replacement of new figure 2.1.3; update of label elements; addition new note 2 to table 2.1.2 on requirement for SDSs.
- 2.3 (Aerosols): update of text on classification criteria; update of decision logic 2.3.1-a; update of section 2.3.6 on the relation to transport classification.
- 2.14 (Oxidising solids): addition of criteria using test 0.3; update of labelling elements.

(iv) Minor changes to the following sections in Part 2:

- 2.8 (Self-reactive): update of label elements.
- 2.12 (Emitting flammable gases): update of label elements.
- 2.15 (Organic peroxides): update of decision logic.2.15.1; update of label elements.

(v) Revision of following sections in Part 3:

- 3.1 (Acute toxicity): Reference to new *in-vitro* test. Indication that harmonised ATE values will be included in Annex VI to CLP. Deletion of reference to the concept of relating the conditions of an acute inhalation test to real life. Indication that not-classified components may influence ATE and, in general, clarification about components to be considered for mixture classification according to the case. Indication to avoid under classification for oral toxicity. Additon of a new example (13) on the application of additivity methods for mixtures with components in different physical forms.
- 3.2 (Skin corrosion): Subsection on non-testing methods updated and clarified the need to assess the relevance. Update of classification criteria. Inclusion of new figure illustrating the tiered evaluation approach. Inclusion of a new figure illustrating the relative weight

	of different available pieces of information to be considered when weight of Evidence (WoE) is applied. Replacement of the decision logic chart with separate decision logics for substances and mixtures, based on the chart from GHS. Clarification about classification of mixture as Category 1 without subcategory. • 3.3 (Serious eye damage/irritation): Clarification of the need for further data when considerations about alkaline/acid reserve suggest no risk added. Interpretation of non-testing methods results enhanced. Mentioned the use of LVET data. Inclusion of new figure illustrating the tiered evaluation approach. Inclusion of reference to new figure on hierarchy of information added in section 3.2. Replacement of the decision logic chart with separate decision logics for substances and mixtures, based on the chart from GHS. • 3.4 (Respiratory or skin sensitisation): Deletion of the relationship between skin and respiratory sensitisation potential. Identification of non-human data brought in line with REACH guidance. Introduction of available non-testing systems. Clarification of the test sample to be used in human diagnostic patch testing. • 3.5 (Germ cell mutagenicity): Reference to OECD TG 488 added. New section on classification of substances containing CMR constituents, additives or impurities included. (iv) Minor changes to the following sections in Part 3: • 3.6 (Carcinogenicity): Removal of reference to supporting evidence for classification under DSD. Update of label elements. New section included on classification of substances containing CMR constituents, additives or impurities. • 3.7 (Reproductive toxicity): New section included on classification of substances containing CMR constituents, additives or impurities. • 3.8 (STOT-SE): Editorial corrections to the examples. (vi) Minor changes to Part 4 to update the terminology when referring to short-term (acute) and long-term (chronic) studies.	
Version 6.0	Part 4 has been updated to provide clarifications, correct errors, delete information considered irrelevant, and add text on new OECD TGs. The update includes the following: • Section 4.1.3.3.1: The paragraph referring to the absence of chronic data has been amended to reflect general data availability and established practice; • Section 4.1.3.3.1; Additional text was added to clarify cases where data on a degradation product may need to be considered; • Section 4.1.3.3.1: A reference to a topic the guidance	Jan 2024

	annexes do not directly comment on was deleted; • At the end of section 4.1.3.3.2: Some text was added to further define instances where Category Chronic 4 may apply; • Section 4.1.3.3.3: Text was added on the fact that M-factors are considered part of the classification; • Section 4.1.4.5: Clarification on deriving classification when using toxicity values calculated from the additivity formula was added; • Section 4.1.4.7.5: Correction to Example D and explanation added; • Section 4.1.7 was deleted as any reference to reclassification from DSD is out of date; • Annex I.2: General statements on most commonly occurring issues during aquatic toxicity testing have been added; • Annex I.2.1.1: General considerations on OECD TG 236 were added; • Annex I.2.1.2: General considerations regarding various relevant OECD TGs added; • Annex I.2.2.1: A more recent change in the respective OECD TG (202) is reflected; • Annex I.2.2.1: Clarifications on invertebrate data beyond *Daphnia Magna* were added; • Annex I.2.2.2: A more recent change in the respective OECD TG protocol (202 part II) is reflected; • Annex I.2.2.2: Clarifications on invertebrate data beyond *Daphnia Magna* were added; • Annex I.2.3.2: Clarifications on aquatic macrophyte data were added; • Annex I.2.3.2: CLP preference on algae as the preferred test species deleted; • Annex I.3.2: Clarification on use of surrogate approach for chronic classification added; • Annex I.4: Clarification on use of data for difficult to test substances added; • Annex II.2: Two first sentences of the paragraph have been deleted as they were vague and did not offer any added value; • Annex II.2.3.6: An additional statement that soil degradation data can be used under certain conditions in the absence of aquatic degradation data has been added; • Annex II.2.3.7: Clarification on the use of anaerobic degradation data has been added; • Annex II.3.1: Clarification on the general guidance for complex substances has been added (also change in I.4.5); • Annex II.3.5: Clarification text on presence of both positive and negative ready biodegradability tests has been added;	

	• Annex III.2.1: Footnote 29 has been deleted as it is out of date; • Annex III.2.1.2: Clarification text on radio-labelled substances has been added; • Annex III.2.2.2, Table III.1 has been deleted; • Annex III.2.2.2, Guidance on (Q)SAR BCFs and their use has been added; • Annex III.5: Text added to emphasise that a conclusion on bioaccumulation is required under CLP and that a conclusion as "inconclusive" is still possible, albeit not preferred; • Annex III.5: More explicit wording added on the conclusion on bioaccumulation, based on the available data; • Annex IV.3: Rapid removal footnote amended to reflect CARACAL decision on rapid removal; • Annex IV.5.4: Correction of error regarding loading rates used to determine chronic M-factors; • Annex IV.5.6: Correction of how alloys are considered under CLP to remove reference to 'special preparations' and accurately reflect CLP Art. 2(27); • Table IV.1: Correction of criteria error on determining M-factors for readily soluble metal compounds; Besides these changes, typos, spelling errors and other formatting issues, such as homogenisation of referencing (both within the document and to external sources), have been addressed. Note, such changes are not substantial and do not alter the content.	

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 replaced 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 primarily assist manufacturers, importers and downstream users in applying the 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 (currently DG Growth). The guidance was handed over to ECHA in summer 2009.

After that the guidance has been revised twice – version 2.0 in April 2012 on the long-term aquatic hazard and version 3.0 in November 2012 in relation to the guidance chapters on setting of specific concentration limits (SCLs) for health hazards.

During 2012/2013, further drafting work was done in close collaboration with European experts, to take account of a range of guidance aspects (for example further guidance on the criteria for respiratory and skin sensitisation, and other health related points, as well as guidance on the criteria for chemically unstable gases and aerosols and other physical hazards related changes) following the 2nd and/or the 4th Adaptation to Technical Progress (ATP) to the CLP (Commission Regulation (EU) No 286/2011 and No 487/2013[1]). This work resulted in publication of version 4.0 in November 2013 and the subsequent corrigendum version 4.1 June 2015 to update the text following the transitional period for the 4th ATP.

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] Commission Regulation (EU) No 286/2011 of 10 March 2011 and Commission Regulation (EU) No 487/2013 of 8 May 2013 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.

Both guidance documents were further updated in 2016 to address the changes due to the 8th ATP (e.g. new alternative methods to classify oxidising solids, changes in the classification for skin corrosion/irritation, serious eye damage/irritation and aerosols, as well as changes in precautionary statements).

Therefore, the current version of the Guidance reflects the changes made by the 8th ATP (Regulation 2016/918) in Annex I to CLP. These changes apply from 1 February 2018.

However:

- The 8th ATP may already be applied on a voluntary basis before that date.
- Substances and mixtures placed on the market before 1 February 2018 shall not be required to be relabelled and repackaged in accordance with the 8th ATP during a period of two years, i.e. before 1 February 2020.

Between 2019 and 2023, the part 4 of the guidance (hazards to the aquatic environment) and annexes I – IV were updated to provide guidance on new OECD TGs, provide clarity on a number of areas, and correct a number of errors/typos. More substantial matters were updated by consulting a PEG established for the purpose, RAC, and Member States/COM via CARACAL. Matters editorial in nature (spelling and typos) were update following a fast track procedure involving only CARACAL. This update represents the 6th update of the CLP guidance (v 6.0).

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LIST OF ABBREVIATIONS

Standard term / Abbreviation	Explanation
ADD	Directive 75/324/EEC on aerosol dispensers[2]
ADN	European Agreement concerning the International Carriage of Dangerous Goods by Inland Waterways (Accord européen relatif au transport international des marchandises dangereuses par voie de navigation intérieure)[3]
ADR	European Agreement concerning the International Carriage of Dangerous Goods by Road (Accord européen relatif au transport international des marchandises dangereuses par route)[4]
ANE	Ammonium Nitrate Emulsion
ASTM	American Society for the Testing of Materials
ATE	Acute Toxicity Estimate
ATP	Adaptation to Technical Progress (ATP) to the CLP Regulation
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
BOD	Biological Oxygen Demand
BP	Boiling point
bw	Body weight

[2] Directive (75/324/EEC) of the Council on the approximation of the laws of the Member States relating to aerosol dispensers [OJ L 147, 9.6.1975, p.40]. Directive as last amended by Commission Directive 2013/10/EU [OJ L 77, 20.03.2013, p.20].

[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.

Standard term / Abbreviation	Explanation
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
COD	Chemical Oxygen Demand
CSA	Chemical Safety Assessment
CSR	Chemical Safety Report
DIN	Deutsches Institut für Normung (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]
EC3	Effective Concentration inducting a stimulation index of 3 in the LLNA test
ECHA	European Chemicals Agency, Helsinki (https://echa.europa.eu/)
ECVAM	European Centre for the Validation of Alternative Methods (http://ihcp.jrc.ec.europa.eu/our_labs/eurl-ecvam)
ED	Effective Dose

[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].

[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].

Standard term / Abbreviation	Explanation
EN	A European Standard
ERV	Ecotoxicity Reference Value
ESAC	ECVAM Scientific Advisory Committee (https://eurl-ecvam.jrc.ec.europa.eu/about-ecvam)
EUH	The hazard statements carried through from DSD and DPD, which are not yet included in the GHS are codified as 'EUH'
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 (or H statement)	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

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

Standard term / Abbreviation	Explanation
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 Code	International Maritime Dangerous Goods Code
IMO	International maritime Organisation
IPCS	International Programme on Chemical Safety (joint programme of WHO, ILO and UNEP)
IR&CSA	Guidance on Information Requirements and Chemical Safety Assessment, ECHA (http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_en.htm)
IRE	Isolated Rabbit Eye
ISO	International Organisation for Standardization
ITDG	Directive 2008/68 on the Inland Transport of Dangerous Goods[9]
ITS	Integrated Testing Strategy
K_{ow}	The n-octanol/water partition coefficient
LEL	Lower Explosion Limit
LD_{50}/LC_{50}	Median (50%) lethal dose/concentration
LFL	Lower Flammability Limit
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

[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].

Standard term / Abbreviation	Explanation
MetHb	Methaemoglobin
M-factor	Multiplying factor
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 All Test Guidelines are available at the OECD homepage: http://www.oecd.org/document/40/0,3343,en_2649_34377_37051368_1_1_1_1,00.html
OP	Oxidising Power
P statement (or PS)	Precautionary statement
PB/PK	Physiologically-based pharmacokinetic
PPARα	Peroxisome proliferator-activated receptor-alpha
PS (or P statement)	Precautionary statement
(Q)SAR	(Quantitative) Structure Activity Relationship

Standard term / Abbreviation	Explanation
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
RTI	Respiratory tract irritation
SADT	Self-Accelerating Decomposition Temperature
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
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

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

[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.

Standard term / Abbreviation	Explanation
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
UEL	Upper Explosion Limit
UFL	Upper Flammability Limit
UGT	UDP-glucuronyltransferase
UN	United Nations
UN-MTC	The UN Manual of Tests and Criteria contains 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 (GHS). More information and the latest revision are available at: http://www.unece.org/trans/danger/publi/manual/manual_e.html.
UN RTDG Model Regulations	UN Recommendations on the Transport of Dangerous Goods - Model Regulations. It covers all modal transport regulations (ADR, RID, ADN, IMDG and ITDG). It is regularly updated and amended every two years. More information and the latest revision are available at: http://www.unece.org/trans/danger/publi/unrec/rev13/13nature_e.html
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)

[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].

Standard term / Abbreviation	Explanation
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
UVCB	Substances of unknown or variable composition, complex reaction products or biological materials
VDI	Verein Deutscher Ingenieure (The Association of German Engineers)
VP	Vapour Pressure
WAF	Water Accommodated Fraction
WoE	Weight of Evidence
WSF	Water soluble fraction

NOTEs to the reader:

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

This symbol highlights text to be noted.

1. PART 1: GENERAL PRINCIPLES FOR CLASSIFICATION AND LABELLING

1.1. INTRODUCTION

1.1.1. The objective of the guidance document

This document is a comprehensive technical and scientific guidance on the application of Regulation (EC) No 1272/2008 on the classification, labelling and packaging of substances and mixtures[13], hereafter referred to as CLP.

CLP amended 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 repealed DSD and DPD from 1 June 2015 (CLP Article 61). CLP was implemented based on the United Nations' Globally Harmonised System of Classification and Labelling of Chemicals (UN GHS) without lowering the protection of human health and the environment, compared to the classification, labelling and packaging system in DSD and DPD. The implementation of GHS into CLP followed various declarations made by the Community to confirm its intention to contribute to GHS development and to implement GHS into EU law.

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

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

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

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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].

1.1.2. Background

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

The EU has had a comprehensive system for the classification and labelling of dangerous substances and mixtures for over 40 years, in the past mainly DSD and DPD. In addition, the Safety Data Sheet (SDS) Directive 91/155/EEC[17] required suppliers to provide more detailed information for professional users. These directives contributed to a single market in chemicals in the EU, based on a high level of protection of human safety and health and the environment.

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

The GHS criteria for classifying hazardous substances and mixtures were developed taking into account existing systems for hazard classification, such as the EU supply and use system, the Canadian and US Pesticide systems, GESAMP[18] hazard evaluation procedure, IMO[19] Scheme for Marine Pollutants, the UN Recommendations on the Transport of Dangerous Goods (UN/RTGD), and the US Land Transport. These systems include supply and subsequent use of chemicals, the sea transport of chemical substances as well as transport of chemical substances by road and rail. The harmonised criteria are therefore intended to identify hazardous chemicals in a common way for use throughout all these systems.

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

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

1.1.3. Hazard classification

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

[17] 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.

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

[19] International Maritime Organisation.

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

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

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

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

1.1.4. Who is responsible for the hazard classification

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

1.1.5. Which substances and mixtures should be classified

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

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

- radioactive substances and mixtures (Directive 96/29/Euroatom[20]);
- 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[21]; and
- certain substances or mixtures in the finished state, intended for the final user:
    - medicinal products, as defined in Directive 2001/83/EC[22],
    - veterinary medicinal products, as defined in Directive 2001/82/EC[23],
    - cosmetic products, as defined in Directive 76/768/EEC[24],
    - medical devices as defined in Directive 90/385/EEC[25] (active implantable medical devices) and 93/42/EEC[26] (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[27]), and
    - food or feeding stuffs as defined in Regulation 178/2002[28], including when they are used as food additives within the scope of Directive 89/107/EEC[29], as a flavouring in foodstuffs within the scope of Directive 88/388/EEC and Decision

[20] 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].

[21] 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].

[22] 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].

[23] 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].

[24] 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].

[25] 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].

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

[27] 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].

[28] 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].

[29] 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].

1999/217/EC[30], as an additive in feeding stuffs within the scope of Regulation (EC) 1831/2003[31], and in animal nutrition within the scope of Directive 82/471/EEC[32].

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

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

1.1.6. What information is needed for classification

1.1.6.1. Information for the classification of substances

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

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

Although data may be provided through the application of REACH, it should be recognised that the data set required by REACH (particularly at lower tonnages) will not necessarily enable the comparison with the criteria for all hazard classes. Information may also be available from other EU legislation for which there are specific requirements for test data to be generated, such as legislation on plant protection products (Regulation (EC) No 1107/2009[33] and Directive

[30] 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].

[31] 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].

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

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

91/414/EEC[34]) and on biocidal products (Regulation (EU) No 528/2012[35] and Directive 98/8/EC[36]), or from various non-EU programmes. Finally, the supplier may decide to conduct new testing in order to fill data gaps, provided that he has exhausted all other means of generating information. Testing on animals must be avoided wherever possible and alternative methods (including *in vitro* testing, the use of (Q)SARs, read-across and/or grouping approaches) must always be considered first, provided they are scientifically validated, sufficiently adequate and reliable.

In the case of a substance containing impurities, additives or other constituents, the classification of the substance should, similar to mixtures, preferably be based on available information (including test data) on the substance except when classifying for CMR properties or when evaluating the bioaccumulation and degradation properties within the 'hazardous to the aquatic environment' hazard class (referred to in sections 4.1.3.3.2 and 4.1.2.9 of Annex I to CLP). In such cases it is strongly recommended that the classification of the substance, similar to mixtures (Articles 6(3), 6(4) and 10 of CLP), is based on information of known CMR constituent(s) as there is no toxicological difference between a mixture and a substance containing other constituent substances[37]. In exceptional cases, data on the substance itself might show relevant effects for classification for CMR and/or bioaccumulation or degradation properties which have not been identified from the information on the constituent substances. These data should then be used, if available.

If, for the purpose of CLP, it is required or decided to generate new data, certain test methods and quality conditions must be met. Studies must be conducted in accordance with the EU test methods (Regulation (EC) 440/2008)[38] or other international test methods validated according to international procedures such as those of the OECD. For physical hazards new tests must be carried out in compliance with a relevant recognised quality system or by laboratories complying with a relevant recognised standard, and for health and environmental hazards in compliance with the principles of Good Laboratory Practice (GLP[39]). Animal tests must comply with the Directive 86/609/EEC[40]. Tests on non-human primates are prohibited for the purposes of CLP. Tests on humans must not be performed for the purpose of CLP. However, existing data obtained from other sources, such as accident records and epidemiological and clinical studies, can be used.

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[34] 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].

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

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

[38] 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].

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

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

1.1.6.2. Information relevant for the classification of mixtures

For mixtures, classification for physical hazards should normally be based on the results of tests carried out on the mixtures themselves (unless, as for substances, a mixture placed on the market for R&D purposes has been manufactured or imported in quantities that are too small to perform physical hazard testing). New tests for physical hazards must be carried out in compliance with a relevant recognised quality system or by laboratories complying with a relevant recognised standard.

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

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

Thus, if no *in vivo* test data are available on a mixture, such data should normally not be generated; rather, all available information on the ingredients[41] of the mixture should be used to derive a classification.

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

1.1.7. Data evaluation and reaching a decision on classification

1.1.7.1. Classification of substances

After the available information has been assembled, a systematic evaluation of this information is necessary in order to derive a classification. The information must be compared with the criteria for classification for each hazard class or differentiation within the hazard class. Differentiation is a distinction depending on the route of exposure or the nature of the effects. A decision should be made as to whether the substance meets the criteria for classification. When this is the case; the classifier should assign one or more hazard categories for each relevant hazard class or differentiation. The substance is then assigned the appropriate hazard communication elements.

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

[41] Note that the term "ingredient" is used in this guidance with the same meaning of "component" to indicate a substance in amixture.

needed to decide whether the results of a particular test or the available information in a Weight of evidence assessment meet the criteria laid down in Annex I.

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

Substances may contain impurities, additives, or other constituents while still meeting the substance definition in CLP. This applies to both mono-constituent, multi-constituent (e.g. reaction masses) and UVCB substances. The classification of such impurities, additives or individual constituents may influence the classification of the substance, in addition to the other hazardous properties. If data on the substance with its components are not available (or for CMRs, see section 1.1.6.1), in principle, the same classification and labelling rules as for mixtures should apply also for such substances[42].

1.1.8. Updating of hazard classifications

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

Please, see also Section 1.1.10 addressing changes in harmonised classifications.

1.1.9. The interface between hazard classification and hazard communication

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

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

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

CLP places emphasis on self-classification by industry of the substances or mixtures they supply. In some cases, substances are subject to harmonised classification at EU level, while

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

mixtures must always be self-classified, except for pesticidal and biocidal products where the Member State competent authorities (MSCAs) decide on the classification as part of the national authorisation scheme (CLP Article 36(2)).

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

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

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

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

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

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

Harmonised classification and labelling of a substance provides for a high level of protection of human health and the environment, and provides legal clarity for different suppliers of the same substance of high concern (i.e. manufacturers of substances, importers of substances or

mixtures, producers of specific articles, downstream users (including manufacturers of mixtures) and distributors).

Part 3 of Annex VI to CLP contains the list of harmonised classifications and labellings (except precautionary statements). All harmonised classifications previously adopted under DSD and listed in Annex I to DSD were translated to CLP classifications and carried over to the list of harmonised classifications in Annex VI to CLP also including the Notes assigned to the entries as referred to in the DSD. This was done to maintain the same level of protection under CLP as under DSD. The harmonisation of classification of substances is a continuous process building on all efforts already done within the EU so far to evaluate hazards of substances that caused concern.

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

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

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

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

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

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

1.1.12. Relation of classification to other EU legislation

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

1.1.12.1. REACH

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

1.1.12.2. Plant Protection Products and Biocides

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

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

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

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

1.1.12.3. Transport legislation

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

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

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

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

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

> ***Article 5(1)*** *Manufacturers, importers and downstream users of a substance shall identify the relevant available information for the purposes of determining whether the substance entails a physical, health or environmental hazard as set out in Annex I*
>
> *[….]*
>
> *The information shall relate to the forms or physical states in which the substance is placed on the market and in which it can reasonably be expected to be used.*
>
> ***Article 6(1)*** *The information shall relate to the forms or physical states in which the mixture is placed on the market and, when relevant, in which it can reasonably be expected to be used.*
>
> ***Article 8(6)*** *Tests that are carried out for the purposes of this Regulation shall be carried out on the substance or on the mixture in the form(s) or physical state(s) in which the substance or mixture is placed on the market and in which it can reasonably be expected to be used.*
>
> ***Article 9(5)*** *When evaluating the available information for the purposes of classification, the manufacturers, importers and downstream users shall consider the forms and physical states in which the substance or mixture is placedon the market and in which it can be reasonably be expected to be used.*

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

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

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

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

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

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

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

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

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

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

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

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

1.2.3.1. Physical hazards

Different forms or physical states of a substance or mixture may result in different physical properties and hazards with possible consequences for the hazard classification of a substance or mixture. Putative forms comprise properties such as crystal structure, particle size, homogeneity (e.g. emulsions) and texture (e.g. viscosity or tablet form). Examples of physical state factors are: surface treatment (e.g. coating), state of aggregation, moisture content, residual solvent, activation or stabilisation.

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

General considerations

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

Specific requirements of certain test methods

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

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

Section 2.0.4 provide further details about the relevance of the physical state for testing purposes.

1.2.3.2. Human health hazards

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

to test for different routes of exposure (oral, dermal, inhalation). Again, due to test complexity, mostly the data for only one exposure route are available.

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

1.2.3.3. Environmental hazards

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

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

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

1.3. SPECIFIC CASES REQUIRING FURTHER EVALUATION – LACK OF BIOAVAILABILITY

1.3.1. Definition

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

1.3.2. Bioavailability

> ***Article 12***
>
> ***Specific cases requiring further evaluation***
>
> *Where, as a result of the evaluation carried out pursuant to Article 9, the following properties or effects are identified, manufacturers, importers and downstream users shall take them into account for the purposes of classification:*
>
> *[…]*
>
> *(b) conclusive scientific experimental data show that the substance or mixture is not biologically available and those data have been ascertained to be adequate and reliable;*
>
> *[…]*

In general, bioavailability is not explicitly evaluated in hazard classification – the observation of systemic toxicity implicitly demonstrates a degree of bioavailability. On the other hand, when no toxicity is demonstrated in a test, this may be a result of either lack of intrinsic toxicity of the substance or lack of bioavailability in the test system employed. Nevertheless, as indicated in Article 12 (b) of CLP there may be cases where a specific evaluation of bioavailability is warranted. Bioavalibility may also need to be considered for grouping and read-across.

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

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

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

1.3.2.1. Human health hazards

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

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

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

Bioavailability of a substance or a substance in mixtures is normally assumed if there are *in vitro* studies available which show the solubility of a substance or mixture in body fluids or artificial simulated body fluids. Furthermore, conclusions on bioavailability of a substance or a mixture may be based on considerations of the physical properties of a substance or derived from Structural Activity Relationships (SAR). Note also that bioavailability is not limited to solubility, local bioavailability and the uptake of (nano)particles also has to be taken into account. Further, a substance or mixture can be transformed, e.g. by gastric fluid so that the substance absorbed may differ from the substance delivered. In certain exceptional circumstances it may be possible that a substance on its own or in a mixture can be considered to be non-bioavailable, based on either appropriate *in vitro* data, e.g. from skin absorption models, SAR considerations or consideration of the physical properties of the substance, if the respective requirements described above have been taken into account in an adequate analysis.

1.3.2.2. Environmental hazards

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

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

Article 9(1) *Manufacturers, importers and downstream users of a substance or a mixture shall evaluate the information identified in accordance with Chapter 1 of this Title by applying to it the criteria for classification for each hazard class or differentiation in Parts 2 to 5 of Annex I, so as to ascertain the hazards associated with the substance or mixture*

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

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

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

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

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

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

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

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

> **Annex I: *1.1.1.3***. *A weight of evidence determination means that all available information bearing on the determination of hazard is considered together, such as the results of suitable in vitro tests, relevant animal data, information from the application of the category approach (grouping, read-across), (Q)SAR results, human experience such as occupational data and data from accident databases, epidemiological and clinical studies and well documented case reports and observations. The quality and consistency of the data shall be given appropriate weight. Information on substances or mixtures related to the substance or mixture being classified shall be considered as appropriate, as well as site of action and mechanism or mode of action study results. Both positive and negative results shall be assembled together in a single weight of evidence determination.*

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

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

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

1.4.1. (Q)SAR

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

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

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

1.4.2. Grouping

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

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

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

1.4.3. Read-across

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

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

1.5. SPECIFIC CONCENTRATION LIMITS AND M-FACTORS

1.5.1. Specific concentration limits

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

Specific concentration limits shall be set by the manufacturer, importer or downstream user where adequate and reliable scientific information shows that the hazard of a substance is evident when the substance is present at a level below the concentrations set for any hazard

class in Part 2 of Annex I or below the generic concentration limits set for any hazard class in Parts 3, 4 and 5 of Annex I.

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

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

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

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

SCLs should take precedence over the generic concentration limits (GCLs) given in the relevant health hazard sections of Annex I to CLP. In case specific concentration limits have been set in Annex VI to CLP, these must be applied. Moreover, manufacturers, importers or downstream users may not set their own SCLs for hazards subject to harmonised classifications in Annex VI to CLP.

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

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

Hazard class	Category	Lower 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	all	yes*	yes*	see Section 3.4 *currently not available;

Hazard class	Category	Lower SCL than GCL	Higher SCLs than GCL (in exceptional circumstances)	Guidance
Skin sensitisation	all	yes	yes*	available in Section 3.4 *currently not available
Germ cell mutagenicity	all	yes*	yes*	see Section 3.5 *currently not available
Carcinogenicity	all	yes	yes	available in Section 3.6
Reproductive toxicity	all	yes	yes	available in Section 3.7 and in Annex IV
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 the application of the summation method for classification of mixtures containing substances that are classified as very toxic. The concept of M-factors has been established to give an increased weight to very toxic substances when classifying mixtures. M-factors are only applicable to the concentration of a substance classified as hazardous to the aquatic environment (categories Acute 1 and Chronic 1) and are used to derive by the summation method the classification of a mixture in which the substance is present. They are,

however, substance-specific and it is important that they are being established already when classifying substances.

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

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

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

1.5.3. Harmonised ATE values

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

1.6. MIXTURES

1.6.1. How to classify a mixture

The classification of mixtures under CLP is for the same hazards as for substances. As a general rule and as is the case with substances, available relevant data on the mixture as a whole should primarily be used to determine classification where applicable, also considering the validity and suitability of the used test method, with regard to testing mixtures in general and the specific mixture of concern. Not all the test methods relevant for substances may be suitable for (all) mixtures and for this reason care has to be taken. Note that for skin sensitisation, care has to be taken so that the doses used do not render the results unreliable. If this cannot be done, further approaches to mixture classification may be applied. When evaluating CMR hazards and biodegradation and bioaccumulation properties, classification of the mixture should according to Article 6(3) and (4) always be based on the ingredient substances for these particular hazard classes. However, if data on a mixture show CMR properties even in absence of data on possible CMR ingredientes, the mixture has to be classified appropriately following Article 6(3).

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

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

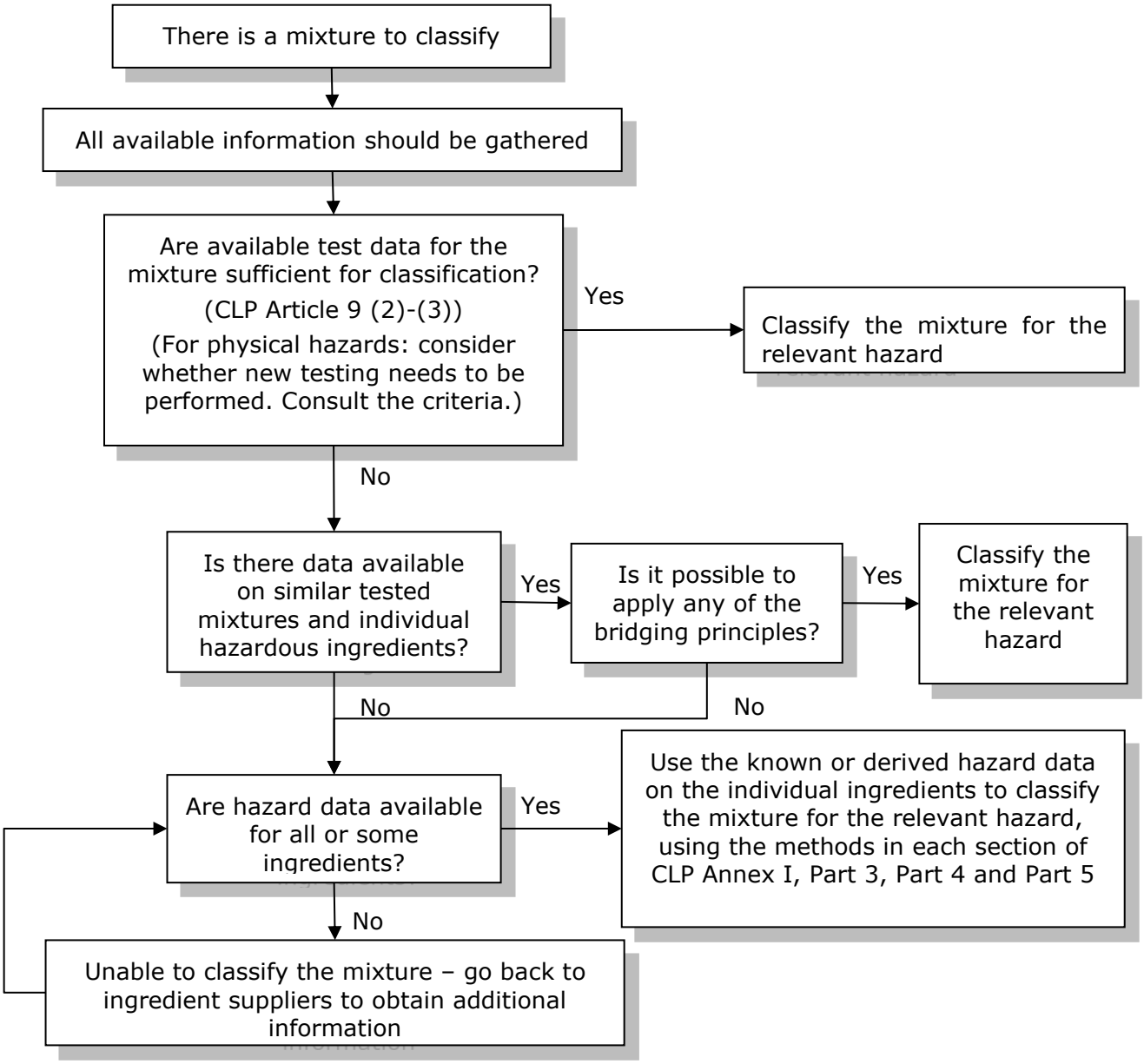
Useful sources for such information are the SDS from the supplier of the substance or the mixture, and the C&L Inventory provided by ECHA, which also includes the harmonised classifications of substances listed in Annex VI to CLP. Also data from registration dossiers are a valuable source of information.

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

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

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

Figure 1.1 How to classify a mixture



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

1.6.2. Classification for physical hazards

The majority of the physical hazards of mixtures should be determined through testing based on the methods or standards referred to in CLP Annex I, Part 2. In a few cases, the classification of mixtures can also be derived through a calculation, if sufficient appropriate data are available

(see CLP Annex I 2.2.4.1 and ISO 10156 for flammable gases, CLP Annex I 2.4.4 and ISO 10156 for oxidizing gases and CLP Annex I, 2.6.4.2 and 2.6.4.3 for flammable liquids).

Test methods for physical hazards are referred to in each physical hazard class chapter of CLP. Most of these test methods can be found in the UN Manual of Tests and Criteria, see the website http://www.unece.org/trans/danger/publi/manual/manual_e.html. A few of these test methods are contained in standards which are also referred to in CLP (see particularly flammable gases, oxidizing gases and flammable liquids). When test result, based on other methods or standards (which are not referred to in CLP) are available, then these data may still be used, provided they are adequate for the purpose of hazard determination. Expert judgement is necessary to conclude whether there is sufficient documentation to assess the suitability of the test used, and whether the test was carried out using an acceptable level of quality assurance and thus on the adequacy of such data for the purposes of classification according to CLP.

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

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

1.6.3. Health and environmental hazards

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

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

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

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

a. Classification derived using data on the mixture itself (see Section 1.6.3.1 of this document), by applying the substance criteria of Annex I to CLP;

b. Classification based on the application of bridging principles (see Section 1.6.3.2 of this document), which make use of test data on similar tested mixtures and ingredient substances; and

c. Classification based on calculation or on concentration thresholds, including SCLs and M-factors.

1.6.3.1. Classification derived using data on the mixture itself

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

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

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

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

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

1.6.3.2. Bridging principles

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

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

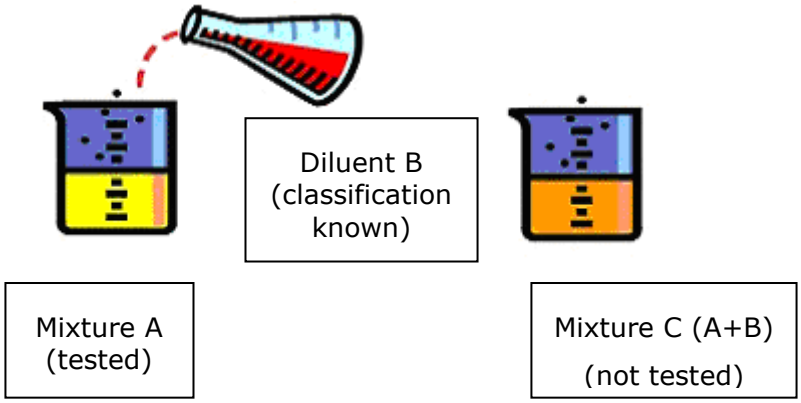
It is necessary to consult Annex I of CLP, Part 3 for health hazards and Part 4 for environmental hazards, before undertaking any of these assessments.

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

1.6.3.2.1. Dilution

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

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



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

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

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

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

In case a mixture is diluted with another mixture, see Section 1.6.4.1 of this document.

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

1.6.3.2.2. Batching

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

1.6.3.2.3. Concentration of highly hazardous mixtures

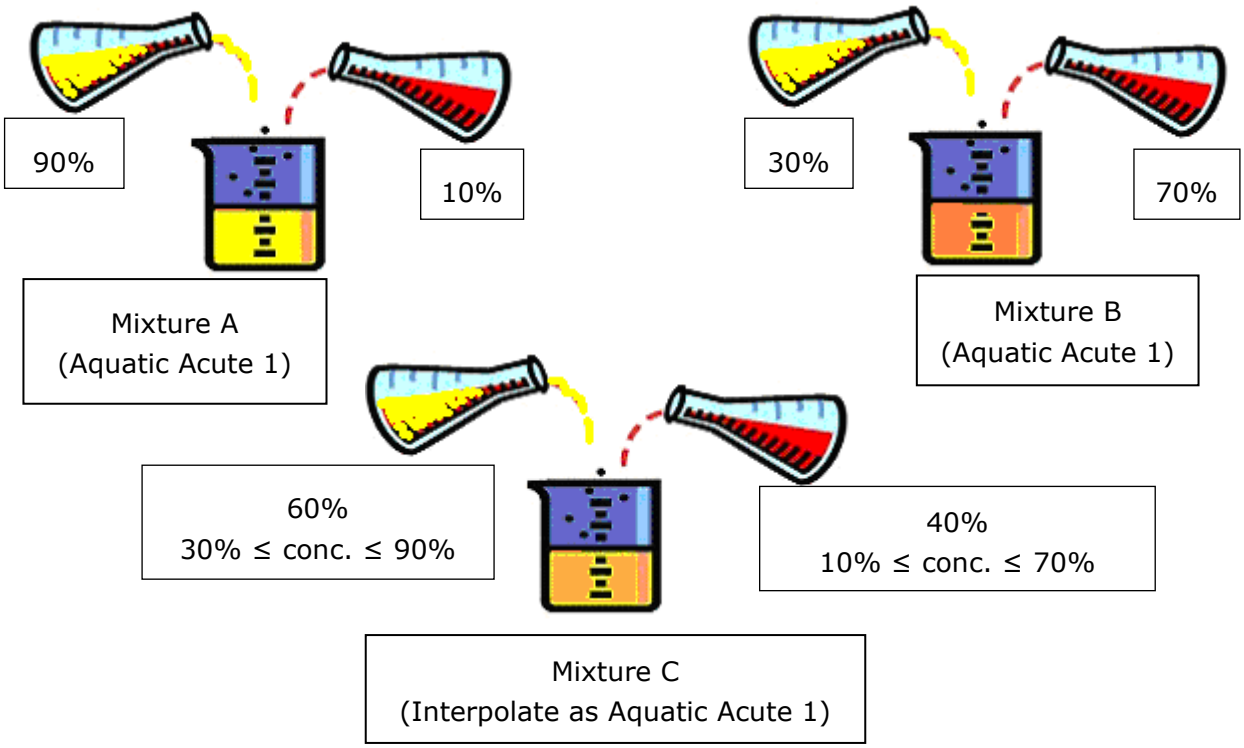
Where a tested mixture is already classified in the highest hazard category or sub-category, an untested mixture which contains a higher concentration of those ingredient substances that are in that category or sub-category should also be classified in the highest hazard category or sub-category (CLP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

1.6.3.2.4. Interpolation within one hazard category

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

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

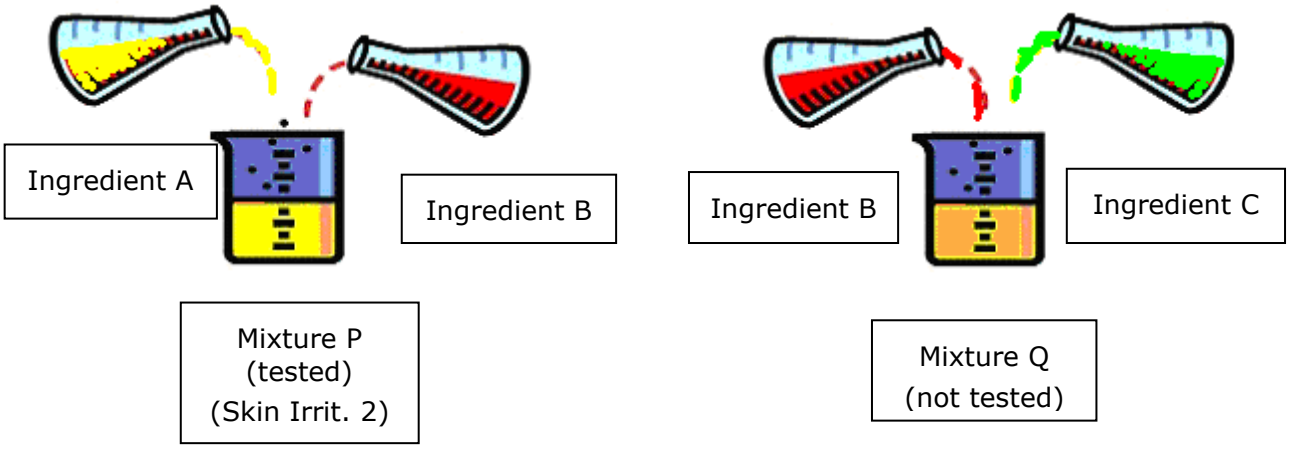
Figure 1.3 Application of the bridging principle: interpolation for determining the aquatic acute hazard classification of a mixture



1.6.3.2.5. Substantially similar mixtures

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

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



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

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

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

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

(b) […]

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

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

Table 1.2

Bridging Principle for changes in the composition of a mixture

Initial concentration range of the constituent	*Permitted variation in initial concentration of the constituent*
≤ 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).*

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

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

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

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

Substance A: $2 \times \pm 0.3 = \pm 0.6$ → 1.4 – 2.6

Substance B: $12 \times \pm 0.1 = \pm 1.2$ → 10.8 – 13.2

1.6.3.2.7. Aerosols (some health hazards only)

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

1.6.3.3. Classification based on calculation or concentration thresholds

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

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

1.6.3.3.1. Classification based on calculation

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

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

Annex I: *3.1.3.6.1.*

[…]

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

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

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 aquatic toxicity:

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

where:
C_i = concentration of component i (weight percentage)
$L(E)C_{50i}$ = (mg/l) LC_{50} or EC_{50} for component i
η = number of components
$L(E)C_{50m}$ = $L(E)C_{50}$ of the part of the mixture with test data

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

(b) Based on chronic aquatic toxicity:

$$\frac{\sum C_i + \sum C_j}{\text{Eq NOEC}_m} = \sum_n \frac{C_i}{\text{NOEC}_i} + \sum_n \frac{C_j}{0{,}1 \times \text{NOEC}_j}$$

Where:
C_i = concentration of component i (weight percentage) covering the rapidly degradable components
C_j = concentration of component i (weight percentage) covering the non-rapidly degradable components
$NOEC_i$ = NOEC (or other recognised measures for chronic toxicity) for component i covering the rapidly degradable components, in mg/l;
$NOEC_j$ = NOEC (or other recognised measures for chronic toxicity) for component i covering the non-rapidly degradable components, in mg/l;
n = number of components, and I and j are running from 1 ton;
$EqNOEC_m$ = Equivalent NOEC of the part of the mixture with test data;
[…]

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

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

1.6.3.3.2. Classification based on concentration thresholds

Generic concentration thresholds

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

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

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

corrosive/irritant substances are present in the mixture below the relevant generic concentration limits. If additivity applies, classification as provided by the summation in CLP Annex I, Table 3.2.3 may be applicable, i.e.:

(10 × 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 individual substances:

- SCLs are described in section 1.5.1 of this document and where they have been established they are included in Table 3.1 of Annex VI to CLP[43] and/or in the C&L Inventory (CLP Article 42). For 'hazardous to the aquatic environment' the Multiplying factors (M-factors) concept[44] is used instead of SCLs, see section 1.5.2 of this guidance. SCLs and M-factors included in Tables 3.1 must be used where applicable and, for classifications not included in Annex VI, SCLs and M-factors notified to the C&L Inventory can be considered and used where applicable.
- Cut-off values that may be different from the generic values and that are to be used in specific cases are given in 1.1.2.2.2(a) and (b) of Annex I to CLP. For example concerning aquatic hazard, for a substance with an established M-factor, the cut-off value is always the generic cut-off value divided by the M-factor; hence, (0.1/M) % (see 1.1.2.2.2(b) and 4.1.3.1 of Annex I to CLP).

1.6.3.3.3. Additivity Vs. non additivity of hazards

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

Additivity is normally not applied for the following hazard classes:

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

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

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

[44] 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.

If the mode of action (MoA) of two substances is the same, additivity can reasonably be assumed. Examples of cases where additivity applies is reprotoxicity of anticoagulant rodenticides (a group of substances affecting the same enzyme in the same way), reprotoxicity of substances releasing boron ions, skin sensitisation by nickel substances and carcinogenicity and mutagenicity of formaldehyde releasers. For the latter group of substances there are notes[45] in Annex VI stating that the levels of releasable formaldehyde from different components of a mixture must be added. This applies regardless whether the substances have a harmonised classification or not, whether the purpose of the substance is to act as a formaldehyde releaser or not and it includes formaldehyde itself.

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

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

Additivity is used for the following hazard classes or differentiations:

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

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

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

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

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

ConcB = the concentration of substance B in the mixture;

[45] The 10th ATP added the following notes in Annex I to CLP:

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

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

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

An example is provided for the hazard class serious eye damage /eye irritation: in case there are only substances classified as eye irritation Category 2 present in a mixture, then their sum must be equal to or exceed the generic concentration limit of 10 % in order for the mixture to be classified in Category 2 as well. Note that only relevant substances (i.e. for eye irritants, above the generic cut-off value of 1%) should be summed up and contribute to mixture classification. Further guidance on the application of SCLs when using the summation method to derive conclusions on skin corrosion / irritation or serious eye damage/eye irritation hazards can be found in Sections 3.2 and 3.3 of 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 component substances, including their individual hazard classification and concentration, is generally required. In the case where one or more mixtures are added to another mixture, the same requirement applies: it is generally necessary to know all component substances, their hazard classifications and their concentrations to be able to derive a correct hazard classification of the final mixture. It is generally not possible to derive the correct hazard classification for the final mixture by using only the hazard classification(s) of the mixtures that were combined to make it. For example, a mixture containing 1% of a Carc. Cat. 1B substance would be classified as Carc. Cat. 1B. Taking 1% of this mixture into another mixture would lead to a concentration of the ingredient causing the carcinogenic classification of 0.01%, i.e. below the GCL. The same situation may occur also for substances classified due to an impurity.

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

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

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

1.6.4.1. Example: Classification of Mixture A

Note that the example only addresses health hazards. For compositional details see Table 1.2 and Table 1.3 below.

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

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

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

Acute toxicity

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

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

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

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

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

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

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

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):

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

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

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

Skin corrosion/irritation

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

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

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

Serious eye damage/eye irritation

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

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

Skin sensitisation

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

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

Table 1.2 Ingredients in Mixture A

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

Table 1.3 Ingredient 'Fragrance mixture'

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

1.6.4.2. Example: Classification of Mixture B

Note that the example only addresses health hazards.

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

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

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

Acute toxicity

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

Following option (i) it is first necessary to calculate the ATE_{mix} of the 'base powder' taking into account the non-ionic surfactant (other components can be excluded as LD_{50} values are > 2000 mg/kg):

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

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

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

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

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

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

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

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

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

Skin corrosion/irritation

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

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

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

Serious eye damage/eye irritation

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

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

Respiratory sensitisation

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

STOT

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

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

Table 1.4 Ingredients in Mixture B

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

Ingredient	% w/w	Oral LD_{50} (rat)	Classification
Polycarboxylate	3.00	> 5000 mg/kg	Not classified
Total:	**100.00**		

Table 1.5 Ingredients 'base powder'

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

1.7. ANNEX VII TO CLP

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

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

The tables contained in Annex VII to CLP show how classifications in accordance with the DSD were converted into the corresponding classification under CLP and included in Table 3.1 of Annex VI to CLP[46]. The tables also aimed to support translation of existing self-classifications in accordance with DSD into classifications in accordance with CLP.

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

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

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

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

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

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

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

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

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

Classifications under DSD or DPD	Potential translation outcomes	Comments
	2) Self-reactive	See Annex VII to this Guidance for additional information on transport classifications
F, R15	Substance or mixture which, in contact with water, emit(s) flammable gas(es)	See Annex VII to this Guidance for additional information on transport classifications

2. PART 2: PHYSICAL HAZARDS

2.0. INTRODUCTION

2.0.1 General remarks about the prerequisites for classification and testing

The purpose of this chapter is to give some general guidance with respect to the classification of physical hazards, the generation of test data 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 of CLP);
2. evaluation of hazard information to ascertain the hazards associated with the substance or mixture (Article 9 of CLP); and
3. a decision on whether the substance or mixture will be classified as hazardous and the degree of hazard, where appropriate, by comparison of the data with agreed hazard classification criteria (Article 13 of CLP).

Generally, for bothsubstances and mixtures, the tests required in Annex I of CLP must be performed unless there is adequate and reliable information already available. 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 a substance or mixture, enquiries should be made to ascertain the availability of data, e.g. flash points, on the substance or mixture.

2.0.2 Safety

In most cases, the classification is based on data derived from testing. 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 Recommendations on the transport of dangerous goods 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.

2.0.3 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, impurities 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.

In some cases, additional parameters like (e.g.) physical condition, particle size and shape, specific surface area, density, crystal structure, may influence the test result. Therefore, these properties should be mentioned in the test report.

The tests must 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).

2.0.4 Physical state

The physical state determines which hazard classes should be considered for testing. As the CLP states[47], hazard classification is based on intrinsic properties of the substance or mixture which are determined not only by its physical state but also its form.

As mentioned in Chapter 1.2 of this guidance, the same solid substance or mixture may have different forms such as flakes, prills, or powder. Furthermore, e.g. a powder may contain particles of different size, and particles of the same size may have different shapes, crystallinity or allotropy etc. These differences may result in different intrinsic properties, and consequently, different physical hazards of the powder. Particle size is crucial for several 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. Therefore not only the physical appearance, but also other parameters should be considered when identifying the form, since they may trigger different classifications of the same substance or mixture.

An example of different classification due to different intrinsic properties of forms is red phosphorus (flammable solid) and white phosphorus (pyrophoric solid) (different allotropes). It is therefore important to evaluate case by case whether available information on the physical properties of the substance and mixture placed on the market, is applicable to the examined form, and whether additional testing should be performed.

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 must 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 must be communicated.

If further testing is required, the choice of the test method should be done after thorough evaluation of its suitability for the substance or mixture, as the properties of the form (e.g. for powders especially size and shape of the particle) may have a significant effect on the test results.

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 a substance or mixture must be regarded as a liquid if either the result of the

[47] CLP Article 5(1), 6(1) and 8(6).

ASTM D 4359-90 test as amended (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'.

2.0.5 Quality

The determination of data must be based on the methods named in Annex I, Part 2 of CLP. For most hazard classes in Annex I, Part 2 of CLP there is reference made to the UN-MTC which gives very detailed descriptions of the test methods. For the classification of flammable gases, oxidising gases and for the determination of the flash point there are references to international standards in Annex I, Part 2 of CLP. Whenever possible, the laboratory should validate the performance of the methods used e.g. by participating in inter-laboratory testing or by using reference materials. 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 hazardous substances and mixtures 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.
>
> […]

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 amended as a relevant recognised standard;
3. other internationally recognised standards of comparable scope.

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

2.1. EXPLOSIVES

2.1.1. Introduction

The requirements in Chapter 2.1 'Explosives' of Annex I of CLP are identical to those in Chapter 2.1 of GHS.

The classification of explosives according to the GHS is almost entirely adopted based on the UN Recommendations on the Transport of Dangerous Goods – Model Regulations (UN RTDG Model Regulations), which are appropriate for transport and also storage of packaged explosives.

The classification of substances, mixtures and articles in the class of explosives and further allocation to a division is a very complex procedure. References to Part I of the UN-MTC and related expertise are necessary.

2.1.2. 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) substances, mixtures and articles not mentioned in points (a) and (b) which are manufactured with a view to producing a practical, explosive or pyrotechnic effect.

Additional remark related to the applicability of 2.1.1.1 (a) (see also UN RTDG Model Regulations, 2.1.1.1 (a)):

- 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;
- explosive behaviour related to the thermal decomposition of organic peroxides and of self-reactive substances and mixtures is covered by those specific hazard classes and therefore not included in the hazard class 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.

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 to their non-wetted or non-diluted counterparts i.e. different hazard classes may apply, depending on the physical properties of the wetted/diluted substance or mixture.

2.1.3. Relation to other physical hazards

For safety reasons, substances, mixtures or articles which have already been classified as Explosives (Class 1 according to the UN RTDG Model Regulations) should not be considered for classification in any other physical hazard classes. Since the explosion hazard is more severe than other physical hazards there is no need to further perform classification tests for other potential physical hazards.

When considering substances and mixtures for classification within the hazard class explosives, the following checks should be performed with respect to other hazard classes:

Substances, mixtures and articles that have been manufactured with a view to producing a practical explosive or pyrotechnic effect, are classified as explosives by definition according to 2.1.1.1(c) of Annex I of the CLP. It should be checked whether such a substance or mixture is an unstable explosive.

Thermally unstable substances or mixtures that are not classified as explosives should be considered for classification as self-reactive substances and mixtures.

Mixtures of oxidising substances and mixtures with combustible material that are not classified as explosives should be considered for classification as self-reactive substances and mixtures, oxidising liquids or oxidising solids.

Due to the complexity of these issues, expert advice should always be sought when dealing with classification of substances and mixtures with potentially explosive properties.

2.1.4. Classification of substances, mixtures or articles as explosives

2.1.4.1. 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.

2.1.4.2. 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-MTC.

The screening procedure may be used for new substances or mixtures which are suspected of having explosive properties. It should not be used for substances and mixtures 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 and/or pressure. The screening procedure is aimed at identifying the presence of such reactive groups and the potential for rapid energy release.

Examples of groups which may indicate explosive properties in organic materials 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).

A substance or mixture is not classified as explosive:

a. when there are no chemical groups associated with explosive properties present in the molecule;

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:

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

Using the formula:

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

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.

If the screening procedure identifies the substance or mixture to be a potential explosive or if it is a mixture containing any known explosives, the classification (acceptance) procedure for the class of explosives (see Section 2.1.4.5.1) has to be applied. If the exothermic decomposition energy of organic materials is less than 800 J/g, a UN gap test is not required, neither according to Series 1 Type (a) nor according to Series 2 Type (a).

2.1.4.3. 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 RTDG, 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 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 RTDG, 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 RTDG, Manual of Tests and Criteria). Intentional explosives (1) shall not be subject to UN Test Series 2.* *Sensitiveness: according to UN Test Series 3 (section 13 of the UN RTDG, Manual of Tests and Criteria).* *Thermal stability: according to UN Test 3(c) (sub-section 13.6.1 of the UN RTDG, Manual of Tests and Criteria).*

	Further tests are necessary to allocate the correct Division.
(1) This comprises substances, mixtures and articles which are manufactured with a view to producing a practical, explosive or pyrotechnic effect.	

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

Classification tests must be performed on the substance or mixture as supplied. 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.

2.1.4.4. Testing and evaluation of hazard information

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

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 2.1.4.5 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.

2.1.4.5. Classification procedure and decision logics

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

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

In the acceptance procedure, intrinsic explosive properties of a substance, mixture or article are determined through tests of its sensitivity, stability and explosion effects. 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 applying the assignment procedure. The further subdivision into compatibility groups A to S is described in detail in the UN RTDG Model Regulations, Section 2.1.2. 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. However, assignment of compatibility groups is not part of the classification system according to CLP.

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 the classification of explosives should be experienced in this field and be familiar with the criteria for classification.

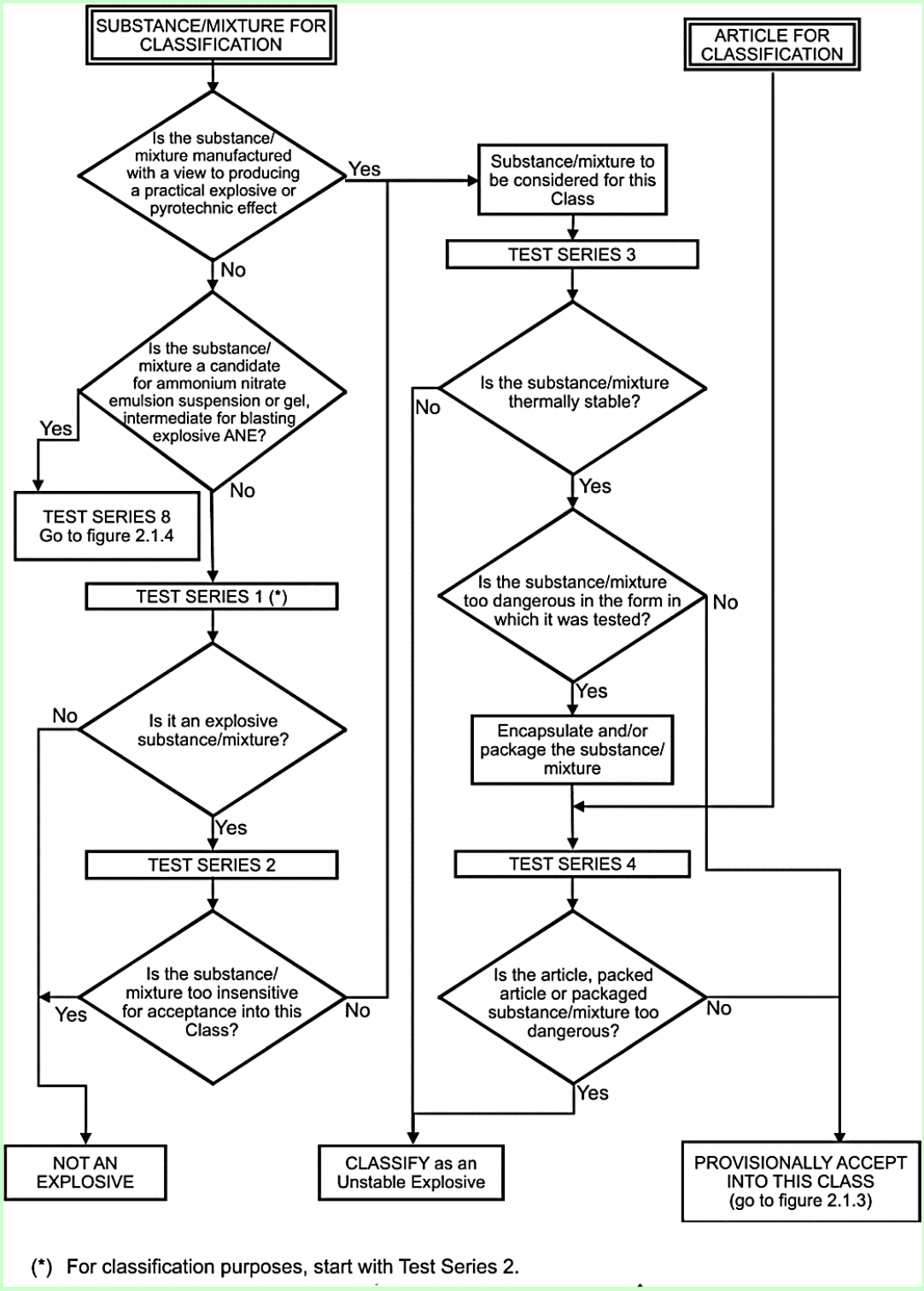
2.1.4.5.1. Acceptance procedure

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 reported below).

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)



(*) For classification purposes, start with Test Series 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 should be conducted. **It may be important for the safety of test personnel that certain tests, using small amounts of material, be conducted first before proceeding to experiment with larger quantities.**

Starting 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 the results of three types of tests to assess possible explosive effects. The question is answered 'Yes' if a '+' is obtained in any of the three types of tests. If the answer is 'No', the substance / mixture is rejected from this class; it is not an explosive. Under certain conditions the test Type 1 (a) can be replaced by certain tests of Test Series F, see UN-MTC, Section 11.3.5.

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, zero gap);

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. Under certain conditions test Type 2 (a) can be replaced by certain tests of Test Series F, see UN-MTC, Section 12.3.4.

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) (with a defined gap e.g. 50 mm);

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 or mixture is manufactured with a view to produce a practical explosive or pyrotechnic effect, it is unnecessary to conduct Test Series 1 and 2 for purposes of classification.

Test Series 3

As stated above it is recommended to carry out Test Series 3 before Test Series 1 and 2 for safety reasons due to the small sample amount needed. It is also recommended to carry out Test Series 3 even if negative results have been obtained in Test Series 1 and/or 2 because only Test Series 3 gives information about the thermal stability and the sensitivity to mechanical stimuli (impact and friction).

Test Series 3 is used to answer the questions 'Is the **substance / mixture** thermally stable?' and 'Is the substance / mixture too dangerous for transport in the form in which it

was tested?' This involves tests for determining the sensitiveness of the substance or mixture 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 or mixture to fire (small scale burning test).

The first question is answered 'No' if a '+' is obtained in Test type 3(c). Then the substance / mixture is considered as thermally unstable and either classified as an unstable explosive or as a self-reactive substance or mixture.

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 packaged to reduce its sensitiveness to external stimuli or is classified as an unstable explosive. Furthermore, the explosive may be desensitized in order to suppress/reduce its explosive properties in which case the classification procedure has to be restarted.

Test Series 4

Series 4 tests are intended to answer the question 'Is the **article**, packaged article or packaged substance or mixture too dangerous to be transported?'. 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 substance or mixture or article is classified as an unstable explosive.

It is important to note that a substance / mixture which fails Test Series 2 (i.e. it is sensitive enough for acceptance into the class of explosives) may still, if properly packaged, leave the class of explosives provided that it 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/or 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 EU test method A.14 in Regulation (EC) No 440/2008 (these are substances with a sensitiveness to impact, determined by UN Test Series 3 (a) (ii) of 40 J or less and/or a sensitiveness to friction, determined by Test Series 3 (b) (i) of 360 N or less).

2.1.4.5.2. 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 the class of explosives. A substance, mixture or article must be assigned to the division which corresponds

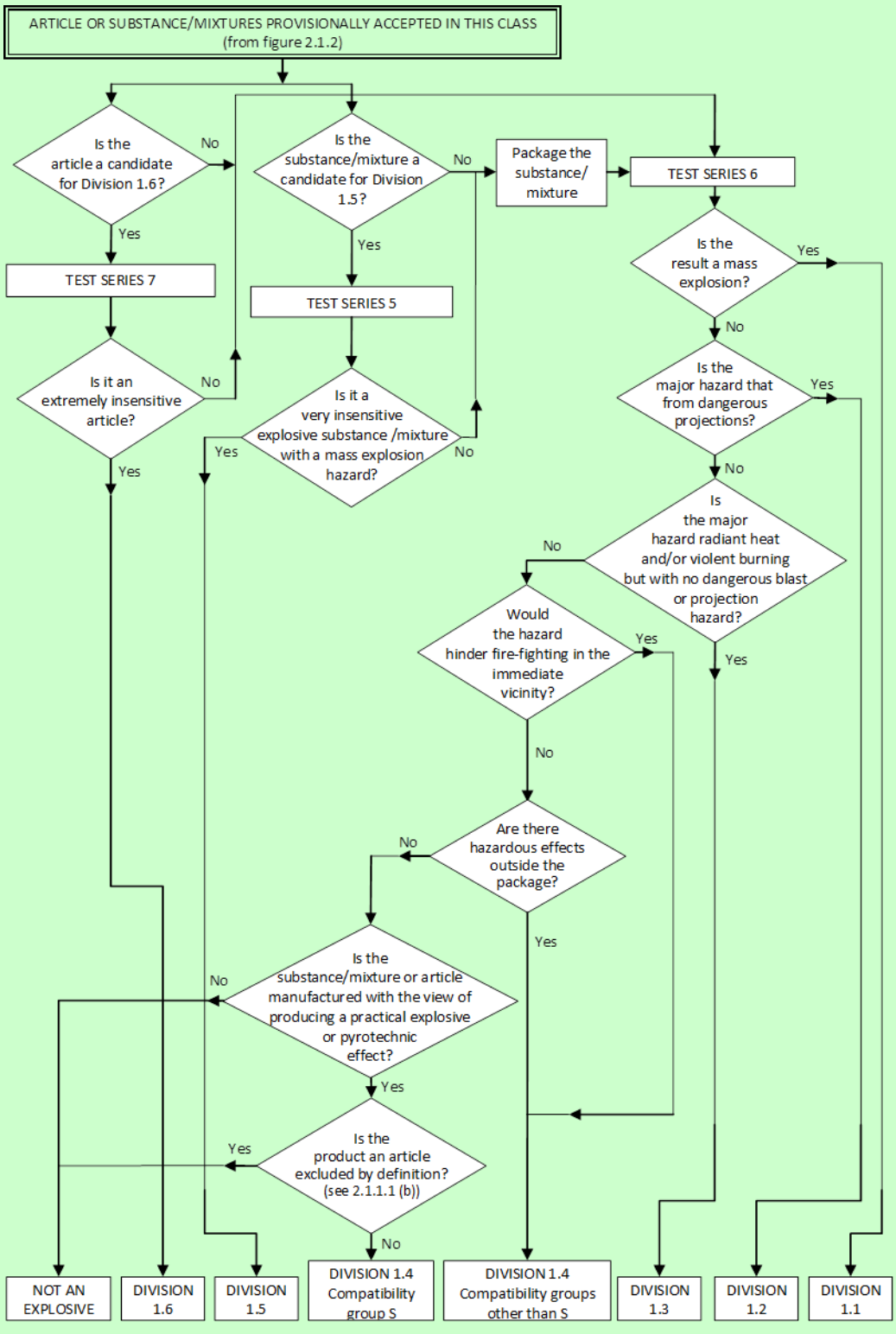
to the results of the tests to which the substance, mixture or article, as offered for supply and use, has been subjected. Other test results, and data gathered from accidents which have occurred, may also be taken into account.

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 the classification of explosives should be experienced in this field and be familiar with the criteria for classification.

Annex I: *Figure 2.1.3*

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



Test Series 5

Test Series 5 is only carried out for explosive substances/mixtures which are very insensitive and therefore candidates for division 1.5. Typical substances/mixtures are blasting agents such as ANFO, slurries, and emulsion explosives.

The results from three types of series 5 tests are used to answer the question 'Is it a very insensitive explosive substance/mixture 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 of transition from deflagration to detonation (French or 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 four 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 the substance, mixture or article to be classified 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 substance, mixture or article 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 substances, mixtures or articles in the condition and form in which they are offered for supply and use.

The four test types 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, mixture 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, mixture 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);

Type 6 (d): a test on an unconfined package of explosive articles to which special provision 347 of Chapter 3.3 of the UN RTDG Model Regulations applies, to determine if there are hazardous effects outside the package arising from accidental ignition or initiation of the contents.

Test types 6 (a), 6 (b), 6 (c) and 6 (d) 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 as 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.

Test type 6 (d) is a test used to determine whether a 1.4S classification is appropriate and is only used if Special Provision 347 of Chapter 3.3 of the UN RTDG Model Regulations applies. The results of test series 6 (c) and 6 (d) indicate if 1.4S is appropriate, otherwise the classification is 1.4 other than S.

If a substance or mixture 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

Test Series 7 aims at military explosives (Extremely Insensitive Substance: EIS or article containing an EIS) 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- MTC, Part I, Section 17.

Test Series 8

The question whether a candidate for ammonium nitrate emulsion or suspension or gel, intermediate for blasting explosives (ANE) is insensitive enough for classification as oxidising is answered by series 8 tests. 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);

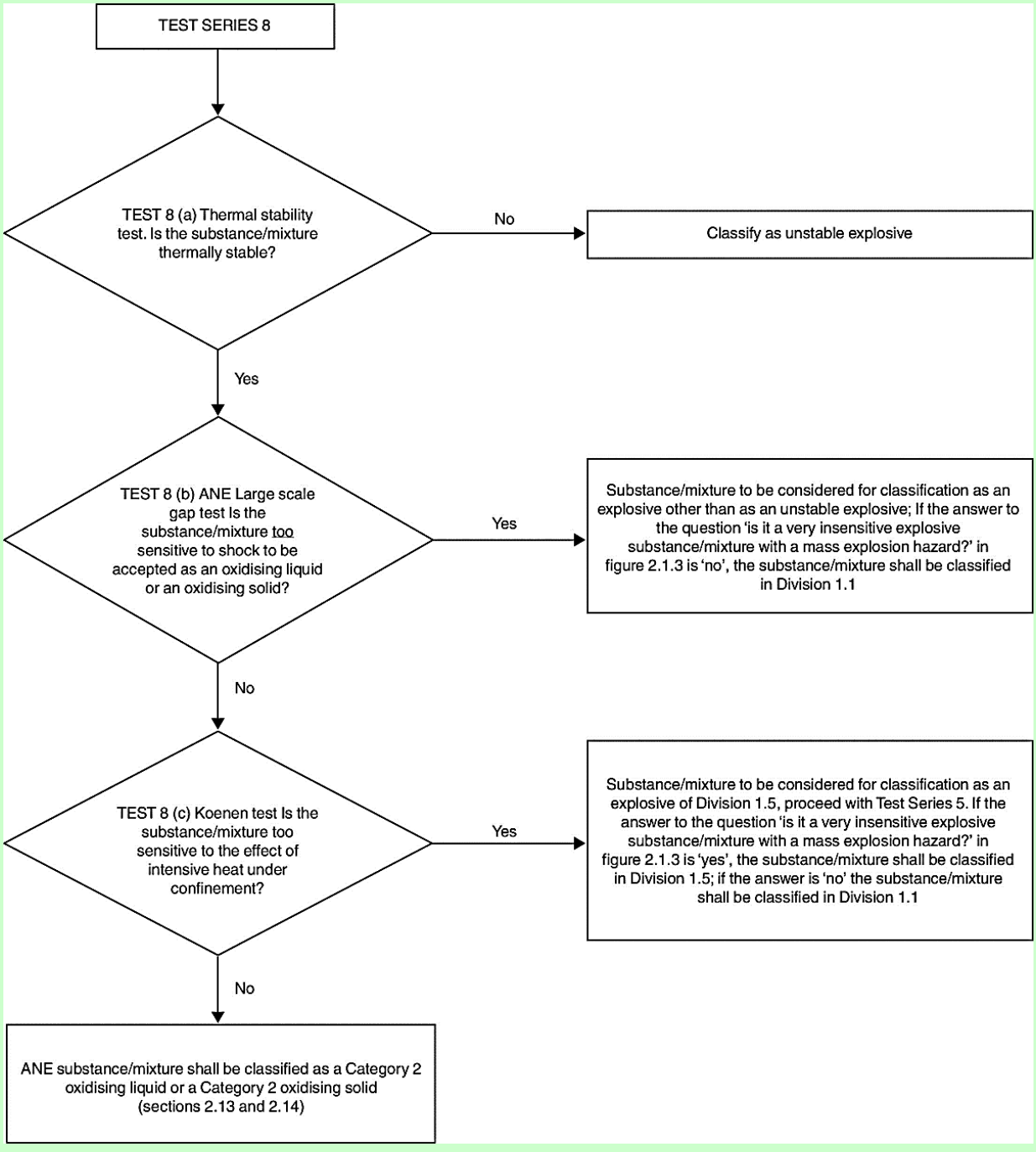
Type 8 (b): a shock test to determine sensitivity to intense shock (ANE gap test); and

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

Test Series 8 is used to establish whether an ammonium nitrate emulsion or suspension or gel, intermediate for blasting explosives (ANE) may leave the class of explosives or not. Substances or mixtures failing any of the tests must 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. If they pass all three tests they are classified as an oxidising liquid or solid.

Annex I: *Figure 2.1.4*

Procedure for the classification of ammonium nitrate emulsion, suspension or gel (ANE)



2.1.5. Hazard communication for explosives

2.1.5.1. Pictograms, signal words, hazard statements and precautionary statements[48]

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*
Pre-cautionary Statement *Prevention*	*P201* *P250* *P280*	*P210* *P230* *P234* *P240* *P250* *P280*	*P210* *P230* *P234* *P240* *P250* *P280*	*P210* *P230* *P234* *P240* *P250* *P280*	*P210* *P234* *P240* *P250* *P280*	*P210* *P230* *P234* *P240* *P250* *P280*	*No pre-cautionary statement*
Pre-cautionary Statement *Response*	*P370 + P372 + P380+P373*	*P370 + P372 + P380 + P373*	*P370 + P372 + P380 + P373*	*P370 + P372 + P380 + P373*	*P370 + P372 + P380 + P373* *P370 + P380 + P375*	*P370 + P372 + P380 + P373*	*No pre-cautionary statement*
Pre-cautionary Statement *Storage*	*P401*	*P401*	*P401*	*P401*	*P401*	*P401*	*No pre-cautionary statement*

[48] The combination statement P370+P372+P380+P373 applies to division 1.4 except for compatibility group S in transport packaging, whereas the combination statement P370+P380+P375 applies to division 1.4 compatibility group S in transport packaging.

Pre-cautionary Statement *Disposal*	*P501*	*P501*	*P501*	*P501*	*P501*	*P501*	*No pre-cautionary statement*

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

The intrinsic 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 substances, mixtures or articles. The type of packaging may significantly influence the test outcome.

Consequently, there are some deficiencies in the hazard communication of the GHS for unpacked or repacked explosive substances and mixtures, especially for substances and mixtures, which are provisionally accepted in the class of explosives but are later rejected from this class due to their packaging in the assignment procedure (see CLP Annex I, Figure 2.1.1 and Figure 2.1.3 and Section 2.1.4.5.1 of this guidance). 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. Musk xylene is an example which illustrates this issue (see Section 2.1.7.2). 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 the tested one 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 the CLP criteria.

2.1.5.2. Additional labelling provisions

2.1.5.2.1. Packaging dependance

Explosives are normally classified in their transport packaging. The packaging itself may be crucial for the classification. This is clear from the Figure 2.1.3 in Section 2.1.4.5.2 especially when it comes to Test Series 6. The assignment of an explosive substance or mixture to a particular Division within the hazard class of explosives is thus only valid for the substance and mixture in the packaging in which it was tested, which is usually the transport packaging. Because of the package-dependence of the classification, paragraph 2.1.2.4 of the Annex I to the CLP prescribes:

> **Annex I: *2.1.2.4.*** *If explosives are unpackaged or repacked in packaging other than the original or similar packaging, they shall be retested.*

Further, according to NOTE 1 to Table 2.1.2 in Section 2.1.3 of Annex I to CLP, unpackaged explosives or explosives repacked in packaging other than the original or similar packaging must have the following label elements:

> **Annex I: 2.1.3.** ***Hazard communication***
>
> […]
>
> NOTE 1: Unpackaged explosives or explosives repackaged in packaging other than the original or similar packaging shall include the following label elements:
>
> (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.

Normally, if explosives are unpackaged or repacked in packaging other than the original or similar packaging the classification procedure needs to be performed again in order to determine which Division the explosive belongs to in the new packaging. The label elements prescribed in NOTE 1 to Table 2.1.2, as quoted above, are the same as those of Division 1.1 and in practice this Division constitutes the most severe classification of a repackaged explosive. (Please note that Table 2.1.2 foresees also the hazard category 'Unstable explosive', which is assigned on the basis of the intrinsic properties of a substance or mixture via Test Series 3 and it is not package dependent). Therefore, the CLP allows labelling of a repackaged explosive with labelling corresponding to Division 1.1 instead of retesting. This, however, overestimates the hazardous properties unless the explosive in fact belongs to Division 1.1.

Many explosives are supplied in inner packages which are placed together in an outer package and where the entity as a whole, i.e. the combination of inner and outer packages, constitutes the transport packaging. According to the UN RTDG Model Regulations and the modal transport regulations (ADR, RID, ADN and IMDG Code, ICAO TI) the classification tests are performed in the transport packaging. Under Article 33(1) of CLP where the hazard pictograms(s) required by CLP relate to the same hazard as in the rules for the transport of dangerous goods, the respective CLP hazard pictogram(s) do not need to appear on the outer packaging.

The classification in accordance with rules on the transport of dangerous goods is almost entirely identical to the corresponding classification procedure used in CLP and hence the CLP classification will automatically be known for the transport packaging. However, the CLP classification for the inner package alone strictly speaking is not known to the manufacturer, importer or downstream user as this will not have been derived from the classification of the transport packaging. On the other hand, it is normally not practicable to perform the required tests on the inner packages. Therefore, normally the same classification as for the transport packaging may be assumed for the inner packages. The labelling requirements for the inner packages are those foreseen in Table 2.1.2 of Annex I to the CLP. However, the following exceptions apply:

- Transport packages in which the packaging is designed such that mass explosion is prevented by the packaging, e.g. by arranging the individual inner packages crosswise (so that they are not neighbouring each other) and by separating them with specified material. This is especially the case when packing instruction P101 according to section 4.1.5 of the ADR applies. In this case the inner package should be labelled in accordance with Note 1 to Table 2.1.2 of Annex I to the CLP (i.e. as Division 1.1 unless tested otherwise).
- Packages in which explosives of different divisions are contained (for such cases see especially the mixed packing provisions MP 20 to MP 24 in section 4.1.10 of the ADR).
- Furthermore, they do not apply if the packaging is changed, as stated in Note 1 to Table 2.1.2 of Annex I to the CLP.

2.1.5.2.2. Supplemental hazard information

Some R-phrases under DSD are not covered by hazard classes in the current GHS. They are included as supplemental hazard statements in Part 1 of Annex II to CLP. The following EU hazard statements are important in connection with explosive properties:

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.

EUH001 must be assigned to explosives which are wetted, diluted, dissolved or suspended with a phlegmatizer in order to reduce or suppress their explosive properties (desensitized explosives in the sense of the foreseen new hazard class for desensitized explosives) and which do not meet the criteria of the hazard class of explosives.

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.

Some substances and mixtures which may react explosively if heated under confinement are not covered adequately by the classification system. This may e.g. be the case for:

- substances or mixtures which are exempted from the class of explosives based on their packaging and according to results of the Test Series 6;
- substances or mixtures with a SADT of more than 75 °C for a 50 kg package which therefore cannot be classified as self-reactive.

EUH044 must be assigned to such substances or mixtures, in order to make the user aware of these properties.

2.1.5.3. Further communication requirements

According to Note 2 to Table 2.1.2, explosive properties of certain substances and mixtures which are exempted from classification as explosives must be communicated to the user via the SDS (when one is required).

Annex I: 2.1.3. *Hazard communication*

[…]

NOTE 2: *Substances and mixtures, as supplied, with a positive result in Test Series 2 in Part I, Section 12, of the UN RTDG, Manual of Tests and Criteria, which are exempted from classification as explosives (based on a negative result in Test Series 6 in Part I, Section 16 of the UN RTDG, Manual of Tests and Criteria,) still have explosive properties. The user shall be informed of these intrinsic explosive properties because they have to be considered for handling – especially if the substance or mixture is removed from its packaging or is repackaged – and for storage. For this reason, the explosive properties of the substance or mixture shall be communicated in Section 2 (Hazards identification) and Section 9 (Physical and chemical properties) of the Safety Data Sheet and other sections of the Safety Data Sheet, as appropriate*

2.1.6. Relation to transport classification

Division 1.1 – 1.6 within Class 1 of the UN RTDG Model Regulations covers explosive substances, mixtures and articles. Normally, the transport classification in accordance with the UN RTDG Model Regulations and the modal transport regulations (ADR, RID, ADN and IMDG Code, ICAO TI) can be used one-to-one when deriving the CLP classification for explosives,

which are packaged in authorised transport packaging. See Annex VII of this guidance for additional information on transport classification in relation to CLP classification.

For the use of other packaging or for unpacked substances and mixtures the additional labelling provisions (see Section 2.1.5.2) have to be observed or re-testing is necessary.

2.1.7. Examples of classification for explosives

Examples are given below for the classification of substances. Equivalent information would be needed for mixtures.

2.1.7.1. Example of substances and mixtures fulfilling the classification criteria

a. RESULTS FROM APPLICATION OF THE ACCEPTANCE PROCEDURE

Step	Test	Conclusion	Rationale
0. General data: 0.1 Name of the substance / mixture: **Hexanitrostilbene**			
1. Is the substance / mixture a candidate for ammonium nitrate emulsion, suspension or gel, intermediate for blasting explosive (ANE)?		No	
2. Is the substance / mixutre manufactured with the view to producing a practical explosive or pyrotechnic effect?		Yes	
3. Test Series 3 3.1 Thermal stability: 3.2 Impact sensitivity: 3.3 Friction sensitivity:	 75 °C / 48 hour test (test 3(c)) BAM Fallhammer test (test 3(a)(ii)) BAM friction test (test 3(b)(i))	 Result: '—', thermally stable Result: Limiting impact energy 5 J Result: Limiting load > 240 N	 '—', not too dangerous in form tested '—', not too dangerous in form tested
4. Is the substance / mixture thermally stable?		Yes	
5. Is the substance / mixture too dangerous in the form in which it was tested?		No	
6. Conclusion:		**PROVISIONALLY ACCEPT INTO THIS CLASS**	

Step	Test	Conclusion	Rationale
10.1 Exit:		Apply the assignment procedure	

b. RESULTS FROM APPLICATION OF THE ASSIGNMENT PROCEDURE

Step	Test	Conclusion	Rationale
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: 2.2 Effect of propagation: 2.4 Effect of fire engulfment:	 Test 6(a) with detonator Type 6(b) with detonator Test 6(c) may be waived because of the result of the 6(b) test.	 Result: detonation, crater Result: detonation of the whole stack of packages, crater	
3. Is the result a mass explosion?		Yes	
4. Conclusion:		**Assignment to Division 1.1**	

2.1.7.2. Example of substances and mixtures not fulfilling the classification criteria

This example is taken from the UN-MTC, Part I, Section 10.5.2, Figure 10.5.

c. RESULTS FROM APPLICATION OF THE ACCEPTANCE PROCEDURE

Step	Test	Conclusion	Rationale
0. General data: 0.1 Name of the substance / mixture: **5-tert-butyl-2,4,6-trinitro-m-xylene (musk xylene)**			
1. Is the substance / mixutre a candidate for ammonium nitrate emulsion, suspension or gel, intermediate for blasting explosive ANE?		No	
2. Is the substance / mixture manufactured with the view to		No	

Step	Test	Conclusion	Rationale
producing a practical explosive or pyrotechnic effect?			
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 / mixture?		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 / mixture 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 (test 3(a)(ii))	Result: Limiting impact energy 25 J", not too dangerous in form tested.	

Step	Test	Conclusion	Rationale
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 / mixture thermally stable?		Yes	
9. Is the substance / mixture too dangerous in the form in which it was tested?		No	
10. Conclusion: 10.1 Exit		**PROVISIONALLY ACCEPT INTO THIS CLASS** Apply the assignment procedure The explosive properties shall be communicated in the safety data sheet in accordance with section 2.1.5.3 above.	

d. RESULTS FROM APPLICATION OF THE ASSIGNMENT PROCEDURE

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

2.2. FLAMMABLE GASES (INCLUDING CHEMICALLY UNSTABLE GASES)

2.2.1. Introduction

The criteria for 'Flammable gases (including chemically unstable gases)' are found in Annex I, Section 2.2 of CLP and are identical to those in Chapter 2.2 of GHS.

2.2.2. Definitions and general considerations for the classification of flammable gases (including chemically unstable gases)

Annex I*: 2.2.1. Definitions*
2.2.1.1 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.
2.2.1.2. A chemically unstable gas means a flammable gas that is able to explode even in the absence of air or oxygen.

The flammable 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.

The hazard class of flammable gases also covers chemically unstable gases as defined above.

2.2.3. Relation to other physical hazards

Annex I: *2.2.2. Classification criteria*
[…]
Note: Aerosols shall not be classified as flammable gases; see Section 2.3.

For flammable gases that are packaged in aerosol dispensers see 2.3 Aerosols. If classified as aerosols, they do not have to be classified as flammable gases in addition.

2.2.4. Classification of substances and mixtures as flammable gases (including chemically unstable gases)

2.2.4.1. Identification of hazard information

Many gases are classified as flammable gases in Annex VI of CLP and more gases are classified as flammable gases in the UN RTDG Model Regulations.

For gases that are not classified as flammable gases in Annex VI of CLP nor in the UN RTDG Model Regulations, there is ample scientific literature giving the flammability range for most gases (e.g. IEC 60079-20-1, *Explosive atmospheres – Part 20-1: Material characteristics for gas and vapour classification – Test methods and data* as amended).

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

Information on a number of chemically unstable gases can be found in the UN-MTC, Section 35. Tables 35.1 and 35.2 within UN-MTC, Section 35.3.2.1 contain information on a number of chemically unstable gases together with their classification and Category.

If information on other gases than the ones mentioned in the above tables is needed a test method for determination of chemical instability of gases and gas mixtures is described in UN-MTC, Section 35. However, it should be noted that this test method is not applicable to liquefied gas mixtures. In case the gaseous phase above a liquefied gas mixture may become chemically unstable after withdrawal, this should be communicated via the SDS.

2.2.4.2. 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 which are often prepared on demand. In most of the cases, the formulator of the gas mixture will use a calculation method as described in ISO 10156 as amended (see Section 2.2.4.4) to determine if the mixture is flammable or not.

If the calculations in accordance with ISO 10156 as amended show that a gas mixture is not flammable it is also not classified as chemically unstable and therefore it is not necessary to carry out the tests for determining chemical instability for classification purposes.

Expert judgement should be applied to decide whether a flammable gas or gas mixture is a candidate for classification as chemically unstable in order to avoid unnecessary testing of gases where there is no doubt that they are stable. Functional groups indicating chemical instability in gases are triple bonds, adjacent or conjugated double-bonds, halogenated double-bonds and strained rings.

Gas mixtures containing only one chemically unstable gas are not considered as chemically unstable and therefore do not have to be tested for classification purposes if the concentration of the chemically unstable gas is below the higher of the following generic concentration limits:

a. the lower explosion limit (LEL) of the chemically unstable gas; or
b. 3 mole%.

Furthermore, for some gases there are also specific concentration limits available and these are indicated in the tables 35.1 and 35.2 within UN-MTC, Section 35.3.2.1.

2.2.4.3. Classification criteria

The criteria for the classification of flammable gases (including chemically unstable gases) are given in the following tables:

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.*
Annex I: *2.2.2* *Table 2.2.2* ***Criteria for chemically unstable gases***	
Category	*Criteria*
A	*Flammable gases which are chemically unstable at 20 °C and a pressure of 101.3 kPa.*
B	*Flammable gases which are chemically unstable at a temperature greater than 20 °C and/or a pressure greater than 101.3 kPa.*

2.2.4.4. Testing and evaluation of hazard information

ISO 10156 as amended describes a test method and a calculation method for the classification of flammable gases. The test method may be used in all cases, but must be used when the calculation method cannot be applied.

The calculation method applies to gas mixtures and can be applied when the T_{Ci} for all flammable components and the K_k for all inert components are available. These are listed for a number for gases in ISO 10156 as amended. In the absence of T_{Ci} value for a flammable gas, the value of the LFL can be used and ISO 10156 proposes the value of 1.5 where no K_k value is listed. The calculation method described in ISO 10156 as amended uses the criterion that a gas mixture is considered non-flammable in air if:

Equation 2.2.4.4.a

$$\sum_{i=1}^{n} \frac{A'_i}{T_{ci}} \leq 1$$

where:

Equation 2.2.4.4.b

$$A'_i = \frac{A_i}{\sum_{i=1}^{n} A_i + \sum_{k=1}^{p} K_k B_k}$$

and where:

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

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

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

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

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

n is the number of flammable gases in the mixture

p is the 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 2.2.4.4.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 2.2.4.4.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 as amended 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 Category 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 as amended).

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

Gases or compressed gas mixtures that are classified as flammable have to be considered for classification as chemically unstable in addition. If the screening procedures described in Section 2.2.4.2 are not conclusive, the gas or gas mixture has to be tested. The test method is described in UN-MTC, Section 35. It uses the same equipment as the test method for oxidising gases according to ISO 10156 as amended and therefore could be applied by laboratories that also carry out the tests for oxidising gases.

2.2.4.5. Decision logic

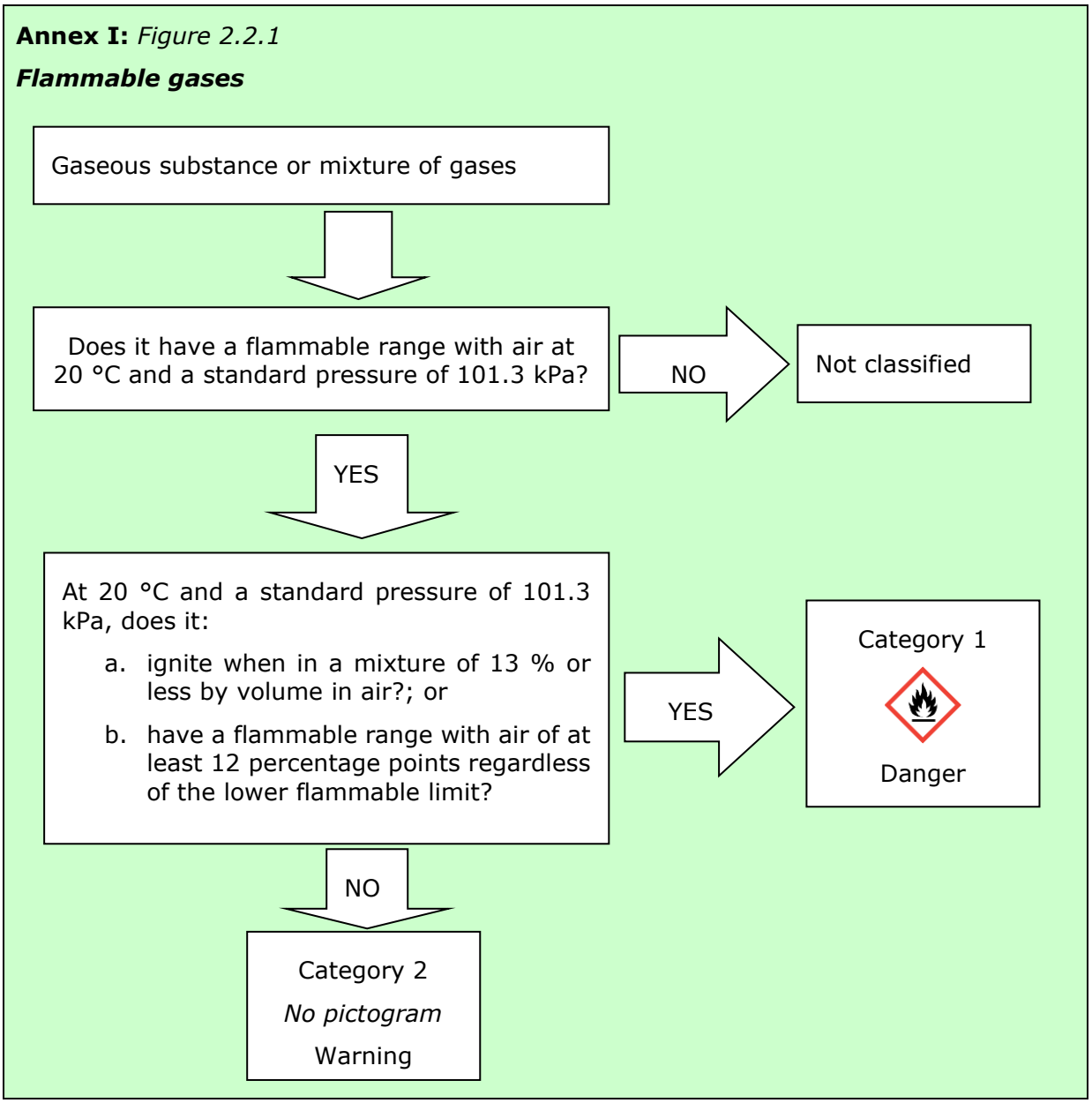
Classification of flammable gases is laid down in the following flow-charts which are applicable according to CLP.

⚠ NOTE: The person responsible for the classification of flammable gases (including chemically unstable gases) should be experienced in this field and be familiar with the criteria for classification.

2.2.4.5.1. Decision logic for flammable gases

Annex I: *Figure 2.2.1*

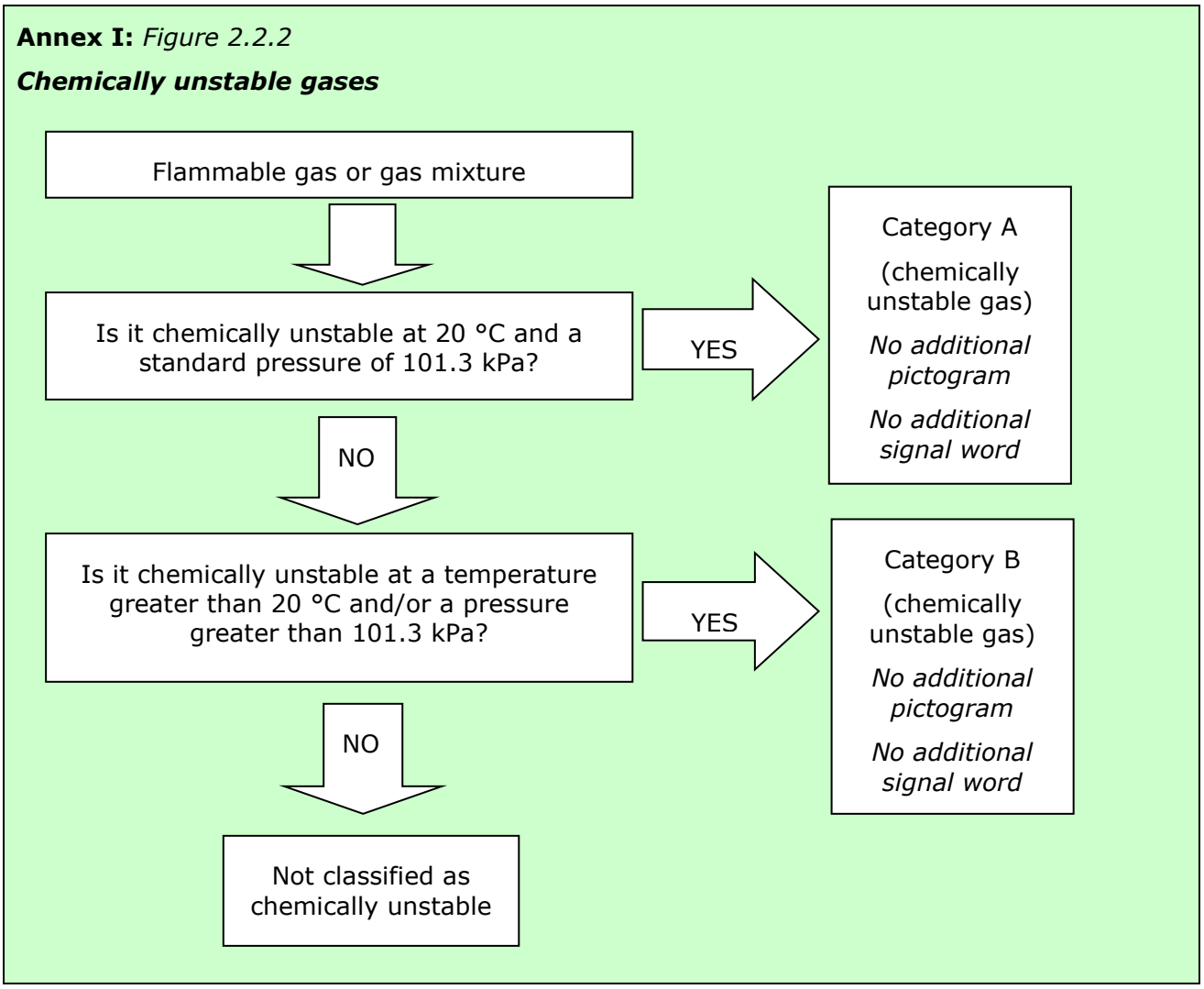
Flammable gases



2.2.4.5.2. Decision logic for chemically unstable gases

Annex I: *Figure 2.2.2*

Chemically unstable gases



2.2.5. Hazard communication for flammable gases (including chemically unstable gases)

2.2.5.1. Pictograms, signal words, hazard statements and precautionary statements

Annex I: *2.2.3.* *Table 2.2.3* ***Label elements for flammable gases (including chemically unstable gases)***				
Classification	*Flammable gas*		*Chemically unstable gas*	
	Category 1	*Category 2*	*Category A*	*Category B*
GHS Pictogram		*No pictogram*	*No additional pictogram*	*No additional pictogram*
Signal Word	*Danger*	*Warning*	*No additional signal word*	*No additional signal word*
Hazard Statement	*H220: Extremely flammable gas*	*H221: Flammable gas*	*Additional hazard statement H230: May react explosively even in the absence of air*	*Additional hazard statement H231: May react explosively even in the absence of air at elevated pressure and/or temperature*
Precautionary Statement Prevention	*P210*	*P210*	*P202*	*P202*
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.

2.2.6. Relation to transport classification

The criteria for flammable gases Category 1 correspond to the criteria that are in use for classifying flammable gases in the UN RTDG Model Regulations. Consequently all gases listed as flammable in the UN RTDG Model Regulations and in the modal transport regulations (ADR, RID, ADN and IMDG Code, ICAO TI) must be classified as Flam.Gas 1; H220. See Annex VII for additional information on transport classification in relation to CLP classification.

2.2.7. Example of classification for flammable gases

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_k in ISO 10156 as amended.**

T_{c1} =	5.5 mole %
T_{c2} =	8.7 mole %
K_1 =	0.55
K_2 =	0.9

***Step 3:* Calculate the equivalent gas contents A'_i for the flammable gases according to** Equation 2.2.4.4.b

$$A'_1 = \frac{2}{(2+6)+(0.55\times 27+0.9\times 65)} = 2.46 \text{ mole \%}$$

$$A'_2 = \frac{6}{(2+6)+(0.55\times 27+0.9\times 65)} = 7.38 \text{ mole \%}$$

***Step 4:* Calculate the flammability of the gas mixture according to** Equation 2.2.4.4.a

$$\sum_{i=1}^{2} \frac{A'_i}{T_{ci}} = \frac{A'_1}{T_{c1}} + \frac{A'_2}{T_{c2}} = \frac{2.46}{5.5} + \frac{7.38}{8.7} = 1.29$$

***Step 5*: Compare the outcome to the criterion in** Equation 2.2.4.4.a

Since 1.29 > 1, this particular gas mixture is considered to be flammable.

2.3. AEROSOLS

2.3.1. Introduction

Identical criteria related to the flammability of aerosols are found in Annex I, Section 2.3 of CLP, Chapter 2.3 of GHS as well as in the Aerosol Dispensers Directive (ADD) 75/324/EEC.

2.3.2. Definitions and general considerations for the classification of 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.*

2.3.3. Relation to other physical hazards

There is no direct relation to other physical hazards.

1. **Annex I, 2.3.2.1.**

[…]

Note 2:

Aerosols do not fall additionally within the scope of Sections 2.2 (flammable gases), 2.5 (gases under pressure), 2.6 (flammable liquids) and 2.7 (flammable solids). Depending on their contents, aerosols may however fall within the scope of other hazard classes, including their labelling elements.

2.3.4. Classification of aerosols

2.3.4.1. Classification criteria

Annex I: ***2.3.2.1.*** *Aerosols shall be classified in one of the three categories of this hazard class, depending on their flammable properties and their heat of combustion. They shall be considered for classification in Category 1 or 2 if they contain more than 1% components (by mass) which are classified as flammable according to the following criteria set out in this Part:*

– Flammable gases (see Section 2.2);

– Liquids with a flash point ≤ 93 °C, which includes Flammable Liquids according to section 2.6;

– Flammable solids (see Section 2.7);

or their heat of combustion is at least 20kJ/g.

Note 1:

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. *An aerosol shall be classified in one of the three 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 Figures 2.3.1(a) to 2.3.1(c) of this Annex and sub-sections 31.4, 31.5 and 31.6 of Part III of the UN RTDG, Manual of Tests and Criteria. Aerosols which do not meet the criteria for inclusion in Category 1 or Category 2 shall be classified in Category 3.*

Note:

Aerosols containing more than 1% flammable components or with a heat of combustion of at least 20 kJ/g, which are not submitted to the flammability classification procedures in this section shall be classified as aerosols, Category 1.

Under the ADD and also in UN-MTC, Section 31, flammability classification for aerosols refers to 'extremely flammable', 'flammable' and 'non-flammable'. This respectively corresponds to the terms 'Aerosol, Category 1', 'Aerosol, Category 2' and 'Aerosol, Category 3' which are used in CLP.

The following identical criteria can be found in both CLP and ADD:

The aerosol is classified as 'Aerosol, Category 3' if it contains 1 % or less flammable components[49] **and** the chemical heat of combustion is less than 20 kJ/g.

The aerosol is classified as 'Aerosol, Category 1' if it contains 85 % or more flammable components **and** the chemical heat of combustion is 30 kJ/g or more.

All other aerosols should be submitted to the appropriate flammability classification procedures in order to select the appropriate Category 1, 2 or 3. However, if these are not submitted to the

[49] Depending on their flash point value, also certain liquids not classified under CLP as Flam. Liq., Cat. 1, 2 or 3, will be considered as flammable components in an aerosol. The CLP hazard class of Flammable liquids covers liquids of flash point ≤ 60 °C while a liquid component in an aerosol is considered flammable when its flash point is ≤ 93 °C.

flammability classification procedures they must be automatically classified as 'Aerosol, Category 1'.

The chemical heat of combustion is determined in accordance with CLP Annex I, 2.3.4.1 which is identical to point 1.10 of the Annex to ADD.

2.3.4.2. 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 classification related to the flammability of aerosols. These test methods are described under point 6.3 of the Annex to ADD and are therefore available in all EU languages. They are also described in the UN-MTC Section 31.

After evaluation according to the appropriate criteria (see previous sections) the aerosol is classified in one of the three categories.

2.3.4.3. Decision logic

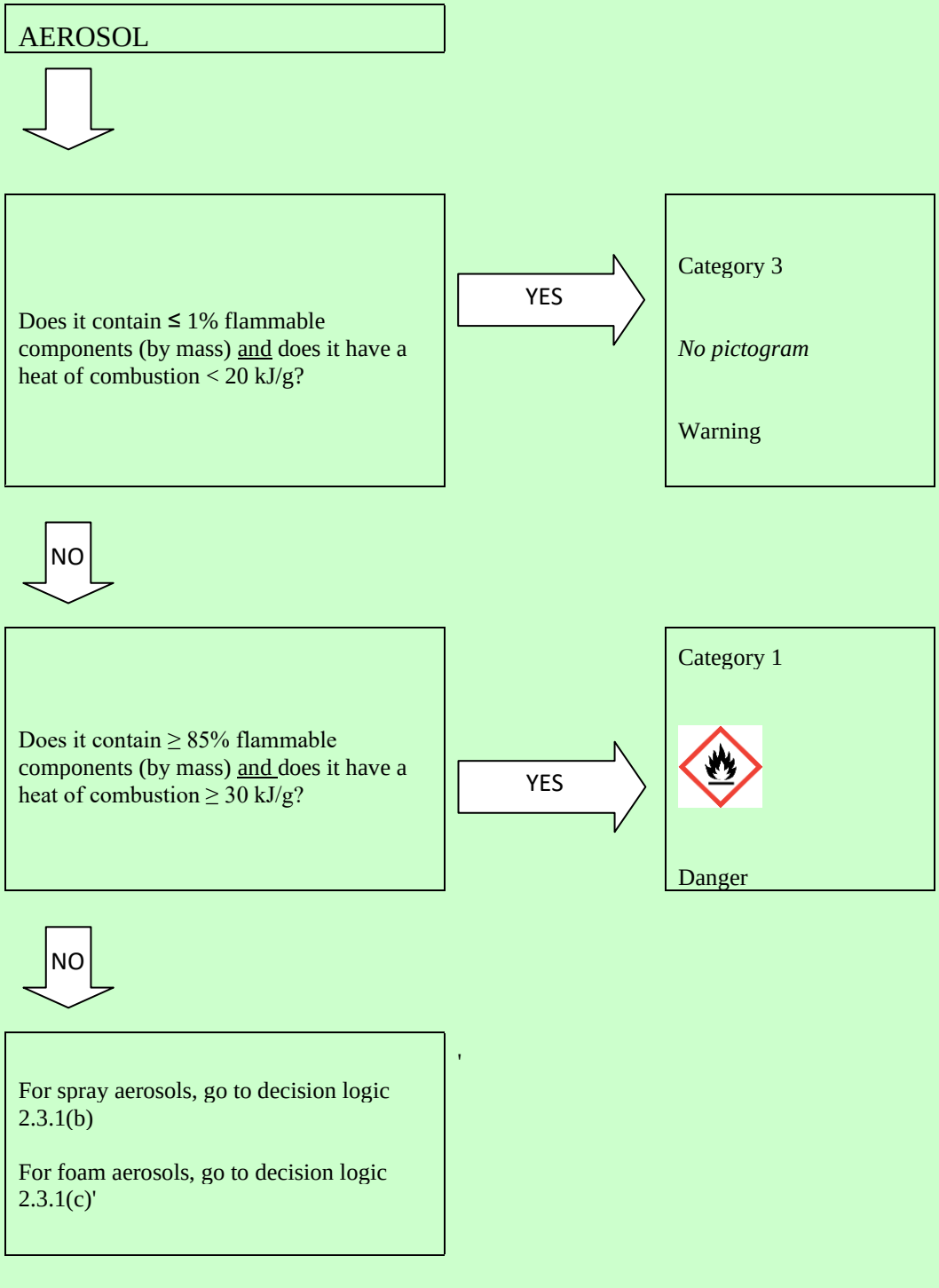
The classification procedure is also laid down in the following flow-charts which are applicable according to CLP.

NOTE: The person responsible for the classification of aerosols should be experienced in this field and be familiar with the criteria for classification.

2.3.4.3.1. Decision logic for aerosols

Annex I: *Figure 2.3.1 (a)*

for aerosols

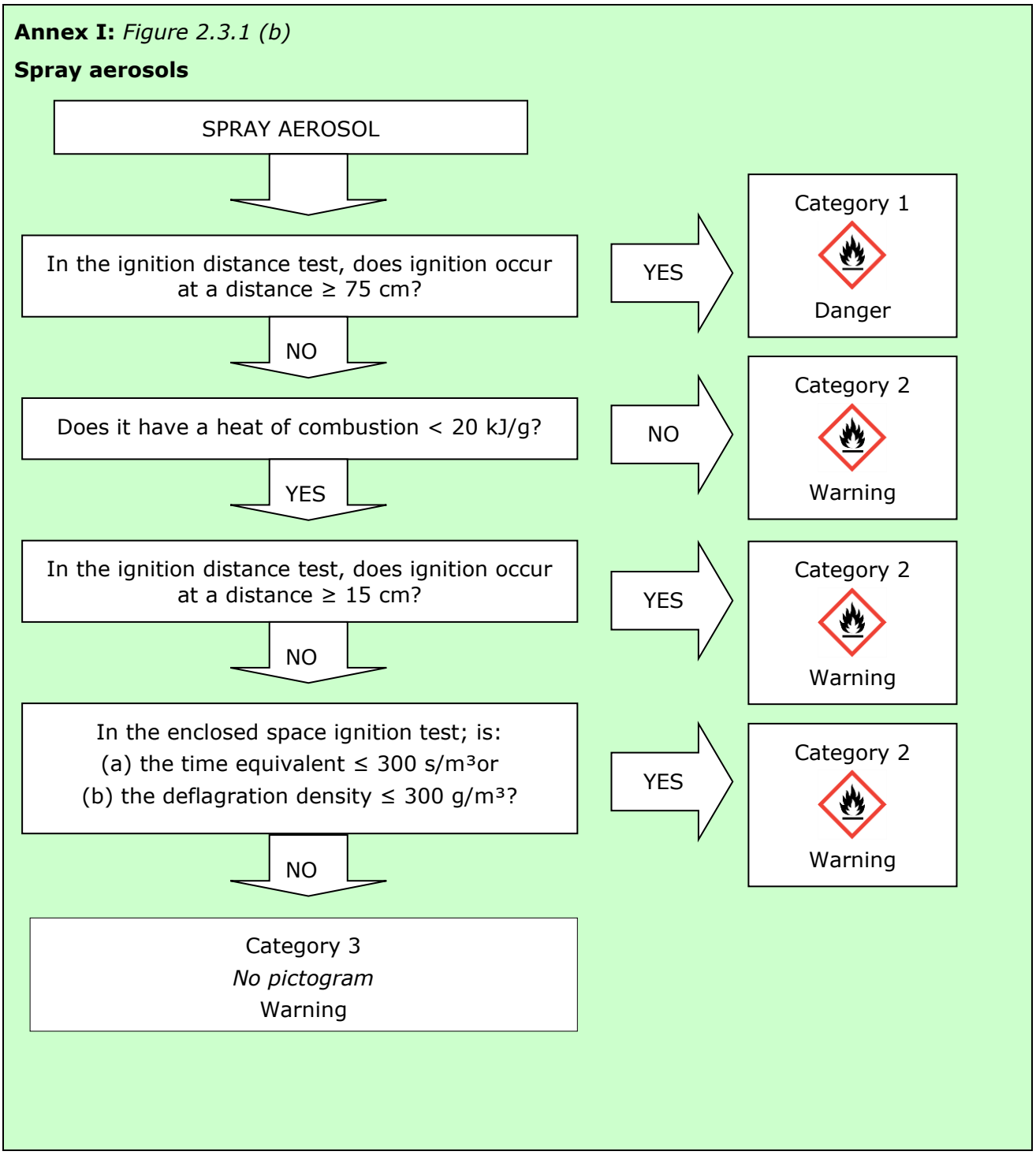


'

2.3.4.3.2. Decision logic for spray aerosols

Annex I: *Figure 2.3.1 (b)*

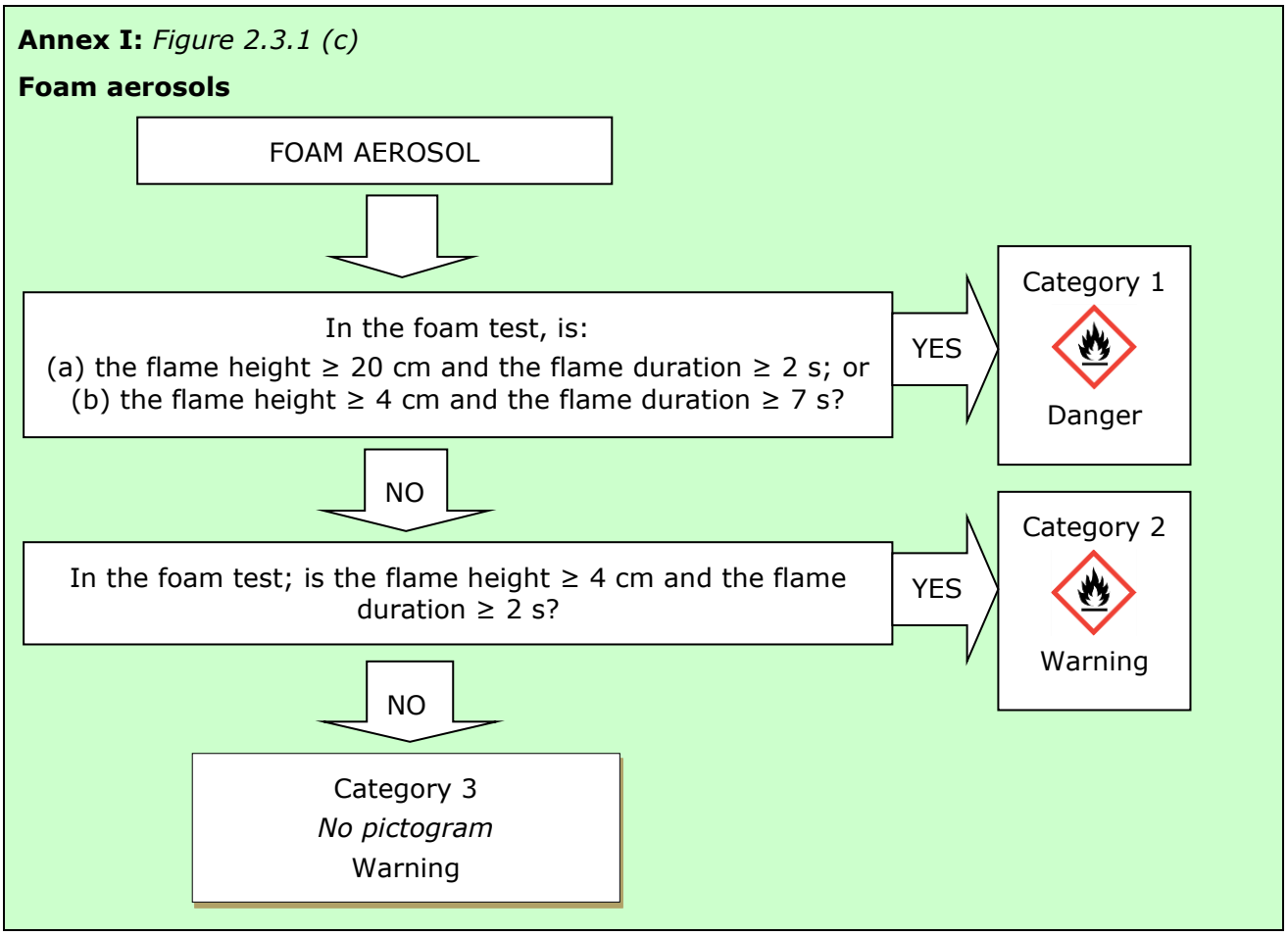
Spray aerosols



2.3.4.3.3. Decision logic for foam aerosols

Annex I: *Figure 2.3.1 (c)*

Foam aerosols



2.3.5. Hazard communication for aerosols

2.3.5.1. Pictograms, signal words, hazard statements and precautionary statements

Annex I: *Table 2.3.1* ***Label elements for aerosols***			
Classification	*Category 1*	*Category 2*	*Category 3*
GHS Pictograms			*No pictogram*
Signal Word	*Danger*	*Warning*	*Warning*
Hazard Statement	*H222: Extremely flammable aerosol* *H229: Pressurised container: May burst if heated.*	*H223: Flammable aerosol* *H229: Pressurised container: May burst if heated.*	*H229: Pressurised container: May burst if heated.*
Precautionary Statement Prevention	*P210* *P211* *P251*	*P210* *P211* *P251*	*P210* *P251*
Precautionary Statement Response			
Precautionary Statement Storage	*P410 + P412*	*P410 + P412*	*P410 + P412*
Precautionary Statement Disposal			

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

2.3.5.2. Additional labelling provisions

The ADD imposes additional labelling requirements on all aerosols, flammable or not.

For example:

Where an aerosol dispenser contains flammable components but is not classified as flammable (i.e. 'Aerosol, Category 3'), the quantity of flammable material contained in the aerosol dispenser must be stated clearly on the label, in the form of the following legible and indelible wording: 'X % by mass of the contents are flammable'.

2.3.6. Relation to transport classification

Aerosol dispensers (UN 1950) belong to Class 2 in the UN RTDG Model Regulations and in the modal transport regulations (ADR, RID, ADN and IMDG Code, ICAO TI). Flammability classification criteria are harmonised between CLP and in the modal transport regulations (ADR, RID, ADN and IMDG Code, ICAO TI).

Aerosols, Category 1 and 2 fall under Division 2.1 (sometimes referred to as Class 2.1 or Group F, FC, TF or TFC depending on their contents with hazardous properties). Aerosols, Category 3 fall under Division 2.2 (sometimes referred to as Class 2.2 or Group A, O, T, C, CO, TC or TOC depending on their contents with hazardous properties). See Annex VII for additional information on transport classification in relation to CLP classification.

2.3.7. Examples of classification for 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.

2.3.7.1. Examples of aerosols fulfilling the classification criteria

Deodorant:	
Composition:	
Butane/propane:	70 % (flammable components, ΔHc = 43.5 kJ/g)
Ethanol:	25 % (flammable components, ΔHc = 24.7 kJ/g)
Others:	5 % (non-flammable components, ΔHc = 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 as **Aerosol, Category 1.**	
Air freshener (wet):	
Composition:	
Butane/propane:	**30 % (flammable components, ΔHc = 43.5 kJ/g)**
Others:	70 % (non-flammable components, ΔHc = 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 as **Aerosol, Category 2.**	
Shaving foam:	
Composition:	
Butane/propane:	4 % (flammable components, ΔHc = 43.5 kJ/g)
Others:	96 % (non-flammable components, ΔHc = 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 classified as **Aerosol, Category 3**.
However, according to the requirements of ADD, the quantity of flammable components must be stated clearly on the label: '4% by mass of the contents are flammable'.

2.3.7.2. Examples of aerosols not fulfilling the classification criteria

By definition, all aerosol dispensers fall under one of the three categories for this hazard class.

2.4. OXIDISING GASES

2.4.1. 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.

2.4.2. 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.*

2.4.3. Relation to other physical hazards

Oxidising gases do not need to be classified in any other hazard class apart from 'Gases under pressure' where appropriate.

2.4.4. Classification of substances and mixtures as oxidising gases

2.4.4.1. Identification of hazard information

There are not many pure gases that are oxidising. Most oxidising gases are identified as such in the UN RTDG Model Regulations and in ISO 10156 *Gases and gas mixtures*: *Determination of fire potential and oxidizing ability for the selection of cylinder valve outlets* as amended.

2.4.4.2. 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 as amended in order to determine the oxidising potential are time consuming and expensive for gas mixtures which are often prepared on demand. In most of the cases, the formulator of the gas mixture will use a calculation method as described in ISO 10156 as amended.

2.4.4.3. 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.*

Note:

'Gases which cause or contribute to the combustion of other material more than air does' means pure gases or gas mixtures with an oxidising power greater than 23.5 % as determined by a method specified in ISO 10156 as amended.

Please note that ISO 10156-2:2005 has been integrated into the revised version ISO 10156:2010. ISO 10156:2010 supersedes EN 720-2:1996 and ISO 10156-2:2005.

2.4.4.4. Testing and evaluation of hazard information

ISO 10156 as amended describes a test method and a calculation method for the classification of oxidising gases. The test method may be used in all cases, but must be used when the calculation method cannot be applied.

The calculation method applies to gas mixtures and can be applied only when the C_i for all oxidising components and the K_k for all inert components are available. These are listed for a number of gases in ISO 10156 as amended. For gas mixtures the calculation method described in ISO 10156 as amended 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:

Equation 2.4.4.4.a

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

Where:

- x_i is the molar fraction of the *i*:th oxidising gas in the mixture, in %
- 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* relative to nitrogen
- B_k is the molar fraction of the *k*:th inert gas in the mixture, in %
- n is the number of oxidising gases in the mixture
- p is the number of inert gases in the mixture

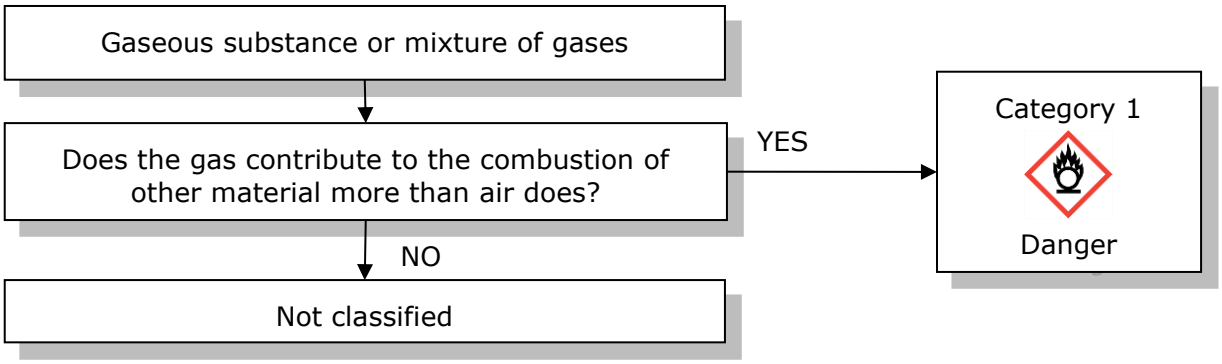
For mixtures containing both flammable and oxidising components, special calculation methods are described in ISO 10156 as amended.

2.4.4.5. Decision logic

Classification of oxidising gases is done according to decision logic 2.4.4.1 as included in the GHS.

NOTE: The person responsible for the classification of oxidising gases should be experienced in this field and be familiar with the criteria for classification.

Figure 2.1 Decision logic for oxidising gases (Decision logic 2.4 of GHS)



2.4.5. Hazard communication for oxidising gases

2.4.5.1. Pictograms, signal words, hazard statements and precautionary statements

Annex I: *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.

2.4.6. Relation to transport classification

Most oxidising gases are classified as such with subsidiary risk 5.1 in the UN RTDG Model Regulations. Consequently all gases listed as oxidising in the UN RTDG Model Regulations and in the modal transport regulations (ADR, RID, ADN and IMDG Code, ICAO TI) must be classified as Ox. Gas 1. See Annex VII for additional information on transport classification in relation to CLP classification.

2.4.7. Example of classification for oxidising gases

2.4.7.1. Example of substances and mixtures not fulfilling the classification criteria

EXAMPLE OF A CLASSIFICATION USING THE CALCULATION METHOD OF ISO 10156 AS AMENDED
Example Mixture: 9 % (O_2) + 16 % (N_2O) + 75 % (N_2)
Calculation steps
Step 1: Ascertain the coefficient of oxygen equivalency (C_i) 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 the Oxidising Power (OP) of the gas mixture according to Equation 2.4.4.4.a

$$OP = \frac{\sum_{i=1}^{n} x_i C_i}{\sum_{i=1}^{n} x_i + \sum_{k=1}^{p} K_k B_k} = \frac{0.09 \times 1 + 0.16 \times 0.6}{0.09 + 0.16 + 0.75 \times 1} = 0.186$$

0.186 < 0.235 (18.6 % < 23.5 %), therefore the mixture is <u>not</u> considered as an oxidising gas.

2.5. GASES UNDER PRESSURE

2.5.1. 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 Class 2 'Gases' in the UN RTDG Model Regulations.

2.5.2. Definitions and general considerations for the classification of gases under pressure

2.5.2.1. 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 substances and mixtures are considered as gases when their boiling point or initial boiling point (BP) is not higher than 20 °C. Substances and mixtures with a boiling point or initial boiling point higher than 20 °C are liquids except those few that develop a vapour pressure higher than 300 kPa at 50 °C; these substances and mixtures are considered as gases because of the pressure hazard 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.

2.5.2.2. 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 at 20 °C, 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.

2.5.3. Relation to other physical hazards

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

2.5.4. Classification of substances and mixtures as gases under pressure

2.5.4.1. Identification of hazard information

Many gases are identified as such in the UN RTDG Model Regulations and many flammable gases and some oxidising gases are identified as gases in Annex VI of CLP. The UN RTDG Model Regulations identifies further if the gas can be packaged as a 'compressed gas', a 'liquefied gas', a 'refrigerated liquefied gas' and a 'dissolved gas'. To determine whether a substance is a gas in

case it is not listed in the UN RTDG Model Regulations and in case of doubt, the following physical characteristics are necessary:

- the boiling point;
- the vapour pressure at 50 °C.

See also *IR & CSA, Chapter R.7a: Endpoint specific guidance*, Section R.7.1.3 (Boiling point), R.7.1.5 (Vapour pressure).

For those substances that meet the definition of a gas (see Section 2.5.2), the critical temperature is also necessary. For the classification of gas mixtures based on the pseudo-critical temperature see Section 2.5.4.3.

The references according to Section 2.6.8 provide good quality data on boiling points, vapour pressure and the critical temperature of substances.

2.5.4.2. Classification criteria

Annex I: *Table 2.5.1* ***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.*
Note: *Aerosols shall not be classified as gases under pressure. See Section 2.3.*	

2.5.4.3. 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* as amended.

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.

$$\text{Pseudo-critical temperature} = \sum_{i=1}^{n} x_i \times T_{Crit_i}$$

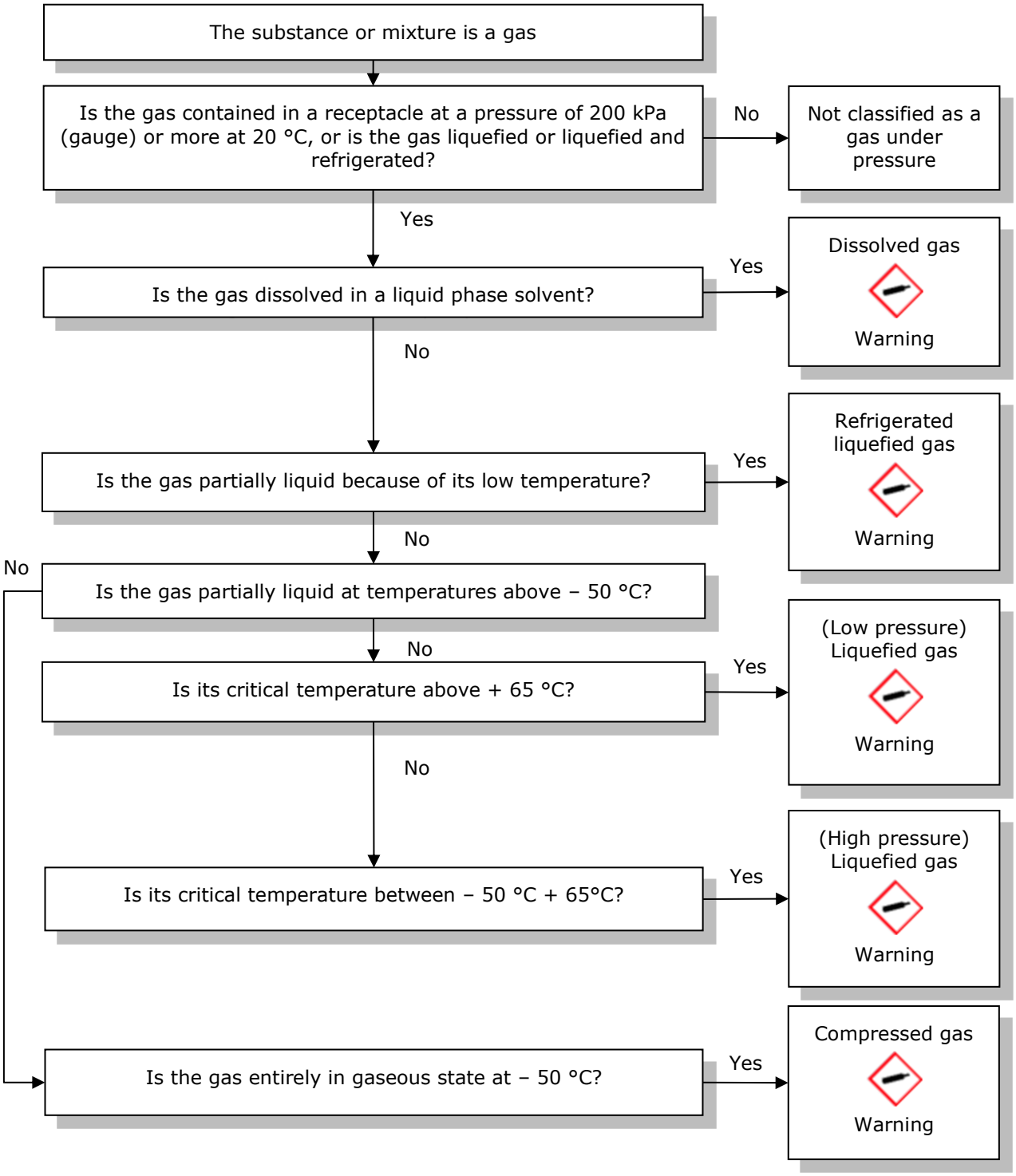
where x_i is the molar concentration of component *i* and T_{Crit_i} is the critical temperature (in °C or in K) of the component *i*.

2.5.4.4. Decision logic

Classification of gases under pressure is done according to decision logic 2.5.4.1 as included in the GHS.

NOTE: The person responsible for the classification of gases under pressure should be experienced in this field and be familiar with the criteria for classification.

Figure 2.2 Decision logic for gases under pressure (Decision logic 2.5 of GHS)



2.5.5. Hazard communication for gases under pressure

2.5.5.1. Pictograms, signal words, hazard statements and precautionary statements

Annex I: *Table 2.5.2* ***Label elements for gases under pressure***				
Classification	*Compressed gas*	*Liquefied gas*	*Refrigerated liquefied gas*	*Dissolved gas*
GHS Pictogram				
Signal Word	*Warning*	*Warning*	*Warning*	*Warning*
Hazard Statement	*H280: Contains gas under pressure; may explode if heated*	*H280: Contains gas under pressure; may explode if heated*	*H281: Contains refrigerated gas; may cause cryogenic burns or injury*	*H280: Contains gas under pressure; may explode if heated*
Precautionary Statements Prevention			*P282*	
Precautionary Statements Response			*P336 + P315*	
Precautionary Statements Storage	*P410 + P403*	*P410 + P403*	*P403*	*P410 + P403*
Precautionary Statements Disposal				
Note: *Pictogram GHS04 is not required for gases under pressure where pictogram GHS02 or pictogram GHS06 appears.*				

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

2.5.6. Relation to transport classification

Gases are listed in UN RTDG Model Regulations and in the transport regulations (ADR, RID, ADN)[50] with an indication of the physical state in their name for compressed gases (e.g. Argon, compressed), for refrigerated liquefied gas (e.g. Oxygen, refrigerated liquid) and for dissolved gas (e.g. Acetylene, dissolved). These indications of the physical state can be used to identify the group of gases under pressure according to CLP. The gas names without an indication of the physical state are 'liquefied gases' by default. See Annex VII for additional information on transport classification in relation to CLP classification.

[50] The classification codes according to the ADR, Sections 2.2.2.1.2 and 2.2.2.1.3 are: 1. Compressed gas; 2. Liquefied gas; 3. Refrigerated liquefied gas; 4. Dissolved gas. A asphyxiant; O oxidizing; F flammable; T toxic; TF toxic, flammable; TC toxic, corrosive; TO toxic, oxidizing; TFC toxic, flammable, corrosive; TOC toxic, oxidizing, corrosive.

2.5.7. Examples of classification for gases under pressure

2.5.7.1. Examples of substances and mixtures fulfilling the classification criteria

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

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):	T_{Crit} = -118.4 °C (= 154.75 K)
Nitrous Oxide (N_2O):	T_{Crit} = +36.4 °C (= 309.55 K)
Nitrogen (N_2):	T_{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'.	

2.6. FLAMMABLE LIQUIDS

2.6.1. Introduction

The criteria for 'Flammable liquids' are found in Annex I, Section 2.6 of CLP and are **not** identical to those of GHS as the respective GHS Chapter 2.6 contains additional classification criteria - Category 4 for flammable liquids.

2.6.2. Definitions and general considerations for the classification of flammable liquids

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

The flash point 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 flash point.

2.6.3. Relation to other physical hazards

For flammable liquids that are packaged in aerosol dispensers, see Section 2.3 on Aerosols. If classified as flammable aerosols, they must not be classified as flammable liquids in addition (see Section 2.3).

2.6.4. Classification of substances and mixtures as flammable liquids

2.6.4.1. Identification of hazard information

For the decision if a substance or mixture is a liquid see Section 2.0.4.

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 2.6.4.3), 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, Chapter R.7a: Endpoint specific guidance*, Section R.7.1.3 (Boiling point), R.7.1.9 (Flash point).

The references in Section 2.6.8 provide good quality data on boiling points (all three references) and flash point (first reference) of substances.

Special care is required when viscous substances or mixtures are tested or when halogenated compounds are present (see Section 2.6.4.4.1).

2.6.4.2. Screening procedures and waiving of testing

2.6.4.2.1. Boiling point

Normally calculation methods based on increments give satisfying results for substances and mixtures. With respect to the criterion for distinguishing between Category 1 and 2 (boiling point of 35 °C) only that method with a mean absolute error lower than 5 °C could be recommended for screening.

2.6.4.2.2. 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 flash point is sometimes not reliable and at this time, it is not possible to predict what the accuracy of a calculated value is. Calculation can be used as a screening test for mixtures, and a flash point 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 (23 °C and 60 °C, respectively). However, the restrictions outlined in the CLP Annex I, 2.6.4.2 must 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 flash point and boiling point experimental determination is recommended.

2.6.4.3. Classification criteria

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

Annex I: *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.

Note:

Aerosols shall not be classified as flammable liquids; see section 2.3.

Annex I: *2.6.4.5.* *Liquids with a flash point of more than 35 °C and not more than 60 °C need not be classified in Category 3 if negative results have been obtained in the sustained combustibility test L.2, Part III, section 32 of the UN RTDG, Manual of Tests and Criteria.*

Gas oils, diesel and light heating oils in the flash point range of 55 °C to 75 °C may be regarded as a whole. The reason is that these hydrocarbon mixtures have varying flash points in that range due to seasonal requirements (EN 590 *Automotive fuels – Diesel- Requirements and Test Methods* as amended). 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.

2.6.4.4. 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 safety characteristics 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 Part F: *Chemical Safety Report*, Part G: *Extending the SDS and Guidance on compilation of safety data sheets* respectively).

2.6.4.4.1. 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 *Determination of flash point - Rapid equilibrium closed cup method* as amended) 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 above the tolerance limits of the method, the lower value should be taken or the determination should be repeated with manual observation. If the experimentally determined flash point 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 no flash point is found up to 60 °C and (partly) halogenated compounds are present or if there is the possibility of loss of volatile flammable or non-flammable components (i.e. the liquid is a candidate for the assignment of EUH018, EUH209 or EUH209A) or if in doubt, the explosion limits should be determined in order to decide whether labelling with EUH018, EUH209 or EUH209A is appropriate. Determination of explosion limits should be carried out according to EN 1839 *Determination of explosion limits of gases and vapours* as amended or ISO 10156 *Gases and gas mixtures – Determination of fire potential and oxidising ability for the selection of cylinder valves outlets* as amended or EN 15794 *Determination of explosion points of flammable liquids* as amended.

Substances

For non-halogenated substances, the flash point 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 flash point.

Within the respective scope, every standard is applicable.

Mixtures

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

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 flash point 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.

2.6.4.4.2. Evaluation of hazard information

Flash points 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 and their limited application range.

If in literature different flash points are found for the same substance the one found as evaluated or recommended has to be preferred.

If in literature different flash points 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.

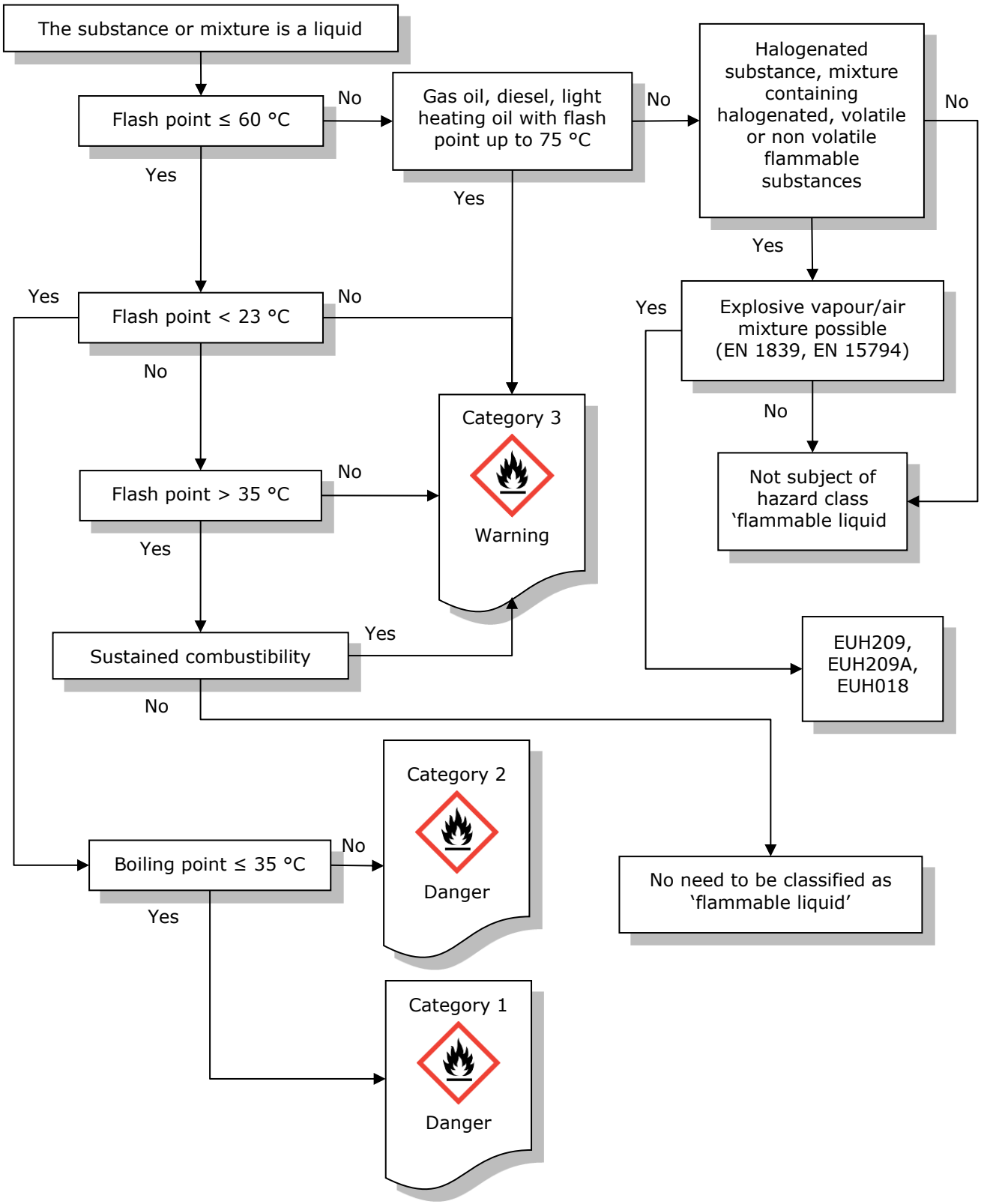
According to the criteria either Category 1, Category 2 or Category 3, including the relevant hazard statement and signal word, have to be assigned (see Section 2.6.5). In case the criteria for EUH018, EUH209 or EUH209A are met, the liquid has to be labelled with the respective supplemental hazard statement as well. In the majority of cases EUH018 covers EUH209 and EUH209A.

2.6.4.5. Decision logic

Compared to the decision logic 2.6 for flammable liquids contained in the GHS chapter 2.6.4.1, this decision logic below is amended to include derogations for gas oil, diesel, light heating, sustained combustibility and for phrases EUH018, EUH209 and EUH209A.

NOTE: The person responsible for the classification of flammable liquids should be experienced in this field and be familiar with the criteria for classification.

Figure 2.3 Amended GHS decision logic for flammable liquids to include derogations for gas oil, diesel, light heating, sustained combustibility and for phrases EUH018, EUH209 and EUH209A



2.6.5. Hazard communication for flammable liquids

2.6.5.1. 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 Storage	*P403 + P235*	*P403 + P235*	*P403 + P235*
Precautionary Statement Disposal	*P501*	*P501*	*P501*

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

2.6.5.2. 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.

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

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. Information about testing can be found in Section 2.6.4.4.1 paragraph 5.

2.6.6. Re-classification of substances and mixtures classified as flammable liquids according to DSD and DPD or already classified for transport

2.6.6.1. Relation to transport classification

Class 3 of the UN RTDG Model Regulations and the modal transport regulations (ADR, RID, ADN and IMDG Code, ICAO TI) cover flammable liquids based on the same criteria as the CLP hazard class flammable liquid. In general there is a correspondence between transport packing groups and CLP hazard categories. However, in many cases specific exceptions apply. Further, the UN RTDG Model Regulations cover substances and mixtures transported above their flash point and desensitized explosives. In practice the information on flash point and boiling point needed for classification is available and it is recommended to classify based on the data rather than use direct translation. See Annex VII for additional information on transport classification in relation to CLP classification.

2.6.7. Examples of classification for flammable liquids

2.6.7.1. Examples of substances and mixtures fulfilling the classification criteria

2.6.7.1.1. Example 1

MIXTURE OF: N-BUTYLACETATE + P-XYLENE + 1,3,5-TRIMETHYLBENZENE (7.9 MOL % + 60.3 MOL % + 31.7 MOL %)	
Initial boiling point (calculated):	140 °C
Flash point (calculated):	26 °C
calculated flash point 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):	30.0 °C
⇨ According to boiling point and measured flash point result: **Flam.Liq. Category 3**	

2.6.7.1.2. Example 2

HYDROCARBONS AND DICHLOROMETHANE (70 VOL % + 30 VOL %)	
Initial Boiling point (calculated):	52 °C
Flash point:	no flash point according to a standard
⇨ Because the hydrocarbon part of the mixture has a flash point by itself (- 12 °C) the question 'Is an explosive vapour/air mixture possible' (EN 1839 as amended, EN 15794 as amended) 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 1: In that case EUH018 covers EUH209 Note 2: The EUH018 must only be assigned if the substance or mixture is classified as hazardous (Article 25 (1) of CLP) **Cannot be classified as flammable liquid because the mixture has no flash point.**	

2.6.7.2. Examples of substances and mixtures not fulfilling the classification criteria

2.6.7.2.1. Example 3

AQUEOUS FORMULATION OF ALIPHATIC POLYURETHANE RESIN	
Boiling point (EC 440/2008, EU test method A.2):	92 °C
Dyn. Viscosity at 20 °C (DIN 53019 as amended):	1938 mPas
Sample is highly viscous, use low heating rate for flash point determination (1 °C /min).	
Flash point (EN ISO 13736 as amended):	42.5 °C
Sustained combustibility test (UN- MTC L.2) at 60.5 °C:	combustion not sustained
Sustained combustibility test (UN-MTC L.2)at 75 °C:	combustion not sustained
⇨ According to the flash point result: Category 3 However, does not necessarily have to be classified as flammable liquid **Category 3** because it did not sustain combustion.	

2.6.8. References

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

William M. Haynes *et al.* (2012) *CRC Handbook of Chemistry and Physics 93rd Edition*. CRC Press, Taylor and Francis, Boca Raton, FL

O'Neil, Maryadele J. *et al.* © (2016, 2012) *The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals* (14th Edition – Version 14.9). Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.

2.7. FLAMMABLE SOLIDS

2.7.1. Introduction

The criteria for 'Flammable solids' are found in Annex I, Section 2.7 of CLP and are identical to those in Chapter 2.7 of GHS.

2.7.2. 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.

Special consideration on particle size

Annex I: *2.7.2.3.*

[…]

Note 1:

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.

[…]

The finer the particle size of a solid substance or mixture, the greater the area exposed to air will be, and since flammability is a reaction with the oxygen in air, the particle size will greatly influence the ability to ignite. Hence it is very important that flammable properties for solids are investigated on the substance or 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, 2.7.2.3.For further information please see Section 1.2 within this Guidance.

2.7.3. 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 aerosol dispensers, see Section 2.3, Aerosols. If classified as flammable aerosols, they must not be classified as flammable solids in addition (see Section 2.7).

2.7.4. Classification of substances and mixtures as flammable solids

2.7.4.1. Identification of hazard information

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 for solids containing flammable liquids.

See also *IR & CSA, Chapter R.7a: Endpoint specific guidance*, Section R.7.1.2 (Melting/freezing point), R.7.1.9 (Flash point).

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.

2.7.4.2. 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. In many cases, a simple screening test (see Section 2.7.4.4) can be used to determine whether a solid should be classified as flammable. Solid substances and mixtures are classified as flammable according to their burning behaviour.

The test method as described in Part III, Sub-section 33.2.1.4.3.1 in the UN-MTC should be applied for screening purposes. Alternatively, the burning index (referred to as 'class number' in VDI 2263) as obtained from the Burning Behaviour test (VDI 2263, part 1) may be used. If a burning index of 3 or less is found, the substance or mixture 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.

2.7.4.3. 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 RTDG, 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 RTDG, Manual of Tests and Criteria in accordance with Table 2.7.1;*

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 2:* *Aerosols shall not be classified as flammable solids; see section 2.3.*	

2.7.4.4. Testing and evaluation of hazard information

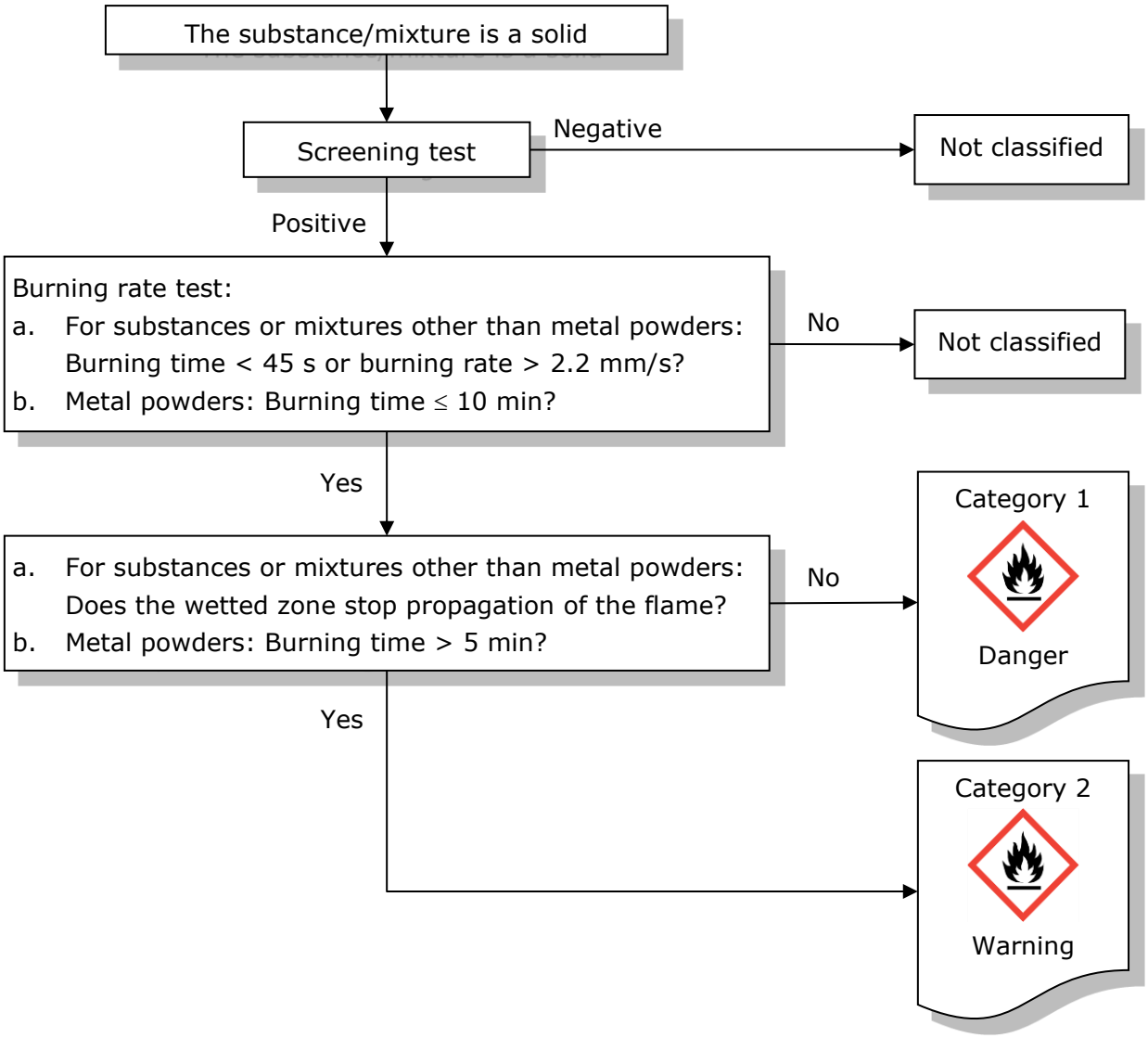
For safety reasons, it is advisable to test for explosive and self-reactive properties first and to rule out pyrophoric behaviour before performing this test. The classification test is described in Part III, Sub-section 33.2.1.4.3.2 of the UN-MTC. The sample should be tested in its commercially relevant 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.

2.7.4.5. Decision logic

Classification of flammable solids is done according to decision logic 2.7.4 as included in the GHS.

NOTE: The person responsible for the classification of flammable solids should be experienced in this field and be familiar with the criteria for classification.

Figure 2.4 Decision logic for flammable solids (Decision logic 2.7 of GHS)



2.7.5. Hazard communication for flammable solids

2.7.5.1. 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.

2.7.6. Relation to transport classification

Division 4.1 within Class 4 of the UN RTDG Model Regulations covers flammable substances, solid desensitized explosives and self-reactive liquids or solids. If a transport classification according to the modal transport regulations (ADR, RID, ADN and IMDG Code, ICAO TI) is available it should be kept in mind that transport classification is based on prioritisation of hazards (see UN RTDG Model Regulations, Section 2.0.3) and that flammable solids have a relatively low rank in the precedence of hazards. Therefore, the translation from transport classification to CLP should be only done if a transport classification for a flammable solid is explicitly available. The conclusion that a substance or mixture not classified as a flammable solid for transport should not be classified as a flammable solid according to CLP is, in general, not correct. See Annex VII for additional information on transport classification in relation to CLP classification.

2.7.7. Examples of classification for flammable solids

2.7.7.1. Example of substances and mixtures fulfilling the classification 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 Test N.1 (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.**	

2.7.7.2. 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.

2.7.8. References

VDI guideline 2263, part 1, 1990, *Test methods for the Determination of the Safety Characteristics of Dusts*

2.8. SELF-REACTIVE SUBSTANCES AND MIXTURES

2.8.1. Introduction

The criteria for 'Self-reactive substances and mixtures' are found in Annex I, Section 2.8 of CLP and are identical to those in Chapter 2.8 of GHS.

In general, substances or mixtures classified as self-reactive substances and mixtures 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 and mixtures that only decompose slowly at temperatures well above the normal storage and transport temperatures (e.g. 75 °C).

The decomposition of self-reactive substances and mixtures 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 or mixture. Decomposition, particularly if no ignition occurs, may result in the evolution of toxic gases or vapours. For certain self-reactive substances and mixtures, the temperature must be controlled during storage and handling. Some self-reactive substances and mixtures 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 and mixtures burn vigorously. Self-reactive substances are, for example, some compounds of the types listed below:

c. Aliphatic azo compounds (-C-N=N-C-);

d. Organic azides (-C-N_3);

e. Diazonium salts (-$CN_2^+Z^-$);

f. N-nitroso compounds (-N-N=O); and

g. Aromatic sulfohydrazides (-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 and mixtures included in the UN RTDG Model Regulations, Section 2.4.2.3.2.3.

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

2.8.2. Definitions and general considerations for the classification of self-reactives

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

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.

2.8.3. Relation to other physical hazards

Neither the burning properties nor the sensitivity to impact and friction form part of the classification procedure for self-reactive substances and mixtures in CLP. These properties may be of importance in safe handling of self-reactive substances and mixtures (see additional tests in Section 2.8.4.3.2).

In addition, the following should be noted:

Explosive properties

The explosive properties do not have to be determined according to the CLP Annex I, Chapter 2.1, because explosive properties are incorporated in the decision logic for self-reactive substances and mixtures. Note that substances and mixtures may have explosive properties when handled under higher confinement.

2.8.4. Classification of substances and mixtures as self-reactive

2.8.4.1. Identification of hazard information

The classification of a self-reactive substance or mixture in one of the seven categories 'types A to G' is dependent on its detonation, deflagration and thermal explosion properties, its response to heating under confinement, its explosive power and the concentration and the type of diluent added to desensitize the substance or mixture. Specifications of acceptable diluents that can be used safely are given in the UN RTDG Model Regulations, Section 2.4.2.3.5.

The classification of a self-reactive substance or mixture as type A, B or C is also dependent on the type of packaging in which the substance or mixture is tested as it affects the degree of confinement to which the substance or mixture is subjected. This has to be considered when handling the substance or mixture; stronger packaging may result in more violent reactions when the substance or mixture decomposes. This is why it is important that storage and transport is done in packaging, allowed for the type of self-reactive substance and mixture, 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 2.8.4.4). Consequently, the determination of explosive properties as prescribed in the hazard class explosives needs not to be conducted for self-reactive substances and mixtures.

2.8.4.2. Classification criteria

According to CLP, substances and mixtures must be considered for classification in this hazard class as a self-reactive substance or mixture 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 UN RTDG, Manual of Test 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 must be considered for classification in this hazard class unless:

Annex I: *2.8.4.2.*

[…]

(a) 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 Appendix 6 of the UN RTDG, Manual of Tests and Criteria.

[…]

In the CLP decision logic (see Section 2.8.4.4), classification of self-reactive substances or mixtures is based on performance based testing in both small scale tests and, where necessary, some larger scale tests with the substance or mixture in its packaging. The concept of 'intrinsic properties' is, therefore, not necessarily, applicable to this hazard class.

Self-reactive substances or mixtures 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, CLP. The classification principles are given in the decision logic in Figure 2.8.1 of CLP (see Section 2.8.4.4) 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 and mixtures is included in the UN RTDG Model Regulations, Section 2.4.2.3.2.3.

2.8.4.3. Testing and evaluation of hazard information

2.8.4.3.1. 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 and mixtures has to be assessed in order to determine the SADT.

The SADT is defined as the lowest temperature at which self-accelerating decomposition of a substance or mixture may occur 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 or mixture and its packaging.

There is no relation between the SADT of a self-reactive substance and mixture 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 and mixture 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:
2. Self-reactive substances and mixtures need to be subjected to temperature control when the SADT is ≤ 55 ° C.
3. Derivation of control and emergency temperatures:

Type of receptacle	SADT*	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

*i.e. the SADT of the substance/mixture as packaged for transport, handling and storage.

It should be emphasized that the SADT is dependent on the nature of the self-reactive substance or mixture itself, together with the volume and heat-loss characteristics of the packaging or vessel in which the substance or mixture 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 or mixture as tested and when handled properly. Mixing the self-reactive substances and mixtures 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.

2.8.4.3.2. Additional considerations and testing

Explosive properties

The sensitivity of self-reactive substances and mixtures to impact (solids and liquids) and friction (solids only) may be of importance for the safe handling of the substances and mixtures, in the event that these substances and mixtures 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 (a) (ii) and 3 (b) (i) of the UN-MTC. This information should be documented in the SDS.

Burning properties

Although there are currently no dedicated storage guidelines for self-reactive substances and mixtures (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 2.15 on organic peroxides.

Flash point

The flash point for liquid self-reactive substances or mixtures is only relevant in the temperature range where the product is thermally stable. Above the SADT of the self-reactive substance or mixture, flash point determination is not relevant because decomposition products are evolved.

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

Auto-ignition temperature

The determination of the auto ignition temperature is not relevant for self-reactive substances and mixtures, 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 and mixtures vapours when they decompose, can never be excluded. This information should be documented in the SDS.

Self-ignition temperature

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

Control and Emergency temperatures

The Control and Emergency temperatures are based on the SADT as determined by UN Test H.4. The Dewar vessel used in the UN Test H.4 is supposed to be representative for the substance or mixture handled in packages. For handling of the substance or mixture 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 degree of insulation. From that SADT the Control and Emergency temperatures can be derived (see also Section 2.15.4.3)

2.8.4.3.3. Additional classification considerations

Currently, the following properties are not incorporated in the classification of self-reactives under the CLP:

- mechanical sensitivity i.e. impact and friction sensitivity (for handling purposes);
- burning properties (for storage purposes);
- flash point for liquids; and
- burning rate for solids.

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.*

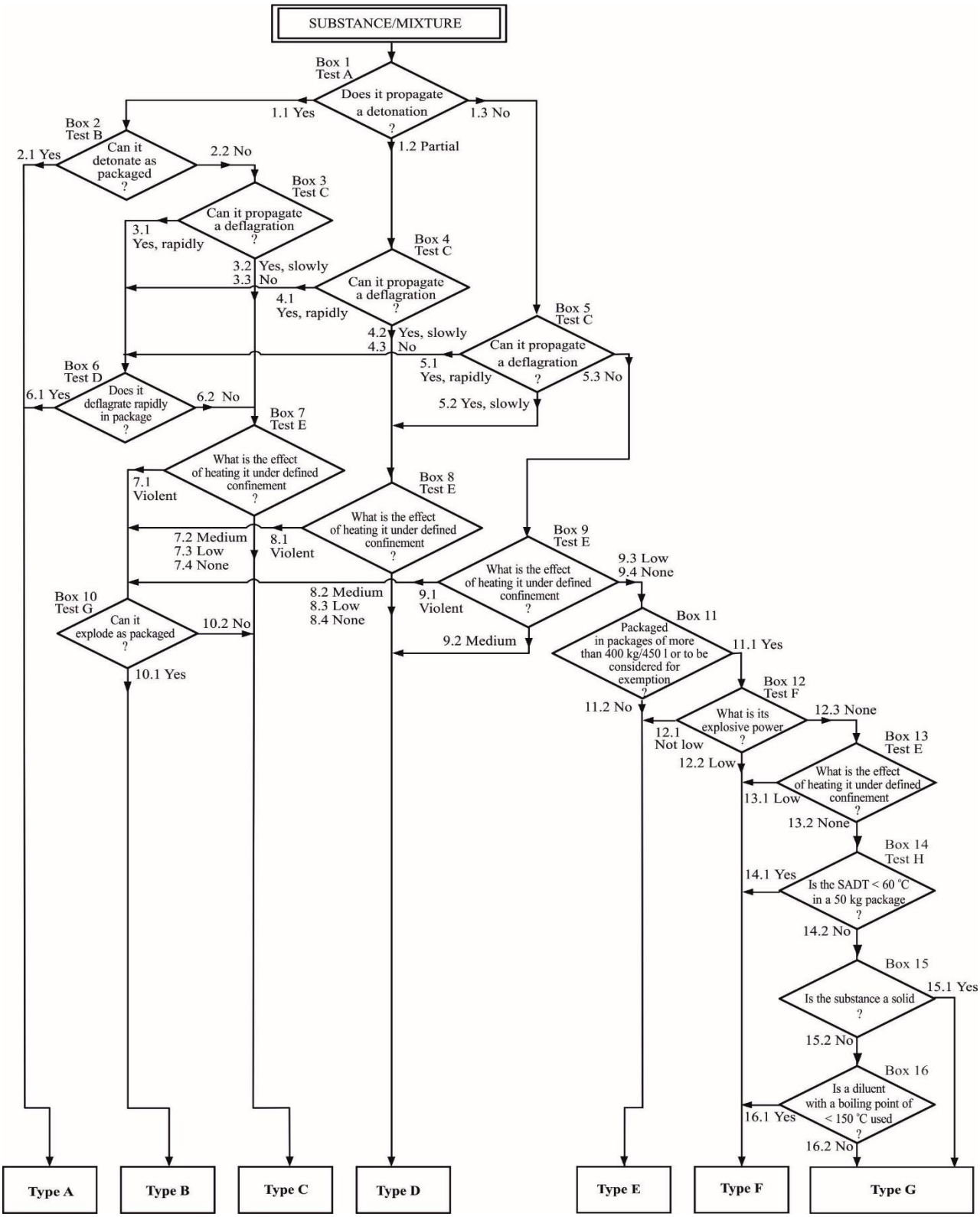
Please note that polymerising substances do not fulfil the criteria for classification as self-reactives. However, there are on-going discussions at the UNSCEGHS on this subject.

2.8.4.4. Decision logic

Classification of self-reactive substances and mixtures is done according to decision logic 2.8 as included in the GHS.

NOTE: The person responsible for the classification of self-reactive substances and mixtures should be experienced in this field and be familiar with the criteria for classification.

Figure 2.5 Decision logic 2.8 for self-reactive substances and mixtures



2.8.5. Hazard communication for self-reactives

2.8.5.1. Pictograms, signal words, hazard statements and precautionary statements

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

Annex I: *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[2]*
GHS pictograms					*There are no label elements allocated to this hazard category*
Signal Word	*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 P234 P235 P240 P280*	*P210 P234 P235 P240 P280*	*P210 P234 P235 P240 P280*	*P210 P234 P235 P240 P280*	
Precautionary statement Response	*P370 + P372 + P380 + P373*	*P370 + P380 + P375 [+P378][1]*	*P370 + P378*	*P370 + P378*	
Precautionary statement Storage	*P403 P411 P420*	*P403 P411 P420*	*P403 P411 P420*	*P403 P411 P420*	
Precautionary statement Disposal	*P501*	*P501*	*P501*	*P501*	

[1] See the introduction to Annex IV for details on the use of square brackets.

[2] Type G has no hazard communication elements assigned but should be considered for properties belonging to other hazard classes.

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

2.8.6. Relation to transport classificationaccording to DSD and DPD or already classified for transport

Division 4.1 within Class 4 of the UN RTDG Model Regulations covers flammable substances, solid desensitized explosives and self-reactive liquids or solids. A list of already classified self-reactive substances is included in UN RTDG Model Regulations, Section 2.4.2.3.2.3. This table includes self-reactive substances of various types from type B to type F. See Annex VII for additional information on transport classification in relation to CLP classification.

2.8.7. Examples of classification for self-reactives

2.8.7.1. Examples of substances and mixtures fulfilling the classification criteria

Substance to be classified: NP

Molecular formula: n.a.

According to CLP Annex I, Section 2.8.2.1, the substance has:

- an energy content of 1452 kJ/kg; and
- a SADT of 45 °C (in 50 kg package);

and consequently it has to be considered for classification in the hazard class self-reactive substances and mixtures.

Test results and classification according to CLP decision logic 2.8.1 for self-reactive substances and mixtures and the UN - MTC, Part II, is as follows:

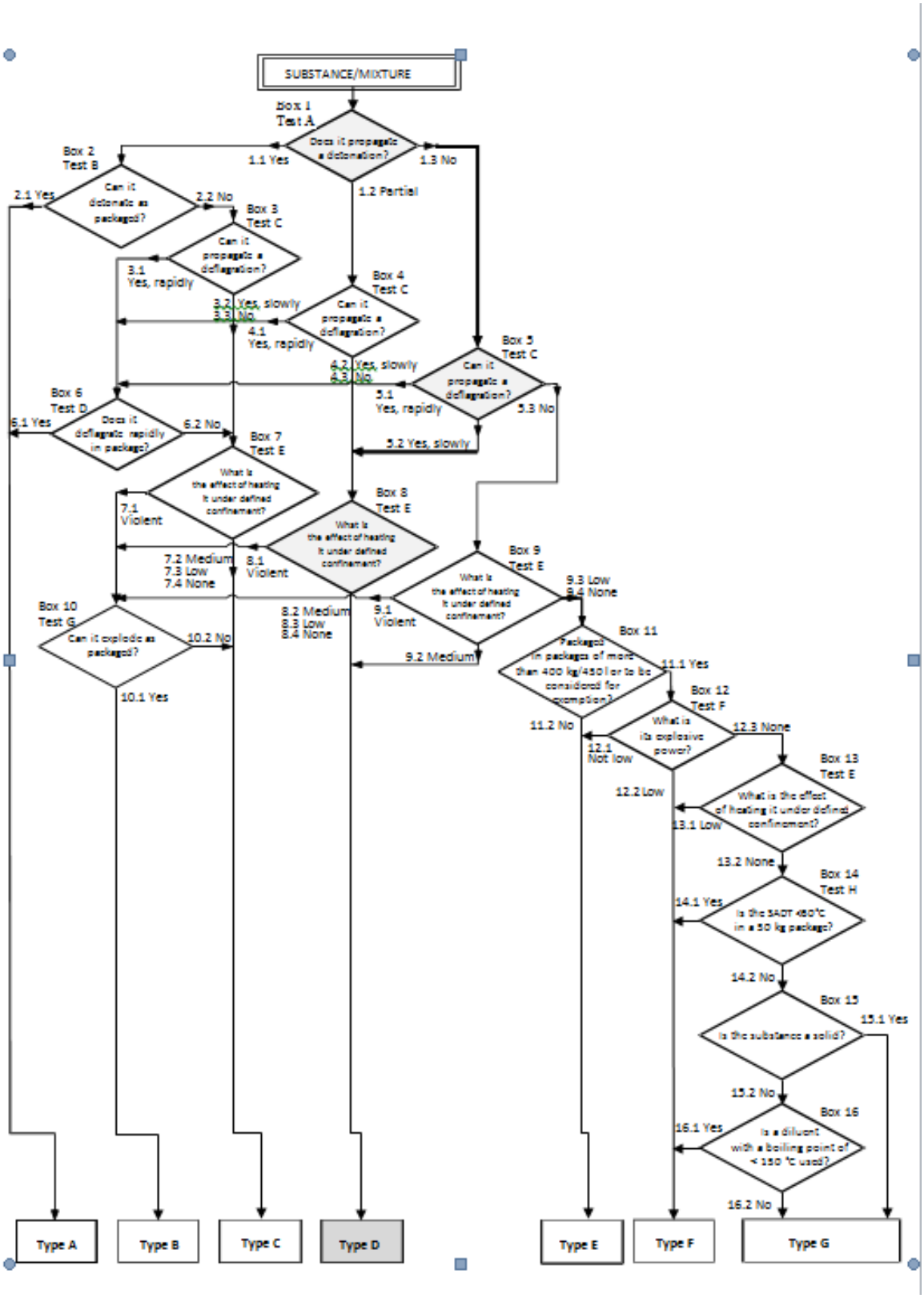
CLASSIFICATION TEST RESULTS	
1. Name of the self-reactive substance or mixture:	NP
2. General data	
2.1. Composition	NP, technically pure
2.2. Molecular formula	n.a.
2.3. Physical form	solid, fine powder
2.4. Colour	brown
2.5. Density (apparent)	460 kg/m^3
3. Detonation (test series A)	
Box 1 of the decision logic	Does the substance 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

CLASSIFICATION TEST RESULTS	
3.4. Result	No
3.5. Exit	1.3
4. Deflagration (test series C)	
Box 5 of the decision logic	Does the substance 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 :	mass 232.5 g. Half life time of cooling of Dewar vessel with 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 (in 50 kg package)

CLASSIFICATION TEST RESULTS	
7. General remarks	The decision logic is given in Figure 2.6
8. Final classification	
Hazard / hazard class:	Self-reactive substance, Type D, solid, temperature controlled
Label	Flame (GHS02)
Signal word	Danger
Hazard statement	H242: 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-MTC, table 28.2.

Figure 2.6 Decision logic for self-reactive substance example: NP, technically pure



2.9. PYROPHORIC LIQUIDS

2.9.1. Introduction

The criteria for 'Pyrophoric liquids' are found in Annex I, Section 2.9 of CLP and are identical to those in Chapter 2.9 of GHS.

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 or mixture 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 and haloacetylene derivatives may show pyrophoricity (Urben, 2007).

There are also pyrophoric substances or mixtures that do not belong to the above mentioned groups of chemicals, i.e. the list above is not exhaustive. Since pyrophoric substances or mixtures 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, 2007).

2.9.2. Definitions and general considerations for the classification pyrophoric liquids

The definition in CLP for pyrophoric liquids is as follows:

Annex I: 2.9.1. *Definition*

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.

2.9.3. Relation to other physical hazards

Pyrophoric substances and mixtures will react spontaneously with air already in small amounts and more or less instantaneously (within minutes). This differentiates them from self-heating substances and mixtures, which also react spontaneously with air but only when in larger amounts and after an extended period of time (hours or days). While liquids in themselves generally do not exhibit self-heating properties due to the limited contact with air (which can occur only at the surface), liquids that are adsorbed onto solid particles should, in general, be considered for classification in the hazard class self-heating substances and mixtures, see Chapter 2.11 of this guidance.

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 and mixtures will also react vigorously with water under the production of flammable gases. Such substances and mixtures may thus be classified in the hazard class substances and mixtures which in contact with water emit flammable gases in addition, see Chapter 2.12 of this guidance. It should be noted in this context that water-reactive substances and mixtures may also to some extent react with the humidity in air, although such a reaction is seldom vigorous. A substance or mixture that spontaneously ignites in air in accordance with the test procedures is to be considered pyrophoric, regardless of the reaction mechanism.

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, see Section 2.6 of this guidance.

2.9.4. Classification of substances and mixtures as pyrophoric liquids

2.9.4.1. Identification of hazard information

Since the tests to determine pyrophoricity are simple and require no special equipment, see Section 2.9.4.4 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 2.9.4.2 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 2.0.4. Naturally, all data sources should be carefully evaluated with regard to reliability and scientific validity.

2.9.4.2. Screening procedures and waiving of testing

In case a liquid is known from practical handling to be pyrophoric no testing is necessary. Such liquids are classified as pyrophoric liquids without testing. This would also be the case if the liquid 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, the classification procedure for pyrophoric liquids need not be applied when experience in manufacture or handling shows that the liquid does not ignite spontaneously on coming into contact with air at normal temperatures (i.e. the liquid is known to be stable at room temperature for prolonged periods of time (days)).

2.9.4.3. Classification criteria

Section 2.9.2.1 of Annex I of CLP specifies the classification criteria:

Annex I: *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.*

2.9.4.4. Testing and evaluation of hazard information

In Section 2.9.2.1 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 RTDG, Manual of Tests and Criteria according to Table 2.9.1:*

The UN Test N.3 for pyrophoricity is quite simple and sufficiently described in Part III, 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 or mixture 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. 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. The filter paper test of UN Test N.3 for pyrophoric liquids should be carried out at 25 ± 2 °C and a relative humidity of 50 ± 5 % (see UN-MTC, Section 33.3.1.5).

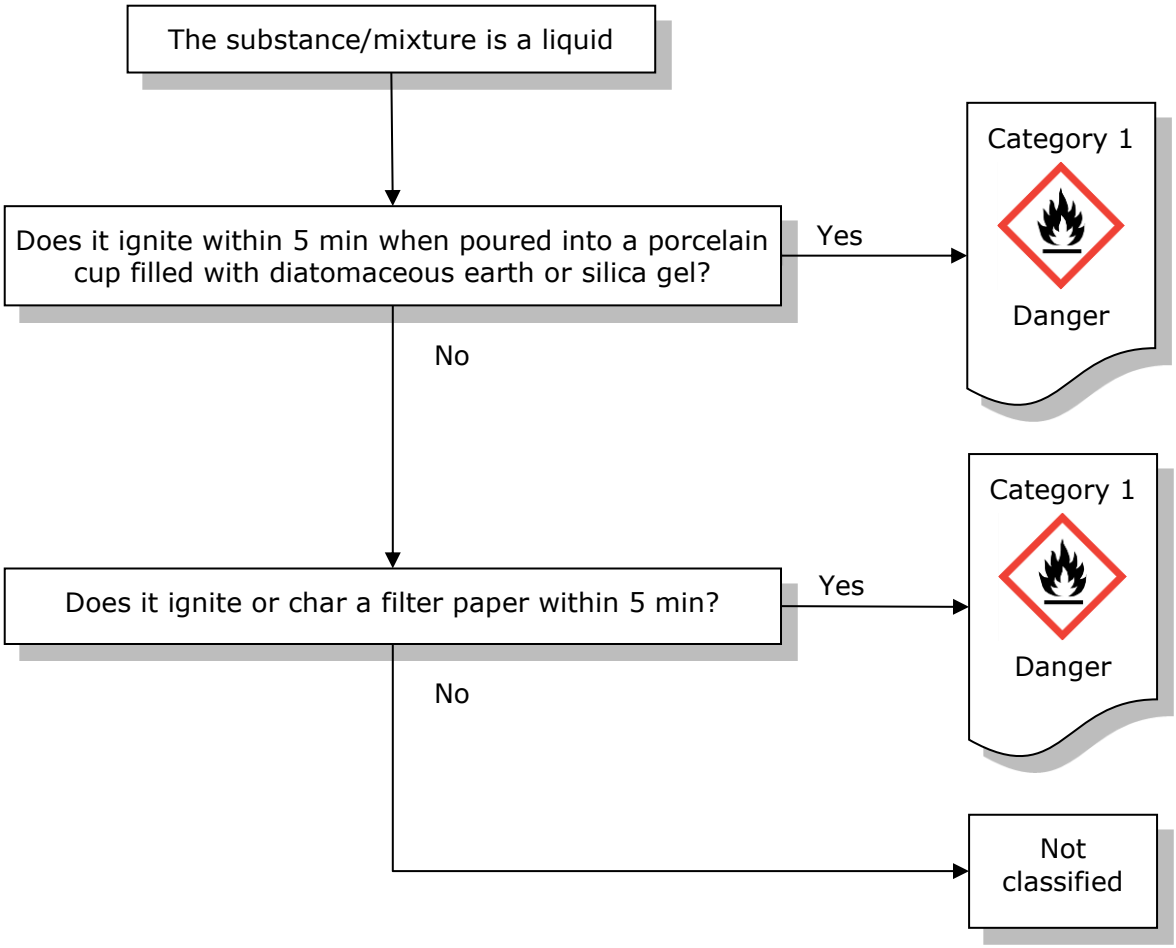
2.9.4.5. Decision logic

Classification of pyrophoric liquids is done according to decision logic 2.9.4.1 as included in the GHS.

NOTE: The person responsible for the classification of pyrophoric liquids should be experienced in this field and be familiar with the criteria for classification.

2.9.4.5.1. Decision logic for pyrophoric liquids

Figure 2.7 Decision logic for pyrophoric liquids (Decision logic 2.9 of GHS)



2.9.5. Hazard communication for pyrophoric liquids

2.9.5.1. Pictograms, signal words, hazard statements and precautionary statements

Annex I: *2.9.3* *Table 2.9.2* ***Label elements for pyrophoric liquids***	
Classification	*Category 1*
GHS Pictogram	
Signal Word	*Danger*
Hazard Statement	*H250: Catches fire spontaneously if exposed to air*
Precautionary Statement Prevention	*P210* *P222* *P231 + P232* *P233* *P280*
Precautionary Statement Response	*P302 + P334* *P370 + P378*
Precautionary Statement Storage	
Precautionary Statement Disposal	

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

2.9.6. Relation to transport classification

Division 4.2 within Class 4 of the UN RTDG Model Regulations covers pyrophoric solids, liquids and self-heating substances and mixtures. UN Test N.3 that is used for classification for pyrophoricity for liquids according to CLP is also used for classification in the subdivision pyrophoric substances and mixtures in Division 4.2: Substances liable to spontaneous combustion according to the UN RTDG Model Regulations. The criteria for Category 1 according to CLP (which is the only category for pyrophoric liquids) and for packing group I in Division 4.2 according to the modal transport regulations (ADR, RID, ADN and IMDG Code, ICAO TI) are also exactly the same. Furthermore, all pyrophoric substances and mixtures are assigned to packing group I within Division 4.2, which is used exclusively for pyrophoric substances and mixtures.

Therefore, any liquid assigned to Division 4.2, packing group I according to the modal transport regulations (ADR, RID, ADN and IMDG Code, ICAO TI) will be classified in Category 1 of the hazard class pyrophoric liquids according to CLP. See Annex VII for additional information on transport classification in relation to CLP classification.

2.9.7. Examples of classification for pyrophoric liquids

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

2.9.7.1. Examples of substances and mixtures fulfilling the classification criteria

2.9.7.1.1. Example 1

Name:	Pyrpherdine
Physical state:	Liquid
Pyrophoric properties:	Unknown, therefore the UN Test N.3 of the UN-MTC was applied. However, when opening the receptacle in order to perform the test, Pyrpherdine self-ignited.
Classification:	Pyrophoric liquid, Category 1

2.9.7.1.2. Example 2

Name:	Qulipyr
Physical state:	Liquid
Pyrophoric properties:	Unknown, therefore the UN Test N.3 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

2.9.7.2. Examples of substances and mixtures not fulfilling the classification criteria

2.9.7.2.1. Example 3

Name:	Notpyratal
Physical state:	Liquid
Pyrophoric properties:	Unknown, therefore UN 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

2.9.8. References

Urben, Peter G. (2007). *Bretherick's Handbook of Reactive Chemical Hazards*, Volumes 1-2 (7th Edition). Elsevier.

2.10. PYROPHORIC SOLIDS

2.10.1. Introduction

The criteria for 'Pyrophoric solids' are found in Annex I, Section 2.10 of CLP and are identical to those in Chapter 2.10 of GHS.

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 self-ignition temperature for a pyrophoric substance or mixture 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, 2007). 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 solids that do not belong to the above mentioned groups of chemicals, i.e. the list above is not exhaustive. Since pyrophoric solids ignite *spontaneously* in air, pyrophoricity is a very dangerous property. In case of doubt it should therefore be thoroughly investigated whether a given solid is pyrophoric. More information on pyrophoric solids can e.g. be found in *Bretherick's Handbook of Reactive Chemical Hazards* (Urben, 2007).

2.10.2. Definitions and general considerations for the classification pyrophoric solids

The definition in CLP for pyrophoric solids is as follows:

> **Annex I: *2.10.1. Definition***
>
> *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

> **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.*

The finer the particle size of a solid, 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 or 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.

2.10.3. Relation to other physical hazards

Pyrophoric solids will react spontaneously with air already in small amounts and more or less instantaneously (within minutes). This differentiates them from self-heating substances and mixtures, which also react spontaneously with air but only when in larger amounts and after an extended period of time (hours or days). A solid which is not classified as a pyrophoric solid may thus belong to the hazard class self-heating substances and mixtures, and should be considered for classification in that hazard class, see Chapter 2.11 of this guidance.

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 in addition see Chapter 2.12 of this guidance. It should be noted in this context that water-reactive substances or mixtures 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, see Chapter 2.7 of this guidance, i.e. they may be 'readily combustible solids'.

2.10.4. Classification of substances and mixtures as pyrophoric 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 is taken from literature or other data sources anyway, it is of utmost importance that the correct physical form is considered, see Section 2.0.4. 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 solid is known from practical handling to be pyrophoric no testing is necessary. Such solids are classified as pyrophoric solids without testing. This would also be the case if the solid 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, 2.10.4, the classification procedure for pyrophoric solids 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 or mixture is known to be stable at room temperature for prolonged periods of time (days)).

2.10.4.3. Classification criteria

Section 2.10.2.1 of Annex I of CLP specifies the classification criteria:

Annex I: *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 2.10.2.1 of Annex I of CLP reference to the test-methods are made:

> **Annex I: *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 RTDG, Manual of Tests and Criteria in accordance with Table 2.10.1:*

UN Test N.2 for pyrophoricity is quite simple and sufficiently described in Part III, Section 33 of the UN-MTC. No special equipment is needed. Essentially the solid is exposed to air to see if it ignites.

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 solid 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.

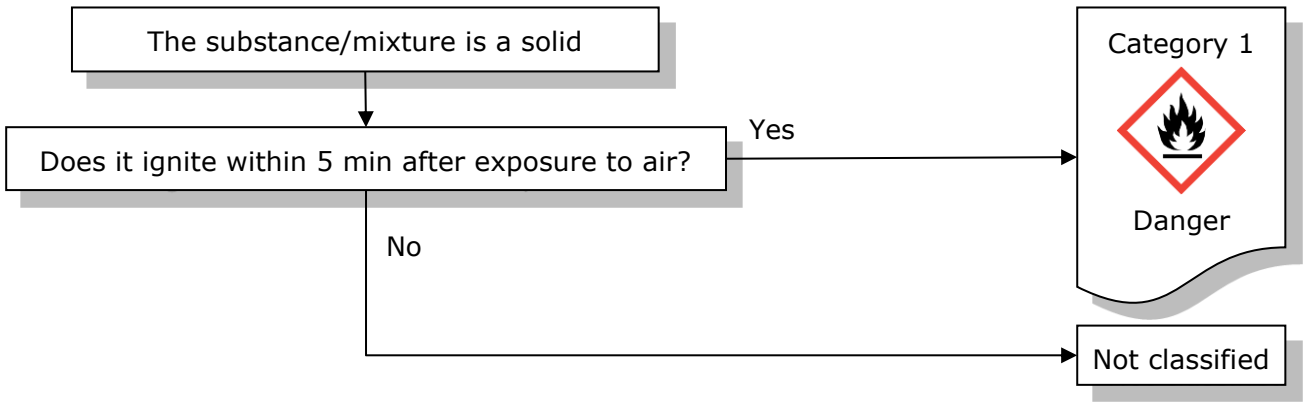
2.10.4.5. Decision logic

Classification of pyrophoric solids is done according to decision logic 2.10.4.1 as included in the GHS.

NOTE: The person responsible for the classification of pyrophoric solids should be experienced in this field and be familiar with the criteria for classification.

2.10.4.5.1. Decision logic for pyrophoric solids

Figure 2.8 Decision logic for pyrophoric solids (Decision logic 2.10 of GHS)



2.10.5. Hazard communication for pyrophoric solids

2.10.5.1. Pictograms, signal words, hazard statements and precautionary statements

Annex I: *2.10.3* *Table 2.10.2* ***Label elements for pyrophoric solids***	
Classification	*Category 1*
GHS Pictogram	
Signal Word	*Danger*
Hazard Statement	*H250: Catches fire spontaneously if exposed to air*
Precautionary Statement Prevention	*P210* *P222* *P231 + P232* *P233* *P280*
Precautionary Statement Response	*P302 + P335 + P334* *P370 + P378*
Precautionary Statement Storage	
Precautionary Statement Disposal	

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

2.10.6. Relation to transport classification

Division 4.2 within Class 4 of the UN RTDG Model Regulations covers pyrophoric solids, liquids and self-heating substances and mixtures. The UN Tests N.2 that is used for classification for pyrophoricity for solids according to CLP is also used for classification in the subdivision pyrophoric substances and mixtures in Division 4.2: Substances liable to spontaneous combustion according to the UN RTDG Model Regulations. The criteria for Category 1 according to CLP (which is the only category for pyrophoric solids) and for packing group I in Division 4.2 according to the modal transport regulations (ADR, RID, ADN and IMDG Code, ICAO TI) are also exactly the same. Furthermore, all pyrophoric substances and mixtures are assigned to packing group I within Division 4.2, which is used exclusively for pyrophoric substances and mixtures.

Therefore, any solid substance or mixture assigned to Division 4.2, packing group I according to the modal transport regulations (ADR, RID, ADN and IMDG Code, ICAO TI) will be classified in Category 1 of the hazard class pyrophoric solids according to CLP. See Annex VII for additional information on transport classification in relation to CLP classification.

2.10.7. Examples of classification for pyrophoric solids

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

2.10.7.1. Examples of substances and mixtures fulfilling the classification criteria

2.10.7.1.1. 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

2.10.7.1.2. Example 2

Name:	Zorapyrole
Physical state:	Solid
Pyrophoric properties:	Unknown, therefore the UN Test N.2 of the UN-MTC was applied.
Test result:	When poured from one meter height according to the test procedure, Zorapyrole self-ignited after two minutes already in the first trial.
Classification:	Pyrophoric solid, Category 1

2.10.7.2. Examples of substances and mixtures not fulfilling the classification criteria

2.10.7.2.1. Example 3

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

2.10.7.2.2. Example 4

Name:	Pyronot
Physical state:	Solid
Pyrophoric properties:	Unknown, therefore UN Test N.2 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

2.10.8. References

Urben, Peter G. (2007). *Bretherick's Handbook of Reactive Chemical Hazards*, Volumes 1-2 (7th Edition). Elsevier.

2.11. SELF-HEATING SUBSTANCES AND MIXTURES

2.11.1. Introduction

The criteria for 'Self-heating substances and mixtures' are found in Annex I, Section 2.11 of CLP and are identical to those in Chapter 2.11 of GHS.

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 low. 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 or mixture pile with the available air in the interspace between the particles.

Since the surface area of a solid substance or mixture exposed to air increases with decreasing particle size, it follows that particle size and shape will greatly influence the propensity of a substance or mixture to self-heat. Therefore it is very important that self-heating properties for solids, and especially powders, are determined for the substance or mixture in the form it is supplied and expected to be used.

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 a substance or a mixture is a process where the gradual reaction of that substance or mixture with oxygen (in the air) generates heat. If the rate of heat production exceeds the rate of heat loss, then the temperature of the substance or mixture will rise which, after an induction time, may lead to self-ignition and combustion.*

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 Determination 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.

EU test method A.16 as described in 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 EU test method A.16 are interpreted towards a CLP classification for self-heating substances and mixtures.

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

Substances or mixtures 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 must be classified in one of the two categories for this class if, in a test performed in accordance with UN Test 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.
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.* ***2.11.2.3.*** *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.*	

2.11.4.4. Testing and evaluation of hazard information

A self-heating substance or mixture must be classified in one of the two categories for this class using UN Test 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 N.4 as described in the latest version of the UN-MTC should be used.

Explosive substances and mixtures 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 behaviour before performing this test. The oven should be equipped with an appropriate pressure-release 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 must 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 and 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-MTC.

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 UN Test 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 with the chosen inert gas is essential in such cases since otherwise much air may be retained between the crystals of the sample in the container.

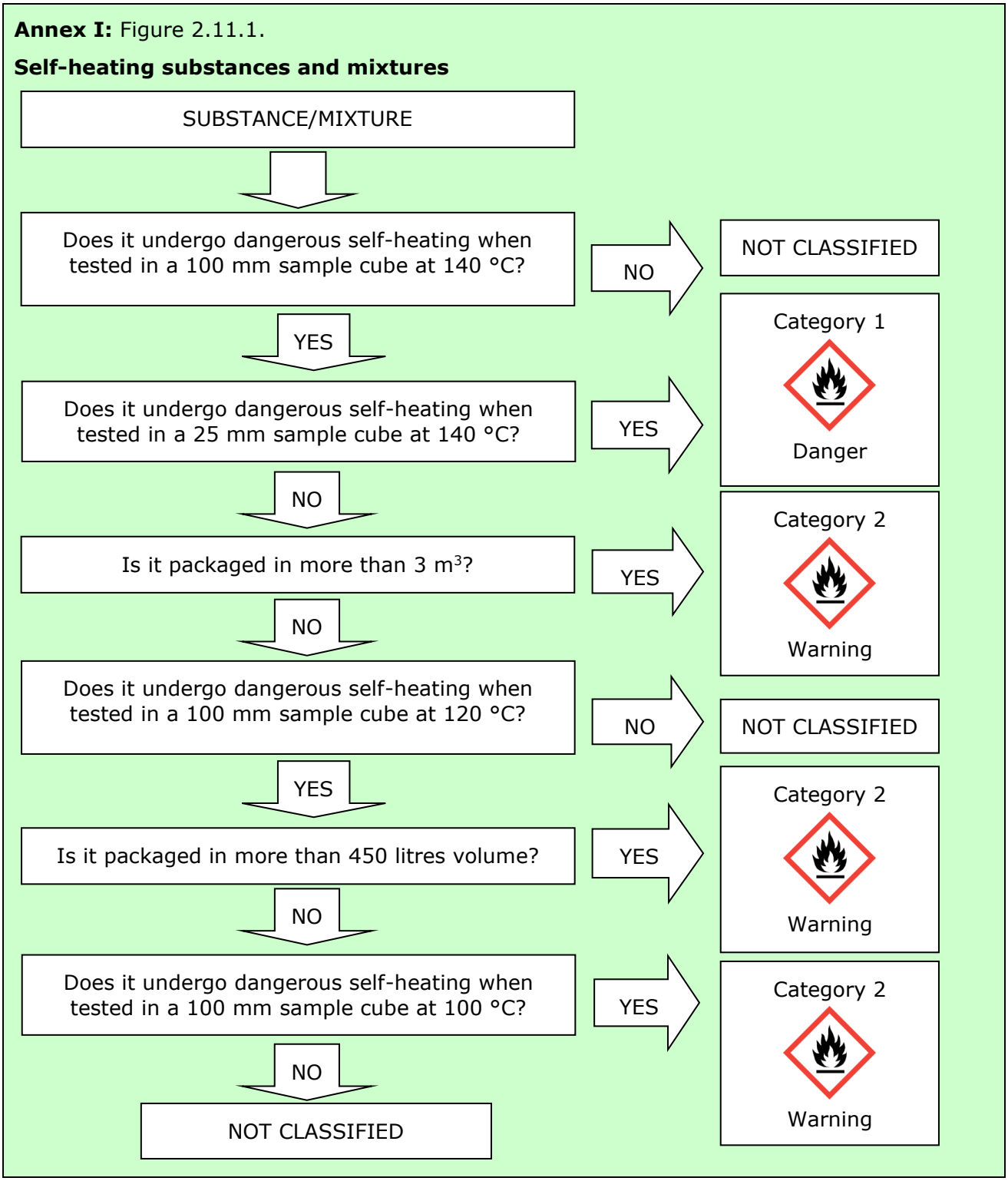
2.11.4.5. Decision logic

The following decision logic for self-heating substances and mixtures is applicable according to CLP.

NOTE: The person responsible for the classification of self-heating substances and mixtures should be experienced in this field and be familiar with the criteria for classification.

Annex I: Figure 2.11.1.

Self-heating substances and mixtures



2.11.4.6. Exemption

The following exemptions apply (see Section 2.11.4.3):

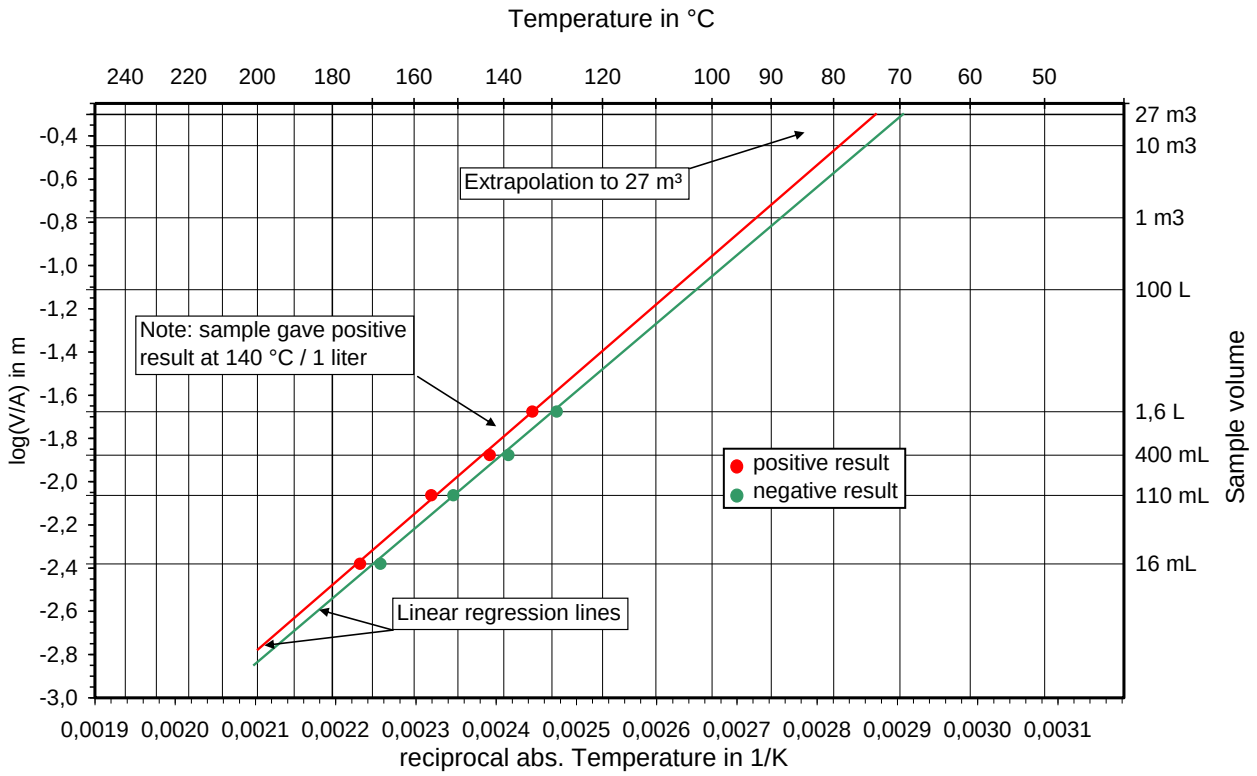
- Substances and mixtures with a temperature of spontaneous combustion higher than 50 °C for a volume of 27 m³ must not be classified as a self-heating substance or mixture.

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

However, the UN-MTC does not provide any guidance on how these values should be determined. The UN test regime is based on the assumption of a cubic sample shape. For the extrapolation to larger volumes, an improved model has to be used. According to Grewer (Grewer, 1994), plotting 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 2.9):

Figure 2.9 Extrapolation towards large volumes



The test setup is essentially the same as in UN 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 over a range of at least four different volumes 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 must 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: *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* *P280*	*P235* *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. Relation to transport classification

Division 4.2 – substances and mixtures liable to spontaneous combustion – within Class 4 of the UN RTDG Model Regulations comprises the following entries:

a. pyrophoric substances and mixtures ;

b. self-heating substances and mixtures.

Whereas pyrophoric substances and mixtures in the modal transport regulations (ADR, RID, ADN and IMDG Code, ICAO TI) are assigned to packing group I, self-heating substances and mixtures 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 UN RTDG Model Regulations, Section 2.0.3) and that self-heating substances and mixtures have a relatively low rank in the precedence of hazards. Therefore, the translation from the modal transport regulations (ADR, RID, ADN and IMDG Code, ICAO TI) to CLP should be only done if a transport classification as self-heating is explicitly available. The conclusion that a substance or mixture not classified as self-heating for transport should not be classified as a self-heating

substance or mixture according to CLP is, in general, not correct. See Annex VII for additional information on transport classification in relation to CLP classification.

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 adsorbed on a large surface.

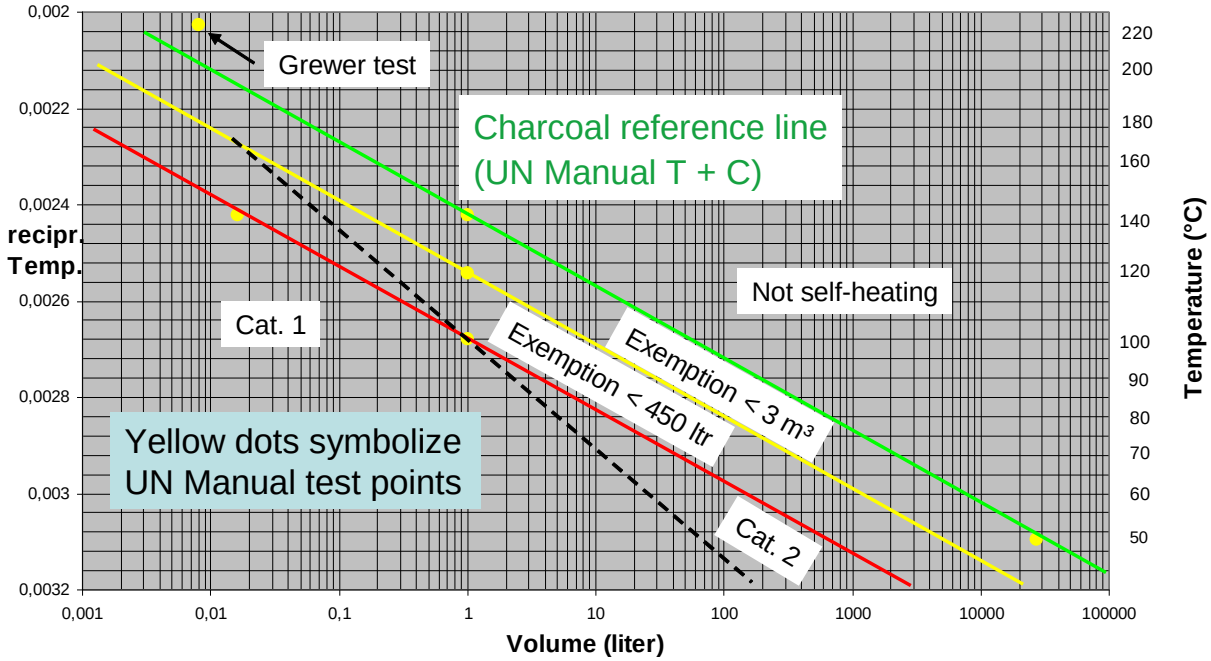
Scientific background

A basic model for the thermal explosion of solids was first developed by Frank-Kamenetzskii (Frank-Kamenetzskii, 1969). 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 2.10). The black dotted line in Figure 2.10 separates Category 1 from Category 2. For examples of results following the Test N.2 see Section 33.3.1.4.5 of UN-MTC.

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 2.10 Volume dependency of the critical temperature for charcoal



2.11.8. References

Grewer, T. (1994). *Thermal hazards of chemical reactions*, Elsevier.

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

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

2.12.1. Introduction

The criteria for 'Substances and mixtures which, in contact with water, emit flammable gases' are found in Annex I, Section 2.12 of CLP and are identical to those in Chapter 2.12 of GHS.

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 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 or mixture 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 2.1 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

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. Relation to other physical hazards

If the chemical identity of the emitted gas is unknown, the gas must be tested for flammability (unless it ignites spontaneously). Other than under DSD/DPD, pyrophporic liquids and

pyrophoric solids have to be considered for classification in this hazard class as well and data about pyrophoric properties are needed prior to testing for this hazard class.

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

2.12.4.1. 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.

See also *IR & CSA, Chapter R.7a: Endpoint specific guidance*, Section R.7.1.7 (Water solubility), R.7.1.14 (Granulometry).

Information about the chemical structure is used to check whether the substance or mixture contains metals and/or metalloids.

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 or mixture is manufactured with water or washed with water (see Section 2.12.4.4.1).

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 must be tested for flammability (see Section 2.2).

In case of pyrophoric substances and mixtures the UN Test N.5 of the UN-MTC, Part III, Section 33.4.1.3.1 must be executed under nitrogen atmosphere. Therefore, data about pyrophoric properties are needed prior to testing.

The melting point, boiling point and information about viscosity are necessary to identify the physical state of the substance or mixture. See also *IR & CSA, Chapter R.7a: Endpoint specific guidance*, Section R.7.1.2 (Melting point/freezing point), R.7.1.3 (Boiling point), R.7.1.18 (Viscosity).

Even though the UN Test N.5 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 UN Test N.5. For further details regarding the test procedure see Section 2.12.4.4.1.

The references in Section 2.12.8 provide good quality data on physical hazards.

2.12.4.2. Screening procedures and waiving of testing

For the majority of substances and mixtures, 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.

2.12.4.3. 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.*

2.12.4.4. Testing and evaluation of hazard information

2.12.4.4.1. Testing procedure

Care must be taken during testing as the emitted gas might be toxic or corrosive.

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 must be carried out by experienced personnel. Some of these factors are described in the following:

2. Apparatus / measuring technique

In UN Test N.5 no special laboratory apparatus / measuring technique to determine the rate of gas evolution is required and no reference material is prescribed. As demonstrated in the past by a round robin test (Kunath, K. *et al*. 2011), the gas evolution rate measured by different apparatuses may vary widely. 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.

3. 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 or mixture is friable, then the complete sample must be ground to a powder before testing to account for a possible reduction in particle size during handling and transport.

In certain cases, grinding 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 provided in the test report.

4. 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 must 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 highly recommended. The results of the blank test should be noted in the test report.

5. Test with demineralised (distilled) water

The UN Test N.5 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 using demineralised water. This should be taken into account when handling substances and mixtures which in contact with water emit flammable gases.

6. Stirring procedures during the test

Stirring of the sample or 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 or 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 moistening of the sample becomes impossible (see Kunath K. *et al*., 2011).

7. Spontaneous ignition

Spontaneous ignition of the evolved gas without contact with an additional ignition source, i.e. without the flame of the gas burner results in classification as Category 1. This does not necessarily mean that the evolved gas is pyrophoric but often the heat of reaction is sufficient to ignite the evolved gas (e.g. the hydrogen evolved when sodium reacts with water).

2.12.4.4.2. Evaluation of hazard information

In order to accurately interpret the test results the evaluating person must 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 criteria for assignment to Category 2 or 3 are gas evolution rates of 20 and 1 litre per kilogram of substance or mixture per hour, respectively, but for Category 1 the relevant criterion is 10 litres per kilogram of substance or mixture over any one minute period (if the gas does not ignite spontaneously). This has to be considered while testing and for correct evaluation of the test results.

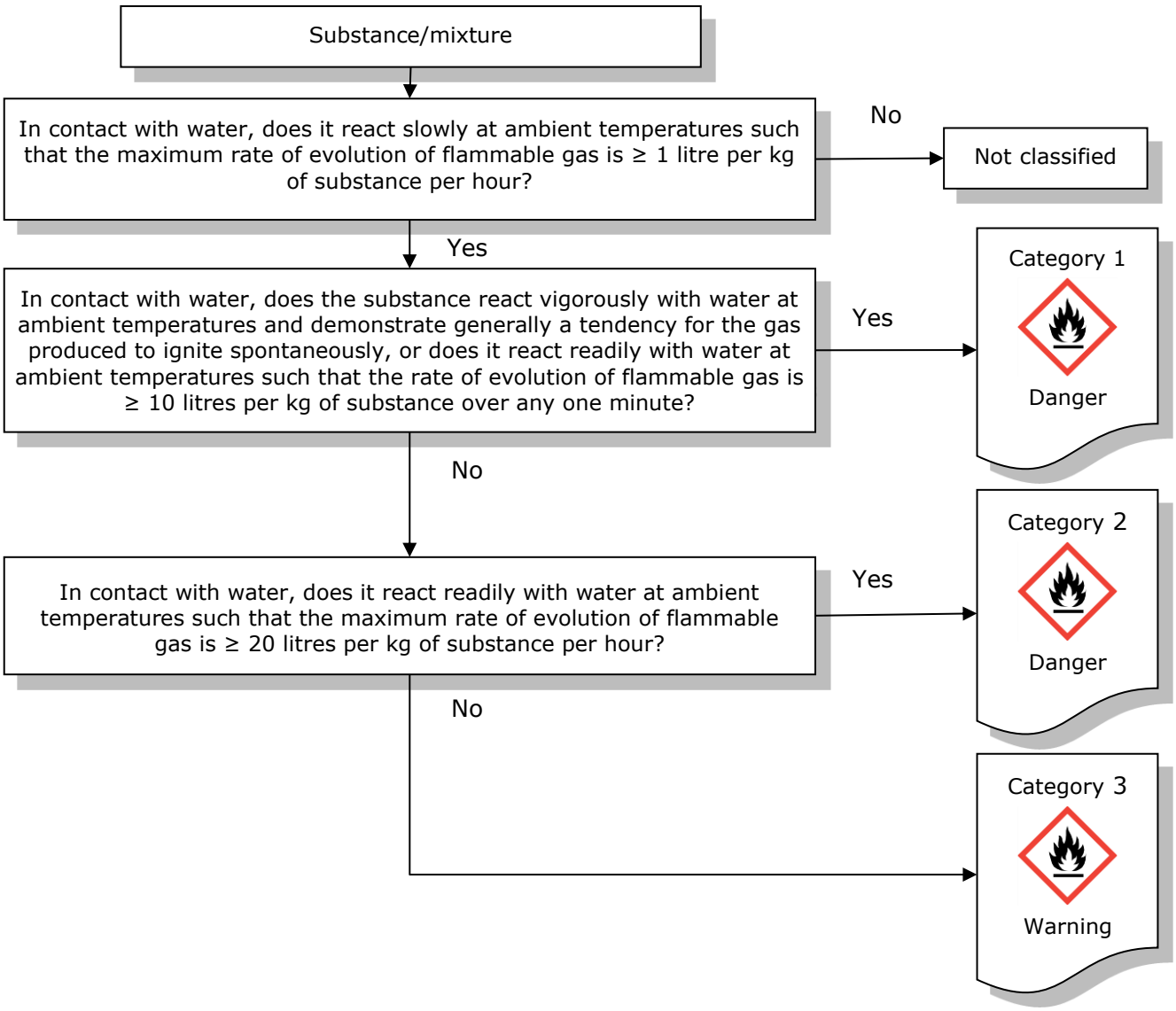
The assignment to the respective hazard class/category will further determine the technical means to be taken to avoid dangerous events which, in combination with other safety characteristics such as i) explosion limits, ii) flash points (applicable only for liquids) or iii) self-ignition temperature,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

2.12.4.5. Decision logic

Classification of substances and mixtures which, in contact with water, emit flammable gases is done according to decision logic 2.12.4.1 as included in the GHS.

NOTE: The person responsible for the classification of substances and mixtures which, in contact with water, emit flammable gases should be experienced in this field and be familiar with the criteria for classification.

Figure 2.11 Decision logic for substances and mixtures which, in contact with water, emit flammable gases (Decision logic 2.12 of GHS)



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

2.12.5.1. Pictograms, signal words, hazard statements and precautionary statements for substances and mixtures

Annex I: *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	*P302 + P335 + P334* *P370 + P378*	*P302 + P335 + 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.

2.12.5.2. Additional labelling provisions

Annex II of CLP provides the following additional labelling provisions for water-reactive substances and mixtures. These statements must 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.*

2.12.6. Relation to transport classification

Division 4.3 within Class 4 of the UN RTDG Model Regulations covers substances and mixtures which in contact with water emit flammable gasses. Substances and mixtures which are classified and/or labelled in Division 4.3 in the modal transport regulations (ADR, RID, ADN and IMDG Code, ICAO TI) are classified as substances and mixtures which, in contact with water, emit flammable gases under CLP. See Annex VII for additional information on transport classification in relation to CLP classification.

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

2.12.7.1. Example of a substance fulfilling the classification criteria

Many different types of chemicals may belong to the hazard class of substances and mixtures which, in contact with water, emit flammable gases, 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, 2007).

2.12.7.1.1. Example 1

PYROPHORIC SUBSTANCE FULFILLING THE CRITERIA FOR CLP CLASSIFICATION	
Substance:	Magnesium alkyls (Index No. 012-003-00-4)
Chemical structure:	R_2Mg
Flammable gas:	Hydrogen
Gas evolution rate:	not applicable
Spontaneous ignition:	not possible due to the nitrogen atmosphere during the UN Test N.5
DSD classification:	F; R14-17
Transport classification:	-
Reference:	Former Annex I to DSD and Annex VI to CLP
⇒ CLP Classification:	**Water-react. 1; H260** **Pyr. Sol. 1; H250**
Supplemental Hazard Information:	**EUH014**

2.12.7.2. Example of a substance not fulfilling the classification criteria

2.12.7.2.1. Example 2

MANGANESE ETHYLENE BIS (DITHIOCARBAMATE) COMPLEX WITH ZINC SALT 88 % (MANCOZEB)	
Gas evolution rate:	0 litres per kilogram of substance per hour.
Spontaneous ignition:	not applicable
Transport classification:	not Class 4.3
Reference:	UN Test N.5, UN-MTC Table 33.4.1.4.5
⇒ CLP Classification:	**Not classified as substance which, in contact with water, emit flammable gases**

2.12.8. References

William M. Haynes *et al.* (2012) *CRC Handbook of Chemistry and Physics 93rd Edition*. CRC Press, Taylor and Francis, Boca Raton, FL

GESTIS-database on hazardous substances: http://www.dguv.de/bgia/en/gestis/stoffdb/index.jsp

O'Neil, Maryadele J. *et al.* (2016, 2012) *The Merck Index - An Encyclopaedia of Chemicals, Drugs, and Biologicals* (14th Edition – Version 14.9). Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.

Urben, Peter G. (2007). *Bretherick's Handbook of Reactive Chemical Hazards*, Volumes 1-2 (7th Edition). Elsevier.

Kunath, K., Lüth, P., Uhlig, S. (2011). *Interlaboratory test on the method UN Test N.5 / EC A.12 "Substances which, in contact with water, emit flammable gases" 2007*.Short report. BAM Bundesanstalt für Materialforschung und –prüfung. Berlin. ISBN 978-3-9814634-1-5. http://www.bam.de/de/service/publikationen/publikationen_medien/short_report_rv_un_n_5.pdf

2.13. OXIDISING LIQUIDS

2.13.1. Introduction

The criteria for 'Oxidising liquids' are found in Annex I, Section 2.13 of CLP and are identical to those in Chapter 2.13 of GHS.

The hazard class oxidising liquids comprises liquid 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 substances or mixtures. This is for example the case when a solid material (e.g. wood) is soaked with an oxidising liquid.

Certain combinations of combustible materials and oxidising substances or mixtures 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 or mixtures.

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

The hazards communication of oxidising liquids 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 testing procedure and criteria for oxidising substances or mixtures do not work properly for ammonium nitrate compounds or solutions, ammonium nitrate based fertilizers and ammonium nitrate emulsions, suspensions or gels. Therefore for classification and labelling of substances or mixtures containing ammonium nitrate, known experience should be used and expert judgement should be sought. For the classification procedures for ammonium nitrate emulsions, suspensions or gels – intermediate for blasting explosives, see Chapter 2.1 of this guidance.

Annex I: *2.13.4.3*

In the event of divergence between test results and known experience in the handling and use of substances or mixtures which shows them to be oxidising, judgments based on known experience shall take precedence over test results.

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

The CLP text comprises the following definition for oxidising liquids.

Annex I: *2.13.1. Definition*

Oxidising liquid means a liquid 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. Relation to other physical hazards

Oxidising liquids that are mixed with combustible materials or reducing agents may have explosive properties and should be considered for classification in the hazard class Explosives (including the applicable screening procedures), see Chapter 2.1 of this guidance.

In rare cases, mixtures with oxidising liquids may exhibit self-reactive behaviour, see Chapter 2.8 of this guidance. Expert judgement should be sought in case of doubt.

The classification procedure and criteria for oxidising substances or mixtures is not applicable for organic peroxides. Under DSD organic peroxides were considered to be oxidising substances or mixtures 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 liquids. Organic peroxides were classified as oxidising (O; R7) according to the DSD, which was not appropriate since the vast majority of them do not exhibit oxidising properties.

Inorganic oxidising liquids are not flammable and therefore do not have to be subjected to the classification procedures for the hazard classes flammable liquids or pyrophoric liquids. Also other liquids that are classified as oxidising liquids are normally not flammable, although a few exemptions may exist. Expert judgement should be sought in case of doubt.

2.13.4. Classification of substances and mixtures as oxidising liquids

2.13.4.1. Identification of hazard information

Oxidising liquids 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 class oxidising liquids. This does not necessarily mean that every substance or mixture containing oxygen and/or halogen atoms should be subjected to the full testing procedure.

2.13.4.1.1. Screening procedures and waiving of testing

Liquids that are classified as explosives should not be subjected to the testing procedures for oxidising liquids.

Organic peroxides should be considered for classification within the hazard class organic peroxides, see Chapter 2.15 of this guidance.

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 liquids. 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 and mixtures. 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 must be performed.

For organic substances or mixtures the classification procedure for this hazard class 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 this hazard class 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 class 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 waiving 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. 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 substance and a non-hazardous inert substance 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 substance. Hence, the mixture can never be classified into a more severe hazard category.
- If an oxidising substance 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 substance. 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 mixture is not necessary provided that the total concentration of all solid oxidisers in the aqueous solution is less than or equal to 20 % (w/w).

2.13.4.2. Classification criteria

The testing procedures for oxidising liquids are based on the capability of an oxidising liquid to enhance the combustion of a combustible material. Therefore, substances and mixtures 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 liquid 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 material mixtures. The higher the pressure rise rate, the stronger the oxidising capability of the liquid tested.

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 RTDG, 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.*

For additional information regarding the use of non-testing data see Section 2.13.4.3 below and Urben, 2007 (see Section 2.13.7).

2.13.4.3. Testing and evaluation of hazard information

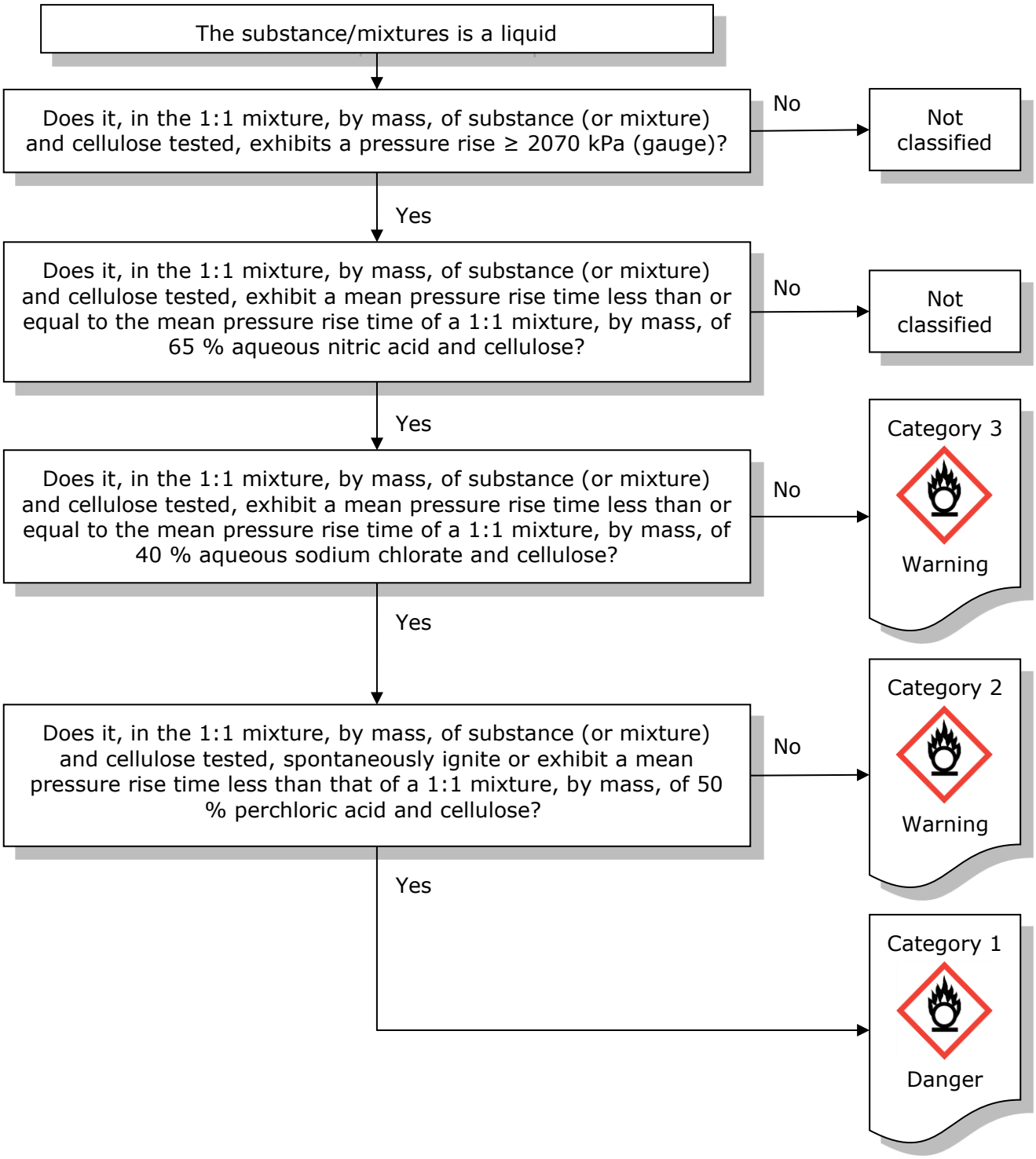
The test methods for oxidising liquids are designed to give a final decision regarding their classification. Apart from testing, also experience in the handling and use of substances or mixtures which shows them to be oxidising is an important additional factor in considering classification in this hazard class. In the event of divergence between test results and known experience, judgement based on known experience should take precedence over test results. However, a substance or mixture must not be classified into a less severe Category based on experience only.

2.13.4.4. Decision logic

Classification of oxidising liquids is done according to decision logic 2.13 as included in the GHS.

⚠ NOTE: The person responsible for the classification of oxidising liquids should be experienced in this field and be familiar with the criteria for classification.

Figure 2.12 Decision logic for oxidising liquids (Decision logic 2.13 of GHS)



2.13.4.5. Hazard communication for oxidising liquids

2.13.4.5.1. Pictograms, signal words, hazard statements and precautionary statements

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

Annex I : *Table 2.13.2* ***Label elements for oxidising liquids***			
	Category 1	*Category 2*	*Category 3*
GHS Pictograms			
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* *P280* *P283*	*P210* *P220* *P280*	*P210* *P220* *P280*
Precautionary Statement Response	*P306 + P360* *P371 + P380 + P375* *P370 + P378*	*P370 + P378*	*P370 + P378*
Precautionary Statement Storage	*P420*		
Precautionary Statement Disposal	*P501*	*P501*	*P501*

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

2.13.5. Relation to transport classification

Division 5.1 within Class 5 of the UN RTDG Model Regulations covers oxidising liquids and oxidising solids, using the same tests and criteria as the CLP. Therefore, a liquid substance or mixture classified as Division 5.1 (sometimes referred to as Class 5.1) according to any of the modal transport regulations (ADR, RID, ADN and IMDG Code, ICAO TI) is normally also classified as an oxidising liquid according to the CLP. Packing Groups I, II and III of the transport regulations correspond directly to Categories 1, 2 and 3 of the CLP, respectively. See Annex VII for additional information on transport classification in relation to CLP classification.

2.13.6. Examples of classification for oxidising liquids

2.13.6.1. 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. For examples of results see Section 34.4.2.5 of UN-MTC.

- Ferric nitrate, saturated aqueous solution
- Lithium perchlorate, saturated aqueous solution
- Magnesium perchlorate, saturated aqueous solution
- Perchloric acid, 55 %
- Sodium nitrate, 45 % aqueous solution

2.13.6.2. Examples of substances and mixtures not fulfilling the classification criteria

- Nickel nitrate, saturated aqueous solution
- Potassium nitrate, 30 % aqueous solution
- Silver nitrate, saturated aqueous solution

2.13.7. Reference

Urben, Peter G. (2007). *Bretherick's Handbook of Reactive Chemical Hazards, Volumes 1-2* (7th Edition). Elsevier.

2.14. OXIDISING SOLIDS

2.14.1. Introduction

The criteria for 'Oxidising solids' are found in Annex I, Section 2.14 of CLP and are identical to those in Chapter 2.14 of GHS.

The hazard class oxidising solids comprises 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 affected by the presence of an oxidising solid. This is for example the case when a liquid fuel (e.g. gas oil) mixes with an oxidising solid. Certain combinations of combustible materials and oxidising substances or mixtures 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 or mixtures.

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 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 testing procedure and criteria for oxidising substances or mixtures do not work properly for ammonium nitrate, ammonium nitrate compounds, ammonium nitrate based fertilizers and ammonium nitrate gels. Therefore, for classification and labelling of substances and mixtures containing ammonium nitrate, known experience should be used and expert judgement should be sought. For the classification procedures for ammonium nitrate gels – intermediate for blasting explosives, see Section 2.1 of this guidance.

Annex I: *2.14.4.3*

In the event of divergence between test results and known experience in the handling and use of substances or mixtures which shows them to be oxidising, judgments based on known experience shall take precedence over test results.

2.14.2. Definitions and general considerations for the classification of oxidising solids

The CLP text comprises the following definition for oxidising solids.

Annex I: *2.14.1. Definition*

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

Special consideration on particle size

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.

Hence it is very important that oxidising properties for solids are investigated on the substance or 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 2 cited in CLP Annex I, 2.14.2.1.

Annex I: *2.14.2.1.*

[…]

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.

2.14.3. Relation to other physical hazards

Oxidising solids that are mixed with combustible materials or reducing agents may have explosive properties and should be considered for classification in the hazard class Explosives (including the applicable screening procedures), see Chapter 2.1 of this guidance.

In rare cases, mixtures with oxidising solids may exhibit self-reactive behaviour, see Chapter 2.8 of this guidance. Expert judgement should be sought in case of doubt.

The classification procedure and criteria for oxidising substances and mixtures 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 comprise a separate hazard class (CLP Annex I, 2.15) and they must not be considered according to the procedures described for oxidising solids. Organic peroxides were classified as oxidising (O; R7) according to the DSD, which was not appropriate since the vast majority of them do not exhibit oxidising properties.

Inorganic oxidising solids are not flammable and therefore do not need to be subject to the classification procedures for the hazard classes flammable solids or pyrophoric solids. Also other solids that are classified as oxidising solids are normally not flammable, although a few exeptions may exist. Expert judgement should be sought in case of doubt.

2.14.4. Classification of substances and mixtures as oxidising solids

2.14.4.1. Identification of hazard information

Oxidising solids may cause, or contribute to, the combustion of other material. Although the definition in Annex I: 2.14.1, quoted above, 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 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.

2.14.4.1.1. Screening procedures and waiving of testing

Solids that are classified as explosives should not be subjected to the testing procedures for oxidising solids.

Organic peroxides should be considered for classification within the hazard class organic peroxides, see Chapter 2.15 of this guidance.

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 solids. 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 and mixtures. The following text provides a guideline for the theoretical evaluation of potential oxidising properties on the basis of its composition and chemical structure. In case of doubt, the full test must be performed.

For organic substances or mixtures the classification procedure for this hazard class need not 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 this hazard class need not be applied if they do not contain oxygen or halogen.

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

Any substance or mixture that complies with the above waiving criteria can be safely regarded to have no oxidising properties and, hence, need not be tested and need not be regarded as 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 substance and a non-hazardous inert substance 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 substance. Hence, the mixture can never be classified into a more severe hazard category.
- If an oxidising substance 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 substance. 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.

2.14.4.2. Classification criteria

The testing procedures for oxidising solids are based on the capability of an oxidising solid to enhance the combustion of a combustible material. Therefore, solids that are submitted to 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 solid and cellulose is then ignited and its behaviour is observed and compared to the behaviour of reference material mixtures.

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.

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 or test O.3 in Part III, sub-section 34.4 3 of the UN RTDG, Manual of Tests and Criteria, in accordance with Table 2.14.1:*

Table 2.14.1

Criteria for oxidising solids

Category	*Criteria using test O.1*	*Criteria using test O.3*
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.*	*Any substance or mixture which, in the 4:1 or 1:1 sample-to-cellulose ratio (by mass) tested, exhibits a mean burning rate greater than the mean burning rate of a 3:1 mixture (by mass) of calcium peroxide 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.*	*Any substance or mixture which, in the 4:1 or 1:1 sample-to-cellulose ratio (by mass) tested, exhibits a mean burning rate equal to or greater than the mean burning rate of a 1:1 mixture (by mass) of calcium peroxide and cellulose 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 or 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.*	*Any substance or mixture which, in the 4:1 or 1:1 sample-to-cellulose ratio (by mass) tested, exhibits a mean burning rate equal to or greater than the mean burning rate of a 1:2 mixture (by mass) of calcium peroxide 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' (IMSBC Code (International Maritime Solid Bulk Cargoes Code, IMO), Appendix 2, Section 5) can be used to assess this hazard. Appropriate information shall be made in the SDS.

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, such as storage in large volumes (multiple tonnes) and either contamination (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 Regulation (EC) No 2003/2003 for ammonium nitrate.

For additional information regarding the use of non-testing data see Section 2.14.4.3 below and Urben, 2007 (see Section 2.14.7).

2.14.4.3. Testing and evaluation of hazard information

The test methods[51] for oxidising solids are designed to give a final decision regarding their classification. It should be recalled that experience in the handling and use of substances or mixtures, besides testing, is an important additional factor in considering classification in this hazard class.

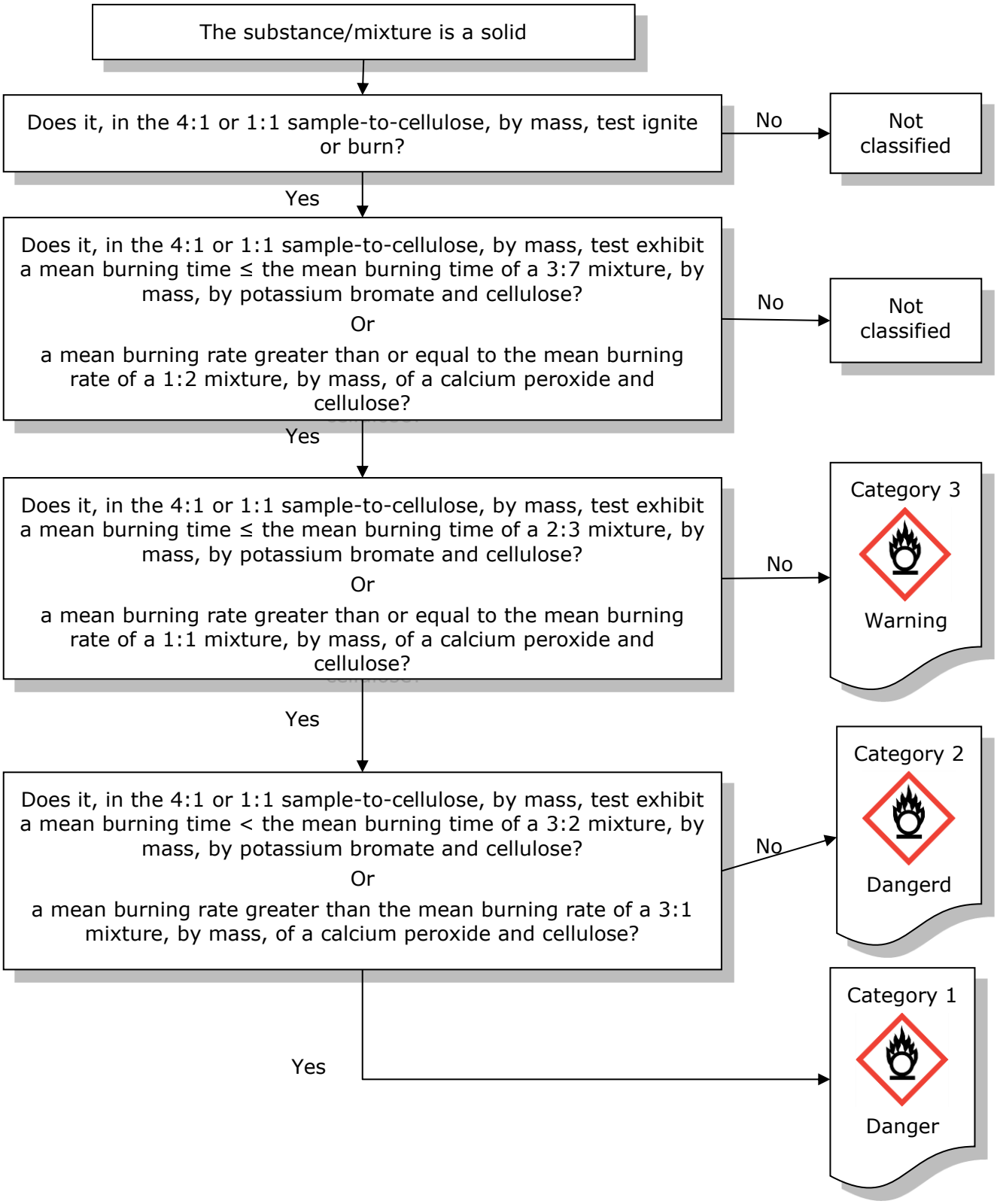
2.14.4.4. Decision logic

Classification of oxidising solids is done according to decision logic 2.14 as included in the GHS.

⚠ NOTE: The person responsible for the classification of oxidising solids should be experienced in this field and be familiar with the criteria for classification.

[51] As from December 2012 an alternative test method for oxidising solids, Test O.3, has been included in the UN MTC (see document ST/SG/AC.10/40/Add.2). Test O.3 is an improved version of Test O.1 using a different reference substance and gravimetric measurements of the burning rate. Reference to Test O.3 has been included in the 5th revised edition of the GHS.

Figure 2.13 Decision logic for oxidising solids (Decision logic 2.14 of GHS)



2.14.4.5. Hazard communication for oxidising solids

2.14.4.5.1. Pictograms, signal words, hazard statements and precautionary statements

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

Annex I: *Table 2.14.2* ***Label elements for oxidising solids***			
	Category 1	*Category 2*	*Category 3*
GHS Pictograms			
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* *P280* *P283*	*P210* *P220* *P280*	*P210* *P220* *P280*
Precautionary Statement Response	*P306 + P360* *P371 + P380 + P375* *P370 + P378*	*P370 + P378*	*P370 + P378*
Precautionary Statement Storage	*P420*		
Precautionary Statement Disposal	*P501*	*P501*	*P501*

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

2.14.5. Relation to transport classification

Division 5.1 within Class 5 of the UN RTDG Model Regulations covers oxidising liquids and oxidising solids, using the same tests and criteria as the CLP. Therefore, a solid substance or mixture classified as Division 5.1 (sometimes referred to as Class 5.1) according to any of the modal transport regulations (ADR, RID, ADN and IMDG Code, ICAO TI) is normally also classified as an oxidising solid according to CLP. Packing Groups I, II and III of the transport regulations correspond directly to Categories 1, 2 and 3 of CLP, respectively. See Annex VII for additional information on transport classification in relation to CLP classification.

2.14.6. Examples of classification for oxidising solids

2.14.6.1. 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. For examples of results see section 34.4.1.5 of UN-MTC.

- Calcium nitrate, anhydrous
- Chromium trioxide
- Potassium nitrite
- Potassium perchlorate
- Potassium permanganate
- Sodium chlorate
- Sodium nitrite
- Sodium nitrate
- Strontium nitrate, anhydrous

2.14.6.2. Examples of substances and mixtures not fulfilling the classification criteria

- Calcium nitrate, tetrahydrate
- Cobalt nitrate, hexahydrate

2.14.7. Reference

Urben, Peter G. (2007). *Bretherick's Handbook of Reactive Chemical Hazards, Volumes 1-2* (7th Edition). Elsevier.

2.15. ORGANIC PEROXIDES

2.15.1. Introduction

The criteria for 'Organic peroxides' are found in Annex I, Section 2.15 of CLP and are identical to those in Chapter 2.15 of GHS.

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 and mixtures which may have various properties. However, the type of peroxide is determined by testing.

2.15.2. Definitions and general considerations for the classification of organic peroxides

In CLP, the following definition is given for 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.*

2.15.3. Relation to other physical hazards

In addition to the definition (CLP Annex I, 2.15.1), organic peroxides may:

a. be flammable;

b. 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 UN RTDG Model Regulations, 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. However, these properties may be of importance for the safe handling of organic peroxides (see Section 2.15.4.3.2, additional testing).

In addition, the following should be noted:

Explosive properties

The explosive properties do not have to be determined according to the CLP Annex I, Chapter 2.1, because explosive properties are incorporated in the decision logic for organic peroxides. Note that organic peroxides may have explosive properties when handled under higher confinement.

Flammable properties

The hazard statement for flammable properties for liquid organic peroxides should be based on the appropriate category for flammable liquids, as long as the flash point is relevant, (see Section 2.15.4.3.2). The translation table in Annex VII to CLP can be used for this.

2.15.4. Classification of substances and mixtures as organic peroxides

2.15.4.1. 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, deflagration and thermal explosion properties, its response to heating under confinement, its explosive power and the concentration and the type of diluent added to desensitize the organic peroxide. Specifications of acceptable diluents that can be used safely are given in the UN RTDG Model Regulations, 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 organic peroxide is tested as it affects the degree of confinement to which the organic peroxide is subjected. This has to be considered when handling the organic peroxide; stronger packaging may result in more violent reactions when the organic peroxide 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 of CLP Figure 2.15.1. 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 UN RTDG Model regulations, Section 2.5.3.2.4.

2.15.4.2. 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.*
>
> *[…]*

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 organic peroxide 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(1), 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.

(1) See UN RTDG, Manual of Test 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 Model Regulations, Section 2.5.3.2.4.

2.15.4.3. Testing and evaluation of hazard information

2.15.4.3.1. 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 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 of an organic peroxide may occur 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 organic peroxide 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, consist of the following two elements:

4. 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.

5. Derivation of control and emergency temperatures:

Type of receptacle	SADT *	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

* i.e. the SADT of the organic peroxide 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 organic peroxide 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 organic peroxide 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.

2.15.4.3.2. Additional considerations and testing

Explosive properties

The sensitivity of organic peroxides to impact (solids and liquids) and friction (solids only) may be of importance for the safe handling of the organic peroxide if they have pronounced explosive properties (e.g. they are liable to detonate, to deflagrate rapidly or show a violent effect when heated under confinement). Test methods to determine these properties are described in Test Series 3 of the UN-MTC (see Test 3 (a) (ii) and 3 (b) (i)). This information on the mechanical sensitivity should be included in the SDS.

Burning properties

In some national storage guidelines the burning rate is commonly used for classification for the purposes of storage and consequential storage requirements. Test methods are incorporated in these national storage regulations.

Flash point

The flash point for liquid organic peroxides is only relevant in the temperature range where the organic peroxide is thermally stable. Above the SADT of the organic peroxide determination of the flash point is not relevant because decomposition products are evolved.

NOTE: In case a flash point determination seems reasonable (expected flash point 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 flash point.

Auto-ignition temperature

The determination of the auto ignition temperature is not relevant for organic peroxides. Available test methods are for non-decomposing vapour phases but the vapours of organic peroxides decompose during execution of the test and auto ignition of these organic peroxide vapours can never be excluded. This information should be included in the SDS.

Self-ignition temperature

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

Control and Emergency temperatures

The Control and Emergency temperatures are based on the SADT as in most cases determined by UN Test H.4. The Dewar vessel used in the UN Test H.4 is supposed to be representative for the organic peroxide handled in packages. For handling the organic peroxide 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 2.15.4.3.1).

2.15.4.3.3. Additional classification considerations

Currently the following properties are not incorporated in the classification of organic peroxides under the CLP:

- mechanical sensitivity i.e. impact and friction sensitivity (for handling purposes);
- burning properties (for storage purposes);
- flash point for liquids; and
- burning rate for solids.

Furthermore:

Annex I: ***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.

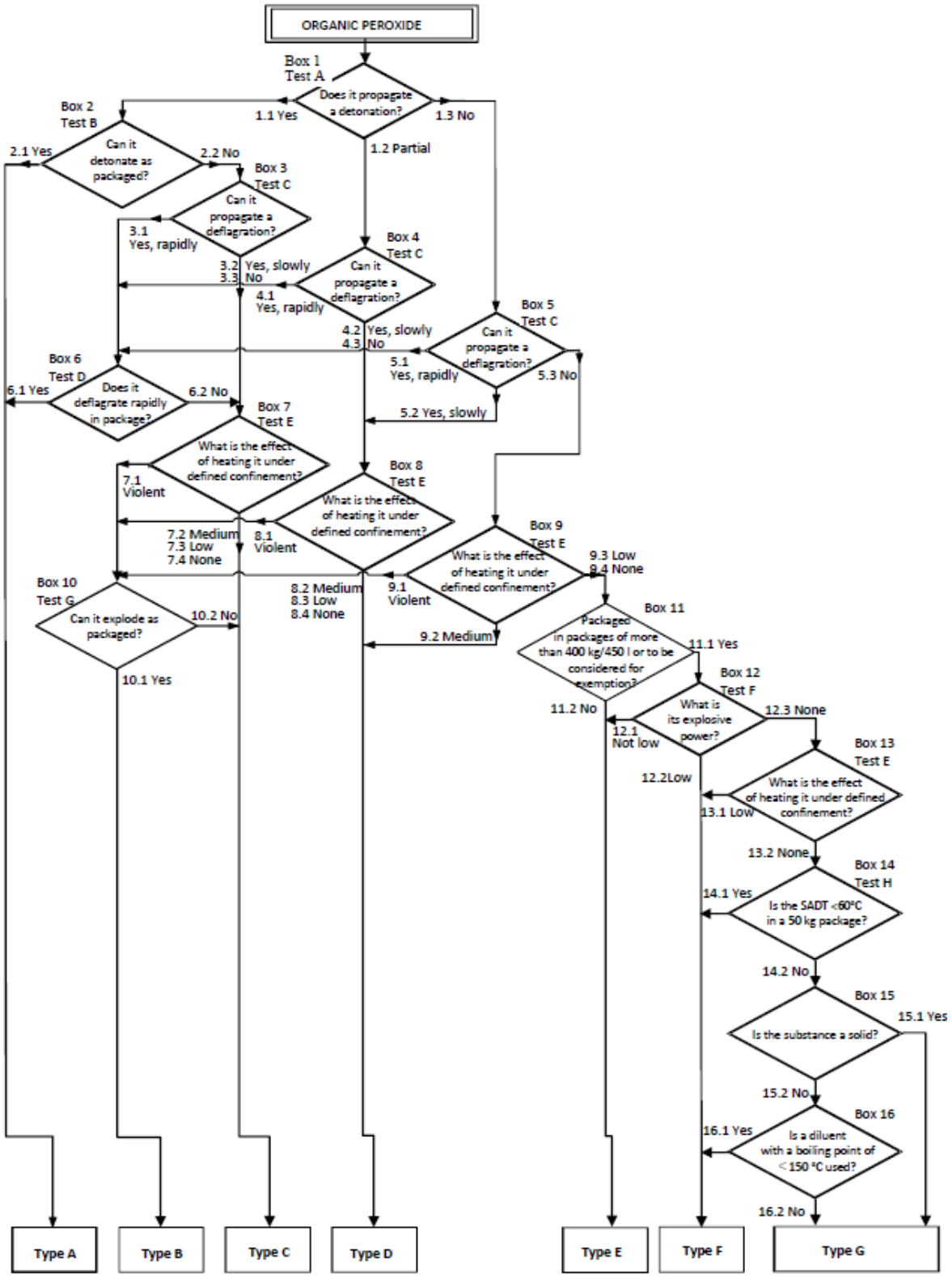
Formulated commercial organic peroxides are classified according to their SADT.

2.15.4.4. Decision logic

The decision logic for organic peroxides is applicable according to CLP.

⚠ NOTE: The person responsible for the classification of organic peroxides should be experienced in this field and be familiar with the criteria for classification.

Figure 2.14 Decision logic 2.15 for organic peroxides



2.15.5. Hazard communication for organic peroxides

2.15.5.1. Pictograms, signal words, hazard statements and precautionary statements

According to CLP the following label elements must be used for organic peroxide 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 Word	*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* *P234* *P235* *P240* *P280*	*P210* *P234* *P235* *P240* *P280*	*P210* *P234* *P235* *P240* *P280*	*P210* *P234* *P235* *P240* *P280*	
Precautionary statement Response	*P370 + P372 + P380 + P373*	*P370 + P380 + P375[+ P378]*[1]	*P370 + P378*	*P370 + P378*	
Precautionary statement Storage	*P403* *P410* *P411* *P420*	*P403* *P410* *P411* *P420*	*P403* *P410* *P411* *P420*	*P403* *P410* *P411* *P420*	
Precautionary statement Disposal	*P501*	*P501*	*P501*	*P501*	

[1] *See introduction to Annex I for details on the use of square brackets.*

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

2.15.5.2. 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 UN RTDG Model Regulations, section 2.5.3.2.4.

2.15.6. Relation to transport classification

Division 5.2 within Class 5 of the UN RTDG Model Regulations covers organic peroxides. A list of currently classified organic peroxides is included in the UN RTDG Model Regulations, 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 UN RTDG Model Regulations 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 2.15.4.4, 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. See Annex VII for additional information on transport classification in relation to CLP classification.

2.15.7. Examples of classification for organic peroxides

2.15.7.1. Examples of substances and mixtures fulfilling the classification criteria

Substance to be classified: Example Peroxide

Molecular formula: n.a.

According to CLP Annex I, Section 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:	Example Peroxide
2. General data	
2.1. Composition:	Example Peroxide, 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

CLASSIFICATION TEST RESULTS	
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:	Can 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 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)

CLASSIFICATION TEST RESULTS	
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:	Can it explode as packaged?
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 with400 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 x[52]
9. Final classification	
Hazard class:	Organic peroxide, Type C, liquid, temperature controlled
Label:	Flame (GHS02)
Signal word:	Danger
Hazard statement:	H242: 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-MTC, table 28.2.

[52] Not attached to this example.

2.15.7.2. Additional remarks

Explosive properties

As shown in Section 2.15.7.1 a substance and a mixture may have explosive properties when handled under greater confinement and where the packaging in which it was tested in UN Test G.1 (see point 6 of classification test results above) is changed. Such information should be given in the SDS.

The example in Section 2.15.7.1 shows a violent effect when heated under confinement (see point 5.3 of the above results). Consequently, also the impact sensitivity according to UN Test series 3, test 3 (a) (ii), BAM Fallhammer should be determined. For this example it amounts to 20 J. Such information should be given in the SDS.

Burning properties

For the example in Section 2.15.7.1 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.

Flash point

The example substance thermally decomposes before the temperature at which the vapour can be ignited is reached (see Section 2.15.4.3.2) and consequently a flash point cannot be determined.

2.16. CORROSIVE TO METALS

2.16.1. Introduction

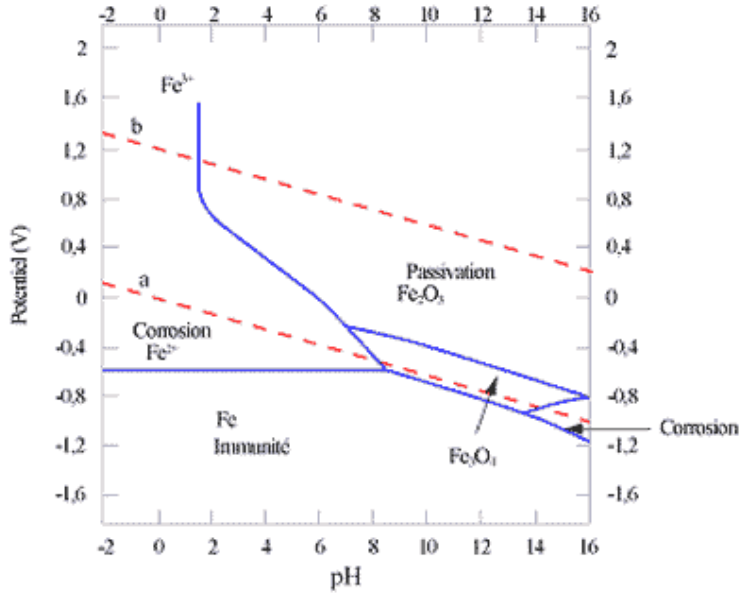
The criteria for 'Corrosive to metals' are found in Annex I, Section 2.16 of CLP and are identical to those in Chapter 2.16 of GHS.

The hazard class corrosive to metals 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 occurring 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 chemical 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 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 and mixtures that are liable to attack carbon steel or aluminium, two of the most common metals that may come in contact with chemical substances (containment material, reactor material). The classification scheme applied here must 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, must be selected for testing.

2.16.2. 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.

2.16.3. Relation to other physical hazards

There is no direct relation to other physical hazards.

2.16.4. Classification of substances and mixtures as corrosive to metals

2.16.4.1. 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. Neither the corrosivity of gases nor the formation of corrosive gases is currently covered by CLP classes and are therefore **not** applicable here.

According to the classification criteria only substances and mixtures for which the application of the UN Test C.1 (described in part III, Section 37.4.1.1 of the UN-MTC) is relevant and needs to be considered. Application of classification criteria in the UN-MTC, Section 37.4 excludes solids, while 'liquids and solids that may become liquids (during transport)', have to be considered for such a classification.

The wording 'solids that may become liquids' was developed for UN RTDG Model Regulations 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 UN 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 2.16.4.4.2). 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. 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 must 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 UN Test 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).

See also IR & CSA, Chapter R.7a: Endpoint specific guidance, Section R.7.1.2 (Melting point/freezing point).

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.

2.16.4.2. 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 2.16.7).

Generally extreme pH-values point to a higher likelihood that the substance or mixture is corrosive. However, it cannot lead to immediate classification in the hazard class corrosive to metals. As a proof of that, Figure 2.15 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 UN Test C.1 was 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.

2.16.4.3. 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: *Table 2.16.1*

Criteria for substances and mixtures corrosive to metals

Category	*Criteria*
1	*Corrosion rate on either steel or aluminium surfaces exceeding 6,25 mm per year at a test temperature of 55 °C when tested on both materials.*

2.16.4.4. Testing and evaluation of hazard information

2.16.4.4.1. 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 UN Test 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 2.2 (Section 37.4.1.4.1 of the UN- MTC) translates the corresponding minimum mass loss rates leading to classify the test substance or mixture 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 Section 2.4.2), the values in Table 2.2 and Table 2.3 need adjustments due to the fact that the corrosion process depends on the surface of specimen.

Table 2.2 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 2.3 (Section 37.4.1.4.2 of the UN-MTC) indicates the criteria leading to classification of the test substance or mixture as corrosive to metals for standard metal specimens, according to time of exposure, for reasons of localised corrosion process.

Table 2.3 Minimum intrusion depths after exposure times (corresponding to the criterion of localized corrosion of 6.25 mm/year)

Exposure time	Min. intrusion depth
7 days	120 μm
14 days	240 μm
21 days	360 μm
28 days	480 μm

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 UN 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

.

2.16.4.4.2. 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-MTC, 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 or mixture (1.5 L, according to the UN-MTC) 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 2.15.4.1, 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 UN C.1 test protocol). In no case will simple dilution of the solid substance or mixture in any quantity of water lead to satisfactory testing of the substance or mixture for corrosion to metals.

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 UN Test C.1

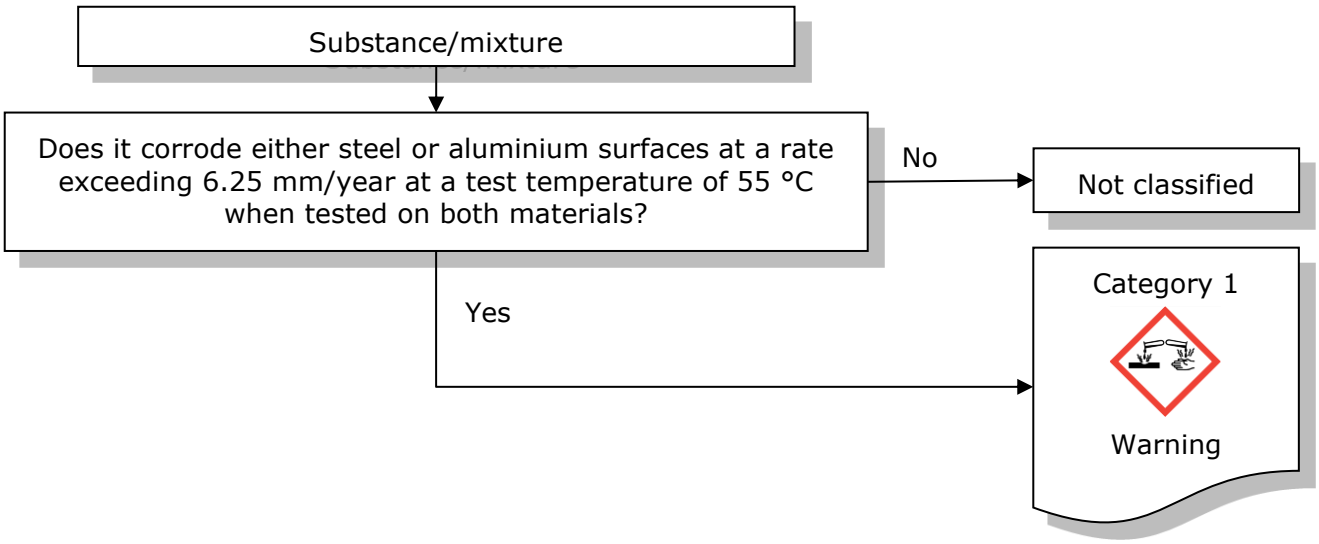
Figure 2.16 Example of testing equipment available on the market to perform UN Test C.1

2.16.4.5. Decision logic

Classification of substances and mixtures corrosive to metals is done according to decision logics 2.16.4.1 as included in the GHS.

NOTE: The person responsible for the classification of substances and mixtures corrosive to metals should be experienced in this field and be familiar with the criteria for classification.

Figure 2.17 Decision logic for substances and mixtures corrosive to metals (Decision logic 2.16 of GHS)



2.16.5. Hazard communication for substances and mixtures corrosive to metals

2.16.5.1. 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 and mixtures that are classified in this hazard class corrosive to metals but will not induce corrosive action on other more corrosive resistant metals (e.g. platinum) than those serving as reference materials.

Label elements must 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	
Note: *Where a substance or mixture is classified as corrosive to metals but not corrosive to skin and/or eyes, the labelling provisions set out in Section 1.3.6 shall be used.*	

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

Further, in Section 1.3.6 of CLP Annex I a derogation from labelling requirements for substances or mixtures classified as corrosive to metals but not corrosive to skin and/or eyes is provided.

Annex I: *1.3.6 Substances or mixtures classified as corrosive to metals but not classified as skin corrosion or as serious eye damage (Catgory 1)*

Substances or mixtures classified as corrosive to metals but not classified as skin corrosion or as serious eye damage (Catgory 1) which are in the finished state as packaged for consumer use do not require on the label the hazard pictogram GHS05.

2.16.6. Relation to transport classification

Class 8 of the UN RTDG Model Regulations covers substances and mixtures that are classified for corrosivity to skin, metals or both. Valuable information can be obtained from UN RTDG Model Regulations and the modal transport regulations (ADR, RID, ADN and IMDG Code, ICAO TI). Existing test results obtained in the context of the modal transport regulations (ADR, RID, ADN and IMDG Code, ICAO TI) may be applied since the UN Test C.1 serves as reference for testing in both classification systems. See Annex VII for additional information on transport classification in relation to CLP classification.

2.16.7. 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 UN Test C.1 results) in comparison with predicted results for skin corrosion hazard.

Table 2.4 Examples of classified and non classified substances and mixtures in Class 2.16

Note: 'Corroded' means corrosion attack in the sense of UN Test C.1;

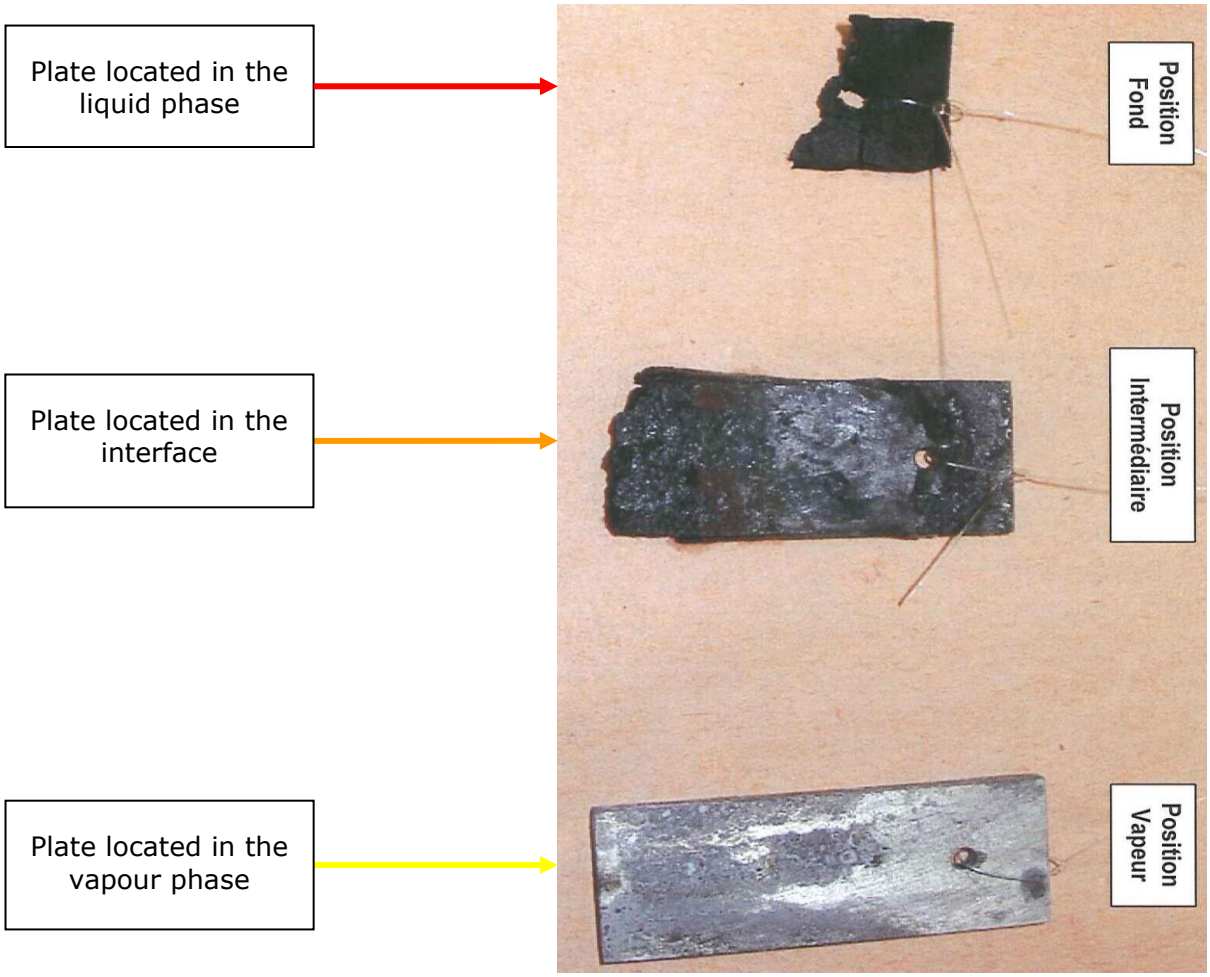
'Not corroded' means corrosion resistant in the sense of UN Test C.1;

'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

2.16.7.1. Example of metal specimen plates after exposure to a corrosive mixture

Figure 2.18 Example of corroded metal plates after testing according to UN Test C.1 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).

2.16.8. 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. PART 3: HEALTH HAZARDS

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 or mixture. 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 different hazard classes covering effects after single or brief exposure – 'Acute toxicity' and 'STOT-SE (Specific Target Organ Toxicity – Single Exposure)', skin irritation/corrosion and eye damage. These are independent of each other and may all 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 multiple classification, even where the criteria for different classes are fulfilled. In such a case the most appropriate (the most severe hazard) 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, when it is observed in the absence of a classification for lethality (see Section 3.8 of this Guidance). Mortalities during the first 72 h after first treatment (in a repeated dose study) may also be considered for the assessment of acute toxicity.

For more details see Guidance on 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 must be considered for each route of exposure, using the appropriate approach as described in Section 3.1.2.2 and Section 3.1.2.3 of this Guidance. If different hazard categories are assigned, the most severe hazard category must be used to select the appropriate pictogram and signal word on the label for acute toxicity. For each relevant route of exposure, the hazard statement will correspond to the classification of this specific route.

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 sources such as 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 Guidance on 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 of this Guidance).

(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.' (Guidance on 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 (see Guidance on IR&CSA, Section R.7.4.3.1, for further information). 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 evident toxicity rather than lethality as indications of acute toxicity.

The animal studies are listed in the Guidance on 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 hazard 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) LD_{50} (oral, dermal) or LC_{50} (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*

Note (b)				
Dermal (mg/kg bodyweight) *See: Note (a)* *Note (b)*	*ATE ≤ 50*	*50 < ATE ≤ 200*	*200 < ATE ≤ 1000*	*1000 < ATE ≤ 2000*
Gases (ppmV ([1])) *see: Note (a)* *Note (b)* *Note (c)*	*ATE ≤ 100*	*100 < ATE ≤ 500*	*500 < ATE ≤ 2500*	*2500 < ATE ≤ 20000*
Vapours (mg/l) *see: Note (a)* *Note (b)* *Note (c)* *Note (d)*	*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)* *Note (c)*	*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 is derived using the LD_{50}/LC_{50} where available.

(b) The acute toxicity estimate (ATE) for the classification of a substance in a mixture is derived using:

- *the LD_{50}/LC_{50} 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.*

(c) The ranges of the acute toxicity estimates (ATE) 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.

(d) For some substances the test atmosphere will not just be a vapour but will consist of a mixture of liquid and vapour phases. For other substances 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.

NOTE regarding CLP Annex I, Table 3.1.1, Note (c):

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 these values may be adjusted to a 4-hour equivalent using Haber's law ($C \cdot t = k$) for direct comparison with the criteria. The formula may be refined to ($C^n \cdot t = k$) where 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 (Guidance on 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 the Guidance on 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.

3.1.2.2.1. Harmonised ATE values

From 2016 harmonised ATE values are gradually included in Annex VI. These values must be applied when classifying mixtures containing the substance just as any other harmonised item regardless of any other ATE value derived from testing of the substance.

3.1.2.2.2. Minimum classification

For certain entries in Annex VI there is an asterisk indicating that it is the minimum classification. In case the substance has a minimum classification this is the lowest classification possible, however, if there is data indicating that a more stringent classification is warranted the classification has to be adapted accordingly. This is due to translation from the old DSD legislation.

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 of this Guidance. 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 of this Guidance) 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 of this Guidance). 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 or 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) in Section 3.1.5.1.1 of this Guidance.

If there are no exact or quantitative lethal dose data the procedure described in CLP Annex I, 3.1.3.6.2.1(b) (see Section 3.1.3.3.5 of this Guidance) would have to be followed using Table 3.1.2 (see Section 3.1.3.3 of this Guidance) 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) in Section 3.1.5.1.2 of this Guidance.

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*
>
> **Annex I: *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 the Guidance on IR&CSA, Section R.7.4.4.1. *In vitro* data cannot be used as a stand alone. However, NRU data can be used as part of a weight of evidence evaluation.

Animal data:

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, CLP Annex I, 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 (b) to Table 3.1.1. This cATpE can be used in the additivity formulae (CLP 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} values or LD_{50}/LC_{50} values 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 sex and age of the animals, the animal strains used, the experimental protocols, the purity of the substance and form or phase in which it was tested (e.g. the particle size distribution of any dusts or mists 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 less than the 14 days, the time to be used according to the OECD guidelines, and effects are observed at the end of the study, the resulting LD_{50} might be misleading. Such information should be included in the weight of evidence consideration.

If there is available test data from a 28 day study to 1000 mg/kg bw/day and no effects are seen, it can be concluded that the substance does not fullfill the criteria for acute toxicity (for further details see Appendx 7.4-1 to Guidance R.7a, especially Section 2.4). If a substance is not acutely toxic by the oral route it can also be assumed that it is not acutely toxic by the dermal route.

Annex I: 3*.1.2.3.* *Specific considerations for classification of substances as acutely toxic by the inhalation route*

Annex I: *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 estimated as follows:

SVC [mg/l] = 0.0412 x MW x vapour pressure (vapour pressure in hPa at 20°C).

The conversion from mg/l to ppm assuming an ambient pressure of 1 atm = 101.3 kPa and 25°C is: ppm= 24,450 x 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 OECD GD 39).

Considerations with respect to physical forms or states or 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 of this Guidance.

Special considerations concerning aerosols (dusts and mists):

Annex I: ***3.1.2.3.2.*** *Of particular importance in classifying for inhalation toxicity is the use of well articulated values in the highest hazard categories for dusts and mists. Inhaled particles between 1 and 4 microns mean mass aerodynamic diameter (MMAD) will deposit in all regions of the rat respiratory tract. This particle size range corresponds to a maximum dose of about 2 mg/l. In order to achieve applicability of animal experiments to human exposure, dusts and mists would ideally be tested in this range in rats.*

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 dusts and mists 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

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.*

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 of this Guidance.

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 of this Guidance then this will normally lead to classification for acute toxicity, irrespective of other information available. Please refer also to the Guidance R7a and in particular to especially to Appendix R7.4-1.

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.

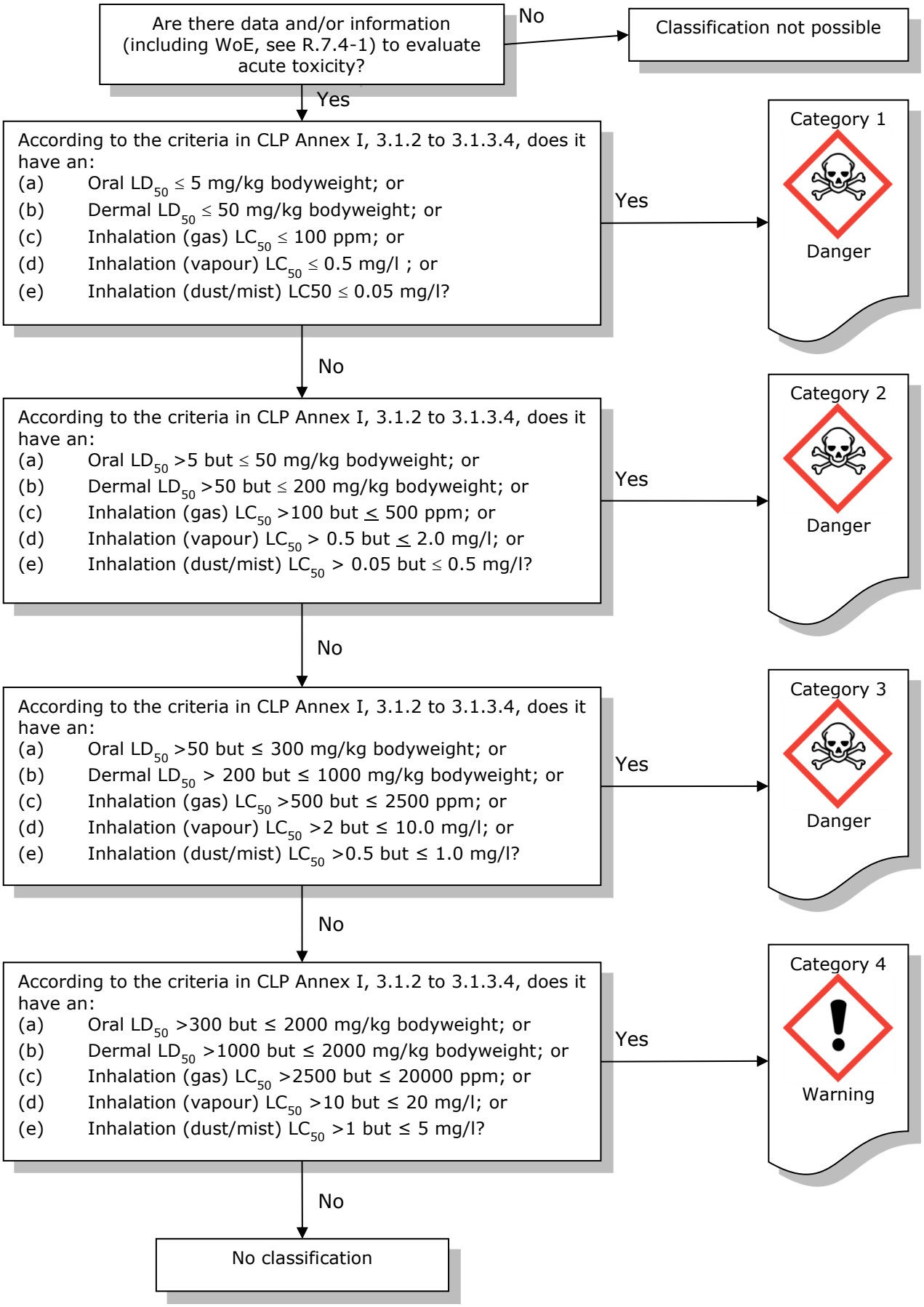
3.1.2.5. Setting of specific concentration limits

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 of this Guidance). 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 for classification of substances

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 are 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 result in three different categories being assigned to the different routes. The route of exposure will then be specified in the corresponding hazard statement.


Are there data and/or information (including WoE, see R.7.4-1) 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 LD50 ≤ 5 mg/kg bodyweight; or
(b) Dermal LD50 ≤ 50 mg/kg bodyweight; or
(c) Inhalation (gas) LC50 ≤ 100 ppm; or
(d) Inhalation (vapour) LC50 ≤ 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 LD50 >5 but ≤ 50 mg/kg bodyweight; or
(b) Dermal LD50 >50 but ≤ 200 mg/kg bodyweight; or
(c) Inhalation (gas) LC50 >100 but ≤ 500 ppm; or
(d) Inhalation (vapour) LC50 > 0.5 but ≤ 2.0 mg/l; or
(e) Inhalation (dust/mist) LC50 > 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 LD50 >50 but ≤ 300 mg/kg bodyweight; or
(b) Dermal LD50 > 200 but ≤ 1000 mg/kg bodyweight; or
(c) Inhalation (gas) LC50 >500 but ≤ 2500 ppm; or
(d) Inhalation (vapour) LC50 >2 but ≤ 10.0 mg/l; or
(e) Inhalation (dust/mist) LC50 >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 LD50 >300 but ≤ 2000 mg/kg bodyweight; or
(b) Dermal LD50 >1000 but ≤ 2000 mg/kg bodyweight; or
(c) Inhalation (gas) LC50 >2500 but ≤ 20000 ppm; or
(d) Inhalation (vapour) LC50 >10 but ≤ 20 mg/l; or
(e) Inhalation (dust/mist) LC50 >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, 3.1.3.3.5, 3.1.3.3.6 and 3.1.3.4 of this Guidance).

3.1.3.2. Identification of hazard information

Where relevant and reliable toxicological information from human evidence or animal studies is available on a mixture, this should be used to derive the appropriate classification. Where such information on the mixture itself is not available, information on similar tested mixtures and, the component substances in the mixture must be used, as described in Section 3.1.3.3 of this Guidance.

Alternatively, the hazard information on all individual components in the mixture could be identified as described in Section 3.1.2.2 of this Guidance.

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 components and there is no relevant evidence to suggest acute toxicity by multiple routes. When there is relevant evidence of toxicity by multiple routes of exposure, classification is to be conducted for all appropriate routes of exposure. All available information shall be considered. The pictogram and signal word used shall reflect the most severe hazard category and all relevant hazard statements shall be used.*

The classification must be considered for each route of exposure. If different hazard categories are assigned, the most severe hazard category will be used to select the appropriate pictogram and signal word on the label for acute toxicity. 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 (as described in Section 3.1.2.3 of this Guidance). 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 or mist 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 of this Guidance).

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.*

In order to apply bridging principles, there needs to be sufficient data on similar tested mixtures as well as the ingredients of the mixture (see Section 1.6.3 of this Guidance).

When the available identified information is inappropriate for the application of bridging principles then the mixture should be classified based on its ingredients as in Section 3.1.3.3.3, 3.1.3.3.5, 3.1.3.3.6 and 3.1.3.4 of this Guidance.

3.1.3.3.3. When data are available for all ingredients

Annex I: *3.1.3.3.*

(c) If the converted acute toxicity point estimates for all components of a mixture are within the same category, then the mixture should be classified in that category.

(d) When only range data (or acute toxicity hazard category information) are available for components in a mixture, they may be converted to point estimates in accordance with Table 3.1.2 when calculating the classification of the new mixture using the formulas in sections 3.1.3.6.1 and 3.1.3.6.2.3.

Annex I: *3.1.3.6.* *Classification of mixtures based on ingredients of the mixture (Additivity formula)*

Annex I: *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 hazard categories shown in Table 3.1.1;

(b) ignore ingredients that are presumed not acutely toxic (e.g., water, sugar);

(c) ignore components if the data available are from a limit dose test (at the upper threshold for Category 4 for the appropriate route of exposure as provided in Table 3.1.1) and do not show acute toxicity.

Components that fall within the scope of this section are considered to be components with a known acute toxicity estimate (ATE). See note (b) to Table 3.1.1 and section 3.1.3.3 for appropriate application of available data to the equation below, and section 3.1.3.6.2.3.

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.

In case an ingredient has a harmonised ATE this value must be used in the formula above. If no harmonised ATE is available, then the ATE should be derived as stated in 3.1.2.3. The cATpE (mentioned in 3.1.2.3.2) is used when ATE values are not known. If there is a harmonised classification and the only known ATE value does not support classification in that hazard category, then the cATpE should be considered.

3.1.3.3.4. Special case for acute inhalation toxicity

For mixtures containing some substance(s) tested for inhalation toxicity as vapours and others as dust/mist or gas, the additivity formula cannot be used directly as the ATE ranges are different. Therefore for acute inhalation toxicity additivity has initially to be used separately for each relevant physical form (i.e. gas, vapour and/or dust/mist), using the appropriate category limit in CLP Annex I, Table 3.1.1. As a first step, the fraction of toxicity is calculated for each form/state:

fraction = ∑ (limit / ATE) x $concentration_s$ /100

Where limit = the upper border of the range of ATE values of a hazard category (Table 3.1.1 of CLP) for the state/form in question and $concentration_s$ = the concentration (%) of components tested for this state/form.

The most severe category where the sum of fractions for the three states/forms are ≥ 1 would apply (see example 13 in section 3.1.5.5).

In case of > 10% of ingredient(s) with unknown acute toxicity, the value is corrected as 1 minus concentration of unknowns/100.

In case no ATE values but only classification of the ingredients is known, the converted Acute Toxicity point Estimates (cATpEs) as shown in Table 3.1.2 of Annex I (see below) should be used.

In addtiton to the new example 13, examples 12a and 12b are also provided in section 3.1.5 (see note to the examples).

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 use in the formulas for the classification of mixtures

Exposure routes	*Classification category or experimentally obtained acute toxicity range estimate*	*Converted acute toxicity point 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* *50 < Category 2 ≤ 200* *200 < Category 3 ≤ 1000* *1000 < Category 4 ≤ 2000*	*5* *50* *300* *1100*
Gases (ppmV)	*0 < Category 1 ≤ 100* *100 < Category 2 ≤ 500* *500 < Category 3 ≤ 2500* *2500 < Category 4 ≤ 20000*	*10* *100* *700* *4500*
Vapours (mg/l)	*0 < Category 1 ≤ 0,5* *0,5 < Category 2 ≤ 2* *2,0 < Category 3 ≤ 10,0* *10,0 < Category 4 ≤ 20,0*	*0,05* *0.5* *3* *11*
Dust/mist (mg/l)	*0< Category 1 ≤ 0,05* *0,05 < Category 2 ≤ 0,5* *0,5 < Category 3 ≤ 1,0* *1,0 < Category 4 ≤ 5,0*	*0,005* *0,05* *0,5* *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 cATpEs are equal to the upper limit of the next lower category, for example the cATpE of oral Category 2 (5 mg/kg bw) is equal to the upper limit of oral Category 1 (also 5 mg/kg bw).

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. In such cases, CLP Annex I, 3.1.3.3.(c) should be applied.

Annex I: *3.1.3.3.(c)* *If the converted acute toxicity point estimates for all components of a mixture are within the same category, then the mixture should be classified in that category.*

As a result, the mixtures in the examples highlighted above would be classified in Categories 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.

3.1.3.3.5. When data are <u>not</u> available for all ingredients

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]) When mixtures contain components that do not have acute toxicity data for each route of exposure, acute toxicity estimates may be extrapolated from the available data and applied to the appropriate routes (see Section 3.1.3.2). However, specific legislation may require testing for a specific route. In those cases, classification shall be performed for that route based upon the legal requirements.

<u>Derivation of ATEs from available information:</u>

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 CLP Annex I, Table 3.1.2. The other option, based on expert judgement in substantiated cases, is the use of the directly derived ATE values.

a. <u>Route-to-route extrapolation (CLP Annex I, 3.1.3.6.2.1.(a))</u>

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 an 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 ensured 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. Further information and guidance on dermal absorption can be found on the OECD and EFSA websites – OECD (http://www.oecd.org/chemicalsafety/testingofchemicals/48532204.pdf) and EFSA (http://www.efsa.europa.eu/en/efsajournal/doc/2665.pdf).

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 the 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 (Guidance on IR&CSA, Chapter R7c, Table R.7.12-10).

Valid information indicating that the deposition and/or absorption rate for the extrapolated route is lower would allow a higher equivalent derived ATE (see Section 3.1.5.1.9 Example 9 of this Guidance).

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 an appreciable absorption of the substance. Thus, depending on the kinetic and physico-chemical properties and kind of mixture, varying ATEs will result. For example, butyn-1,4-diol causes no mortality in rats when dermally applied as a solid at 5000 mg/kg bw, whereas when an aqueous solution of butyn-1,4-diol is administered, a dermal LD_{50} of 659 and 1240 mg/kg bw in male and female rats, respectively, and an oral LD_{50} of about 200 mg/kg bw in both sexes can be determined.

For more details on inter-route extrapolation see the Guidance on IR&CSA, Section R.7c. 12.2.4. examples 8 and 9 which 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 by taking into account the potency (i.e. the magnitude of the lethal dose reported) of the effects in humans. 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 3.1.5.1.1 Example 1 of this Guidance). 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 subsequent use in the formulae (see Section 3.1.5.1.2 Example 2 of this Guidance). See also Section 3.1.2.3.1 of this Guidance for more details.

c. Evidence from other toxicity tests

Standard acute toxicity studies should be the primary source of information for acute toxicity classification. However, when such data are not available or only data from non-reliable studies exist, information from studies conducted for other endpoints can be used for acute toxicity classification. For example, data on early effects from repeated dose testing can be used. These studies will not usually provide an exact 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. Furthermore, it can also be concluded that no classification is warranted for instance by a 28-day repeated dose toxicity study that is performed with 1000 mg/kg bw/day and no adverse effects are observed (refer to Appendix 7.4-1 of Guidance R.7a). In addition, a substance not acutely toxic after oral exposure is not considered as acutely toxic via dermal exposure (see Guidance R.7a).

Example:

Available information: In a range finding study with respect to repeated dose toxicity daily oral doses of 1000 mg/kg bw 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 ATE is >2000 mg/kg bw since 2 doses following (within roughly) 24 h are not lethal (see Section 3.1.2.2 of this Guidance). 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 3.1.2.3.2 of this Guidance) may be used according to Note (a) to CLP 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 according 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.

Further guidance on how to apply this provision is given in Section 3.1.3.3.6 of this Guidance.

Annex I: ***3.1.3.6.2.3.*** *If the total concentration of the relevant 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 relevant 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:*

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

3.1.3.3.6. Ingredients 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%; CLP Annex I, 3.1.3.3 (a)) for which there is no adequate acute toxicity data then the mixture must be classified on the basis of the ingredients with known toxicity, with an additional statement on the label and in the SDS to indicate that the mixture consists of 'x percent' of component(s) of unknown acute 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 CLP Annex I, 3.1.3.6.1 must be used. However, in cases where these ingredients constitute over 10%, a modified additivity formula in CLP Annex I, 3.1.3.6.2.3 must be used, which adjusts for the presence of a significant proportion of ingredients of unknown toxicity. This reflects the greater uncertainty as to the true toxicity of the mixture).

Annex I: Excerpt of 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 for those hazard classes where the generic cut-off values may be best described in volume percentages.*

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 3.1.3.6.2.3 (see Section 3.1.5.3.1 Example 11 of this Guidance). 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.

3.1.3.3.7. Non-classified components

For mixtures containing ingredients with ATE values that are more than 2000 mg/kg (i.e. non-classified components), such ingredients need not be considered in the calculation of ATEs with the formula presented in CLP Annex I: 3.1.3.6.1. However, in cases where no acute toxicity data are available for some ingredients or a mixture contains ingredients with unspecified ATE values which could fall within the classifiable limits, then the formula of CLP Annex I: 3.1.3.6.2.3 has to be used for calculation of ATEs to adjust for the concentrations of ingredients with unknown acute toxicities.

3.1.3.4. Generic concentration limits for substances triggering classification of mixtures

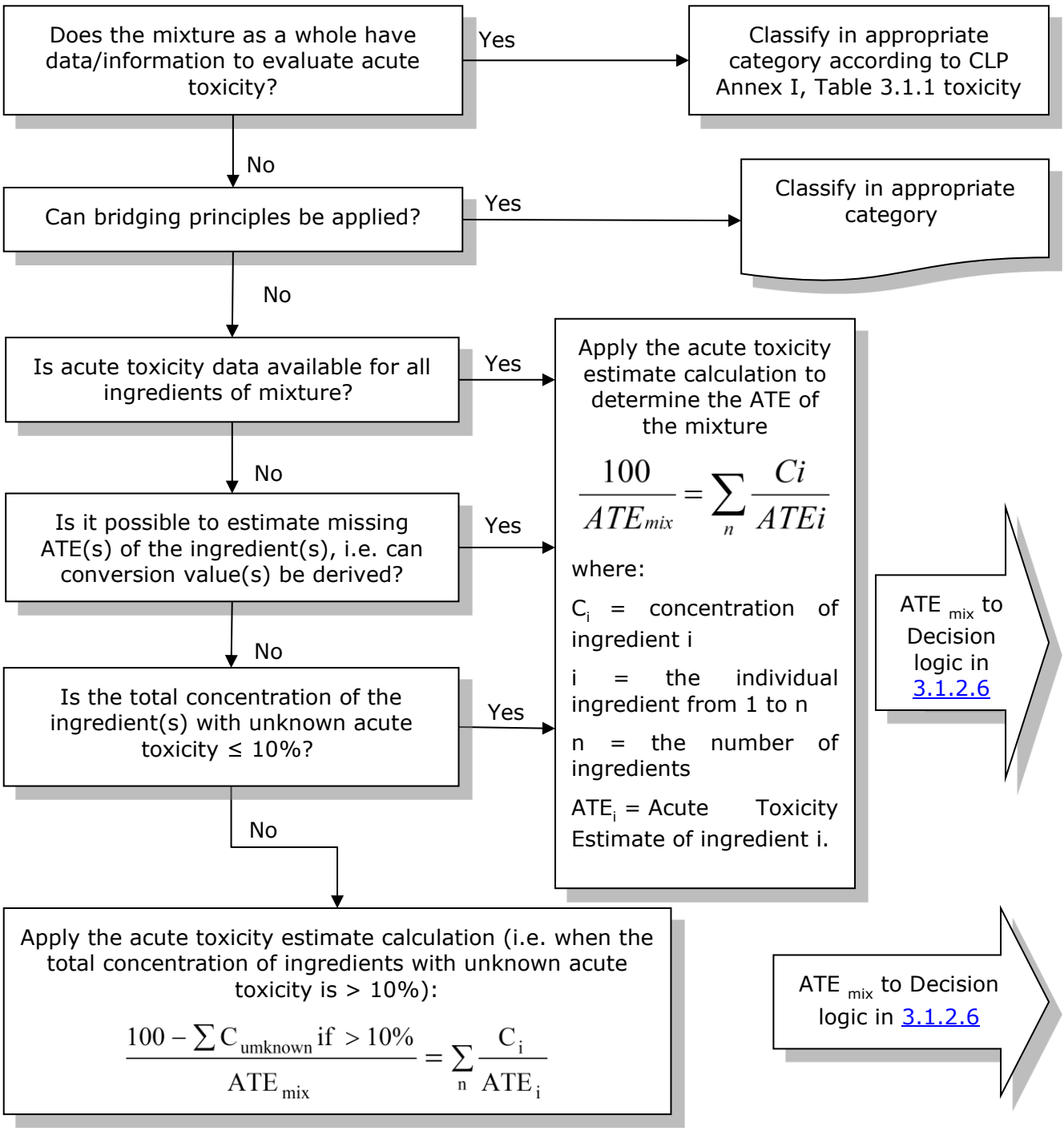
Generic concentration limits as such are not applicable for acute toxicity classification; therefore specific concentration limits are also not applicable (see Section 3.1.2.5 of this Guidance). Nevertheless, according to CLP Annex VI, 1.2.1 the classification for entries with the reference * in the column specific concentration limits is of special concern; the * means that those entries had an SCL in CLP Annex VI, Table 3.2 originating from Annex I to DSD. 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) is necessary. The assessment must 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 CLP Annex I, 3.1.3.6.1 as ATEs or cATpEs (CLP Annex I, Table 3.1.2).

3.1.3.5. Decision on classification

The assessment of classification has to be performed with respect to all the relevant routes of exposure (oral, dermal, inhalation) on the basis of all adequate reliable data. If there is evidence of toxicity by multiple routes of exposure classification is warranted for all these routes, however the label should include one pictogram and a signal word reflecting the most severe hazard category. If, for example, a mixture fulfils the criteria for oral toxicity Category 4 and for inhalation Category 2, then the mixture will be classified in Category 4 for oral toxicity and Category 2 for inhalation toxicity and assigned the corresponding hazard statements; it will be labelled with the acute toxicity Category 2 pictogram (skull and cross bones) and the signal word 'Danger' and both the hazard statements for inhalation Category 2 (H330) and oral Category 4 (H302) (see CLP Annex I Table 3.1.3 in next section 3.1.4.1 of this Guidance).

3.1.3.6. Decision logic for classification of mixtures

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.


Does the mixture as a whole have data/information to evaluate acute toxicity?
Yes
Classify in appropriate category according to CLP Annex I, Table 3.1.1 toxicity
No
Can bridging principles be applied?
Yes
Classify in appropriate category
No
Is acute toxicity data available for all ingredients of mixture?
Yes
Apply the acute toxicity estimate calculation to determine the ATE of the mixture
$\frac{100}{ATE_{mix}} = \sum_{n} \frac{Ci}{ATEi}$
where:
C_i = concentration of ingredient i
i = the individual ingredient from 1 to n
n = the number of ingredients
ATE_i = Acute Toxicity Estimate of ingredient i.
ATE mix to Decision logic in 3.1.2.6
No
Is it possible to estimate missing ATE(s) of the ingredient(s), i.e. can conversion value(s) be derived?
Yes
No
Is the total concentration of the ingredient(s) with unknown acute toxicity ≤ 10%?
Yes
No
Apply the acute toxicity estimate calculation (i.e. when the total concentration of ingredients with unknown acute toxicity is > 10%):
$\frac{100 - \sum C_{umknown} \text{ if } > 10\%}{ATE_{mix}} = \sum_{n} \frac{C_i}{ATE_i}$
ATE mix to Decision logic in 3.1.2.6

3.1.4. Hazard communication in the 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*	*P302 + P350* *P310*	*P302 + P352* *P312*	*P302 + P352* *P312*

	P322 *P361* *P363*	*P322* *P361* *P363*	*P322* *P361* *P363*	*P322* *P363*
Precautionary Statement Response (dermal)	*P302 + P352* *P310* *P321* *P361 +* *P364*	*P302 + P352* *P310* *P321* *P361 +* *P364*	*P302 + P352* *P312* *P321* *P361 +* *P364*	*P302 + P352* *P312* *P321* *P362 +P364*
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 substance or a mixture fulfils the classification criteria with respect to different routes the pictogram and signal word will be based on the most severe one, however the hazard statements for each route must be included on the label.

Article 26 1 (b)

If the hazard pictogram 'GHS06' applies, the hazard pictogram 'GHS07' shall not appear.

3.1.4.2. Additional labelling provisions

In addition to the statement required under CLP Annex I, 3.1.3.6.2.2, it would be appropriate to specify the relevant exposure route of toxicity concerned on a case-by-case basis: For example 'x percent of the mixture consists of component(s) of unknown acute oral toxicity'. In the case of different values being available for the % of ingredients having unknown acute toxicity (as a result of different route of exposure), the % value to be included in the sentence on the label should be selected based on the route where the % of ingredients having unknown toxicity is the highest.

Annex I: *3.1.3.6.2.2.* *In the event that a component without any useable information for classification is used in a mixture at a concentration ≥ 1 %, 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 components only, with the additional statement on the label and in the SDS that: "x percent of the mixture consists of component(s) of unknown acute toxicity", taking into account the provisions set out in section 3.1.4.2.*

Annex I: *3.1.4.2*

The acute toxicity hazard statements differentiate the hazard based on the route of exposure. Communication of acute toxicity classification should also reflect this differentiation. If a substance or mixture is classified for more than one route of exposure then all relevant classifications should be communicated on the safety data sheet as specified in Annex II to Regulation (EC) No 1907/2006 and the relevant hazard communication elements included on the label as prescribed in section 3.1.3.2. If the statement "x % of the mixture consists of ingredient(s) of unknown acute toxicity" is communicated, as prescribed in section 3.1.3.6.2.2, then, in the information provided in the safety data sheet, it can also be differentiated based on the route of exposure. For example, "x % of the mixture consists of ingredient(s) of unknown acute oral toxicity" and "x % of the mixture consists of ingredient(s) of unknown acute dermal toxicity

In case section 3.1.3.6.2.2 applies and the statement 'x % of the mixture consists of ingredient(s) of unknown acute toxicity' has to be communicated, the same statement can be differentiated on the basis of the route of exposure in the safety data sheet (SDS) in accordance with CLP Annex I 3.1.4.2. For example on the label and in the SDS the following should appear: 'x % of the mixture consists of ingredient(s) of unknown acute toxicity'; in the SDS the route of exposure can also be specified, for example 'x % of the mixture consists of ingredient(s) of unknown acute oral toxicity' and 'x % of the mixture consists of ingredient(s) of unknown acute dermal toxicity'. In case of different values being available for the % of ingredients having unknown toxicity (as a result of a different route of exposure), the % value to be included in the sentence on the label should be selected based on the route where the % of ingredients having unknown toxicity is the highest.

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 substance or mixture must 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 of this Guidance). 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 (see Chapter 3.2.4.2 of this Guidance).

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, although this 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 supplementarily labelled with EUH071, if there is a possibility of exposure via inhalation taking into consideration the saturated vapour concentration and the possibility of exposure to particles or droplets of inhalable size as appropriate (see also Chapter 3.8.2.5 of this Guidance. It is strongly recommended to apply the precautionary statement P260: Do not breathe dust/fume/gas/mist/vapours/spray.

Toxic by eye contact:

Annex II: *1.2.5 EUH070 — 'Toxic by eye contact'*

For substances or mixtures where an eye irritation test has resulted in overt signs of systemic toxicity or mortality among the animals tested, which is likely to be attributed to absorption of the substance or mixture through the mucous membranes of the eye. The statement shall also be applied if there is evidence in humans for systemic toxicity after eye contact.

The statement shall also be applied where a substance or a mixture contains another substance labelled for this effect, if the concentration of this substance is equal to, or greater than 0,1 %, unless otherwise specified in part 3 of Annex VI.

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.

Liberation of toxic gases

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.

Annex II: ***1.2.1 EUH031 — 'Contact with acids liberates toxic gas'***

For substances and mixtures which react with acids to evolve gases classified for acute toxicity in category 3 in dangerous amounts, such as sodium hypochlorite, barium polysulphide.

Annex II: ***1.2.3. EUH032 — 'Contact with acids liberates very toxic gas'***

For substances and mixtures which react with acids to evolve gases classified for acute toxicity in category 1 or 2 in dangerous amounts, such as salts of hydrogen cyanide, sodium azide.

3.1.5. Examples of classification for acute toxicity

⚠ NOTE: The classification proposals for the examples refer only to acute toxicity.

3.1.5.1. Examples of substances fulfilling the criteria for classification

3.1.5.1.1. 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 bw	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 bw' (IPCS, Environmental Health Criteria 196, Methanol, WHO, 1997)	Category 3	The minimum lethal dose reported of 300 mg/kg bw is used as equivalent ATE; according to CLP Annex I, Table 3.1.1 the resulting classification is Category 3
Remarks	Test data in rats from mixtures containing methanol should not be used directly in additivity formula		

3.1.5.1.2. 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	Category 3 (oral, dermal, inhalation)	The extensive and consistent human experience is considered to be sufficiently robust by expert judgement to

	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.		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 CLP Annex I, Table 3.1.2 for Category 3; e.g. cATpE dermal = 300 mg/kg bw, which then falls into a higher category than the rabbit data.
Remarks	none		

3.1.5.1.3. Example 3

Application	**No exact LD_{50} value available. Expert judgement needed.**		
	Test Data	**Classification**	**Rationale**
Available information	Corrosive volatile liquid (not classified for skin corrosion). 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 (in addition to the labelling provisions for Acute tox Cat. 4): Corrosive pictogram (pictogram is not mandatory, it may be added) (see Annex I: Note 1 of Table 3.1.3) Additional Hazard statement: EUH071 Corrosive to the respiratory tract		

3.1.5.1.4. 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, the LD_{50} was estimated to be between 50 mg/kg bw and 200 mg/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 CLP Annex I, Table 3.1.2)
Remarks	none		

3.1.5.1.5. Example 5

Application	Use of CLP Annex I, 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 OECD TG 403 in rats. The following LC_{50} was calculated: LC_{50}: 4500 ppm/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 (CLP Annex I, Table 3.1.1), this value corresponds to Category 4. Therefore Category 4 Acute Inhalation Toxicity classification is warranted.
Remarks	none		

3.1.5.1.6. Example 6

Application	Time extrapolation; Note (c) in CLP Annex I, Table 3.1.1; Haber's law		
	Test Data	**Classification**	**Rationale**
Available information	Solid substance Animal data:	Category 3	The classification criteria for acute inhalation toxicity in CLP Annex I, Table 3.1.1 refer to a 4h exposure time;

	The acute inhalation toxicity was studied in rats in a GLP-compliant study performed in principle according to OECD TG 403 in rats, but with respect for transport only with 1-h exposure. The LC_{50} (1-h) of 3 mg/l was calculated.		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) = (3 mg/l **:** 4) = 0.75 mg/l, thus Category 3 classification is warranted according to CLP Annex I, Table 3.1.1.
Remarks	none		

3.1.5.1.7. 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 bw (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	Classification according to criteria for acute inhalation and oral toxicity in CLP Annex I, Table 3.1.1.
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		

3.1.5.1.8. Example 8

Application	Route-to-route extrapolation: oral to inhalation (Section 3.1.3.3.5 of this Guidance). Expert judgement.		
	Test Data	**Extrapolated inhalation ATE/CATpE**	**Rationale**
Available information	Animal data: LD_{50} oral rat: 250 mg/kg bw (Category 3) 100 % oral absorption assumed a) No specific kinetic information b) Robust kinetic information allows the conclusion that only 50% is absorbed due to an exhalation rate of 50 %.	0.5 mg/l/4h (cATpE) 2.6 mg/l/4h (ATE)	a) Using the extrapolation formula 1 mg/kg bw = 0.0052 mg/l/4h: 250 x 0.0052 mg/l/4h = 1.3 mg/l/4h → Category 2 according to CLP Annex I, 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 CLP Annex I, 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		

3.1.5.1.9. Example 9

Application	Route-to-route extrapolation: oral to dermal (Section 3.1.3.3.5 of this Guidance). 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 bw LD_{50} dermal 1080 mg/kg bw	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

3.1.5.2. Examples of substances not fulfilling the criteria for classification

3.1.5.2.1. 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 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: – LC50: 19 mg/l/4h (no GLP) – LC50: 23 mg/l/4h (TG 403, GLP) – LC50: 28 mg/l/4h (TG 403, GLP)	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 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	none		

3.1.5.3. Example of mixtures fulfilling the criteria for classification

3.1.5.3.1. Example 11

Application	**Application of the 'Relevant ingredient' (CLP Annex I, 3.1.3.3 (a)) and 'Generic cut-off values to be taken into account' concepts (CLP Annex I, Table 1.1) for mixtures with data gaps using the equation in CLP Annex I, 3.1.3.6.2.3.** **For dermal and inhalation routes, there is no acute toxicity data available for ingredients 2 and 4. For ingredients 1, 3 and 5 the data indicates no classification for acute toxicity.**		
	Test Data	**Classification (ingredient)**	**Rationale**
Available information	Animal data (oral rat):		
Ingredient 1 (4%)	LD_{50}: 125 mg/kg bw	Oral Category 3	Apply the equation in CLP Annex I, 3.1.3.6.2.3:
Ingredient 2 (92%)	No data available	-	$\frac{100-(\sum C_{unknown} if\ >10\%)}{ATE_{mix}} = \sum_n \frac{C_i}{ATE_i}$
Ingredient 3 (3%)	LD_{50}: 1500 mg/kg bw	Oral Category 4	$\frac{100-92}{ATE_{mix}} = \frac{4}{125} + \frac{3}{1500} + \frac{0.2}{10} =$
Ingredient 4 (0.9%)	No data available	-	$= 0.032 + 0.002 + 0.02 = 0.054$
Ingredient 5 (0.2%)	LD_{50}: 10 mg/kg bw	Oral Category 2	ATEmix = 148 mg/kg bw → Category 3
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 available for the complete mixture (CLP 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 available (CLP Annex I, 3.1.3.5.1). 3. Classification based on ingredient data for the mixture can be considered (CLP Annex I, 3.1.3.6). 4. Applying the 'relevant ingredients' concept from CLP 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 CLP 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 CLP Annex I, 3.1.3.6.2.3 must be used. This corrected calculation adjusts for the total percentage of the ingredient with unknown acute toxicity. 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, CLP Annex I, 3.1.3.6.1 (a). 7. Applying the guidance in Note (b) to CLP Annex I, 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**: '92% of the mixture consists of components of unknown acute toxicity.' (See Section 3.1.4.2 of this guidance)		

3.1.5.3.2. Example 12a

Note: Examples 12a and 12b assume that it is known that only one physical form (i.e. mist in example 12a and vapour in example 12b) can occur during any reasonably expected use of the mixture including when the mixture is used to produce a new mixture. This would need to be justified. If toxicity data for more than one form is used, the converted ATE value has to be used even if an ATE value is available, according to these examples.

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/4 h)		
Ingredient 1 solid (6%)		Category 4	Conv. ATE (mg/L/4 h) = 1.5 mg/L/4 h
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/4 h) = 1.5 mg/L/4 h, 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/4 h → Category 4 NOTE: The mixture of 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.		

3.1.5.4. Examples of mixtures not fulfilling the criteria for classification

3.1.5.4.1. Example 12b

See Note under example 12a.

Application	Different phases in inhalation exposure. Extrapolation.		
	Test Data	**Classification**	**Rationale**
Available information	Use/exposure as vapour Animal data (rat): LC_{50} (mg/L/4 h)		
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 CLP Annex I, 3.1.3.6.1 as information is available for all ingredients. There are 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. $100/ATE_{mix}$ = 0 + 0 + 0 + 40/11 + 0 = 3.64 → ATE_{mix} =27.5 mg/L/4 h, which is above the upper generic concentration limit for vapour → NC		

3.1.5.5. Example of the application of the additivity method for mixtures for acute inhalation toxicity with ingredient substances in different physical forms (gas, vapour, mist or dust).

3.1.5.5.1. Example 13

Application	Information on acute inhalation toxicity for all ingredients			
	Test data (LC_{50} acute inhalation)	**Tested form**	**Classification (ingredient)**	**Reference**

Nicotine (1.9%)	0.19 mg/L	mist	Category 2	RAC 2015
Diacetyl (6%)	2.25 < LC_{50} < 5.2 mg/L [4-hr]	vapour	Category 3	BASF. 1993. Study on the acute inhalation toxicity LC50 of Diacetyl FCC as a vapor in rats 4 hour exposure. Project No. 1310247/927010. BASF
Propylene glycol (65%)	Not acutely toxic			REACH registration
Glycerine (27.1%)	Not acutely toxic			REACH registration
Rationale	1. No test information on the mixture 2. No test information on similar mixtures 3. Sufficient information on all ingredients. Therefore the summation method is applicable. As the two ingredients which are acutely toxic have test data for different forms (mist and vapour), it is not clear which ATE range is applicable to the mixture. Therefore, the fraction of the acute toxicity of the mixture is calculated for each ingredient substance and category and added. When the sum of the fractions is one or higher for a category, that category is applicable to the mixture. (See also 3.1.3.3.4) For diacetyl, no LC_{50} was derived but only a range. Therefore, the converted ATE value in accordance with Table 3.1.2 was applied resulting in an ATE of 3 mg/L which is inside the observed LC_{50} range. Applied formula: $((\text{limit/ATE}) * \text{concentration}/100)_{mist} + ((\text{limit/ATE}) \times \text{concentration}/100)_{vapour}$ limit= the upper border of ATE values for a hazard category (Table 3.1.1., Annex I, CLP) concentration= concentration of a component tested in a state/form Category 1 is not applicable as none of the ingredients are classified as category 1. Category 2: (0.5/0.19) * 1.9/100 (nicotine) + (2/3) * 6/100 (diacetyl) = 0.05 + 0.04 = 0.09 which is below 1 meaning not category 2. Category 3: (1.0/0.19) * 1.9/100 (nicotine) + 10/3 * 6/100 (diacetyl) = 0.10 + 0.20 = 0.30 which is below 1 meaning not category 3. Category 4: (5/0.19) * 1.9/100 (nicotine) + (20/3) * 6/100 (diacetyl) = 0.50 + 0.40 = 0.90 which is below 1 meaning not category 4.			

	No classification for acute toxicity by the inhalation route is warranted

3.1.6. References

OECD (2009) Series on testing and assessment number 39: Guidance document on acute inhalation toxicity testing ENV/JM/MONO(2009)28 (21 July 2009).

ECETOC (2003) TR 86: 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 human 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 (e.g. for diagnostic purposes) the selection of individuals and the control groups must be carefully considered. A critical review of the value of human studies is provided in the Guidance on IR&CSA Section R.4.3.3 and more specific considerations for skin corrosion/irritation are given in the Guidance on IR&CSA Section R.7.2.4.2.

Data indicates that human skin is, in most cases, less sensitive than the skin of 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 models based on combinations of (Q)SARs and databases (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 (Commission Regulation (EC) No 440/2008) or by methods based on internationally recognised scientific principles.

Before using the non-testing methods as referred to in the following sections, it should be checked whether the methods are sufficiently validated (or considered valid in case of (Q)SAR and expert systems) against the criteria for classification according to CLP (and not validated against the old DSD criteria which differed slightly from the CLP criteria).

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 (Guidance on IR&CSA Section R.7.2.3.1).

Thus, in the absence of evidence to the contrary, classification as Skin Irritation Category 2 should be considered for peroxides, whereas the classification for a hydroperoxide would normally be Skin Corrosive Category 1. Appropriate evidence must be provided in order to consider no classification of substances with oxidising properties.

3.2.2.1.2.2. pH and acid/alkaline reserve

> **Annex I: *3.2.2.2.5.*** *Likewise, pH extremes like ≤ 2 and ≥ 11,5 may indicate the potential to cause skin effects, especially when associated with significant acid/alkaline reserve (buffering capacity). Generally, such substances are expected to produce significant effects on the skin. In the absence of any other information, a substance is considered as corrosive to skin (Skin Corrosion Category 1) if it has a pH ≤ 2 or a pH ≥ 11,5. However, if consideration of alkali/acid reserve suggests the substance may not be corrosive despite the low or high pH value, this needs to be confirmed by other data, preferably by data from an appropriate validated in vitro test.*

Prediction of skin corrosivity based on pH extremes shows a very high specificity (>90%) and therefore a low number of false positives (R.7.2.4.1, IR&CSA guidance). 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. The higher the buffer capacity, the higher in general the potential for corrosivity.

3.2.2.1.2.3. Non-testing methods: (Q)SARs and expert systems

Non-testing methods such as (Q)SARs and expert systems (a diverse group of models consisting of combinations of SARs, QSARs and databases) may be considered on a case-by-case basis. Structural alerts are substructures in the substance that are considered to reflect some kind of chemical or biochemical reactivity that underlies the toxicological effect. The occurrence of a structural alert for a substance suggests the presence of an effect, based on the notion that structural analogues that have exhibited corrosion (or irritation) potential can be used to predict a corrosive or irritant effect for the substance of interest, or to tailor further testing and assessment. The absence of one of the known structural alerts for irritation and corrosion alone does not prove absence of effect, as knowledge of structural alerts for irritation and corrosion might be incomplete.

(Q)SAR systems that also account for skin effects are for example ACD Percepta, Hazard Expert, CASE Ultra, Discovery studio Acellrys (former TOPKAT). Derek Nexus is a knowledge-based expert system that gives toxicity predictions. These systems go beyond the structural similarity considerations encompassing also other parameters such as topology, geometry and surface properties. Not all of the models were developed with EU regulatory purposes in mind, so it is important to assess in each case whether the endpoint or effect being predicted corresponds to the regulatory endpoint of interest.

The expert system BfR-DSS[53] has been recommended in the Guidance on IR&CSA Section R.7.2.4 since there is currently 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', https://eurl-ecvam.jrc.ec.europa.eu/laboratories-research/predictive_toxicology/qsar_tools/toxtree. The BfR alerts ("inclusion rules") for corrosion and irritation have also been incorporated into the OECD QSAR Toolbox (http://www.qsartoolbox.org/).

[53] Decision Support System (DSS) developed by the German Federal Institute for Risk Assessment (BfR) to assess certain hazardous properties of pure chemicals.

In the absence of any other existing data, conclusion on the presence of an effect can be reached if the (Q)SAR or expert system has been shown to adequately predict the presence of the classified effect. In case of negative (Q)SAR data the need for classification cannot be excluded.

If existing other data (e.g. *in vitro* or *in vivo* data) contradicts these conclusions on the presence or absence of an effect then a weight of evidence approach must be applied. The suitability of the model (reliability, relevance) should be very carefully checked to make sure that the prediction is fit for purpose, and the applicability of the model to the substance should also be justified.

Since a formal adoption procedure for the non-testing methods (as mentioned above) 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 Guidance on IR&CSA Section R.6.1.

3.2.2.1.2.4. Testing methods: *in vitro* methods

Table R.7.2-2 in the Guidance on IR&CSA lists the status of validation and regulatory acceptance for *in vitro* test methods for skin corrosion and skin irritation. The information given below is current at the time of publication, however further information on newly adopted OECD Test Guidelines can be found on the OECD website (http://www.oecd.org/env/chemicalsafetyandbiosafety/testingofchemicals/oecdguidelinesforthetestingofchemicals.htm). Furthermore, up to date information on OECD and EU test guidelines can be found also on the ECHA website (https://www.echa.europa.eu/support/oecd-eu-test-guidelines).

In vitro methods for skin corrosion

The OECD has accepted 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 EU Test Methods Regulation (EC) No 440/2008 and in OECD Test Guidelines (OECD TG):

- The transcutaneous electrical resistance (TER; using rat skin) test (OECD TG 430 / TM B.40)
- Reconstructed human epidermis (RHE) tests (OECD TG 431 / TM B.40 bis)
- The *in vitro* membrane barrier test method (OECD TG 435)

Positive *in vitro* results on corrosivity 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 at present does not allow subcategorisation within the corrosive category, the membrane barrier test allows for the differentiation into the three Categories 1A, 1B and 1C. The reconstructed human epidermis (RHE) models included in the OECD TG 431 i.e. EpiDerm™ SCT, Episkin™, SkinEthic™ RHE and epiSC® support the sub-categorisation into Category 1A, however they cannot discriminate between Categories 1B and 1C. The applicability domain of the three tests outlined here (TER-, RHE- and membrane barrier test) with regard to the alkalinity and acidity of the tested substance should be carefully considered to decide which test(s) are most appropriate for the actual substance.

The TER and the RHE 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/ESAC, 2000).

In vitro methods for skin irritation

The OECD has adopted an *in vitro* skin irritation test guideline i.e. OECD TG 439 (TM B. 46) that currently contains four test methods i.e. EpiDerm™ SIT, EpiSkin™, SkinEthic™ RHE and LabCyte EPI – MODEL24 SIT. These test methods can reliably distinguish non-classified from classified substances but cannot distinguish between corrosives and irritants when used alone. Thus, in the case of positive results, the potential corrosive properties should be excluded or confirmed based on data obtained from an *in vitro* skin corrosion test. It should be noted that conclusions on the applicability domain of the four methods rest mainly on the optimisation and validation data set. All four methods are valid for the classification of substances for skin irritation according to CLP criteria.

Information on the current developments of *in vitro* tests and methodology can be found on the ECVAM website (http://ihcp.jrc.ec.europa.eu/our_labs/eurl-ecvam).

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 no 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 OECD TG 404 (TM B.4) is the standard *in vivo* test for the hazard assessment under REACH. However, according to Annex VIII of REACH (at or above 10 tonnes/year) an *in vivo* test should only be performed in case the *in vitro* studies (as required in Annex VII) are not applicable or the results of these studies are not adequate for classification.

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 (OECD TG 402; OECD TG 410), guinea pig skin sensitisation studies (OECD TG 406) and from irritation studies in hairless mice.

3.2.2.2. Classification criteria

Annex I: 3.*2.2.1.1.* *Skin corrosion*

Annex I: *3.2.2.1.1.1.* *A substance is corrosive to skin when it produces destruction of skin tissue, namely, visible necrosis through the epidermis and into the dermis in at least one tested animal after exposure for up to 4 hours.*

Annex I: *3.2.2.1.1.2.* *Corrosive substances shall be classified in Category 1 where data is not sufficient for sub-categorisation.*

Annex I: *3.2.2.1.1.3.* *When data are sufficient substances shall be classified in one of the three sub-categories 1A, 1B, or 1C in accordance with the criteria in Table 3.2.1.*

Annex I: *3.2.2.1.1.4.* *Three sub-categories are provided within the corrosion category: sub-category 1A – where corrosive responses are noted following up to 3 minutes exposure and up to 1 hour observation; sub-category 1B – where corrosive responses are described following exposure greater than 3 minutes and up to 1 hour and observations up to 14 days; and sub-category 1C – where corrosive responses occur after exposures greater than 1 hour and up to 4 hours and observations up to 14 days.*

Table 3.2.1

Skin corrosion category and subcategories

Category	***Criteria***
Category 1[1]	*Destruction of skin tissue, namely, visible necrosis through the epidermis and into the dermis, in at least one tested animal after exposure ≤ 4 h*
Sub-Category 1A	*Corrosive responses in at least one animal following exposure ≤ 3 min during an observation period ≤ 1 h*
Sub-Category 1B	*Corrosive responses in at least one animal following exposure > 3 min and ≤ 1 h and observations ≤ 14 days*
Sub-Category 1C	*Corrosive responses in at least one animal after exposures > 1 h and ≤ 4 h and observations ≤ 14 days*

[1] *See the conditions for the use of Category 1 in paragraph (a) of Section 3.2.2.*

Annex I: *3.2.2.1.2. Skin irritation*

Annex I: *3.2.2.1.2.1. A substance is irritant to skin when it produces reversible damage to the skin following its application for up to 4 hours. The major criterion for the irritation category is that at least 2 of 3 tested animals have a mean score of ≥ 2.3 and ≤ 4.0.*

Annex I: *3.2.2.1.2.2. A single irritation category (Category 2) is presented in Table 3.2.2, using the results of animal testing.*

Annex I: *3.2.2.1.2.3. Reversibility of skin lesions is also considered 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.*

Annex I: *3.2.2.1.2.4. Animal irritant responses within a test can be variable, as they are with corrosion. 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.

Table 3.2.2

Skin irritation category[a]

Category	***Criteria***
Irritation (Category 2)	*(1) Mean score 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.*

[a)] Grading criteria are understood as described in Regulation (EC) No 440/2008.

3.2.2.3. Evaluation of hazard information

Annex I: *3.2.2.2.1.* *A tiered approach to the evaluation of initial information shall be considered, where applicable, recognising that not all elements may be relevant.*

Annex I: *3.2.2.2.7.* *The tiered approach provides guidance on how to organize existing information on a substance and to make a weight of evidence decision about hazard assessment and hazard classification.*

Although information might be gained from the evaluation of single parameters within a tier (see Section 3.2.2.2.1), consideration shall be given to the totality of existing information and making an overall weight of evidence determination. This is especially true when there is conflict in information available on some parameters.

The tiered approach for the evalution of the information applied in order to make a decision about the skin corrosion/skin irritation hazard properties is illustrated in Figure 3.1 below. The approach in the figure was adopted by the UNSCEGHS in December 2012 (with exception of the added footnotes g) and h)).

Figure 3.1 Tiered evaluation for skin corrosion/skin irritation

Step	Parameter	Finding	Conclusion
1a:	Existing human or animal skin corrosion/irritation data [a]	→ Skin corrosive	→ Classify as skin corrosive [b]
	↓		
	Not corrosive/Insufficient/Inconclusive/No data		
	↓		
1b:	Existing human or animal skin corrosion/irritation data [a]	→ Skin irritant	→ Classify as skin irritant [g]
	↓		
	Not irritant/Inconclusive Insufficient//No data		
	↓		
1c:	Existing human or animal skin corrosion/irritation data [a]	→ Not skin corrosive or skin irritant	→ Not classified [g]
	↓		
	No/Inconclusive Insufficient/ data		
	↓		
2:	Other, existing skin data in animals [c]	→ Yes; other existing data showing that substance may cause	→ May be deemed to be skin corrosive [b] or skin irritant [g]
	↓		

Step	Parameter	Finding	Conclusion
		skin corrosion or skin irritation	
	No/Negative/ Insufficient/Inconclusive data ↓		
3:	Existing *ex vivo/in vitro* corrosivity data [d] →	Positive: Skin corrosive →	Classify as skin corrosive [b]
	↓ No/Negative/ Insufficient/Inconclusive data ↓		
	Existing *ex vivo/in vitro* irritation data →	Positive: Skin irritant →	Classify as skin irritant [g]
	↓ ↘	Negative: not skin irritant →	Not classified [g]
	No/ Insufficient/Inconclusive data ↓		
4:	pH-based assessment (with consideration of acid/alkaline reserve of the chemical) [e] →	pH ≤ 2 or ≥ 11.5 [i] with high acid/alkaline reserve or no data for acid/alkaline reserve →	Classify as skin corrosive [g]
	↓		

Step	Parameter	Finding	Conclusion
	Not pH extreme, no pH data or extreme pH with data showing low/no acid/alkaline reserve[h] ↓		
5:	**Validated Structure Activity Relationship (SAR) methods** → ↓	**Skin corrosive** →	**Deemed to be skin corrosive [b]**
		Skin irritant →	**Deemed to be skin irritant**
	No/Inconclusive Insufficient/data ↓		
6:	**Consideration of the total weight of evidence [f]** → ↓	**Skin corrosive** →	**Deemed to be skin corrosive [b]**
		Skin irritant →	**Deemed to be skin irritant**
7:	**Not classified**		

(a) *Existing human or animal data could be derived from single or repeated exposure(s), for example in occupational, consumer, transport or emergency response scenarios; or from purposely-generated data from animal studies conducted according to validated and internationally accepted test methods. Although human data from accident or poison centre databases can provide evidence for classification, absence of incidents is not itself evidence for no classification as exposures are generally unknown or uncertain.*

(b) *Classify in the appropriate category/sub-category, as applicable.*

(c) *All existing animal data should be carefully reviewed to determine if sufficient skin corrosion/irritation evidence is available. In evaluating such data, however, the reviewer should bear in mind that the reporting of dermal lesions may be incomplete, testing and observations may be made on a species other than the rabbit, and species may differ in sensitivity in their responses.*

(d) *Evidence from studies using validated protocols with isolated human/animal tissues or other, non-tissue-based, though validated, protocols should be assessed.*

(e) Measurement of pH alone may be adequate, but assessment of acid or alkali reserve (buffering capacity) would be preferable.

(f) All information that is available should be considered and an overall determination made on the total weight of evidence. This is especially true when there is conflict in information available on some parameters. Expert judgment should be exercised prior to making such a determination. Negative results from applicable validated skin corrosion/irritation in vitro tests are considered in the total weight of evidence evaluation.

(g) In case there is a conflict in available data, e.g. negative/irritation human data but positive/corrosive in vitro data, a weight of evidence assessment should be performed, see footnote f. (This footnote was not included in the figure in the 5th rev of GHS, but is based on 3.2.1.2. and 3.2.2.2.7, Annex I, CLP).

(h) Non corrosivity needs to be confirmed by other data and preferably by data from an appropriate validated in vitro test. (This footnote was not included in the figure in the 5th rev of GHS, but is based on 3.2.2.2.5, Annex I, CLP).

(i) For the case of mixtures with no human or animal data on skin corrosion/irritation but with extreme pH see Figure 3.3 in 3.2.3.2.1.1.

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 and on the extent and duration of the exposure. Further guidance on evaluation of human data for skin corrosion/irritation can be found in the Guidance on IR&CSA Section R.7.2.4.2.

The criteria in CLP Annex I, Tables 3.2.1 and 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. For instance, the *in vitro* membrane barrier test method is mainly applicable for acids and bases and is not applicable for solutions with pH values between 4.5 and 8. Normally, recommendations for classification according to GHS criteria based on the results of an *in vitro* test are mentioned in the corresponding OECD test guideline. In particular OECD TG 431 concludes that some results fall in the category 1B/1C. Category 1B/1C is not an option in CLP. However, a WoE assessment may lead to a conclusion about the subcategory but if this is not the case, category 1 should be assigned[54].

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

[54] Please, note that the issue concerning the subcategorization of skin corrosivity is currently under discussion.

- 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 only be 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. Skin Irritation Category 2 is used if at least 2 animals show a mean score of 2.3 or above. Other test methods, however, have used 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 guidance needs to be applied (adopted by the UNSCEGHS in June 2011):

The average score is determined per animal (see Example 3, Section 3.2.5.1.3).

In the case of **6** rabbits the following applies:

a. Classification as skin corrosive – Category 1 if destruction of skin tissue (visible necrosis through the epidermis and into the dermis) occurs in at least one animal after exposure up to 4 hours.

b. Classification as skin irritant – Category 2 if at least 4 out of 6 rabbits show a mean score per animal of ≥ 2.3 ≤ 4.0 for erythema/eschar or for oedema;

In the case of **5** rabbits the following applies:

a. Classification as skin corrosive – Category 1 if destruction of skin tissue (visible necrosis through the epidermis and into the dermis) occurs in at least one animal after exposure up to 4 hours.

b. Classification as skin irritant – Category 2 if at least 3 out of 5 rabbits show a mean score per animal of ≥ 2.3 ≤ 4.0 for erythema/eschar or for oedema;

In the case of **4** rabbits the following applies:

a. Classification as skin corrosive – Category 1 if destruction of skin tissue (visible necrosis through the epidermis and into the dermis) occurs in at least one animal after exposure up to 4 hours.

b. Classification as skin irritant – Category 2 if at least 3 out of 4 rabbits show a mean score per animal of ≥ 2.3 ≤ 4.0 for erythema/eschar or for oedema;

Other dermal tests on animals

Relevant data may also be available from animal studies that were conducted for other primary purposes than the investigation of skin corrosion/irritation. For example, in line with Section 3.2.2.2.3 of Annex I to CLP, acute dermal toxicity data may be used for classification as 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.

If the substance is proven to be either an irritant or a corrosive in an acute dermal toxicity test carried out with rabbits with the undiluted test substance (liquids) or with a suitable suspension (solids), the following applies. In case of signs of skin corrosion, classify as Skin Corrosive (subcategorisation as 1A, 1B or 1C, where possible). In all other cases: calculate or estimate the amount of test substance per cm^2 and compare this to the test substance concentration of 80 µl or 80 mg/cm^2 employed in the EU B.4/OECD TG 404 for dermal corrosion/irritation test with rabbits. If in the same range and adequate scoring of skin effects is provided, classify or not as Skin Irritant Category 2. If not in the same range and inadequate scoring of skin effects, use the data in a Weight-of-Evidence analysis and proceed.

In case the test was performed in other species, which may be less sensitive (e.g. rat), evaluation must be made with caution. Usually, the rat is the preferred species for toxicity studies within the EU. The limit dose level of 2000 mg/kg bw of a solid is normally applied as a 50% suspension in a dose volume of 4 ml/kg bw onto a skin surface area of about 5x5 cm. Assuming a mean body weight of 250 g, a dose of 1 ml of the suspension will be applied to an area of 25 cm^2, i.e 20 mg test substance per cm^2. In case of an undiluted liquid, 0.5 ml is applied to 25 cm^2, i.e. 20 µl/cm2. Considering the fact that (i) the rat skin is less sensitive compared to rabbit skin, (ii) much lower exposures are employed and (iii), in general, the scoring of dermal effects is performed less accurately, the results of dermal toxicity testing in rats will not be adequate for classification with respect to skin irritation. Only in case of evidence of skin corrosivity in the rat dermal toxicity test can the test substance be classified as Skin Corrosive Category 1. All other data should be used in a Weight of Evidence.

Regarding data from skin sensitisation studies, the skin of guinea pigs is less sensitive than that of rats which is, in turn, is less sensitive than that of rabbits. Only in the case of evidence of skin corrosivity in the sensitisation test (Maximisation or Buhler) with the neat material or dilutions of solids in water, physiological saline or vegetable oil, should the test substance be classified as Skin Corrosive Category 1. However, care should be exercised when interpreting findings from guinea pig studies, particularly from maximisation protocols, as intradermal injection with adjuvant readily causes necrosis. All other data should be used for Weight of Evidence only. Information on irritant properties from skin sensitisation tests cannot be used to conclude on a specific classification regarding acute skin irritation but may be used in a Weight-of-Evidence analysis. In general, irritation data from the Local Lymph Node Assay are not usable. The test substance is applied to the dorsum of the ear by open topical application, and specific vehicles for enhancement of skin penetration are used.

3.2.2.3.3. Weight of evidence

According to Article 9(1) CLP, the criteria should be applied to available data. However, sometimes it is not straightforward or simple to apply the criteria and according to Article 9(3) a

weight of evidence and expert judgement should be applied in such cases when the criteria cannot be applied directly.

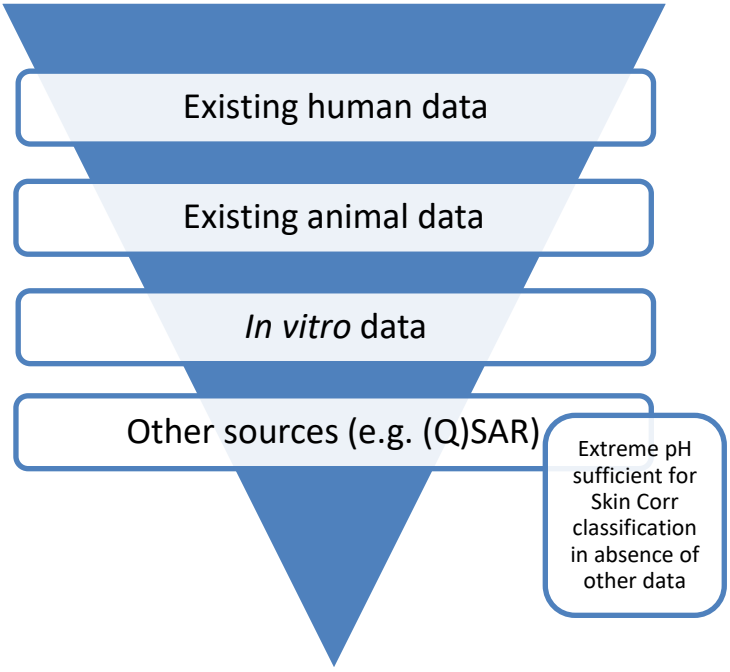
A weight of evidence determination means that all available and scientifically justified information bearing on the determination of hazard is considered together, such as physico-chemical parameters (e.g., pH, reserve alkalinity/acidity), information from the application of the category approach (grouping, 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 should be given appropriate weight. Both positive and negative results should be assembled together in a single weight of evidence determination (see 1.1.1.3, Annex I, CLP and Section 1.4 in this guidance). Note that non testing methods may normally not enable subcategorsation of corrosive substances.

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.*

The following Figure 3.2 provides an illustration of the assessment of available data, in the case of conflicting results, to decide the weight to be assigned to different types of data (see also Figure 3.1). It needs to be noted that the relative weights indicated in the figure assume comparable quality of the data. WoE considerations need to take into account, on a case-by-case basis, the quality, nature, relevance and applicability domain of the different types of data available. The figure illustrates a decreasing weight of the information from top to bottom.

Figure 3.2 Simplified illustration of the relative weight of the available information



When contradicting data of comparable quality belongs to different "hierarchical levels", the following considerations should be made:

- When there are positive data which belong to a higher level in the hierarchy than the available negative data, more weight should normally be given to the positive data.
- When the negative data belong to a level which is higher than the positive data, the full available dataset should be assessed in a WoE approach (as, for example, existing good quality positive animal data could overrule negative human data and negative good quality *in vitro* data could overrule positive QSAR data).

More information and guidance on the relevance of the different types of information, as well as on quality assessment, is provided in OECD guidance no 203[55] and in the Guidance R.7a.

For additional guidance, if both human and animal data are available, see the Guidance on IR&CSA Section R.7.2.3.2.

3.2.2.4. Decision on classification

Where the comparison of the information with the criteria leads to a decision that 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 Corrosion 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.*

[55] Available at http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2014)19&doclanguage=en. See in particular section B, part 2, module 8.

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, such 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' OECD TG 404[56] 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 generating data specifically for the purpose of setting SCLs is not a requirement according to the CLP Regulation. Article 8(1) CLP specifies that new tests may only be performed (in order to determine the hazard of a substance or mixture) if all other means of generating information has been exhausted and Article 7(1) specifies that where new tests are carried out, tests on animals must be undertaken only when no other alternatives, which provide adequate reliability and quality of data, are possible. The GCLs must be applied for the classification of a mixture on the basis of its ingredient substances classified for skin irritation and corrosivity, if there are no already existing specific data justifying an SCL which is lower or, in exceptional cases, higher than the GCL (see Article 10(1), CLP). Therefore, information will

[56] 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.

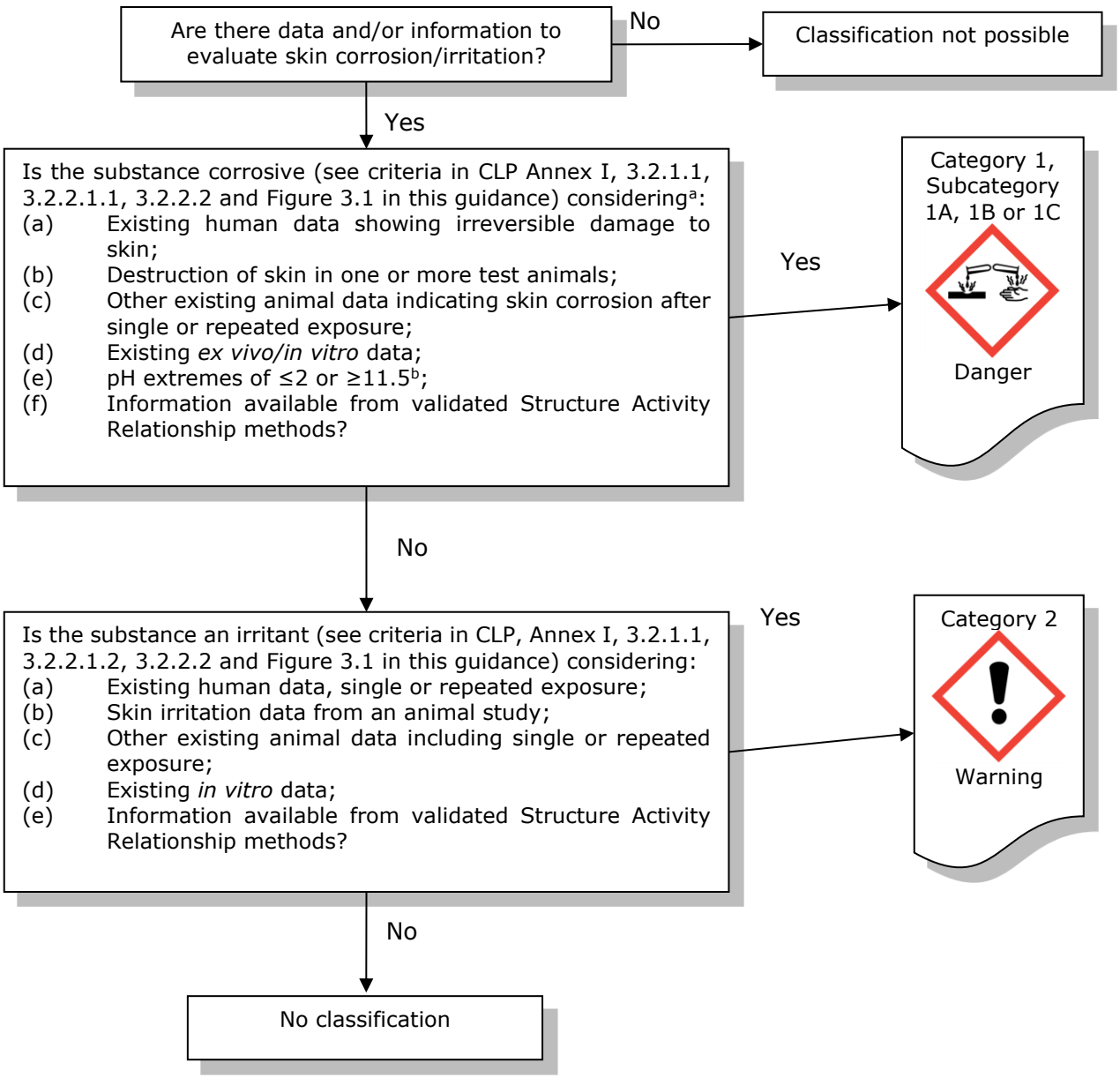
always be available, for mixtures containing substances already classified for skin corrosion/irritation, making it possible to identify the hazard for the mixture by using the GCLs (Article 9(4), CLP).

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 3.1) to CLP includes examples of substances for which a higher or lower SCL was set under Directive 67/548/EEC (old DSD system) and which were transferred to CLP.

3.2.2.6. Decision logic for classification of substances

The decision logic, which is based on the one provided in the GHS, is reported as additional guidance here below. It is strongly recommended that the person responsible for classification, studies the criteria for classification, as well as the guidance above, before and during use of the decision logic.



[a] Taking into account consideration of the total weight of evidence if necessary.

[b] Not applicable if consideration of pH and acid/alkaline reserve indicates substances may not be corrosive and confirmed by other data, preferably by data from an appropriate validated *in vitro* test.

3.2.3. Classification of mixtures for skin corrosion/irritation

3.2.3.1. Identification of hazard information

As for substances, the procedure for evaluating mixtures for classification purposes, 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, *in vitro* data and finally physico-chemical properties available on the mixture. (The tiered approach to evaluate data for skin corrosion/irritation as illustrated in Figure 3.1, should be taken into account also for mixtures in case of relevant and reliable data on the complete 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. Although human data from accident or poison centre databases can provide evidence for classification, absence of incidents is not itself evidence for no classification, as exposures may be unknown or uncertain. See Section 3.2.2.1 of this Guidance 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 should be applied if possible. If the bridging principles are not applicable, an assessment on the basis of data for the components of the mixture must be applied.

3.2.3.2. Classification criteria for mixtures

Based on available information, the approaches below should be used for classification of a mixture for skin corrosivity and irritation in the following sequence (Article 9, CLP and Figure 1.1):

a. Classification derived using data on the mixture itself, by applying the substance criteria of Annex I to CLP;

b. Classification based on the application of bridging principles, which make use of test data on similar tested mixtures and ingredient substances;

c. Classification based on ingredients as described in 3.2.3.3, Annex I, CLP.

3.2.3.2.1. When data are available for the complete mixture

Annex I: *3.2.3.1.1.* *The mixture shall be classified using the criteria for substances, taking into account the tiered approach to evaluate data for this hazard class.*

Annex I: *3.2.3.1.2.* *When considering testing of the mixture, classifiers are encouraged to use a tiered weight of evidence approach as included in the criteria for classification of substances for skin corrosion and irritation (section 3.2.1.2 and 3.2.2.2), to help ensure an accurate classification as well as to avoid unnecessary animal testing. In the absence of any other information, a mixture is considered corrosive to skin (Skin Corrosion Category 1) if it has a pH ≤ 2 or a pH ≥ 11.5. However, if consideration of acid/alkaline reserve suggests the mixture may not be corrosive despite the low or high pH value, this needs to be confirmed by other data, preferably by data from an appropriate validated in vitro test.*

Additional simplified guidelines for the assessment of available data on the mixture when WoE needs to be applied, is provided in Section 3.2.2.3.3 (see Figure 3.2).

There is 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 ensured 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.

Low values of acid or alkaline reserve indicate a low buffer capacity. Mixtures showing a low buffer capacity are less or even not corrosive or irritant. The relation is quantitatively expressed by: - pH + 1/12 alkaline reserve >= 14.5 or pH - 1/12 acid reserve <= -0.5. If the sums are

>= 14.5 or <= -0.5 the mixture has to be considered as corrosive (see Decision logic 3.2.3.4, step 1a).

If the additional consideration of the acid/alkaline reserve according to Young *et al.* (1987, 1994) suggests that classification for corrosion may not be warranted, this needs to be confirmed by other data, preferably by data from an appropriate and validated *in vitro* test, applicable for the mixture. The consideration of acid/alkali reserve should not be used alone to exonerate mixtures from classification.

Where it is decided to base the classification of a mixture upon consideration of pH alone, Skin Corrosion Category 1 should be applied.

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 according to Article 10(1)), 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:

Figure 3.3 Mixture without human or animal data on skin corrosion/irritation 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 Corrosion Category 1.
Is the mixture tested in an OECD adopted *in vitro* skin corrosivity test, considered valid and applicable for the mixture? **NO ➔** **YES** **↓**	Classify as corrosive, Skin Corrosion Category 1
Does the mixture demonstrate corrosive properties in an OECD adopted *in vitro* skin corrosivity test considered valid and applicable for the mixture? **YES ➔** **NO** **↓**	Classify as corrosive. If discrimination between Skin Corr. 1A/1B/1C is not possible, Skin Corr. 1 must be chosen.
Does the mixture demonstrate irritant properties in an OECD adopted *in vitro* skin irritation test considered valid and applicable for the mixture? **YES ➔** **NO** **↓**	Classify as skin irritant, Skin Irritation Category 2
Consideration of the total weight of all available evidence, in particular in case of conflicting data, including the extreme	

pH, negative/inconclusive results from e.g. validated skin corrosion/irritation *in vitro* tests, and the results from the application of the methods based on the ingredients in the mixture in CLP Annex I, sections 3.2.3.3.2-3.2.3.3.3 (Table 3.2.3)/3.2.3.3.4.1-3.2.3.3.4.3 (Table 3.2.4) ➔	Classify: Category 1, 2, no classification

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 use of the pH-acid/alkali reserve approach, potentially leading to a change of the 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-acid/alkali reserve method cannot be a basis for modifying the classification but should be considered in the weight of evidence analysis.

If a mixture with corrosive constituents also contains surfactants (e.g. tensids or detergent substances), it can be assumed that corrosivity might be amplified (Kartono & Maibach 2006). Even if only one corrosive substance with an assigned SCL is present in such a mixture, the possible synergistic effect has to be taken into account when classifying the mixture.

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 steps described in the above decision logic should be followed.

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 corrosion/irritation potential, 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 ingredients of the mixture (see Section 1.6.3.2 of this Guidance).

When the available identified information is inappropriate for the application of the bridging principles then the mixture should be classified based on its ingredients as described in Sections 3.2.3.2.3 and 3.2.3.3 of this Guidance.

3.2.3.2.3. When data are available for all ingredients or only for some ingredients

3.2.3.2.3.1. Ingredients that should be taken into account for the purpose of classification

Annex I: *3.2.3.3.1.* *[…] The 'relevant ingredients' of a mixture are those which are present in concentrations ≥ 1% (w/w for solids, liquids, dusts, mists and vapours and v/v for gases), unless there is a presumption (e.g., in the case of corrosive ingredients) that an ingredient present at a concentration < 1% can still be relevant for classifying the mixture for skin corrosion/irritation.*

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 corrosive or irritant to skin when data are available on the ingredients, but not on the mixture as a whole, is based on the theory of additivity, such that each skin corrosive or skin irritant ingredient contributes to the overall skin corrosive or skin irritant properties of the mixture*

in proportion to its potency and concentration. A weighting factor of 10 is used for skin corrosive ingredients 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 skin irritant. The mixture is classified as corrosive or irritant to skin when the sum of the concentrations of such components exceeds a concentration limit.

Annex I: *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 corrosive or irritant 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. Although the general approach is the additivity principle, which has been successfully used under the DPD and more recently, the supplier must ascertain whether the additivity approach is applicable. The first step would then be to identify all the relevant 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 it is important to also consider effects that could occur in the mixture, such as surfactant interaction, neutralisation of acids/bases when identifying the properties of the complete mixture (including pH and the acid/alkaline reserve) in addition to considering contributions of individual ingredients.

Additivity may not apply where the mixture contains substances mentioned in CLP Annex I, 3.2.3.3.4.1-3.2.3.3.4.3, see Section 3.2.3.2.3.3 of this Guidance.

Application of SCLs when applying the additivity approach

The generic concentration limits (GCLs) are specified in CLP Annex I, Table 3.2.3. However, according to CLP Article 10(6), SCLs take precedence over GCLs. Thus, if a given substance has an SCL set in accordance with Article 10(1), CLP, then this limit has to be taken into account when applying the summation (additivity) method for skin corrosion/irritation (see Examples 4 and 5).

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:

$$\text{Sum of } (\text{ConcA} / \text{clA}) + (\text{ConcB} / \text{clB}) + \ldots. + (\text{ConcZ} / \text{clZ}) \text{ is } \geq 1$$

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.

The formula should be used in a stepwise procedure in the following order:

1. Should the mixture be classified in Category 1 A? Only Cat. 1A ingredient substances are added.
2. Should the mixture be classified in Category 1B? Cat. 1A and 1B ingredient substances are added.
3. Should the mixture be classified in Category 1C? Cat. 1A, 1B and 1C ingredient substances are added.
4. Should the mixture be classified in Category 1? Cat. 1A, 1B, 1C and 1 ingredient substances are added.

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 Sections 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 to the skin at concentrations < 1%.

Annex I: *3.2.3.3.4.2.* *For mixtures containing strong acids or bases the pH shall be used as a classification criterion (see Section 3.2.3.1.2) since pH is a better indicator of skin corrosion than the concentration limits in Table 3.2.3.*

Annex I: *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 Corrosion Category 1 if it contains ≥ 1% of an ingredient classified as Skin Corrosion or as Skin Irritation (category 2) when it contains ≥ 3% of a skin 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.*

Annex I: *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 at or above the generic concentration limits mentioned in Tables 3.2.3 and 3.2.4 in Section 3.2.3.3.6. 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 at or 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 approach shall be applied, as described in Section 3.2.2.2.*

Annex I: *3.2.3.3.6.* *If there are data showing that (an) ingredient(s) is/are corrosive or irritant to skin at a concentration of < 1 % (skin corrosive) or < 3 % (skin 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 as skin corrosion (Category 1, 1A, 1B or 1C)/skin irritation (Category 2) that trigger classification of the mixture as skin corrosion/skin irritation where the additivity approach applies

Sum of ingredients classified as:	Concentration triggering classification of a mixture as:	
	Skin Corrosion	Skin Irritation
	Category 1 (see note below)	Category 2
Skin corrosion Sub-Category 1A, 1B, 1C or Category 1	≥ 5%	≥ 1% but < 5%
Skin irritation Category 2		≥ 10%

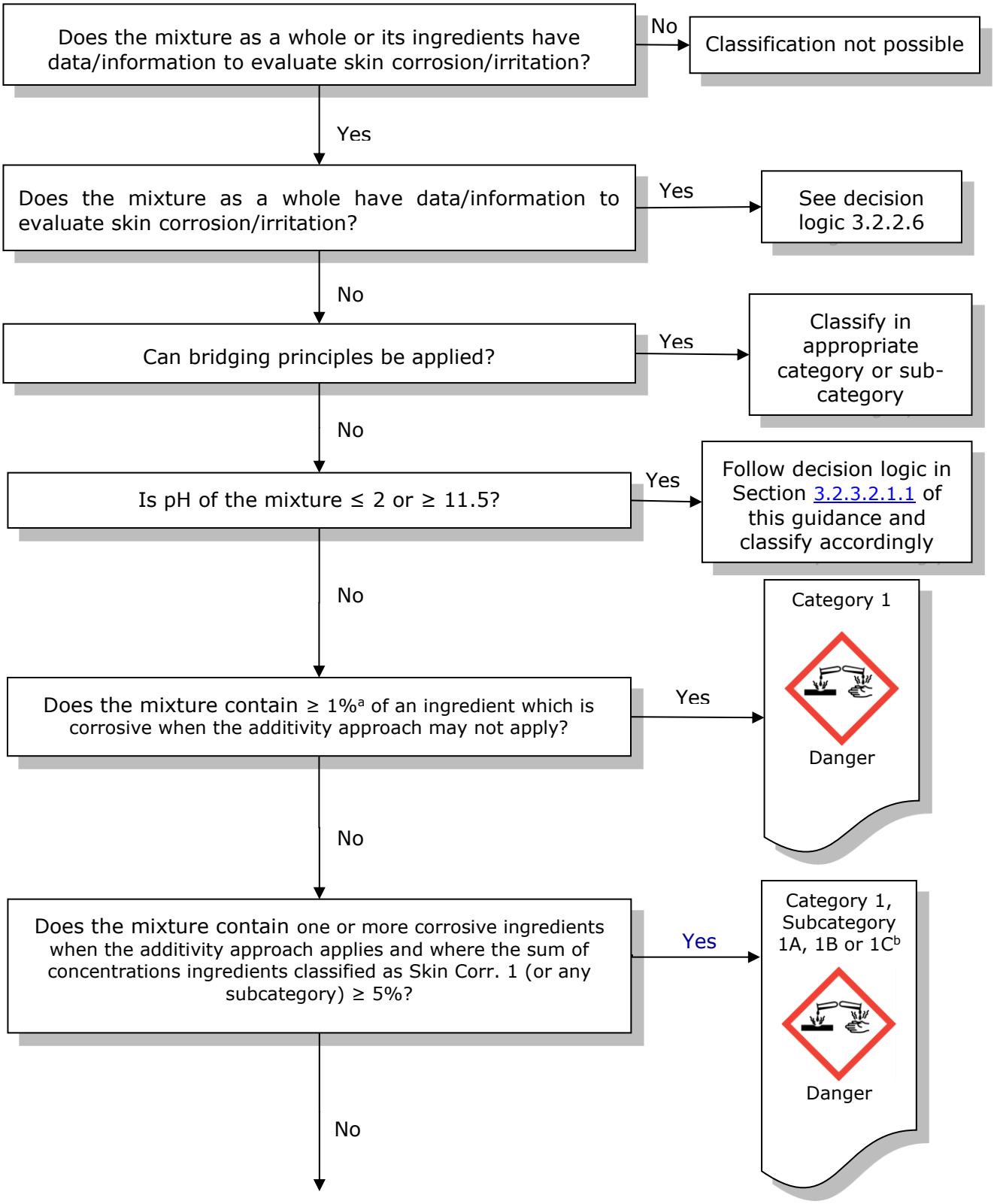
(10 x Skin corrosion Sub-Category 1A, 1B, 1C or Category 1) + Skin irritation Category 2		≥ 10%
Note *The sum of all ingredients of a mixture classified as Skin Corrosion Sub-Category 1A, 1B or 1C respectively, shall each be ≥ 5% respectively in order to classify the mixture as either Skin Corrosion Sub-Category 1A, 1B or 1C. If the sum of the ingredients classified as Skin Corrosion Category 1A is < 5% but the sum of the ingredients classified as Skin Corrosion Category 1A+1B is ≥ 5%, the mixture shall be classified as Skin corrosion Category 1B. Similarly, if the sum of the ingredients classified as Skin Corrosion Category 1A+1B ingredients is < 5% but the sum of the ingredients classified as Sub-Category 1A+1B+1C ingredients is ≥ 5% the mixture shall be classified as Skin Corrosion Category 1C. Where at least one relevant ingredient in a mixture is classified as Category 1 without sub-categorisation, the mixture shall be classified as Category 1 without sub-categorisation if the sum of all ingredients corrosive to skin is ≥ 5 %.*		

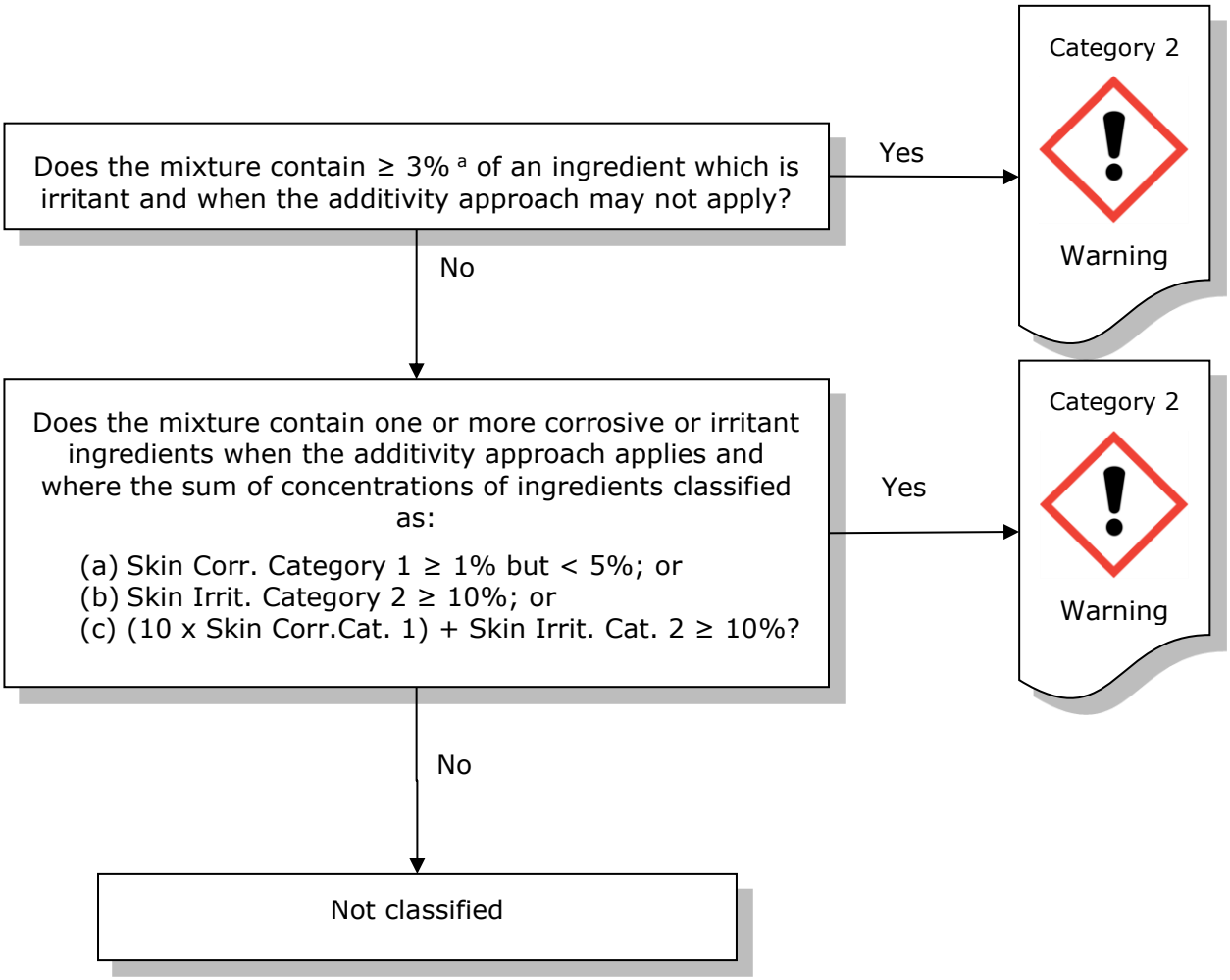
3.2.3.3.2. When the additivity approach is not applicable

Annex I: *Table 3.2.4* ***Generic concentration limits of ingredients of a mixture that trigger classification of the mixture as skin corrosion/skin irritation, where the additivity approach does not apply***		
Ingredient:	*Concentration:*	*Mixture classified as:*
Acid with pH ≤ 2	*≥ 1%*	*Skin corrosion Category 1*
Base with pH ≥ 11,5	*≥ 1%*	*Skin corrosion Category 1*
Other skin corrosive (Sub-Categories 1A, 1B, 1C or Category 1) ingredients	*≥ 1%*	*Skin corrosion Category 1*
Other skin irritant (Category 2) ingredients, including acids and bases	*≥ 3%*	*Skin irritation Category 2*

3.2.3.4. Decision logic for classification of mixtures

The decision logic, based on the one provided in the GHS, is presented here below as additional guidance. 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.


Does the mixture as a whole or its ingredients have data/information to evaluate skin corrosion/irritation?
No
Classification not possible
Yes
Does the mixture as a whole have data/information to evaluate skin corrosion/irritation?
Yes
See decision logic 3.2.2.6
No
Can bridging principles be applied?
Yes
Classify in appropriate category or sub-category
No
Is pH of the mixture ≤ 2 or ≥ 11.5?
Yes
Follow decision logic in Section 3.2.3.2.1.1 of this guidance and classify accordingly
No
Does the mixture contain ≥ 1%[a] of an ingredient which is corrosive when the additivity approach may not apply?
Yes
Category 1
Danger
No
Does the mixture contain one or more corrosive ingredients when the additivity approach applies and where the sum of concentrations ingredients classified as Skin Corr. 1 (or any subcategory) ≥ 5%?
Yes
Category 1, Subcategory 1A, 1B or 1C[b]
Danger
No



[a] Where relevant < 1%, see Section 3.2.3.3.1 of Annex I of CLP.

[b] See note to Table 3.2.3 in Annex I of CLP for details on use of Category 1 subcategories.

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.*

Table 3.2.5

Label elements for skin corrosion/irritation

Classification	*Sub-Categories 1A / 1B / 1C and Category 1*	*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 + P364*
Precautionary Statement Storage	*P405*	
Precautionary Statement Disposal	*P501*	

Article 26 1 (d)

If the hazard pictogram 'GHS05' applies, the hazard pictogram 'GHS07' shall not appear for skin and eye irritation.

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, such substances and mixtures have to be supplementary labelled with EUH071, if there is a possibility of exposure via inhalation taking into consideration the saturated vapour concentration and the possibility of exposure to particles or droplets of inhalable size as appropriate, (see also Chapter 3.8.2.5 of this Guidance). 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. Examples of classification for skin corrosion/irritation

3.2.5.1. Examples of substances fulfilling the criteria for classification

3.2.5.1.1. 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 a 4-hour application time are listed in the following table:

Animal Nr.	Degree of erythema after [observation time]						Degree of oedema after [observation time]						∅ 24/48/72 h ≥2.3 ?	
	1h	24h	48h	72h	7d	14d	1h	24h	48h	72h	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 Irritation Category 2

Rationale: The classification is made on the basis of 2/3 'positive responder' exceeding 2.3 mean score for erythema.

3.2.5.1.2. 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: The classification is based on the destruction of the tissue after 1 hour of exposure.

3.2.5.1.3. Example 3: 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:

Animal Nr	Observation time												Pos responder	
	1h	24h	48h	72h	7d	14d	1h	24h	48h	72h	7d	14d		
	Erythema						Oedema						Eryth e-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 is 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.

3.2.5.2. Examples of mixtures fulfilling the criteria for classification

Where the mixture is made up of ingredients with no assigned SCLs, the appropriate summation(s) and generic concentration limits from CLP Annex I, Table 3.2.3 should be used.

3.2.5.2.1. Example 4: Mixture without extreme pH, with ingredients with SCLs

Ingredient	Skin corrosion / irritation classification	Concentration (% w/w)	SCL
Substance A	Skin Irrit. 2	3.8	Not assigned
Substance B	Not classified	0.5	
Base E	Skin Corr. 1B	5.4	C ≥ 10 %: Skin Corr. 1B 5 % ≤ C < 10 %: Skin Irrit. 2
Substance D	Not classified	4	
Substance F	Skin Corr. 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 base but not any surfactant. Additivity is considered to apply.

Substance B, substance D and water can be disregarded as they are not classified for skin corrosion/irritation.

SCLs are neither assigned to substance F nor substance A, thus GCLs apply for these ingredients. SCLs are assigned to Base E (see Section 3.2.3.2.3.2 of this Guidance, Application of SCLs when applying the additivity approach).

Skin Corr. 1:

(% substance F/GCL) + (% base E/SCL) = (2/5) + (5.4/10) = 0.94 ⇨ < 1, thus the mixture is not classified as Skin Corr. 1

Skin Irrit. 2:

(% substance F/GCL) + (% base E/SCL) + (% substance A/GCL) = (2/1) + (5.4/5) + (3.8/10) = 3.46 which is > 1, thus the mixture is classified Skin Irrit. 2

3.2.5.2.2. Example 5: Mixture without extreme pH, and non-applicability of the additivity approach

Ingredient	Wt%	Classification	Information
Ingredient 1	4	Skin Corr. 1A	pH = 1.8
Ingredient 2	5	Skin Irr. 2	-
Ingredient 3	5	Skin Irr. 2	-
Ingredient 4	86	-	No data available

The pH of the mixture is 4.0, thus extreme pH provisions do not apply. There are no test data on the mixture (apart from a pH). Bridging principles do not apply since data on a similar mixture was not available. Classification of the mixture based on ingredient data can be considered.

Ingredient 1 with a pH = 1.8 is an ingredient for which additivity might not apply (see 3.2.3.3.4.1-2-3 and Table 3.2.4, Annex I, CLP). Expert judgment would be needed to determine whether or not additivity applies. Knowledge of the components is important. Given the limited information in this example, the classifier of this mixture chose to apply non-additivity as a conservative approach. Without information on the mode of action of Ingredient 1, the mixture could be corrosive regardless of the overall pH. Therefore, the criteria described in paragraph 3.2.3.3.4.1-2-3 were applied (including "*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 a an ingredient classified in Category 1A, 1B or 1C respectively or as Category 2 when it contains ≥ 3% of an irritant ingredient*.").

Thus, the mixture should be classification as Skin Corrosion Category 1A because the mixture contains an ingredient 1 (Skin Corr. 1A) at a concentration ≥ 1%.

3.2.5.3. Examples of mixtures not fulfilling the criteria for classification

3.2.5.3.1. Example 6: Mixture without extreme pH, with ingredients with SCLs

Ingredient	Skin corrosion / irritation classification	Concentration (% w/w)	SCL
Surfactant C	Skin Irrit. 2	0.4	Not assigned
Substance G	Skin Irrit. 2	3.0	Not assigned
Substance A	Skin Irrit. 2	0.7	Not assigned
Substance H	Skin Corr. 1A	3.0	C ≥ 70 %: Skin Corr. 1A 50 % ≤ C < 70 %: Skin Corr. 1B 35 % ≤ C < 50 %: Skin Irrit. 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 one surfactant. Additivity is considered to apply[57].

Substance D and water can be disregarded as they are not classified for skin corrosion/irritation. Also surfactant C and substance A can be disregarded as both are present at below 1%.

No SCL is assigned to substance G, thus GCL apply for this ingredient.

Skin Corr. 1:

[57] Please note that in cases where a mixture with corrosive constituents also contains surfactans, it can be assumed that corrosivity migh be amplified.

The mixture contains 3% substance H, the only ingredient classified as Skin Corr. 1. As this is below the 50% SCL for substance H, the mixture is not classified as Skin Corr. 1.

Skin Irrit. 2:

(% substance H/SCL) + (% substance G/GCL) = (3/35) + (3/10) = 0.39 which is < 1, thus the mixture is not classified Skin Irrit. 2.

3.2.6. References

ECETOC (2002), Use of human data in hazard classification for irritation and sensitisation, Monograph No 32, Brussels ISSN 0773-6374-32

ECVAM/ESAC (2000) Statement on the application of the CORROSITEX® Assay for skin corrositivity testing. Online: http://ihcp.jrc.ec.europa.eu/our_labs/eurl-ecvam

ECVAM/ESAC (2007) Statement on the validity of in-vitro tests for skin irritation. Online: http://ecvam.jrc.it/

ECVAM/ESAC (2008) Statement on the validity of in-vitro tests for skin irritation testing. Online: http://ecvam.jrc.it/

ECVAM/ESAC (2009) Statement on the performance under UN GHS of three in-vitro assays for skin irritation testing and the adaptation of the reference chemicals and defined accuracy values of the ECVAM skin irritation performance standards. Online: http://ecvam.jrc.it/

Kartono F & Maibach H. (2006) Irritants in combination with a synergistic or additive effect on the skin response: an overview of tandem irritation studies. Contact Dermatitis 54(6), 303-12.

Spielmann, H., Hoffmann, S., Liebsch, M., Botham, P., Fentem, J., Eskes, C., Roguet, R., Cotović, J., Cole, T., Worth, A., Heylings, J., Jones, P., Robles, C., Kandárová, H., Gamer, A., Remmele, M., Curren, R., Raabe, H., Cockshott, A., Gerner, I. and Zuang, V. (2007) The ECVAM International Validation Study on In Vitro Tests for Acute Skin Irritation: Report on the Validity of the EPISKIN and EpiDerm Assays and on the Skin Integrity Function Test. ATLA 35, 559-601.

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

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 the Guidance on IR&CSA Section R.4.3.3 and more specific considerations for eye damage/irritation are given in the Guidance on IR&CSA Section R.7.2.9.

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.

Before using the methods as referred to in the following sections, it should be checked whether the methods are sufficiently validated (or considered valid in case of (Q)SAR and expert systems) against the criteria for classification according to CLP (and not validated against the old DSD criteria which differed slightly from the CLP criteria).

3.3.2.1.3. 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, or direct oxidative impact, may damage/destroy biological materials. This applies, for example, to organic peroxides, which can be assumed to be eye irritants, unless evidence suggests otherwise (Guidance on IR&CSA Sections R.7.2.8 and R.7.2.4.1).

Thus, in the absence of evidence to the contrary, a hydro peroxide should be considered to be classified as Eye Damage Category 1, whereas Eye Irritation Category 2 should be considered for peroxides. Appropriate evidence must be provided in order to consider no classification of substances with oxidising properties.

3.3.2.1.4. pH and the acid/alkaline reserve

Annex I: ***3.3.2.2.4.*** *Likewise, pH extremes like ≤ 2 and ≥ 11,5 may produce serious eye damage, especially when associated with significant acid/alkaline reserve (buffering capacity).*

Generally such substances are expected to produce significant effects on the eyes. In the absence of any other information, a substance is considered to cause serious eye damage (Category 1) if it has a pH ≤ 2 or ≥ 11,5. However, if consideration of acid/alkaline reserve suggests the substance may not cause serious eye damage despite the low or high pH value, this needs to be confirmed by other data, preferably by data from an appropriate validated in vitro test.

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 or low buffering capacity should not be used alone to exonerate from classification as corrosive, which needs to be confirmed by other data, preferably by a validated *in vitro* test (see also Section 3.2.3.2 of this Guidance).

Further information and/or reasoning is needed to conclude whether the substance causes eye irritation.

3.3.2.1.5. Non-testing methods: (Q)SARs and expert systems

Non-testing methods such as (Q)SARs and expert systems (a diverse group of models consisting of combinations of SARs, QSARs and databases) 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 as alerts to indicate an effect. (Q)SAR systems that also account for eye effects are for example ACD Percepta, CASE Ultra, Discovery studio Accelrys (former TOPKAT), Derek Nexus. For more detailed guidance, consult the Guidance on IR&CSA Section R.6 ('QSAR and grouping of chemicals'). OECD QSAR Toolbox and ToxTree contain BfR rules[58] for eye irritation/corrosion.

In the absence of any other existing data, conclusions on the presence or absence of an effect can be made if the (Q)SAR or expert system has been shown to make an adequate prediction (see Figure 3.4). The suitability of the model (reliability, relevance) should be very carefully checked to make sure that the prediction is fit for purpose, and the applicability of the model to the substance should also be justified. The predicted endpoint should be adequate for classification and labelling. In case of negative QSAR data the need for classification cannot be excluded.

Since a formal adoption procedure for 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 Guidance on IR&CSA Section R.6.1.

3.3.2.1.5.1. Testing methods: in vitro methods

The OECD has at present adopted five *in vitro* test guidelines for assessing eye hazard potential. Four *in vitro* tests methods have been adopted for the identification of substances inducing serious eye damage, i.e. the Isolated Chicken Eye (ICE) test (OECD TG 438; TM B.48), the Bovine Corneal Opacity and Permeability (BCOP) test (OECD TG 437; TM B.47), the Fluorescein Leakage (FL) test (OECD TG 460), the short time exposure (STE) test (OECD TG 491). In addition, there are three validated test methods without an OECD test guideline i.e. Cytosensor Microphysiometer (CM)[59] test, Isolated Rabbit Eye (IRE) test and the Hen's Egg Test on Chorio-

[58] The German Federal Institute for Risk Assessment (BfR) has developed a Decision Support System (DSS) to assess certain hazardous properties of pure chemicals.

[59] A draft OECD TG available at http://www.oecd.org/env/ehs/testing/DRAFT%20Cytosensor%20TG%20(V9)%2021%20Dec%2012_clean.pdf.

allantoic Membrane (HET-CAM) test[60]. These tests are recommended for use as part of a tiered-testing strategy for regulatory classification and labelling (e.g. Top-Down Approach [61]). A substance can be considered as causing serious eye damage (Category 1) based on positive results in the ICE test, the BCOP test, the FL test, the STE test, CM test IRE test or the HET-CAM test[62]. Four adopted OECD TGs can be used for identifying substances not causing serious eye damage/eye irritation which are the ICE test, BCOP test, STE test and Reconstructed human Cornea-like Epithelium (RhCE) (OECD TG 492). In addition, the validated CM test method can be used for identifying substances not causing serious eye damage or eye irritation. Negative results from the ICE, BCOP, STE, RhCE and CM test methods can be used for classification purposes, i.e. 'bottom-up approach'[8]. For other test methods the negative *in vitro* corrosivity responses in these tests must be followed by further testing (see section R.7.2.9.1 in the Guidance on IR&CSA).

There are no *in vitro* tests with regulatory acceptance for eye irritation at present.

Further information on newly adopted OECD Test Guidelines can be found on the OECD website: (http://www.oecd.org/env/chemicalsafetyandbiosafety/testingofchemicals/oecdguidelinesforthetestingofchemicals.htm).

Information on the current developments of *in vitro* tests and methodology can be found on the ECVAM website (http://ihcp.jrc.ec.europa.eu/our_labs/eurl-ecvam).

3.3.2.1.5.2. Testing methods: In vivo methods

Testing for eye irritation should not be carried out on substances known or predicted to be corrosive to skin and classified as such. Such substances are automatically considered to be severely damaging to the eye and are classified but not labelled for serious eye damage in addition to skin corrosion.

The *in vivo* test in rabbits according to OECD TG 405 (TM B.5) is the standard *in vivo* test for the hazard assessment under 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 in the LVET test, 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) in the LVET test, as compared with the standard 0.1 ml).

No new tests should be performed according to LVET as stated by ESAC in its conclusion on the use of LVET data for the purpose of classification and labelling in 2009 (ECVAM/ESAC, 2009b).

Existing data from the LVET test could be considered for the purpose of classification and labelling, but must be carefully evaluated. The differences mentioned above may result in a classification in a lower category (or no classification) based on LVET data, than if the classification were based on data derived from the standard in vivo test (OECD TG 405 (TM B.5)). Thus, positive data from the LVET test could be a trigger for considering classification in

[60] ICCVAM published a report on the HET-CAM in 2010 http://iccvam.niehs.nih.gov/docs/ocutox_docs/InVitro-2010/Body.pdf.

[61] The top-down approach should be used when available information suggests that the substance may cause serious eye damage. The bottom-up approach, on the other hand, should be followed only when available information suggests that the substance may not be irritant to the eye.

[62] ICCVAM published a report on the HET-CAM in 2010 http://iccvam.niehs.nih.gov/docs/ocutox_docs/InVitro-2010/Body.pdf.

Category 1 on its own, but data from this test indicating Category 2 classification or no classification are not conclusive for a category 2 classification or no classification respectively.

Consideration should be given on a case-by-case basis to the limited use of LVET data as supplementary *in vivo* data in a weight of evidence determination in order to assess if the criteria for classification are met. A weight of evidence could include, for example, the results of appropriate validated *in vitro* tests, relevant and conclusive human and animal data, extreme pH. The applicability domain is limited to detergent and cleaning products (ECVAM/ESAC, 2009b).

3.3.2.2. Classification criteria

Annex I: *3.3.2.1.1*. *Serious eye damage (Category 1)*

3.3.2.1.1.1. *A single hazard category (Category 1) is adopted for substances that have potential to seriously damage the eyes. This hazard category includes as criteria the observations 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. Hazard classification as Category 1 also contain substances fulfilling the criteria of corneal opacity ≥ 3 or iritis > 1,5 observed in at least 2 of 3 tested animals, because severe lesions like these usually do not reverse within a 21 days observation period.*

[…]

Table 3.3.1

Serious eye damage[a]

Category	*Criteria*
Category 1	*A substance that produces:* *(a) in at least 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* *(b) in at least 2 of 3 tested animals, a positive response of:* *(i) corneal opacity ≥ 3 and/or* *(ii) iritis > 1,5* *calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material.*

[a] Grading criteria are understood as described in Regulation (EC) No 440/2008

Annex I: *3.3.2.1.2.* *Eye irritation (Category 2)*

3.3.2.1.2.1. *Substances that have the potential to induce reversible eye irritation shall be classified in Category 2 (eye irritation).*

3.3.2.1.2.2. *For those substances where there is pronounced variability among animal responses, this information shall be taken into account in determining the classification*

[…]

Table 3.3 2

Eye irritation[a]

Category	*Criteria*
Category 2	*Substances that produce in at least in 2 of 3 tested animals, a positive response of:* *(a) corneal opacity ≥ 1 and/or* *(b) iritis ≥ 1, and/or* *(c) conjunctival redness ≥ 2 and/or* *(d) 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*
[a] Grading criteria are understood as described in Regulation (EC) No 440/2008	

The classification criteria apply to results of the standard animal *in vivo* test, OECD TG 405, and are possible to apply to the results of the LVET. However, the differences between the LVET and OECD TG 405 test methods, may result in a classification in a lower category (or no classification) based on LVET data, than if the classification were based on data derived from the standard *in vivo* test (OECD TG 405 (TM B.5)). See also 3.3.2.1.5.2 above.

3.3.2.3. Evaluation of hazard information

Annex I: *3.3.2.2.1*. *A tiered approach to the evaluation of initial information shall be considered where applicable, recognising that not all elements may be relevant.*

Annex I: *3.3.2.2.6.* *The tiered approach provide guidance on how to organize existing information and to make a weight of evidence decision about hazard assessment and hazard classification. Animal testing with corrosive substances shall be avoided whenever possible. Although information might be gained from the evaluation of single parameters within a tier (see 3.3.2.1.1), consideration should be given to the totality of existing information and making and overall weight of evidence determination. This is especially true when there is conflict in information available in some parameters.*

The tiered approach for the evaluation of the information applied in order to make a decision about the serious eye damage/eye irritation hazard properties is illustrated by the Figure 3.4 below. The figure was adopted by the UNSCEGHS in December 2012 (with exception of the added footnotes g) and h)).

Figure 3.4 Tiered evaluation for serious eye damage/eye irritation[63]

(see also Figure 3.1)

Step	Parameter	Finding	Conclusion
1a:	Existing human or animal serious eye damage/eye irritation data [a]	→ Serious eye damage	→ Classify as causing **serious eye damage**
	↓	↘ Eye irritant	→ Classify as **eye irritant** [f]
	Negative/Insufficient/Inconclusive/No data		
	↓		
1b:	Existing human or animal data, skin corrosion	→ Skin corrosion	→ Deemed to cause and classify as **serious eye damage**
	↓		
	Negative /Insufficient/Inconclusive/No data		
	↓		
1c:	Existing human or animal serious eye damage/eye irritation data [a]	→ Existing data showing that substance does not cause serious eye damage or eye irritation	→ **Not classified** [f]
	↓		
	No/Insufficient/Inconclusive data		
	↓		
2:	Other, existing skin/eye data in animals [b]	→ Yes; other existing data showing that substance may cause serious eye damage	→ May be deemed to cause **serious eye damage**
	↓	↘ Yes; other existing data showing that substance may cause eye irritation	→ May be deemed to be an **eye irritant** [f]
	No/Insufficient/Inconclusive data		
	↓		

[63] Adopted by the UNSCEGHS in December 2012.

Figure 3.4 Tiered evaluation for serious eye damage/eye irritation[63]

(see also Figure 3.1)

Step	Parameter	Finding	Conclusion
3:	Existing *ex vivo/in vitro eye* data [c]	Positive: serious eye damage	Classify as causing **serious eye damage**
		Positive: eye irritant	Classify as **eye irritant** [f, h]
		Negative: not eye irritant	Not classified [f]
	No/Insufficient/Inconclusive data		
4:	pH-based assessment (with consideration of acid/alkaline reserve of the chemical) [d]	pH ≤ 2 or ≥ 11.5[i] with high acid/alkaline reserve or no data for acid/alkaline reserve	Classify as causing **serious eye damage** [f]
	Not pH extreme, no pH data or extreme pH with data showing low/no acid/alkaline reserve[g]		
		Serious eye damage	Deemed to cause **serious eye damage**
5:	Validated Structure Activity Relationship (SAR) methods	Eye irritant	Deemed to be **eye irritant**
		Skin corrosive	Deemed to cause **serious eye damage**
	No/Insufficient/Inconclusive data		
6:	Consideration of the total weight of evidence [e]	Serious eye damage	Deemed to cause **serious eye damage**
		Eye irritant	Deemed to be **eye irritant**
7:	**Not classified**		

(a) Existing human or animal data could be derived from single or repeated exposure(s), for example in occupational, consumer, transport, or emergency response scenarios; or from purposely-generated data from animal studies conducted according to validated and internationally accepted test methods. Although human data from accident or poison centre databases can provide evidence for classification, absence of incidents is not itself evidence for no classification as exposures are generally unknown or uncertain;

(b) Existing animal data should be carefully reviewed to determine if sufficient serious eye damage/eye irritation evidence is available through other, similar information. It is recognized that not all skin irritants are eye irritants. Expert judgment should be exercised prior to making such a determination;

(c) *Evidence from studies using validated protocols with isolated human/animal tissues or other non-tissue-based, validated protocols should be assessed. A positive test result from a validated in vitro test on skin corrosion would lead to the conclusion to classify as causing serious eye damage;*

(d) *Measurement of pH alone may be adequate, but assessment of acid/alkaline reserve (buffering capacity) would be preferable;*

(e) *All information that is available on a substance should be considered and an overall determination made on the total weight of evidence. This is especially true when there is conflict in information available on some parameters. The weight of evidence including information on skin irritation may lead to classification for eye irritation. Negative results from applicable validated in vitro tests are considered in the total weight of evidence evaluation.*

(f) *In case of contradicting data, e.g. negative/irritation human data but positive/serious eye damage in-vitro data, a weight of evidence assessment should be performed, see footnote e. (This footnote was not included in Figure 3.4 in the 5th rev of GHS, but is based on 3.3.1.2 and 3.3.2.2.6, Annex I, CLP)*

(g) *Non corrosivity needs to be confirmed by other data preferably by data from an appropriate validated in vitro test. (This footnote was not included in Figure 3.4 in the 5th rev of GHS, but is based on 3.3.2.2.4, Annex I, CLP)*

(h) *Note: currently there are no scientifically valid or internationally accepted in vitro test methods for the direct identification of Cat 2 eye irritants.*

(i) *For the cases of mixtures with no human or animal data on serious eye damage/eye irritation but with extremeoH, see* Figure 3.5 in *section 3.3.3.2.1.1 for additional guidance.*

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 extent and duration of the exposure needs also to be taken into account as absence of effect may be due to washing off the eyes shortly after exposure. In such cases the absence of effects may not indicate the absence of hazard. 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 the Guidance on IR&CSA Section R7.2.4.2.

3.3.2.3.2. Evaluation of non-human data

3.3.2.3.2.1. Ex vivo/*in vitro* data

A substance can be considered as causing serious eye damage (Category 1) based on positive results in the ICE test, the BCOP test, FL test, STE test, IRE test, CM test or the HET-CAM test[64]. Negative results from the ICE, BCOP, STE, RhCE and CM test methods can be used for classification purposes i.e. 'bottom-up approach', but for other test methods the negative *in vitro* corrosivity responses in these tests must be followed by further testing (Guidance on IR&CSA Section R.7.2.9). Normally, recommendations for classification according to GHS criteria based on the results of an *in vitro* test are mentioned in the corresponding OECD test guideline.

There are currently no validated *in vitro* eye irritation test methods available.

[64] ICCVAM published a report on the HET-CAM in 2010 http://iccvam.niehs.nih.gov/docs/ocutox_docs/InVitro-2010/Body.pdf.

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 CLP Annex I, Tables 3.3.1 and 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 WoE should be considered.

If considered as reversible, 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, Section 3.3.5.1.1). 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 CLP Annex I, Tables 3.3.1 and 3.3.2, classification has to be assigned accordingly.

Tests that have been conducted with more than three animals

Older test methods used up to six rabbits. In such cases, the current UNSCEGHS Guidance needs to be applied (adopted in June 2011) (see also Example 2, section 3.3.5.1.2):

In the case of **6** rabbits, the following applies:

a. Classification for serious eye damage – Category 1 if:

   i. 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(ii) at least 4 out of 6 rabbits show a mean score per animal of ≥ 3 for corneal opacity and/or > 1.5 for iritis

b. Classification for eye irritation – Category 2 if at least 4 out of 6 rabbits show a mean score per animal of:

   i. ≥ 1 for corneal opacity and/or

   ii. ≥ 1 for iritis and/or

   iii. ≥ 2 conjunctival erythema (redness) and/or

   iv. ≥ 2 conjunctival oedema (swelling) (chemosis)

   and which fully reverses within an observation period of normally 21 days.

In the case of **5** rabbits, the following applies:

c. Classification for serious eye damage – Category 1 if:

i. 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

d. at least 3 out of 5 rabbits show a mean score per animal of ≥ 3 for corneal opacity and/or > 1.5 for iritis.

i. Classification for eye irritation – Category 2 if at least 3 out of 5 rabbits show a mean score per animal of:

ii. ≥ 1 for corneal opacity and/or

iii. ≥ 1 for iritis and/or

iv. ≥ 2 conjunctival erythema (redness) and/or

v. ≥ 2 conjunctival oedema (swelling) (chemosis)

and which fully reverses within an observation period of normally 21 days.

In the case of **4** rabbits, the following applies:

e. Classification for serious eye damage – Category 1 if:

i. 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

ii. at least 3 out of 4 rabbits show a mean score per animal of

≥ 3 for corneal opacity and/or

> 1.5 for iritis

f. Classification for eye irritation – Category 2 if at least 3 out of 4 rabbits show a mean score per animal of:

i. ≥ 1 for corneal opacity and/or

ii. ≥ 1 for iritis and/or

iii. ≥ 2 conjunctival erythema (redness) and/or

iv. ≥ 2 conjunctival oedema (swelling) (chemosis)

and which fully reverses within an observation period of normally 21 days.

In this case the irritant categories 1 and 2 are used if 4 of 6 rabbits show a mean score per animal as outlined in the criteria. Likewise, if the test was performed with 4 or 5 animals, for at least 3 individuals the mean score per animal 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. However, the differences between the LVET and OECD TG 405 test methods, may result in a classification in a lower category (or no classification) based on LVET data, than if the classification was based on data derived from the standard *in vivo* test (OECD TG 405 (TM B.5)). See also 3.3.2.1.5.2 above.

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 CLP Annex I, Tables 3.3.1 and 3.3.2 are not 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

According to Article 9(1) CLP, the criteria should be applied to available information. However, sometimes it is not straightforward or simple to apply the criteria and according to Article 9(3) a weight of evidence and expert judgement should be applied in such cases when the criteria cannot be applied directly.

A weight of 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 (see also 1.1.1.3, Annex I, CLP and Section 1.4 of this guidance).

> **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 additional guidance, if both human and animal data are available, see the Guidance on IR&CSA Section R.7.2.3.3.2.

Additional guidelines on the assessment of available information when WoE needs to be applied is provided in Section 3.2.2.3.3 (see Figure 3.2).

3.3.2.4. Decision on classification

A skin corrosive substance is also classified for serious eye damage which is indicated in the hazard statement for skin corrosion (H 314: Causes severe skin burns and eye damage). However, although classification for both endpoints (Skin Corr. 1 and Eye Dam. 1) is required and has to be addressed in the safety data sheet, the hazard statement H318 'Causes serious eye damage' is not indicated on the label because of redundancy (CLP Article 27).

In other cases, if the comparison of the information related to serious eye damage/eye irritation with the criteria shows that the criteria are met, the substance is classified for serious eye damage or eye irritation.

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, such 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' OECD TG 405[65] 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 generating data specifically for the purpose of setting SCLs is not a requirement according to the CLP Regulation. Article 8(1) of CLP specifies that new tests may only be performed (in order to determine the hazard of a substance or mixture) if all other means of generating information has been exhausted and Article 7(1) specifies that where new tests are carried out, test on animals shall be undertaken only when no other alternatives,

[65] 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.

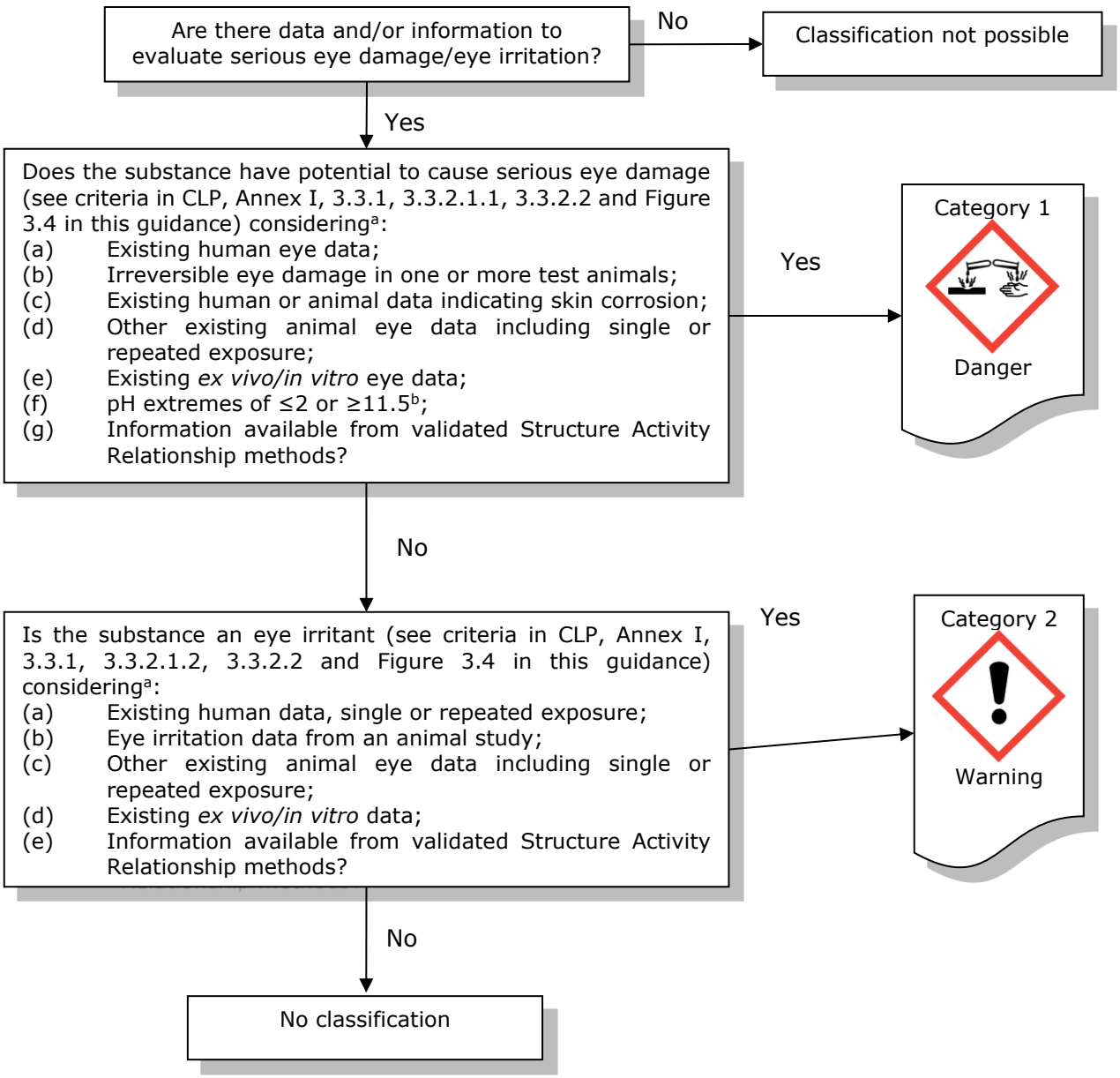
which provide adequate reliability of data, are possible. The GCLs must be applied for the classification of a mixture on the basis of its ingredient substances classified as causing serious eye damage or as an eye irritant, if there are no already existing specific data justifying an SCL which is lower or, in exceptional cases, higher than the GCL (see Article 10(1), CLP). Therefore, information will *always* be available, for mixtures containing substances already classified for serious eye damage/eye irritation, making it possible to identify the hazard for the mixture by using the GCLs (Article 9(4), CLP).

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 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) which have been included in CLP.

3.3.2.6. Decision logic for classification of substances

The decision logic, based on that provided by the GHS, is reported as additional guidance below. It is strongly recommended that the person responsible for classification study the criteria for classification before and during use of the decision logic.



[a] Taking into account consideration of the total weight of evidence as needed.

[b] Not applicable if consideration of pH and acid/alkaline reserve indicates the substance may not cause serious eye damage and confirmed by other data, preferably by data from an appropriate validated *in vitro* test.

3.3.3. Classification of mixtures for serious eye damage/eye irritation

3.3.3.1. Identification of hazard information

As for substances, 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, *ex vivo*/*in vitro* and finally physico-chemical properties, available on the mixture (as illustrated in Figure 3.4, above).

If valid test data are available for the whole mixture they have precedence. If no such data exist, the so called bridging principles should be applied if possible. If the bridging principles are not applicable an assessment on the basis of data for the components of the mixture must be applied.

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 human data cannot be taken as evidence of the mixture being non-hazardous. See Section 3.3.2.1.1 of this Guidance for further information on the identification of human data.

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.

3.3.3.2. Classification criteria for mixtures

The information available related to serious eye damage and eye irritation, 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, by applying the substance criteria of Annex I to CLP

b. Classification based on the application of bridging principles, which make use of test data on similar tested mixtures and ingredient substances

c. Classification based on calculation and/or on concentration thresholds, including SCLs and M-factors.

3.3.3.2.1. When data are available for the complete mixture

Annex *I: 3.3.3.1.1.* *The mixture shall be classified using the criteria for substances, and taking into account the tiered approach to evaluate data for this hazard class.*

Annex I*: 3.3.3.1.2.* *When considering testing of the mixture classifiers are encouraged to use a tiered weight of evidence approach as included in the criteria for classification of substances for skin corrosion and serious eye damage/eye irritation to help ensure an accurate classification, as well as avoid unnecessary animal testing. In absence of any other information, a mixture is considered to cause serious eye damage (Category 1) if it has a pH ≤ 2,0 or ≥ 11,5. However, if consideration of alkali/acid reserve suggests the mixture may not cause serious eye damage despite the low or high pH value, this needs to be confirmed by other data, preferably data from an appropriate validated in vitro test.*

As for substances, where the criteria cannot be applied directly to available identified information, a weight of evidence determination using expert judgement should be used according to CLP Article 9(3) when evaluating the data in order to be able to apply the criteria to the information (according to CLP Article 9(1)) (see 3.3.2.3.3. Weight of evidence above).

The integration of all information to come to a final hazard assessment based on weight of evidence in general requires in-depth toxicological expertise.

For guidance on the assessment of the information available for mixtures when WoE needs to be applied, please see Figure 3.2 in Section 3.2.2.3.3.

There are a number of available *in vitro* test systems that have been validated to identify substances causing serious eye damage (Category 1) and/or no classification (see Section 3.3.2.1.5.1), that are considered to be valid also for mixtures. However, not all available *in vitro* test systems work equally well for all types of mixtures. The specific applicability domain,

including limitations of the use of the test methods for mixtures should be considered. Thus, prior to testing a mixture in a specific *in vitro* assay for classification purposes, it has to be ensured 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.

There are no *in vitro* tests with regulatory acceptance for eye irritation at present. A proposal to combine results of multiple in vitro tests to identify eye irritants has been presented in a draft OECD Guidance document (ref. OECD 2015).

3.3.3.2.1.1. 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 (see 3.2.3.2.1.1.)

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 according to Article 10(1), CLP), 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.

Figure 3.5 Mixture not classified as Skin Corr. 1 and without animal or human data on serious eye damage/eye irritation 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. 1 and serious eye damaging, Eye Dam. 1.
Is the mixture tested for serious eye damaging properties in an OECD adopted or internationally accepted scientifically valid *in vitro* test considered to be valid and applicable for the mixture? **NO ➔** **YES** **↓**	Classify as serious eye damaging, Eye Dam. 1.
Does the mixture demonstrate serious eye damaging properties in an OECD adopted or internationally accepted scientifically valid *in vitro* test considered valid and applicable for the mixture? **YES ➔** **NO** **↓**	Classify as serious eye damaging, Eye Dam. 1.
Consideration of the total weight of available evidence, in particular in case of conflicting data, including extreme pH, negative/inconclusive results from (e.g.) eye irritation *in vitro* tests and results from the application of the methods based on the ingredients in the mixture in CLP Annex I, 3.3.3.3.2-3.3.3.3.3 (Table 3.3.3) / 3.3.3.3.4.1-3.3.3.3.4.3 (Table 3.3.4) ➔	

	Classify: Category 1, Category 2, no classification.

Thus, 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, preferably an appropriate validated in vitro test (CLP Annex I, Section 3.3.3.1.2). The mixture must be classified as Serious Eye damage Category 1 if the supplier decides 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 and considered appropriately valid and applicable for the mixture or the methods based on ingredients.

It must be noted 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-acid/alkali reserve method cannot be a basis for modifying the classification but should be considered in the weight of evidence analysis.

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 steps described in the above decision logic shall be followed.

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/eye 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 on the ingredients of the mixture (see Section 1.6.3 of this Guidance).

When the available identified information is inappropriate for the application of the bridging principles then the mixture should be classified based on its ingredients as described in Sections 3.3.3.2 and 3.3.3.3 of this Guidance.

3.3.3.2.3. When data are available for all ingredients or only for some ingredients of the mixture

3.3.3.2.3.1. Ingredients that should be taken into account for the purpose of classification

Annex I: ***3.3.3.3.1.*** *[…] The 'relevant ingredients' of a mixture are those which are present in concentrations ≥ 1% (w/w for solids, liquids, dusts, mists and vapours and v/v for gases), unless there is a presumption (e.g. in the case of corrosive ingredients) that an ingredient present at a concentration < 1% can still be relevant for classifying the mixture for serious eye damage/eye irritation.*

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 seriously damaging to the eye/eye irritant when data are available on the ingredients, but not on the mixture as a whole, is based on the theory of additivity, such that each skin corrosive or serious eye damaging/eye irritation ingredient contributes to the overall serious eye*

damage/eye irritation properties of the mixture in proportion to its potency and concentration. A weighting factor of 10 is used for skin corrosive and serious eye damaging ingredients 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 eye 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.

Annex I: *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 seriously damaging to the eye or as eye irritant.*

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. Although the general approach is the additivity principle which has been successfully used under the DPD and more recently, the supplier must ascertain whether the additivity approach is applicable where all relevant ingredients should be considered. The first step would then be to identify all the relevant 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, it is important to also consider effects that could occur in the whole mixture, such as surfactant interaction, neutralisation of acids/bases apart from effects of the entire mixture (i.e. pH and the alkaline reserve) and not only consider the contribution of individual ingredients.

Additivity may not apply where the mixture contains substances mentioned in CLP Annex I, 3.3.3.3.4.1- 3.3.3.3.4.3 which may be corrosive/irritant at concentrations below 1%, see Section 3.3.3.2.3.3 of this Guidance.

Application of SCLs when applying the additivity approach

The generic concentration limits are specified in Table 3.3.3. However, CLP Article 10(5) indicates that specific concentration limits (SCLs) take precedence over generic concentration limits. Thus, if a given substance has an SCL set in accordance with Article 10(1), CLP, 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

$$\text{Sum of } (\text{ConcA} / \text{clA}) + (\text{ConcB} / \text{clB}) + \ldots + (\text{ConcZ} / \text{clZ}) \text{ is } \geq 1$$

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.

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 seriously damaging to the eye/eye irritant at concentrations < 1 %.*

Annex I: *3.3.3.3.4.2.* *For mixtures containing strong acids or bases the pH shall be used as classification criteria (see section 3.3.3.1.2) since pH will be a better indicator of serious eye*

damage (subject to consideration of acid/alkali reserve) than the generic concentration limits of Table 3.3.3.

Annex I: ***3.3.3.3.4.3.*** *A mixture containing skin corrosive or serious eye damaging/eye 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 Serious Eye Damage (Category 1) if it contains ≥ 1 % of a skin corrosive or serious eye damaging ingredient and as Eye Irritation (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.*

Annex I: ***3.3.3.3.5.*** *On occasion, reliable data may show that the effects of serious eye damage/eye irritation of an ingredient will not be evident when present at a level at or above the generic concentration limits mentioned in Tables 3.3.3 and 3.3.4 in section 3.3.3.3.6. In these cases the mixture shall be classified according to those data (see also Articles 10 and 11). On other occasions, when it is expected that the skin corrosion/irritation hazards or the effect of serious eye damage/eye irritation an ingredient will not be evident when present at a level at or 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.*

Annex I: ***3.3.3.3.6.*** *If there are data showing that (an) ingredient(s) may be corrosive to the skin or seriously damaging to the eye/eye irritating at a concentration of < 1 % (corrosive to the skin or seriously damaging the eye) or < 3 % (eye 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 corrosion (Category 1, 1A, 1B or 1C) and/or serious eye damage (Category 1) or eye irritation (Category 2) that trigger classification of the mixture as eye damage/eye irritation where additivity approach applies

Sum of ingredients classified as:	*Concentration triggering classification of a mixture as:*	
	Serious eye damage	*Eye irritation*
	Category 1	*Category 2*
Skin corrosion Sub-Category 1A, 1B, 1C or Category 1 + Serious eye damage (Category 1)(a)	*≥ 3 %*	*≥ 1 % but < 3 %*
Eye irritation (Category 2)		*≥ 10 %*
10 x (Skin corrosion Sub-Category 1A, 1B, 1C or Skin corrosion Category 1 + Serious eye damage (Category 1)) + Eye irritation (Category 2)		*≥ 10 %*

([a]) If an ingredient is classified as both Skin Corrosion Sub-Category 1A, 1B, 1C or Category 1 and Serious Eye Damage (Category 1), its concentration is considered only once in the calculation.

3.3.3.3.2. When the additivity approach is not applicable

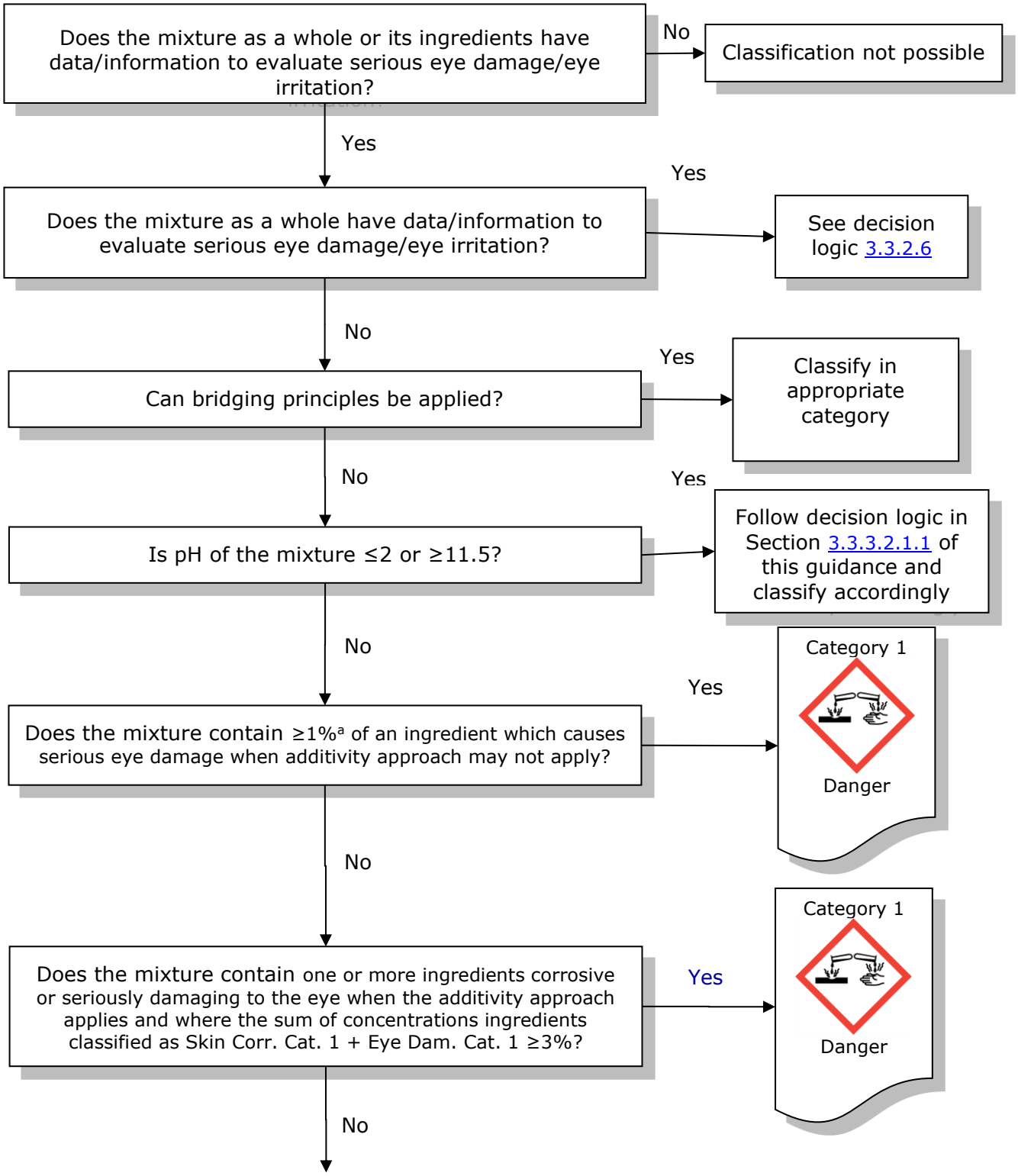
Annex I: *Table 3.3.4*

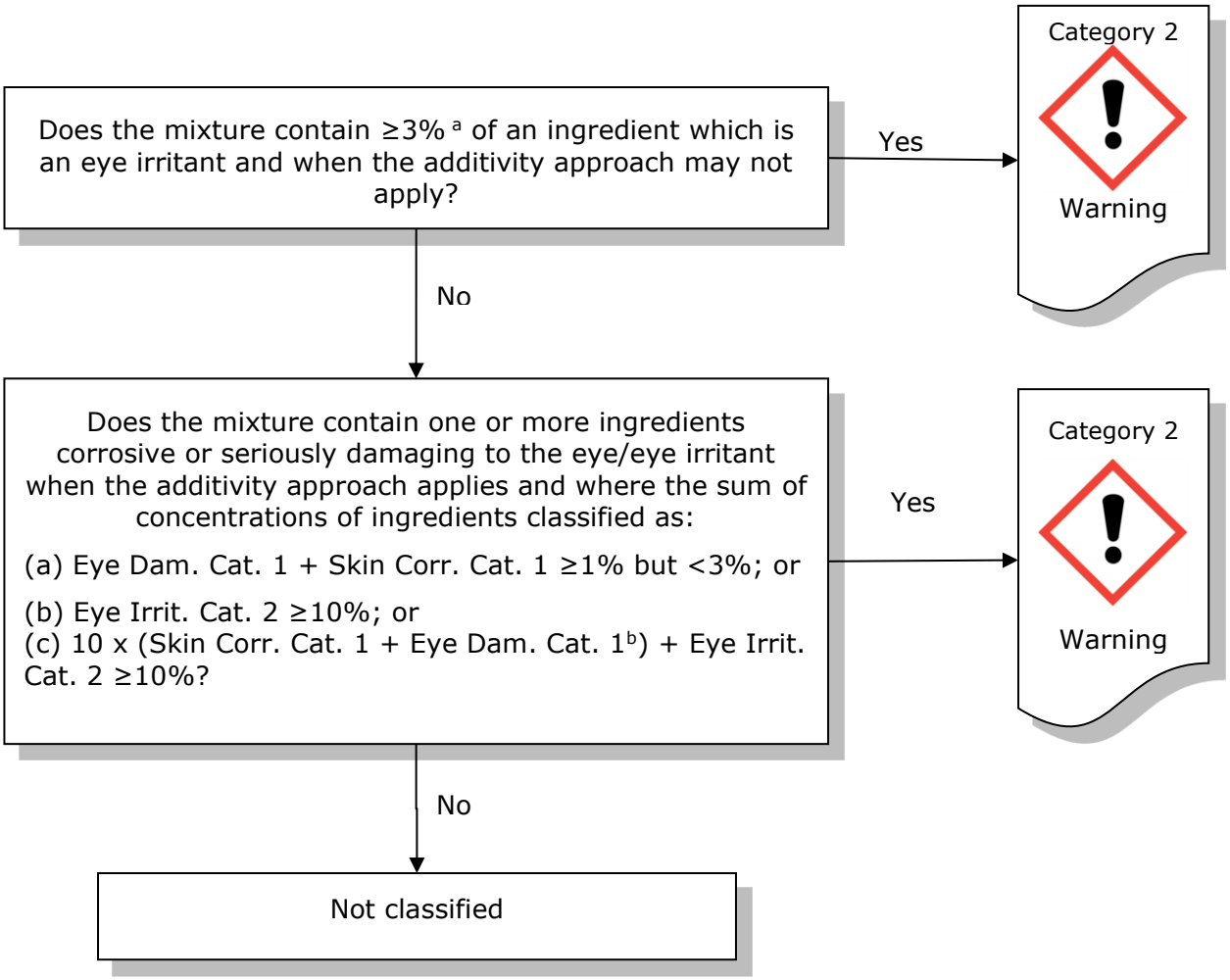
Generic concentration limits of ingredients of a mixture as serious eye damage (Category 1) or eye irritation (Category 2), where the additivity approach does not apply

Ingredient	*Concentration*	*Mixture classified as*
Acid with pH ≤ 2	*≥ 1%*	*Serious eye damage (Category 1)*
Base with pH ≥ 11,5	*≥ 1%*	*Serious eye damage (Category 1)*
Other ingredient classified as skin corrosion (Sub-Category 1A, 1B, 1C or Category 1) or serious eye damage (Category 1)	*≥ 1%*	*Serious eye damage (Category 1)*
Other ingredient classified as eye irritation (Category 2)	*≥ 3%*	*Eye irritation (Category 2)*

3.3.3.4. Decision logic for classification of mixtures

The decision logic, based on the one provided in the GHS, is presented here below 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.


Does the mixture as a whole or its ingredients have data/information to evaluate serious eye damage/eye irritation?
No
Classification not possible
Yes
Does the mixture as a whole have data/information to evaluate serious eye damage/eye irritation?
Yes
See decision logic 3.3.2.6
No
Can bridging principles be applied?
Yes
Classify in appropriate category
No
Is pH of the mixture ≤2 or ≥11.5?
Yes
Follow decision logic in Section 3.3.3.2.1.1 of this guidance and classify accordingly
No
Does the mixture contain ≥1%[a] of an ingredient which causes serious eye damage when additivity approach may not apply?
Yes
Category 1
Danger
No
Does the mixture contain one or more ingredients corrosive or seriously damaging to the eye when the additivity approach applies and where the sum of concentrations ingredients classified as Skin Corr. Cat. 1 + Eye Dam. Cat. 1 ≥3%?
Yes
Category 1
Danger
No



[a] Where relevant < 1%, see Section 3.3.3.3.1 of Annex I of CLP.

[b] If an ingredient is classified as both skin Category 1 and eye Category 1 its concentration is considered only once in the calculation.

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.*

Table 3.3.5

Label elements for serious eye damage/eye irritation([a])

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) Where a chemical is classified as skin corrosion Sub-Category 1A, 1B, 1C or Category 1, labelling for serious eye damage/eye irritation can be omitted as this information is already included in the hazard statement for skin corrosion Category 1 (H314).'		

A skin corrosive mixture is considered to also cause serious eye damage which is indicated in the hazard statement for skin corrosion, H314: Causes severe skin burns and eye damage. Thus, in this case a mixture has to be classified for both classifications (Skin Corr. 1 and Eye Dam. 1) but the hazard statement H318 'Causes serious eye damage' is not indicated on the label because of redundancy (CLP Article 27).

3.3.5. Examples of classification for serious eye damage/eye irritation

3.3.5.1. Examples of substances fulfilling the criteria for classification

3.3.5.1.1. 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 No.	Evaluation after …					Positive responder? Ø Score …	
	1 hr	24 hrs	48 hrs	72 hrs	21 days	≥ 1	≥ 3
1	0	2	2	2	0	Yes	No
		Ø 24/48/72 h animal 1 is 2					
2	2	2	2	2	0		

		Ø 24/48/72 h animal 2 is 2				Yes	No
3	2	2	1	1	0		
		Ø 24/48/72 h animal 3 is 1.3				Yes	No

Effects are reversible

Iris:

Animal No.	**Evaluation after …**					**Positive responder? Ø Score …**	
	1 hr	**24 hrs**	**48 hrs**	**72 hrs**	**21 days**	**≥ 1**	**> 1.5**
1	0	1	1	1	0		
		Ø 24/48/72 h animal 1 is 1				Yes	No
2	1	1	1	1	0		
		Ø 24/48/72 h animal 2 is 1				Yes	No
3	1	1	1	1	0		
		Ø 24/48/72 h animal 3 is 1				Yes	No

Effects are reversible

Conjunctiva – Erythema:

Animal No.	**Evaluation after …**					**Positive responder? Ø Score …**	
	1 hr	**24 hrs**	**48 hrs**	**72 hrs**	**21 days**	**≥ 2**	
1	2	2	2	2	0		
		Ø 24/48/72 h animal 1 is 2				Yes	
2	1	1	1	1	0		
		Ø 24/48/72 h animal 2 is 1				No	
3	1	1	1	1	0		
		Ø 24/48/72 h animal 3 is 1				No	

Effects are reversible

Conjunctiva – Swelling:

Animal No.	Evaluation after …					Positive responder? Ø Score …	
	1 hr	24 hrs	48 hrs	72 hrs	21 days	≥ 2	
1	0	3	3	3	0		
		Ø 24/48/72 h animal 1 is 3				Yes	
2	2	2	2	1	0		
		Ø 24/48/72 h animal 2 is 1.7				No	
3	2	3	2	2	0		
		Ø 24/48/72 h animal 3 is 2.3				Yes	

Effects are reversible

Classification according to CLP: Eye irritant Category 2

Rationale: Cornea 'positive responder' ≥ 1: 3/3 animals

and/or Conjunctiva 'positive responder' ≥ 2: 2/3 animals

and/or Iris 'positive responder' ≥ 1: 3/3 animals

3.3.5.1.2. Example 2: Test carried out with more than 3 rabbits

Cornea:

Animal No.	Evaluation after …							Positive responder? Ø Score …	
	1h	24h	48h	72h	7d	14d	21d	≥ 3	≥ 1
1	1	2	3	3	1	1	0		
		Ø 24/48/72h = 2.7						no	yes
2	1	2	2	3	1	1	0		
		Ø 24/48/72h = 2.3						no	yes
3	1	2	3	3	2	1	0		
		Ø 24/48/72h = 2.7						no	yes
4	1	2	4	4	2	1	0		
		Ø 24/48/72h = 3.3						yes	yes

Effects are reversible

Iris:

Animal No.	Evaluation after …							Positive responder? Ø Score …	
	1h	24h	48h	72h	7d	14d	21d	> 1.5	≥ 1
1	0	0	0	0	0	0	0		
		Ø 24/48/72h = 0						no	no
2	0	0	0	0	0	0	0		
		Ø 24/48/72h = 0						no	no
3	0	1	1	1	1	0	0		
		Ø 24/48/72h = 1						no	yes
4	0	0	0	0	0	0	0		
		Ø 24/48/72h = 0						no	no

Effects are reversible

Conjunctiva – Erythema:

Animal No.	Evaluation after …							Positive responder? Ø Score …	
	1h	24h	48h	72h	7d	14d	21d	≥ 2	
1	2	2	2	1	1	1	0		
		Ø 24/48/72h = 1.7						no	
2	2	2	2	1	1	0	0		
		Ø 24/48/72h = 1.7						no	
3	2	2	2	1	1	1	1		
		Ø 24/48/72h = 1.7						no	
4	2	2	2	1	0	0	0		
		Ø 24/48/72h = 1.7						no	

Effects are irreversible

Conjunctiva – Swelling:

Animal No.	Evaluation after …							Positive responder? Ø Score …	
	1h	24h	48h	72h	7d	14d	21d	≥ 2	
1	2	2	2	1	1	1	0		
		Ø 24/48/72h = 1.7						no	
2	2	2	1	1	1	0	0		
		Ø 24/48/72h = 1.3						no	
3	2	2	2	1	1	1	1		
		Ø 24/48/72h = 1.7						no	
4	2	2	2	1	1	1	1		
		Ø 24/48/72h = 1.7						no	

Effects are irreversible

Classification according to CLP: Serious eye damage Category 1

Rationale: Conjunctiva with irreversible effects

3.3.5.2. Examples of mixtures fulfilling the criteria for classification

3.3.5.2.1. 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 CLP Annex I, Table 3.3.3 should be used.

Ingredient	Skin / eye classification	Concentration (% w/w)	SCL
Substance A	Eye Dam. 1	1.8	Not assigned
Substance B	Eye Irrit. 2	0.5	Not assigned
Substance C	Eye Dam. 1	5.4	Not assigned
Substance D	Not classified	4.0	
Acid E	Skin Corr. 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 an acid but no surfactant. 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 Dam. 1 ingredients as well as 2% acid E so the summation {Skin corrosion Cat 1A, 1B, 1C + Eye Dam. 1} applies and is > 3%, thus mixture is classified Eye Dam. 1.

3.3.5.2.2. Example 4: Application of the additivity approach for mixtures containing ingredients which may have SCLs

Ingredient	Skin / eye classification	Concentration (% w/w)	SCL
Substance A	Eye Dam. 1	2.0	Not assigned
Substance B	Eye Irrit. 2	0.5	Not assigned
Substance C	Skin Corr. 1B	5.4	C ≥ 10 %: Skin Corr. 1B 5 % ≤ C < 10 %: Eye Irrit. 2
Substance D	Not classified	4.0	
Substance E	Skin Corr. 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. 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 substance A, thus generic concentration limits (GCL) apply for these ingredients

Eye Dam. 1

(% Substance A / GCL) + (% Substance C / SCL) + (% Substance E / GCL) = (2/3) + (5.4/10) + (2/3) = 1.9 ⇨ > 1 thus mixture is classified Eye Dam. 1

3.3.5.2.3. 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
Substance B	Eye Dam.1	0.7	Not assigned
Substance C	Eye Irrit. 2	74.9	Not assigned
Substance D	Eye Dam.1	8.5	C ≥ 25 %: Eye Dam.1 10 % ≤ C < 25 %: Eye Irrit. 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. Additivity is considered to apply.

Substance E can be disregarded as it is not classified for serious eye damage/eye irritation. Substance B can also be disregarded as present below 1%.

SCLs are not assigned to substance C, thus GCL apply for this ingredient

Eye Dam. 1

Mixture contains 8.5% substance D, the only 'relevant' ingredient classified as Eye Dam.1. As this is below the 25% SCL for substance D, the mixture is not classified Eye Dam.1

Eye Irrit. 2

(%substance D/ SCL) + (%substance C / GCL) = (8.5/10) + (74.9/10) which is > 1 thus mixture is classified Eye Irrit. 2

3.3.6. References

ECVAM/ESAC (2009a) Statement on the scientific validity of cytotoxicity/cell-function based in vitro assays for eye irritation testing. Online: http://ecvam.jrc.it/

ECVAM/ESAC (2009b) Statement on the use of existing low volume eye test (LVET) data for weight of evidence decisions on classification and labelling of cleaning products and their main ingredients. Online: http://ecvam.jrc.it/

Griffith J.F., Nixon G.A., Bruce R.D., Reer P.J., Bannan E.A. (1980), Dose-response studies with chemical irritants in the albino rabbit eye as a basis for selecting optimum testing conditions for predicting hazard to the human eye. *Toxicol Appl Pharmacol* **55**, 501-513.

Scott L., Eskes C., Hoffmann S., Adriaens E., Alepée N., Bufo M., Clothier R., Facchini D., Faller C., Guest R., Harbell J., Hartung T., Kamp H., Varlet B.L., Meloni M, McNamee P., Osborne R., Pape W., Pfannenbecker U., Prinsen M., Seaman C., Spielmann H., Stokes W., Trouba K., Berghe C.V., Goethem F.V., Vassallo M., Vinardell P., Zuang V. (2010), A proposed eye irritation testing strategy to reduce and replace in vivo studies using Bottom-Up and Top-Down approaches. *Toxicol in Vitro* **24**, 1-9.

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. *Toxicol 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.

3.4. 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.*

Annex I: ***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 (Dotson et al, 2015). Please refer also to the Guidance on IR&CSA, Section R.7.3.

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.*

Annex I*: 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.*

Annex I*: 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 in Annex II, section 2.8.*

Annex I: ***3.4.1.6.*** *The hazard class Respiratory or Skin Sensitisation is differentiated into:*

- Respiratory Sensitisation and;

- Skin Sensitisation.

3.4.2. Classification of substances for sensitisation

3.4.2.1. Classification of substances for respiratory sensitisation

3.4.2.1.1. Identification of hazard information

There are no formally recognised and validated animal or *in vitro* tests for respiratory sensitisation. However there may be data from human observations indicating respiratory sensitisation in exposed populations or other sufficient evidence, including read-across.

3.4.2.1.1.1. Identification of human data

Relevant information with respect to respiratory sensitisation may be available from case reports, epidemiological studies, medical surveillance, reporting schemes. For more details see the Guidance on IR&CSA, Section R.7.3.9.2.

3.4.2.1.1.2. Identification of non human data

No formally recognised and validated animal or *in vitro* tests currently ~~e~~xist for respiratory sensitisation. However, data from some animal studies may be indicative of the potential of a substance to cause respiratory sensitisation in humans (CLP Annex I, 3.4.2.1.3) and may provide supportive evidence in case human evidence is available. These data may provide supportive evidence and should be used in a weight of evidence assessment. For further information see the Guidance on IR&CSA, Section R.7.3.9.1.

3.4.2.1.2. Classification criteria for substances

Annex I*: 3.4.2.1.* *Respiratory sensitisers*

Annex I*: 3.4.2.1.1.* *Hazard categories*

Annex I: *3.4.2.1.1.1.* *Respiratory sensitisers shall be classified in Category 1 where data are not sufficient for sub-categorisation.*

Annex I: *3.4.2.1.1.2.* *Where data are sufficient a refined evaluation according to 3.4.2.1.1.3 shall allow the allocation of respiratory sensitisers into sub-category 1A, strong sensitisers, or sub-category 1B for other respiratory sensitisers.*

Annex I: *3.4.2.1.1.3.* *Effects seen in either humans or animals will normally justify classification in a weight of evidence approach for respiratory sensitisers. Substances may be allocated to one of the two sub-categories 1A or 1B using a weight of evidence approach in accordance with the criteria given in Table 3.4.1 and on the basis of reliable and good quality evidence from human cases or epidemiological studies and/or observations from appropriate studies in experimental animals.*

Annex I*: 3.4.2.1.1.4.* *Substances shall be classified as respiratory sensitisers in accordance with the criteria in Table 3.4.1:*

Table 3.4.1

Hazard category and sub-categories for respiratory sensitisers

Category	*Criteria*
Category 1	*Substances shall be classified as respiratory sensitisers (Category 1) where data are not sufficient for sub-categorisation 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.*
Sub-category 1A:	*Substances showing a high frequency of occurrence in humans; or a probability of occurrence of a high sensitisation rate in humans based on animal or other tests ([1]). Severity of reaction may also be considered.*
Sub-category 1B:	*Substances showing a low to moderate frequency of occurrence in humans; or a probability of occurrence of a low to moderate sensitisation rate in humans based on animal or other tests ([1]). Severity of reaction may also be considered.*

([1]) At present, recognised and validated animal models for the testing of respiratory hypersensitivity are not available. Under certain circumstances, data from animal studies may provide valuable information in a weight of evidence assessment.

There is currently no clear way of establishing sub-categories for respiratory sensitisation, however if compelling evidence were available such as observations in the workplace, it may be possible to determine a sub-category.

Classification into sub-categories is required when data are sufficient. When Category 1A cannot be excluded, Category 1 should be applied instead of Category 1B. High frequency and low to moderate frequency cannot be defined as specific concentrations or percentages for human study data because, when considering human evidence, it is necessary to take into account the size of the exposed population and the extent and conditions of exposure, including frequency. It is necessary, therefore, to reach a view on a case-by-case basis.

3.4.2.1.3. Evaluation of hazard information

3.4.2.1.3.1. Human data

Substances shall be classified as respiratory sensitisers if there is evidence in humans or other sufficient evidence, including read-across that the substance can lead to specific respiratory hypersensitivity.

Annex I*: 3.4.2.1.2 Human evidence*

Annex I: *3.4.2.1.2.1.* *Evidence that a substance can lead to specific hypersensitivity will normally be based on human experience. In this context, hypersensitivity is normally seen as asthma, but other hypersensitivity reactions such as rhinitis/conjunctivitis and alveolitis are also considered. The condition will have the clinical character of an allergic reaction. However, immunological mechanisms do not have to be demonstrated.*

Annex I: *3.4.2.1.2.2.* *When considering the human evidence, it is necessary for a decision on classification to take into account, in addition to the evidence from the cases:*

(a) the size of the population exposed;

(b) the extent of exposure.

[…]

Annex I: *3.4.2.1.2.3.* *The evidence referred to above could be:*

(a) clinical history and data from appropriate lung function tests related to exposure to the substance, confirmed by other supportive evidence which may include:

(i) in vivo immunological test (e.g. skin prick test)

(ii) in vitro immunological test (e.g. serological analysis);

(iii) studies that indicate other specific hypersensitivity reactions where immunological mechanisms of action have not been proven, e.g. repeated low-level irritation, pharmacologically mediated effects;

(iv) a chemical structure related to substances known to cause respiratory hypersensitivity;

(b) data from one or more positive bronchial challenge tests with the substance conducted according to accepted guidelines for the determination of a specific hypersensitivity reaction.

Annex I: *3.4.2.1.2.4.* *Clinical history shall include both medical and occupational history to determine a relationship between exposure to a specific substance and development of respiratory hypersensitivity. Relevant information includes aggravating factors both in the home and workplace, the onset and progress of the disease, family history and medical history of the patient in question. The medical history shall also include a note of other allergic or airway disorders from childhood, and smoking history.*

Annex I*: 3.4.2.1.2.5.* *The results of positive bronchial challenge tests are considered to provide sufficient evidence for classification on their own. It is however recognised that in practice many of the examinations listed above will have already been carried out.*

3.4.2.1.3.2. Non human data

Annex I: *3.4.2.1.3. Animal studies*

Annex I*: 3.4.2.1.3.1.* *Data from appropriate animal studies (*) which may be indicative of the potential of a substance to cause sensitisation by inhalation in humans (**) may include:*

(a) measurements of Immunoglobulin E (IgE) and other specific immunological parameters in mice;

(b) specific pulmonary responses in guinea pigs.

(*) At present, recognised and validated animal models for the testing of respiratory hypersensitivity are not available. Under certain circumstances, data from animal studies may provide valuable information in a weight of evidence assessment.

(**) The mechanisms by which substances induce symptoms of asthma are not yet fully known. For preventative measures, these substances are considered respiratory sensitisers. However, if on the basis of the evidence, it can be demonstrated that these substances induce symptoms of asthma by irritation only in people with bronchial hyper reactivity, they should not be considered respiratory sensitisers.

No formally recognised and validated animal tests currently exist for respiratory sensitisation. However data from some animal studies may be indicative of the potential of a substance to cause respiratory sensitisation in humans (CLP Annex I, 3.4.2.1.3) and may provide supportive evidence in case human evidence is available (see also Section 3.4.2.1.2 above). This information may also be combined with information on structural alerts for respiratory sensitisation (see the Guidance on IR&CSA, Section R.7.3.9.1) and information on the skin sensitising properties of a substance and should be used in a weight of evidence assessment.

Information on sensitizing activity of substances, such as that identified using contact sensitivity studies, may also be taken into consideration in a weight of evidence assessment. Based on a assessment including mostly non-standrad versions of the LLNA, using BALB/c instead of CBA/Ca strains mice, substance for which there were convincing negative data in the LLNA (at an appropriate test concentration and with the exception of large substances such as enzymes) most probably lacks the potential for respiratory allergy (Dearman R.J., 2013). It should be noted that negative data on skin sensitisation cannot be used to negate data fulfilling the classification criteria for respiratory sensitisation.

3.4.2.1.4. Decision on classification

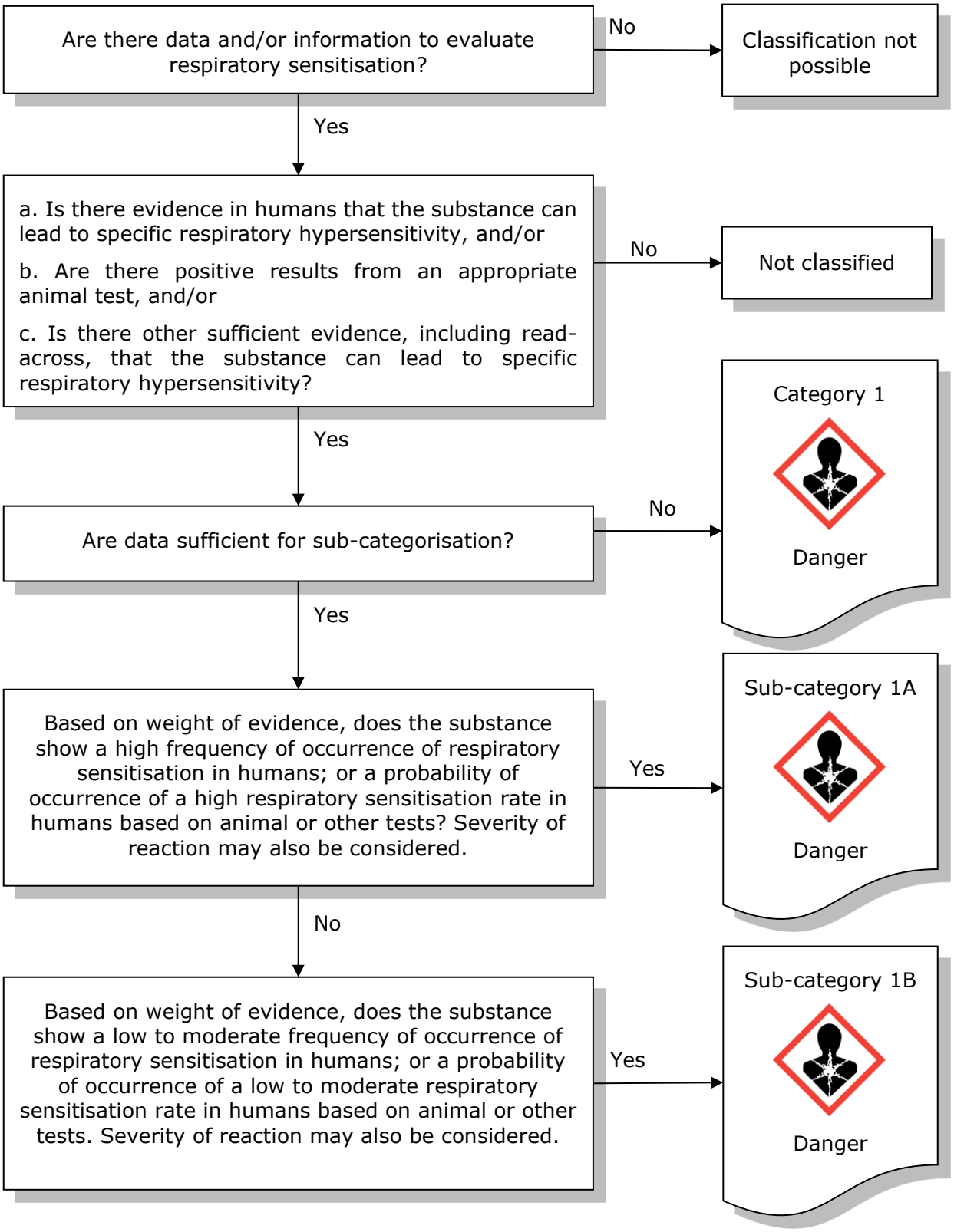
According to CLP Annex I, Section 3.4.2.1.1.4 substances fulfilling the criteria for respiratory sensitisation will be classified as such in Category 1 (and in Sub-category 1A or 1B when sufficient data are available),

3.4.2.1.5. Setting of specific concentration limits

Respiratory sensitisers cannot be identified reliably on the basis of animal tests 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 alone. Moreover, there is no concept available to set SCLs on the basis of human data for respiratory sensitisers.

3.4.2.1.6. 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.



3.4.2.2. Classification of substances for skin sensitisation

3.4.2.2.1. Identification of hazard information

With respect to identification of relevant information for skin sensitisation see the Guidance on IR&CSA, Section R.7.3.4.

3.4.2.2.1.1. Identification of human data

Relevant information with respect to skin sensitisation may be available from case reports, epidemiological studies, medical surveillance and reporting schemes based on human patch testing. For more details see the Guidance on IR&CSA, Section R.7.3.4.2.

3.4.2.2.1.2. Identification of non human data

At present no formally validated non-testing systems exist to predict skin sensitising potential. However data such as structural alert data or data to show that the chemical structure of a molecule is similar to that of known sensitisers (e.g. QSARs or expert systems) may form part of the weight of evidence for classification (see also Guidance on IR&CSA, Section R.7.3.4).

The subject of in vitro testing for skin sensitisation has also been dealt with in the Guidance on IR&CSA, Section R.7.3.4. Validated *in vitro/in chemico* methods exist with the aim to identify a sensitising potential of a chemical. These include OECD TG442C (Peptide/protein binding), TG442D (keratinocyte response) and TG 442E (monocytic/dendritic cell response). The *in vitro/in chemico* tests are not regarded as stand alone tests and the result from such a test should be used together with other data in an overall WoE assessment. Further, at present there is no agreed strategy on how to use *in vitro/in chemico* methods for direct estimation of sensitising potency, but data from such tests can be used in a WoE assessment together with other data in order to assess skin sensitisation potency. See also the Guidance on IR&CSA, especially Section R.7.3.4.1.

Information on the current developments of *in vitro* tests and methodology can be found on the ECVAM website (http://ihcp.jrc.ec.europa.eu/our_labs/eurl-ecvam).

There are three standard 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 assay. They are further described in the Guidance on IR&CSA, Section R.7.3.4, and in the context of classification in Section 3.4.3.2 of this Guidance.

3.4.2.2.2. Classification criteria for substances

Annex I: *3.4.2.2.* *Skin Sensitisers*

Annex I*: 3.4.2.2.1**.* *Hazard categories*

Annex I*: 3.4.2.2.1.1.* *Skin sensitisers shall be classified in Category 1 where data are not sufficient for sub-categorisation.*

Annex I*: 3.4.2.2.1.2.* *Where data are sufficient a refined evaluation according to section 3.4.2.2.1.3 allows the allocation of skin sensitisers into sub-category 1A, strong sensitisers, or sub-category 1B for other skin sensitisers.*

Annex I*: 3.4.2.2.1.3.* *Effects seen in either humans or animals will normally justify classification in a weight of evidence approach for skin sensitisers as described in section 3.4.2.2.2. Substances may be allocated to one of the two sub-categories 1A or 1B using a weight of evidence approach in accordance with the criteria given in Table 3.4.2 and on the basis of reliable and good quality evidence from human cases or epidemiological studies and/or observations from appropriate studies in experimental animals according to the guidance values provided in sections 3.4.2.2.2.1 and 3.4.2.2.3.2 for sub-category 1A and in sections 3.4.2.2.2.2 and 3.4.2.2.3.3 for sub-category 1B.*

Annex I*: 3.4.2.2.1.4.* *Substances shall be classified as skin sensitisers in accordance with the criteria in Table 3.4.2:*

Table 3.4.2 ***Hazard category and sub-categories for skin sensitisers***	
Category	*Criteria*
Category 1	*Substances shall be classified as skin sensitisers (Category 1) where data are not sufficient for sub-categorisation in accordance with the following criteria:* *(a) if there is evidence in humans that the substance can lead to sensitisation by skin contact in a substantial number of persons; or* *(b) if there are positive results from an appropriate animal test (see specific criteria in paragraph 3.4.2.2.4.1).*
Sub-category 1A:	*Substances showing a high frequency of occurrence in humans and/or a high potency in animals can be presumed to have the potential to produce significant sensitisation in humans. Severity of reaction may also be considered.*
Sub-category 1B:	*Substances showing a low to moderate frequency of occurrence in humans and/or a low to moderate potency in animals can be presumed to have the potential to produce sensitisation in humans. Severity of reaction may also be considered.*

Classification into sub-categories is required when data are sufficient. When Category 1A cannot be excluded, Category 1 should be applied instead of Category 1B. This is particularly important if only data are available from certain tests showing a high response after exposure to a high concentration but where lower concentrations, which could show the presence of effects at lower doses, have not been tested (in line with some test protocols where a maximised dose should be used).

When considering human evidence, it is necessary to take into account the size of the population exposed and the extent of exposure and frequency, and thus the consideration is on a case by case basis. Human data should be incorporated with animal data to decide on `the sub-categorisation.

Diagnostic patch testing is the gold standard in diagnosing contact allergy in dermatitis patients (see e.g. Johansen et al, 2015). Patch test concentrations and substances must be suitable for the purpose, not causing false negatives, false positives, irritant reactions or inducing contact allergy (skin sensitisation). The vehicle is important for the outcome of a diagnostic patch test, the most commonly used being petrolatum. Patch test concentrations are not based on concentrations used in products. The used concentrations may be too low and lead to a false negative reaction. Data from the testing of unselected, consecutive dermatitis patients is more standardised than testing which is undertaken on a specific patient group (e.g. those with facial eczema) or worker group (e.g. individuals with a particular type of exposure) and often involves patch testing with materials beyond those normally used, i.e. 'the standard series', as for example the European baseline series. To detect and confirm new sensitisers, suitable patch test concentrations have to be set, which is a laborious task. For many substances, standardised commercial patch tests are lacking.

For a newly identified skin sensitiser, which might also be a substance newly introduced onto the market, or a substance not included in the baseline diagnostic patch test series, the high severity of responses might be used as an indication that classification as Category 1A is appropriate. For example, where the substance has caused:

- Hospitalisation due to acute skin reaction
- Chronic dermatitis (lasting > 6 months)
- Generalised (systemic/whole body) dermatitis

It should be noted that the severity/strength of diagnostic patch test reactions normally cannot be used for this purpose.

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

3.4.2.2.3. Evaluation of hazard information

3.4.2.2.3.1. Human data

The classification of a substance can be based on human evidence, such as positive data from patch testing, epidemiological studies showing allergic contact dermatitis caused by the substance, positive data from experimental studies in man and/or well documented episodes of allergic contact dermatitis, using a weight of evidence approach (see Section 3.4.2.2.3.7 of this Guidance for details).

Criteria for sub-categorisation are listed in CLP Annex I, 3.4.2.2.2.1 and 3.4.2.2.2.2:

> **Annex I*: 3.4.2.2.2.1.*** *Human evidence for sub-category 1A can include:*
>
> *(a) positive responses at ≤ 500 µg/cm^2 (HRIPT, HMT – induction threshold);*
>
> *(b) diagnostic patch test data where there is a relatively high and substantial incidence of reactions in a defined population in relation to relatively low exposure;*
>
> *(c) other epidemiological evidence where there is a relatively high and substantial incidence of allergic contact dermatitis in relation to relatively low exposure.*
>
> **Annex I*: 3.4.2.2.2.2.*** *Human evidence for sub-category 1B can include:*
>
> *(a) positive responses at > 500 µg/cm^2 (HRIPT, HMT – induction threshold);*
>
> *(b) diagnostic patch test data where there is a relatively low but substantial incidence of reactions in a defined population in relation to relatively high exposure;*
>
> *(c) other epidemiological evidence where there is a relatively low but substantial incidence of allergic contact dermatitis in relation to relatively high exposure.*

HRIPT: Human Repeat Insult Patch Test; HMT: Human Maximisation Test

CLP Article 7 (3) states 'Tests on humans shall not be performed for the purposes of this Regulation. However, data obtained from other sources, such as clinical studies, can be used for the purposes of this Regulation.' Thus human induction studies such as HRIPT or HMT must not be performed, although historical data may be used as weight of evidence for the sub-categorisation. To provide further guidance on the types of human data that may be considered as data from other sources, please refer to the following table:

Table 3.1 Types of Human Studies

Type	Subjects	Endpoint studied	Comments
Human Repeated Insult Patch Test (HRIPT) & Human Maximization Test (HMT)	Healthy volunteers	Induction of sensitisation	This is not a clinical study and is only of historical relevance. New studies for this regulation are not permitted.
Diagnostic patch test from individual clinics or collated clinic data	Eczema patients attending dermatology clinics	Elicitation (as an indicator of previous sensitisation)	Primary source of clinical information on the occurrence of skin sensitisation
Dose response study (e.g. patch test serial dilution; repeated open application test)	Sensitised individuals (usually from diagnostic patch tests)	Elicitation	Not yet a standardised protocol, but provides an indication of the degree of sensitivity and of safe limits of exposure. Mainly used as confirmatory tests and in research.
Epidemiology study	Eczema patients, selected occupational groups, other selected groups, or general population	Elicitation	Large general population studies are scarce; focused studies in selected populations are more common and provide insights on frequency of sensitisation compared to exposure

The purpose of the material that follows is the provision of guidance concerning the evaluation of human data, particularly with respect to balancing considerations of exposure against the clinical evidence regarding the frequency of skin sensitisation. The concept of 'guidance' should be applied generally to all of the numeric criteria – they represent indicators derived from expert opinion and are not to be taken as proven absolute values. Application of this guidance should permit sub-categorisation where the human data on exposure and sensitisation is clear.

Table 3.2 Relatively high or low frequency of occurrence of skin sensitisation*

Human diagnostic patch test data	High frequency	Low/moderate frequency
General population studies	≥ 0.2 %	< 0.2 %
Dermatitis patients (unselected, consecutive)	≥ 1.0 %	< 1.0 %
Selected dermatitis patients (aimed testing, usually special test series)	≥ 2.0 %	< 2.0 %
Work place studies:		
1: all or randomly selected workers	≥ 0.4 %	< 0.4 %
2: selected workers with known exposure or dermatitis	≥ 1.0 %	< 1.0 %
Number of published cases	≥ 100 cases	< 100 cases

* Only one or two types of information may be sufficient for sub-categorisation.

The figure of 0.2% for the general population is intended to reflect that the frequency of contact allergy in dermatitis patients is approximately 5 (range 2-10) times higher than in the general population (Mirshahpanah and Maibach, 2007).

The figure of 1% for consecutive (i.e. unselected) dermatitis patients is based on the generally agreed consideration that a contact allergy frequency of ≥ 1% in such patients is of high concern.

The figure of 0.4% for unselected workers in a workplace is derived from the use in REACH of a 2 times higher assessment factor for the general population than for workers.

It is important to note that the data from the testing of unselected, consecutive dermatitis patients is more standardised than testing which is undertaken on a specific patient group (e.g. those with facial eczema) or worker group (e.g. individuals with a particular type of exposure). Such clinical studies may be conducted on patients selected according to a particular type of eczema or based on their likelihood of occupational exposure and often involves patch testing with materials beyond those normally used i.e. 'the standard series' (Andersen *et al*, 2011). It is important to consider also that there may be variations in positive patch test frequency related to age, gender or region.

Table 3.3 Relatively high or low exposure *

Exposure data	Relatively low exposure (weighting)	Relatively high exposure (weighting)
Concentration / dose	< 1.0% < 500µg/cm^2 (score 0)	≥ 1.0% ≥ 500µg/cm^2 (score 2)
Repeated exposure	< once/daily (score 1)	≥ once/daily (score 2)
Number of exposures (irrespective of concentration of sensitizer)	<100 exposures (score 0)	≥100 exposures (score 2)

* To achieve the exposure index (see text below) a response in each row is necessary.

The scores in Table 3.3 represent weightings whose purpose is to enable an exposure index to be derived which best reflects our understanding of the relative importance of dose versus frequency of exposure. An additive exposure index of 1-4 equates to low exposure, whereas 5-6 reflects high exposure.

Careful consideration has to be given regarding the release (migration) of a sensitising substance from a solid object, and not the concentration. Ideally, skin exposure is best expressed in dose per unit area, but it is recognised that this data is often not available, hence concentration may be used as a surrogate indicator of exposure.

Table 3.4 Sub-categorisation decision table

	Relatively low frequency of occurrence of skin sensitisation	Relatively high frequency of occurrence of skin sensitisation
Relatively high exposure (score 5-6)	Sub-category 1B	Category 1 or case by case evaluation
Relatively low exposure (score 1-4)	Category 1 or case by case evaluation	Sub-category 1A

3.4.2.2.3.2. Non human data

Annex I*: 3.4.2.2.3.2.* *Animal test results for sub-category 1A can include data with values indicated in Table 3.4.3*	
Table 3.4.3 **Animal test results for sub-category 1A**	
Assay	*Criteria*
Local lymph node assay	*EC3 value ≤ 2 %*
Guinea pig maximisation test	*≥ 30 % responding at ≤ 0,1 % intradermal induction dose or* *≥ 60 % responding at > 0,1 % to ≤ 1 % intradermal induction dose*
Buehler assay	*≥ 15 % responding at ≤ 0,2 % topical induction dose or* *≥ 60 % responding at > 0,2 % to ≤ 20 % topical induction dose*
Annex I*: 3.4.2.2.3.3.* *Animal test results for sub-category 1B can include data with values indicated in Table 3.4.4 below:*	
Table 3.4.4 **Animal test results for sub-category 1B**	
Assay	*Criteria*
Local lymph node assay	*EC3 value > 2 %*
Guinea pig maximisation test	*≥ 30 % to < 60 % responding at > 0,1 % to ≤ 1 % intradermal induction dose or* *≥ 30 % responding at > 1 % intradermal induction dose*
Buehler assay	*≥ 15 % to < 60 % responding at > 0,2 % to ≤ 20 % topical induction dose or* *≥ 15 % responding at > 20 % topical induction dose*

The CLP Regulation allows classification of skin sensitisers in one hazard category, Category 1, which comprises two sub-categories, 1A and 1B.

Annex I: *3.4.2.2.1.1:* *Skin sensitisers shall be classified in Category 1 where data are not sufficient for sub-categorisation.*

Classification into sub-categories is required when data are sufficient (CLP Annex I 3.4.2.2.1.1). When Category 1A cannot be excluded, Category 1 should be applied instead of Category 1B. This is particularly important if only data are available from the guinea pig tests or from the rLLNA showing a high response after exposure to a high concentration but where lower concentrations which could show the presence of such effects at lower doses are absent or in the absence of adequate dose-response information. Unless there is sufficient evidence to place such substances in sub category 1A or 1B, classification in category 1 should be the default

position. In other words, although the criteria in the Table 3.4.4 for classification to subcategory 1B are fulfilled, the classification for subcategory 1A may not be excluded and therefore the substance should be classified as a Category 1 skin sensitiser (see also examples 6 & 7). The REACH information requirements (as amended by Commission Regulation (EU) 2016/1688) for skin sensitisation includes a requirement for a potency assessment, i.e. an assessment of whether a substance "can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A)". The only exception to this is where there is existing animal information available (i.e. a study which was initiated or conducted before 11 October 2016) that does not allow an assessment of potency and thus only a conclusion in category 1 is possible. In such cases no further testing to assess potency is required (further details can be found in the Guidance on IR&CSA, Section R.7.3). Not all substances which need to be classified are registered under REACH, and thus for these substances the data base can be weaker and not sufficient to conclude on potency and therefore subcategorization is not possible and classification in category 1 is warranted.

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. High potency is determined according to the results from the animal studies as given in CLP Annex I, Table 3.4.3 and low to moderate potency is determined according to the results from the animal studies as given in CLP Annex I, Table 3.4.4. The potency considerations may be used as a basis for setting specific concentration limits (see Section 3.4.2.2.5 of this Guidance). The three currently recognised and officially accepted animal test methods for skin sensitisation defined by OECD Test Guidelines are the Mouse Local Lymph Node Assay (LLNA) OECD TG 429 and its variations OECD TG 442A and 442B, Guinea Pig Maximisation Test by Magnusson & Kligman (GPMT) and the Buehler assay in the guinea pig OECD TG 406. 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 animal method of first choice, in case *in vitro/in chemico* assays are not considered relevant. 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 the Guidance on IR&CSA, Section R.7.3.5.1).

Test results from the LLNA, GPMT and the Buehler assay can 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 3.5 Definition of significant skin sensitising effect

Test	Result
Mouse local lymph node assay (LLNA) (OECD TG 429)*	Stimulation Index ≥ 3
LLNA: DA (OECD TG 442A),*	Stimulation Index ≥ 1.8
LLNA: BrdU-ELISA (OECD TG 442B)*	Stimulation Index ≥ 1.6
Guinea pig maximisation test (GPMT) (OECD 406)	Redness (Score ≥ 1) in ≥ 30% of the test animals
Buehler assay (OECD 406)	Redness (Score ≥ 1) in ≥ 15% of the test animals

*See further details in the test guidelines

A substance may be classified as 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 test method not officially recognised may also justify classification as a skin sensitiser, but can normally not overrule a negative result obtained in one of the three recognised, animal tests described above. A new animal study should not be conducted in an attempt to negate a clearly positive response in a test method not officially recognised particularly where there is other supporting evidence that the substance is a skin sensitiser.

3.4.2.2.3.2.1. Mouse Local Lymph Node Assay

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 is causally and quantitatively correlated with the acquisition of skin sensitisation (Basketter *et al*. 2002a, 2002b). A correlation has been demonstrated between the concentration of a 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 the 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. However, it should be noted that if the dose interval for LLNA is too low so that all the stimulation indexes are below 3, it is not possible to know whether the higher doses would have generated a stimulation index above 3. Also, if only high doses would be used in an LLNA test, the EC3 value may be associated with great uncertainty since the extrapolation is needed to low doses when the shape of the dose-response curve is not known. It is also known that the choice of vehicle may influence the EC3 value.

Potency may be considered when setting specific concentration limits (see Section 3.4.2.2.5 of this Guidance).

Different variants of the LLNA exist, namely the reduced LLNA (rLLNA) described as an option in OECD TG 429, the LLNA: DA (OECD TG 442A), and the LLNA: BrdU-ELISA (OECD TG 442B). The rLLNA uses fewer animals than the classical LLNA and should only be used in those circumstances where dose-response information is not required (e.g. to confirm a negative prediction of skin sensitising potential) and thus should not be used for sub-categorisation of skin-sensitisers. The last two variants avoid the use of DNA radiolabelling agent and provide quantitative data suitable for dose-response assessment. However, the criteria for determining the positive response is different from that of the traditional LLNA (OECD TG 429). Full details are given in the corresponding OECD Test Guidelines. There is no guidance for sub-categorisation.

3.4.2.2.3.3. Guinea Pig Maximisation Test (GPMT, OECD TG 406)

This test has been used for over 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 substances 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 may be 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.

It should be noted that the guinea pig tests should be conducted at highest induction dose causing mild (Buehler Assay) or mild-to-moderate (GPMT) skin irritation. As a consequence, it is unlikely that substances (except strong irritants) would be tested at low concentration given in Table 3.4.4 triggering classification as a skin sensitiser in sub category 1A.

Potency may be considered when setting specific concentration limits (see Section 3.4.2.2.5 of this Guidance).

3.4.2.2.3.4. Buehler assay (OECD TG 406)

This test has been in use for the last 40 years, 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. Potency can be categorised using the results of the Buehler assay 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 assay.

Potency may be considered when setting specific concentration limits (see Section 3.4.2.2.5 of this Guidance).

It should be noted that the guinea pig tests should be conducted at highest induction dose causing mild (Buehler Assay) or mild-to-moderate (GPMT) skin irritation. As a consequence, it is unlikely that substances (except strong irritants) would be tested at the low concentration given in Table 3.4.4 triggering classification as a skin sensitiser in sub category 1A.

3.4.2.2.3.5. Non-guideline skin sensitisation tests

In vivo test methods which do not comply with recognised guidelines (see Article 8(3) of CLP) are strongly discouraged for the identification of skin sensitisers or assessment of skin sensitising potency. The results of such tests may provide supportive evidence when the tests are scientifically well justified and carefully evaluated. If doubts exist about the validity and the interpretation of the results, the evaluation needs to be done by using a weight-of-evidence approach as described below (see Section 3.4.2.2.3.7 of this Guidance).

3.4.2.2.3.6. 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.

3.4.2.2.3.7. Weight of evidence

Annex I: ***3.4.2.2.4.*** *Specific considerations*

3.4.2.2.4.1. *For classification of a substance, evidence shall include any or all of the following using a weight of evidence approach:*

(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;*

(c) *positive data from appropriate animal studies*

(d) positive data from experimental studies in man (see section 1.3.2.4.7);

(e) well documented episodes of allergic contact dermatitis, normally obtained in more than one dermatology clinic;

(f) severity of reaction may also be considered.

Annex I: *3.4.2.2.4.2.* *Evidence from animal studies is usually much more reliable than evidence from human exposure. However, 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 resolve the question of classification on a case-by-case basis. Normally, human data are not generated in controlled experiments with volunteers for the purpose of hazard classification but rather as part of risk assessment to confirm lack of effects seen in animal tests. Consequently, positive human data on skin sensitisation are usually derived from case-control or other, less defined studies. Evaluation of human data must therefore be carried out with caution as the frequency of cases reflect, in addition to the inherent properties of the substances, factors such as the exposure situation, bioavailability, individual predisposition and preventive measures taken. Negative human data should not normally be used to negate positive results from animal studies. For both animal and human data, consideration should be given to the impact of vehicle.*

Annex I: 3.4.2.2.4.3. *If none of the abovementioned conditions are met, the substance need not be classified as a skin sensitiser. However, a combination of two or more indicators of skin sensitisation as listed below may alter the decision. This shall be considered on a case-by-case basis.*

(a) Isolated episodes of allergic contact dermatitis;

(b) epidemiological studies of limited power, e.g. where chance, bias or confounders have not been ruled out fully with reasonable confidence;

(c) data from animal tests, performed according to existing guidelines, which do not meet the criteria for a positive result described in section 3.4.2.2.3, but which are sufficiently close to the limit to be considered significant;

(d) positive data from non-standard methods;

(e) positive results from close structural analogues.

Annex I: *3.4.2.2.4.4.* *Immunological contact urticaria*

Substances meeting the criteria for classification as respiratory sensitisers may in addition cause immunological contact urticaria. Consideration should be given to classifying these substances also as skin sensitisers. Substances which cause immunological contact urticaria without meeting the criteria for respiratory sensitisers should also be considered for classification as skin sensitisers.

There is no recognised animal model available to identify substances which cause immunological contact urticaria. Therefore, classification will normally be based on human evidence which will be similar to that for skin sensitisation.

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 adequate reliable and representative human data are usually more relevant. 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 (CLP Annex I, 3.4.2.2.4.2).

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.

Non-testing data might be used to supplement and increase confidence in the available experimental data. In some cases, such data might be used to conclude on classification in line with the criteria in the absence 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.

Available *in vitro/in chemico* tests cannot be considered as stand alone tests, but the results from such tests can be used together with other data in a weight of evidence assessment. There is currently no agreed strategy on how to use the results of these methods for potency assessment (see OECD TG442C-E and Guidance on IR&CSA, R.7.3.4.1)

Good quality data on the substance itself have more weight than such data extrapolated from similar substances.

3.4.2.2.4. Decision on classification

According to CLP Annex I, 3.4.2.2.1.4 substances fulfilling the criteria for skin sensitisation will be classified as such in Category 1 (or in Sub-category 1A or 1B when sufficient data are available). In addition substances classified for skin sensitisation can be allocated specific concentration limits as described in Section 3.4.2.2.5 of this Guidance.

3.4.2.2.5. Setting of specific concentration limits

SCLs for skin sensitisation can be set based on the results from animal testing as reported below. SCLs 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 CLP Annex I, 3.4.3.1.1). The setting of SCL is based on potency; potency is already considered for the subcategorisation defining generic concentration limits. SCLs are generally applied for the most potent skin sensitisers classified in 1A.

The following schemes can be used for determination of potency categories for sensitisers. The potency categories given in the 3 tables below are described in Basketter *et al*. (2005a).

For the LLNA(OECD TG 429)

Table 3.6 Skin Sensitisation Potency in the Mouse Local Lymph Node Assay

EC3-value (% w/v)	Potency	Resulting sub-category (*)
≤ 0.2	Extreme	1A
> 0.2 - ≤ 2	Strong	1A
> 2	Moderate	1B

(*) based on Annex I Section 3.4.2.2.3.2. and Section 3.4.2.2.3.3.

For the Guinea Pig Maximisation Test (OECD TG 406)

Table 3.7 Potency on basis of the Guinea Pig Maximisation Test

Concentration for intradermal induction (% w/v)	Incidence sensitised guinea pigs (%)	Potency	Resulting sub-category (*)
≤ 0.1	≥ 60	Extreme	1A
≤ 0.1	≥30 - <60	Strong	1A
>0.1 - ≤ 1.0	≥60	Strong	1A
>0.1 - ≤ 1.0	≥30 - <60	Moderate	1B(**)
> 1.0	≥ 30	Moderate	1B(**)

(*) based on CLP Annex I Section 3.4.2.2.3.2. and Section 3.4.2.2.3.3.

(**) If the concentration used for intradermal induction or the incidence of sensitised guinea pigs is very high, care should be taken to exclude the possibility of the substance being a Cat 1A (a strong or an extreme) sensitiser.

For the Buehler Assay, (OECD TG 406)

Table 3.8 Potency on basis of the Buehler assay

Concentration for topical induction (% w/v)	Incidence sensitised guinea pigs (%)	Potency	Resulting sub-category (*)
≤ 0.2	≥ 60	Extreme	1A
≤ 0.2	≥15 - <60	Strong	1A
>0.2 - ≤ 20	≥ 60	Strong	1A
>0.2 - ≤ 20 (**)	≥15 - <60	Moderate	1B (**)
> 20 (**)	≥ 15	Moderate	1B (**)

(*) based on CLP Annex I Section 3.4.2.2.3.2. and Section 3.4.2.2.3.3.

(**) If the concentration used for topical induction or the incidence of sensitised guinea pigs is very high, care should be taken to exclude the possibility of the substance being a Cat 1A (a strong or an extreme) sensitiser.

The generic concentration limits (GCLs) for the classification of sensitisers in mixtures are given in CLP Annex I, Table 3.4.5 (see Section 3.4.3.3.1 of this Guidance). In some cases, the GCL may not be sufficiently protective and an SCL shall be set in accordance with 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 for classification. As such the recommended SCL should normally be as given in Table 3.9. However, supported by reliable data the SCL could have some other value below the GCL. 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 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 an SCL above the GCL.

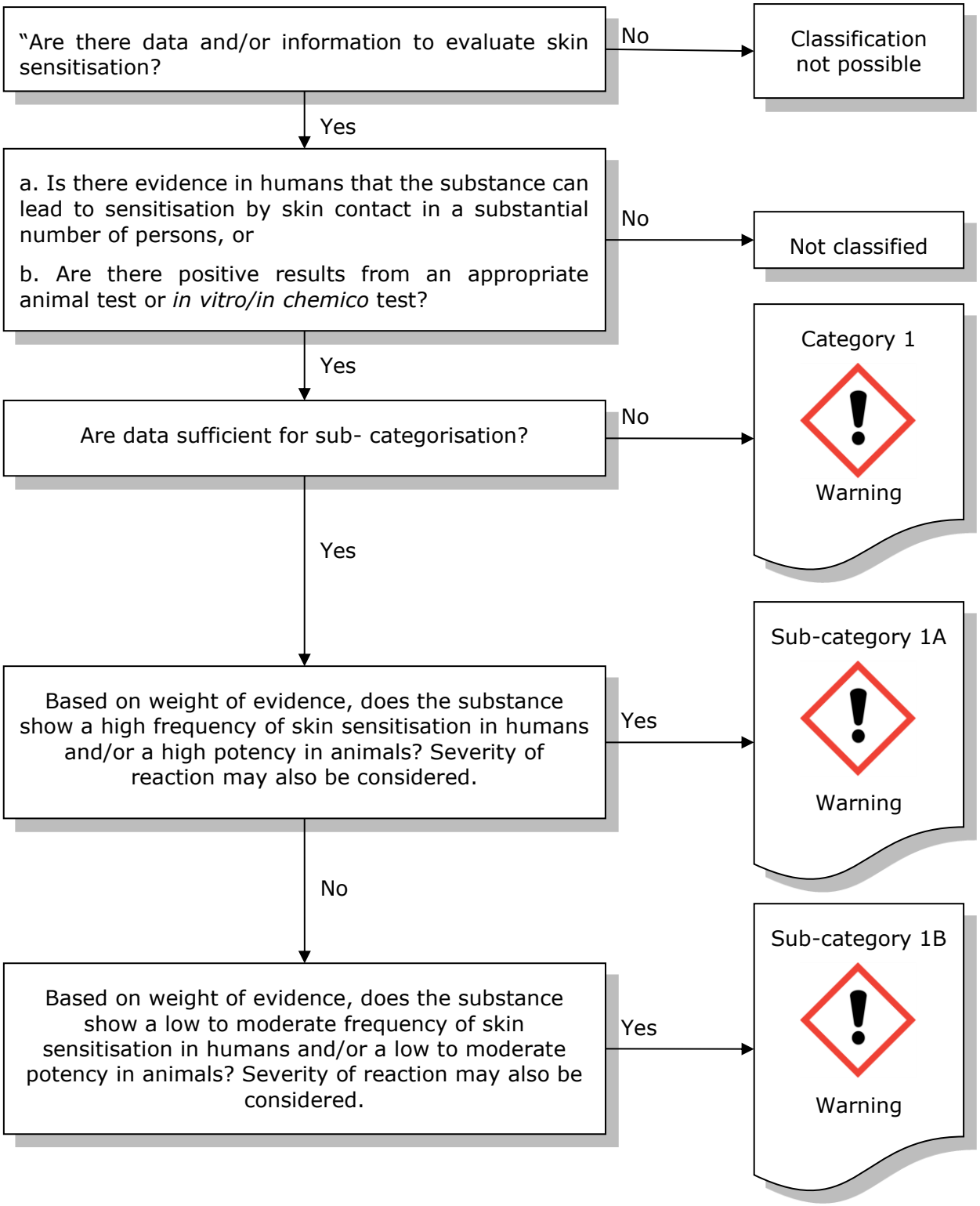
The concentration limits for skin sensitisers categorised according to their sensitisation potency in Table 3.9 are based on the recommendations from an EU expert group on skin sensitisation (Basketter *et al*., 2005a).

Table 3.9 Skin sensitising potency for substances and recommendations on concentration limits

Potency	Concentration Limit (% w/v)
Extreme	0.001 (SCL)
Strong	0.1 (GCL)
Moderate	1 (GCL)

3.4.2.2.6. 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.



3.4.3. Classification of mixtures for respiratory or skin sensitisation

3.4.3.1. Identification of hazard information for respiratory sensitisation

The same principles apply as for substances (see Section 3.4.2.1.1 of this Guidance).

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 Section 3.4.2.2.1 of this Guidance. 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 takes into account effects of possible interactions of its components. For instance, it is known that the 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 the 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 a 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)).

Limitations apply to in chemico and in vitro methods (see the specific OECD test guidelines).

3.4.3.3. Classification criteria for mixtures

When mixtures are classified as sensitizing based on the presence of a sensitizing substance at a concentration at or above the generic or specific concentration limit, no sub-categorisation is required.

3.4.3.3.1. When data are available for all ingredients or only for some ingredients

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 3.4.5 below for solid/liquid and gas respectively.*

Table 3.4.5

Generic concentration limits of components of a mixture classified as either respiratory sensitisers or skin sensitisers that trigger classification of the mixture

Component classified as:	*Concentration triggering classification of a mixture as:*		
	Respiratory sensitiser Category 1		*Skin sensitiser Category 1*
	Solid/Liquid	*Gas*	*All physical states*
Respiratory sensitiser Category 1	*≥ 1,0 %*	*≥ 0,2 %*	
Respiratory sensitiser Sub-category 1A	*≥ 0,1 %*	*≥ 0,1 %*	
Respiratory sensitiser Sub-category 1B	*≥ 1,0 %*	*≥ 0,2 %*	
Skin sensitiser Category 1			*≥ 1,0 %*
Skin sensitiser Sub-category 1A			*≥ 0,1%*
Skin sensitiser Sub-category 1B			*≥ 1,0 %*

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 3.4.2.2.5 of this Guidance) 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 or specific concentration limit, the mixture must be classified for that hazard. If the mixture contains two substances each below the generic or specific concentration limits, the mixture will not be classified.

Annex I: 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 3.4.5, in individuals who are already sensitised to the substance or mixture (see Note 1 to Table 3.4.6).*

Table 3.4.6

Concentration limits for elicitation of components of a mixture

Component classified as:	*Concentration limits for elicitation*		
	Respiratory sensitiser Category 1		Skin sensitiser Category 1
	Solid/Liquid	*Gas*	All physical states
Respiratory sensitiser Category 1	*≥ 0,1 % (Note 1)*	*≥ 0,1 % (Note 1)*	
Respiratory sensitiser Sub-category 1A	*≥ 0,01 % (Note 1)*	*≥ 0,01 % (Note 1)*	
Respiratory sensitiser Sub-category 1B	*≥ 0,1 % (Note 1)*	*≥ 0,1 % (Note 1)*	
Skin sensitiser Category 1			≥ 0,1 % (Note 1)
Skin sensitiser Sub-category 1A			≥ 0,01 % (Note 1)
Skin sensitiser Sub-category 1B			≥ 0,1 % (Note 1)

Note 1:

This concentration limit for elicitation is used for the application of the special labelling requirements section 2.8 of Annex II to protect already sensitised individuals. A SDS is required for the mixture containing a component at or above this concentration. For sensitising substances with specific concentration limit lower than 0,1 %, the concentration limit for elicitation should be set at one tenth of the specific concentration limit.

Further details on the additional labelling provisions to protect already sensitised individuals are provided in Section 3.4.4.1 of this Guidance.

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 the case of skin sensitisation current test methods are based on application of a maximised dose, which can only 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 3.4.3.2 of this Guidance and 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 order to apply bridging principles, there needs to be sufficient data on similar tested mixtures as well as the ingredients of the mixture.

The same limitations apply for the use of existing test results of similar tested mixtures generated with current test methods as those described for any mixture in sections 3.4.3.2. Care must be exercised in evaluating data on mixtures, that the dose used does not render the results inconclusive.

Note that the following bridging principles are not applicable to this hazard class:

- concentration of highly hazardous mixtures
- interpolation within one hazard category

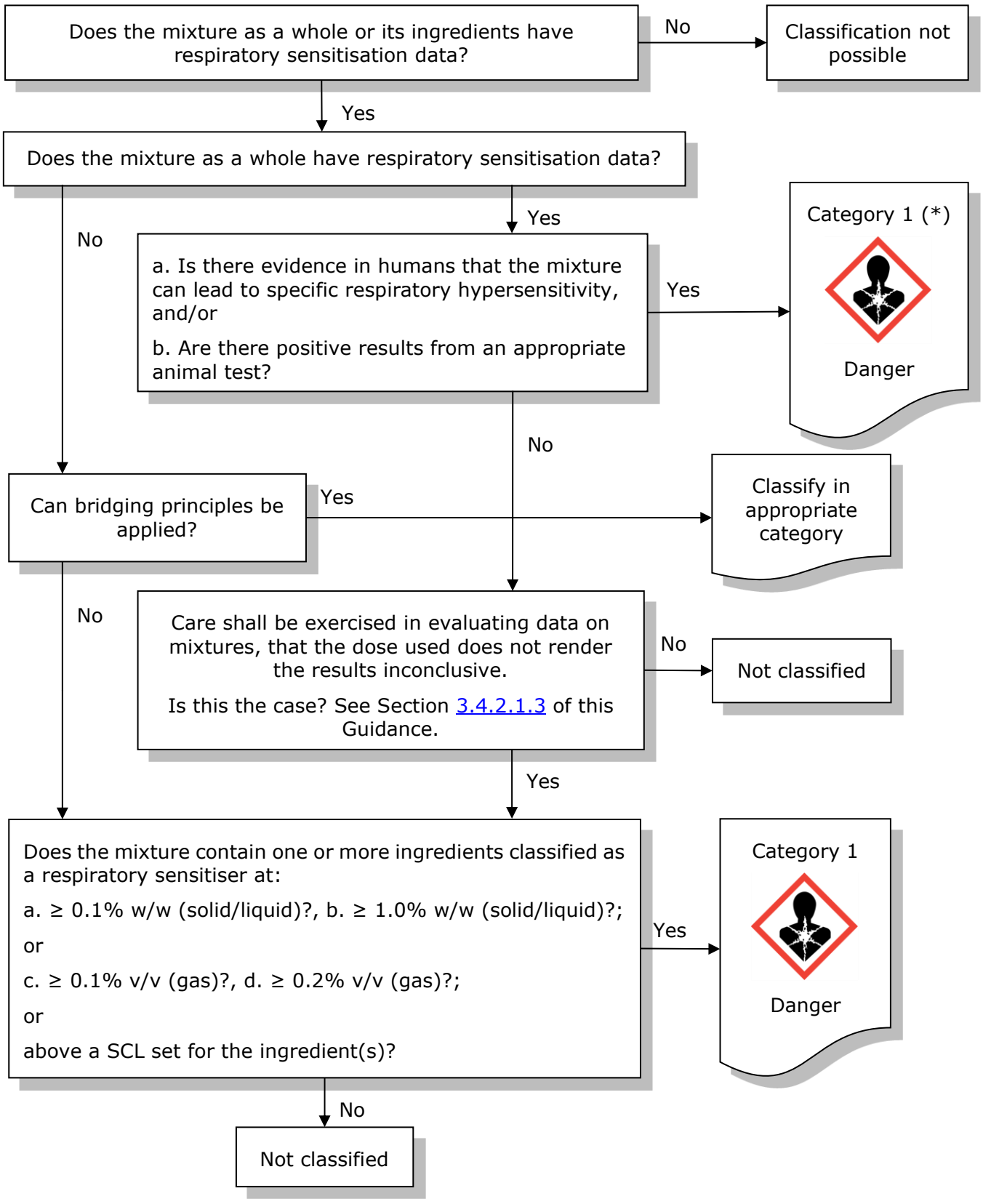
(see CLP Annex 1, 1.1.3.3 and 1.1.3.4).

When the available identified information is inappropriate for the application of the bridging principles then the mixture should be classified using the method described in Section 3.4.3.3.3 of this Guidance.

3.4.3.4. Decision logic for classification of mixtures

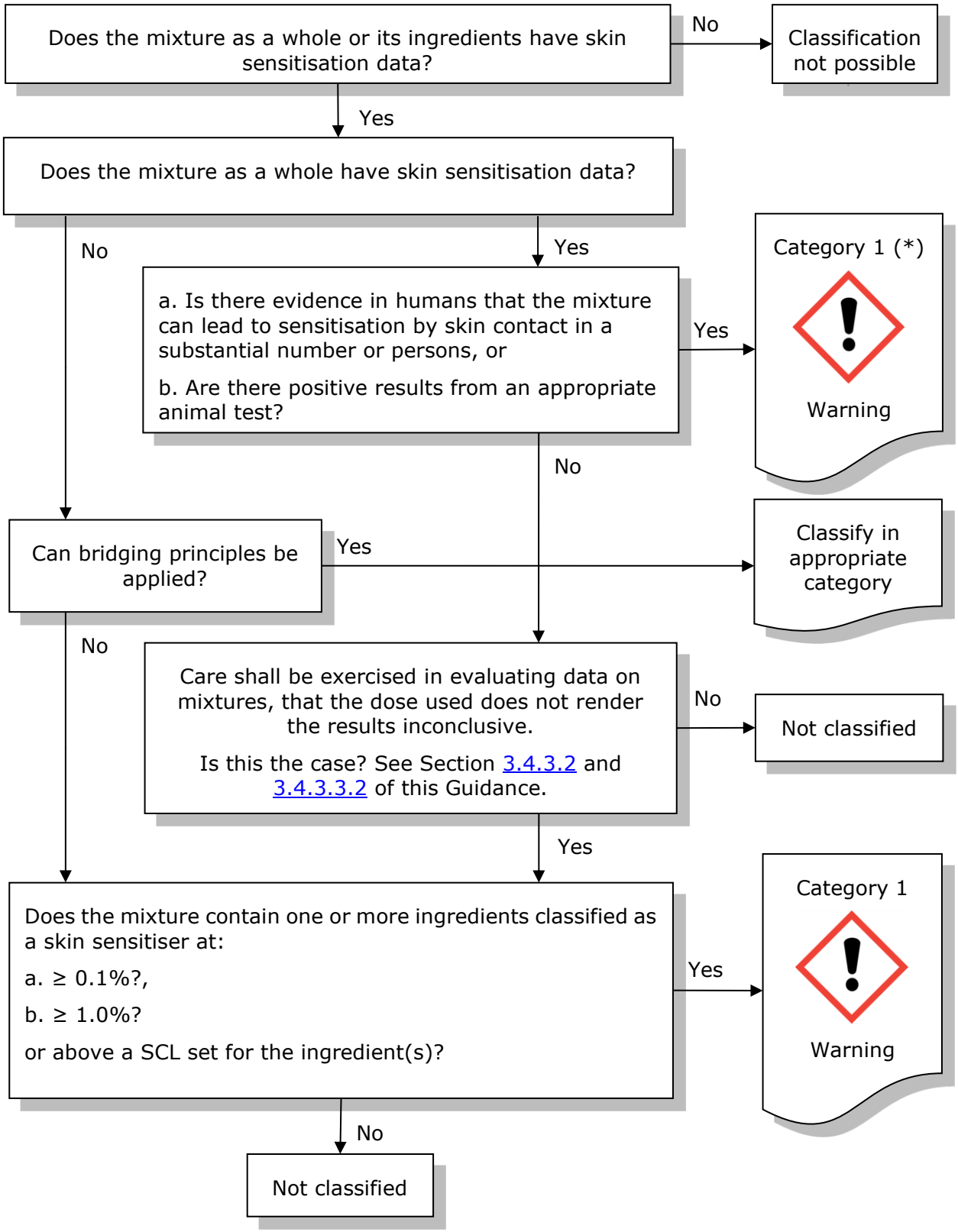
It is strongly recommended that the person responsible for classification study the criteria for classification before and during use of the decision logic.

3.4.3.4.1. Decision logic for classification of mixtures for respiratory sensitisation



(*) can be sub-categorised into 1A or 1B according to decision logic in Section 3.4.2.1.6 of this Guidance.

3.4.3.4.2 Decision logic for classification of mixtures for skin sensitisation



(*) can be sub-categorised into 1A or 1B according to decision logic in Section 3.4.2.2.6 of this Guidance.

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 3.4.7*

Table 3.4.7

Respiratory or skin sensitisation label elements

Classification	*Respiratory sensitisation*	*Skin sensitisation*
	Category 1 and sub-categories 1A and 1B	*Category 1 and sub-categories 1A and 1B*
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 Prevention	*P261* *P284*	*P261* *P272* *P280*
Precautionary Statement Response	*P304 + P341* *P342 + P311*	*P302 + P352* *P333 + P313* *P321* *P363*
Precautionary Statement Response	*P304 + P340* *P342 + P311*	*P302 + P352* *P333 + P313* *P321* *P362 + P364*
Precautionary Statement Storage		

Precautionary Statement Disposal	*P501*	*P501*

Article 26 1 (d)

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.

3.4.4.2. Additional labelling provisions

Annex II: *2.8.* *Mixtures containing at least one sensitising substance*

The label on the packaging of mixtures not classified as sensitising but containing at least one substance classified as sensitising and present in a concentration equal to or greater than that specified in Table 3.4.6 of Annex I shall bear the statement:

EUH208 – 'Contains (name of sensitising substance). May produce an allergic reaction'.

Mixtures classified as sensitising containing other substance(s) classified as sensitising (in addition to the one that leads to the classification of the mixture) and present in a concentration equal to or greater than that specified in Table 3.4.6 of Annex I shall bear the name(s) of that/those substance(s) on the label.

Where a mixture is labelled in accordance with section 2.4 or 2.5, the statement EUH208 may be omitted from the label for the substance concerned.

3.4.5. Examples of classification for skin sensitisation

3.4.5.1. Example of substances and mixtures fulfilling the criteria for classification for skin sensitisation

3.4.5.1.1. 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 (Sub-category 1B) skin sensitiser. The GCL for classification of mixtures containing substance X is 1%.

3.4.5.1.2. 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 (Sub-category 1A) skin sensitiser. The GCL for classification of mixtures containing substance Y is 0.1%.

3.4.5.1.3. Example 3

Herby is a herbicide formulation containing 28 g/l substance X, a Sub-category 1B 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 substance, and in the absence of any additional information, it should be classified as a Category 1 skin sensitiser.

3.4.5.1.4. Example 4

Substance Z being an extreme sensitiser, is classified as a Sub-category 1A. It has a specific concentration limit with regard to skin sensitisation of 0.001%, and due to this property any

mixture containing the substance at a concentration ≥ 0.001% must be classified as a Category 1 skin sensitiser.

3.4.5.1.5. Example 5

Woody is a wood preservative containing two strong sensitising substances (Sub-category 1A): substance A is present at 1% and substance B is present at 0.05%. There are no data for the formulation itself. The mixture will be classified as cat 1 H317, due to the content of substance A (present above the GCL of 0.1%). Substance B is present below the classification limit. The name of both substances should appear on the label, substance A because it determines the classification of the mixture, and substance B because it is present in a concentration above the elicitation level (1/10 of the GCL of 0.1%).

3.4.5.1.6. Example 6

Substance C was tested in a reduced LLNA test in accordance with OECD 429 using a concentration of 25%. This resulted in a stimulation index (SI) of 20 compared to the concurrent control. This is clearly above the SI of 3 required for classification. Therefore, classification as a skin sensitiser is required. However, the available information does not allow calculation of an EC3 value required to determine the sub-categorisation. Although the substance was clearly positive at a high concentration of 25%, it cannot be excluded that also at a concentration of 2% or lower the SI will be 3. Therefore, there is not sufficient data for sub-categorisation. The substance is classified as Skin Sens Cat 1.

3.4.5.1.7. Example 7

Substance D gave a positive response in a guinea pig maximisation test with 90 % responding at 50 % intradermal induction dose. In a Buehler assay 70% responded at 30 % topical induction dose. The response in both GPMT and Buehler assay was > 60% and the substance was not tested at ≤ 1 % intradermal induction dose in the guinea pig maximisation test or at ≤ 20 % topical induction dose in the Buehler assay. Although the criteria for classification to subcategory 1B are fulfilled, the classification for subcategory 1A cannot be excluded and therefore the substance should be classified as a Category 1 skin sensitiser.

3.4.5.1.8. Example 8

If there are contradictory results from two or more skin sensitisation tests, the following examples will give guidance for the classification. Since these are ideal cases, the weight of evidence approach should be applied if studies indicate shortcomings/are not considered fully reliable.

8(a): Substance E was tested in three separate animal tests performed with different test methods. In a Buehler assay no responses were observed with a topical induction dose of 70%. In the LLNA the EC3 value was 0.8%, indicating classification for subcategory 1A. In GPMT, 30 % response was observed with an intradermal induction dose of 0,5 %, indicating classification for subcategory 1B. The substance should be classified for Skin Sens. 1A unless there is sufficient information to discount some of the results.

8(b): Substance F is a skin sensitiser in humans indicating classification for sub-category 1A and in animals indicating classification for sub-category 1B. The substance should be classified for Skin Sens. 1A.

8(c): Substance G is a skin sensitiser in animal tests indicating classification for sub-category 1A and in humans indicating classification for category 1. The substance should be classified for Skin Sens. 1A.

3.4.5.2. Example of substances or mixtures not fulfilling the criteria for classification for skin sensitisation

3.4.5.2.1. Example 9

Substance H was tested at concentrations up to 50% in the LLNA using a recommended and appropriate vehicle. It gave a maximum stimulation index of 2.6 and evidence of a positive dose response. On the basis that the stimulation index was below 3 at a high dose, the substance does not require classification. However, had the highest concentrations been lower, e.g. 10%, and/or a non-standard vehicle used, then further information would have been required before a classification decision could be reached.

3.4.5.2.2. Example 10

Insecto super is an insecticide formulation containing 9 g/l substance X (see Example 1). Substance X is a Sub-category 1B 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 substance is below the GCL of 1%. The label must bear the statement EUH208.

3.4.5.3. Examples of substances fulfilling the criteria for classification for respiratory sensitisation

3.4.5.3.1. Example 11

Five case studies describe the fact that work-related exposure to substance P is associated with asthma or rhinitis. In all of these cases blinded specific bronchial challenge tests with substance P provoked the respiratory symptoms, confirming that substance P is the causal substance.

In a cohort of 51 workers exposed to substance P, 26 (51%) were diagnosed with occupational asthma and 12 of those also suffered from occupational rhinitis. The diagnosis was based on specific bronchial challenge tests with substance P.

There is sufficient human evidence to conclude that substance P should be classified as a category 1 respiratory sensitizer. Sub-categorization was not considered as there is currently no clear way to establish sub-categories.

3.4.5.3.2. Example 12

Work-related exposure to substance Q was associated with occupational asthma and rhinitis in several case studies. In those studies specific bronchial challenges were performed with substance Q and respiratory allergy symptoms could be reproduced, demonstrating that substance Q is the causal agent. In addition, a large retrospective analysis of nine longitudinal studies involving 2,689 persons exposed occupationally to substance Q in a period of 35 years, showed that the incidences of occupational asthma caused by substance Q were 2.7-5.5% in the earliest studies and decreased to 0.3-0.7% in the latest studies.

Guinea pigs were exposed to substance Q by inhalation for 3 hours a day for 5 consecutive days to concentrations of 4, 12, 24, and 48 mg/m^3. Three weeks after the first encounter with the inducing agent, animals were challenged with substance Q at a concentration of 2 mg/m^3. During challenge breathing patterns were affected already at the lowest test concentration in guinea pigs that were sensitized and challenged to substance Q and not in control animals. Additionally, pulmonary inflammation and increased specific IgG1 levels were observed in guinea pigs sensitized and challenged with substance Q.

On the basis of human evidence supported by data from an animal study, substance Q should be classified as a Category 1 respiratory sensitizer. Sub-categorization was not considered as there is currently no clear way to establish sub-categories.

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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.*

Annex I*: 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*

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.*

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 also the Guidance on IR&CSA, Section R.7.7.3.2.

3.5.2.1.2. Identification of non human data

Animal data

There is a number of *in vivo* assays for genotoxicity/mutagenicity testing, with or without OECD TGs. 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 *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 the Guidance on IR&CSA, Section R.7.7.3[66]. These latter tests have, however, been deleted as OECD TGs as of 2014.

In vivo tests in somatic cells which provide information on genotoxicity include, for example, the Comet single cell gel electrophoresis assay[67] for DNA strand breaks. Assays such as gene mutations in transgenic rodent (TGR) models[68] using reporter genes or mammalian erythrocyte micronucleus test for chromosome aberrations can be used for mutagenicity assessment. Please note that of these assays TGR is suitable for germ cells.

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 also the Guidance on IR&CSA, Section R.7.7.3.

Use of other data

See the Guidance on IR&CSA, Section R. 7.7.3.1.

Existing test methods

See the Guidance on IR&CSA, Section R. 7.7.3.1.

[66] The Guidance on IR/CSA, Chapter R.7a (version 4.1).

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[68] OECD TG 488 Transgenic Rodent Somatic and Germ Cell Gene Mutation Assays (26 July 2013).

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 the Guidance on 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 *negative* 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 the Guidance on IR&CSA, Section R.7.7.4.1).

Read-across and (Q)SARs can be used as part of a WoE approach for germ cell mutagenicity classification. If there are positive *in vitro* data from mammalian mutagenicity assays, structural similarities not sufficient for grouping/read-across may still warrant classification.

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 classification of 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.

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 such 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;*

[…]

Supporting evidence in addition to positive results of a valid *in vivo* somatic cell mutagenicity test in mammals is needed to be able to classify a substance as a Category 1B mutagen when no data on mammalian germ cells are available. In the examples provided in the second sentence in the green box, mutagenicity/genotoxicity in germ cells or data showing that the substance or its metabolite(s) interact with the genetic material of germ cells is mentioned. Moreover, genetic damage to germ cells in exposed humans, related to substance exposure, may offer additional information. 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 by application of a WoE approach using expert judgement.

Classification as a Category 2 mutagen

Classification in Category 2 may be based on positive results of at 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 somatic cell 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 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 may be relevant to humans. Note that intraperitoneal injection is since 2016 generally not recommended for new testing without specific scientific justification because it is not an intended route of human exposure. However, existing studies with intraperitoneal injection should be assessed as described in this and the next paragraph

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 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 cannot 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. Classification of substances containing CMR constituents, additives or impurities

From a compositional and a toxicological point of view the situation for substances containing CMR constituents, additives or impurities is the same as for mixtures containing components classified for these endpoints. For this reason the classification procedure for CMR endpoints that is foreseen by CLP for mixtures containing CMR components, is considered applicable also to substances containing CMR constituents, additives or impurities (see Section 1.1.6.1). As discussed in Section 3.5.3 below, mixtures containing components classified as germ cell mutagens shall be normally classified using only the relevant available information for the individual substances in the mixture. Further, in cases where the available test data on the mixture itself demonstrate CMR effects which have not been identified from the information on the individual substances, those data shall also be taken into account. For CMR endpoints the lowest incidence possible to detect in the tests may be by far unacceptable in humans. Thus a dose as high as possible (such as maximal tolerated dose, MTD dose) is needed to be able to detect CMR hazards. Dilution, as would be the case if mixtures or substances containing CMR constituents were tested, would increase the risk that CMR hazards would not be detected.

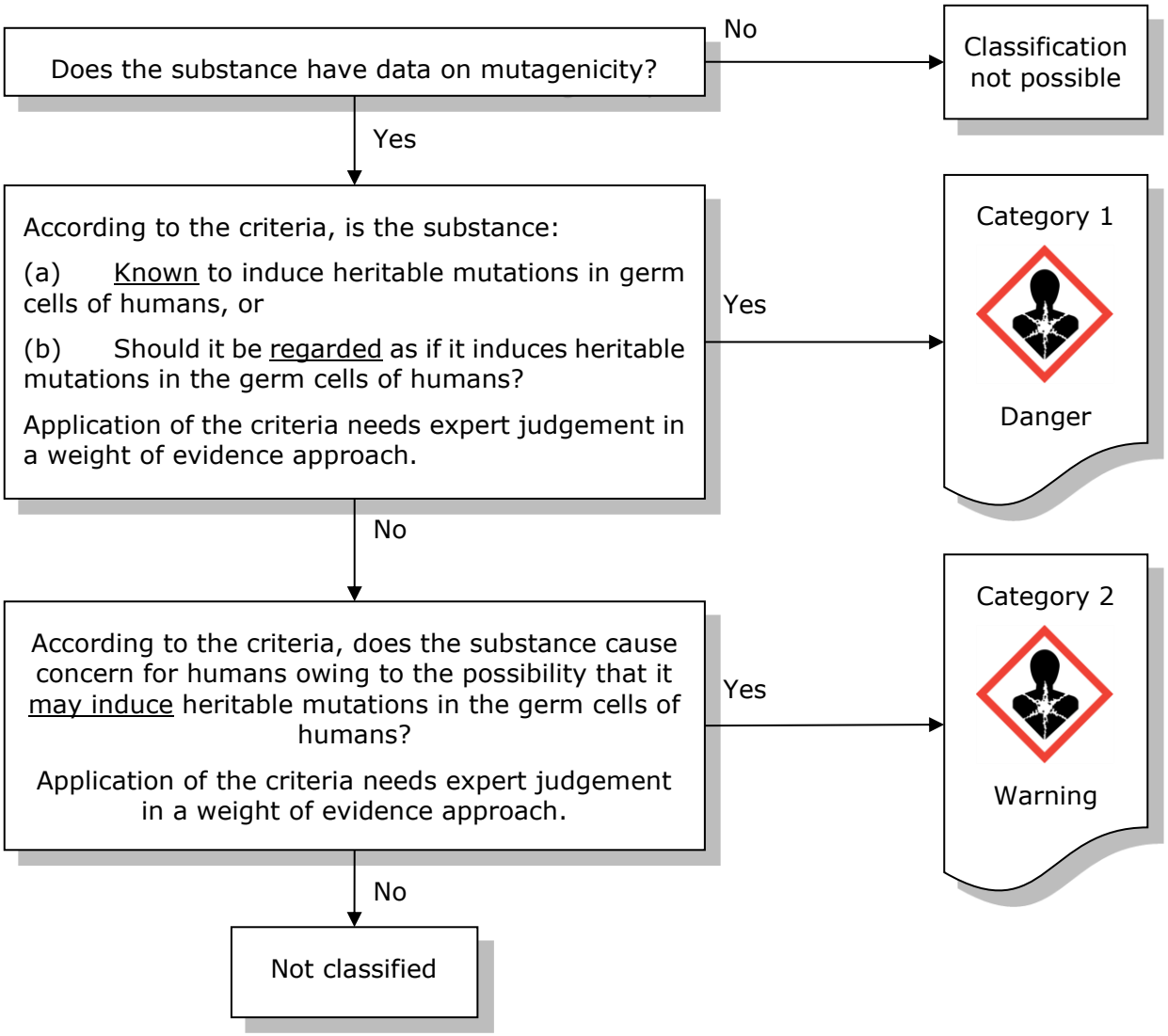
According to article 10 (1) substances in other substances and substances in mixtures are treated in the same way regarding the use of GCLs and SCLs.

3.5.2.6. 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 and substances toxic to reproduction. 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.

3.5.2.7. Decision logic for classification of 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 CLP Article 6(3) and CLP Annex I, 3.5.3.2 and 3.5.3.3).

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.*

Bridging principles will only be used on a case by case basis. Note that the following bridging principles are not applicable to this hazard class:

- concentration of highly hazardous mixtures
- interpolation within one hazard category

(see CLP Annex 1, 1.1.3.3 and 1.1.3.4)

Note that the bridging priciples are relevant only in case of comparable tested mixtures showing mutagenic effects not established from the evaluation of the individual ingredients. Classification for CMR hazards is based on tests with the ingredients.

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.

	Concentration limits triggering classification of a mixture as:

Ingredient classified as:	*Category 1 mutagen*		*Category 2 mutagen*
	Category 1A	*Category 1B*	
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).*			

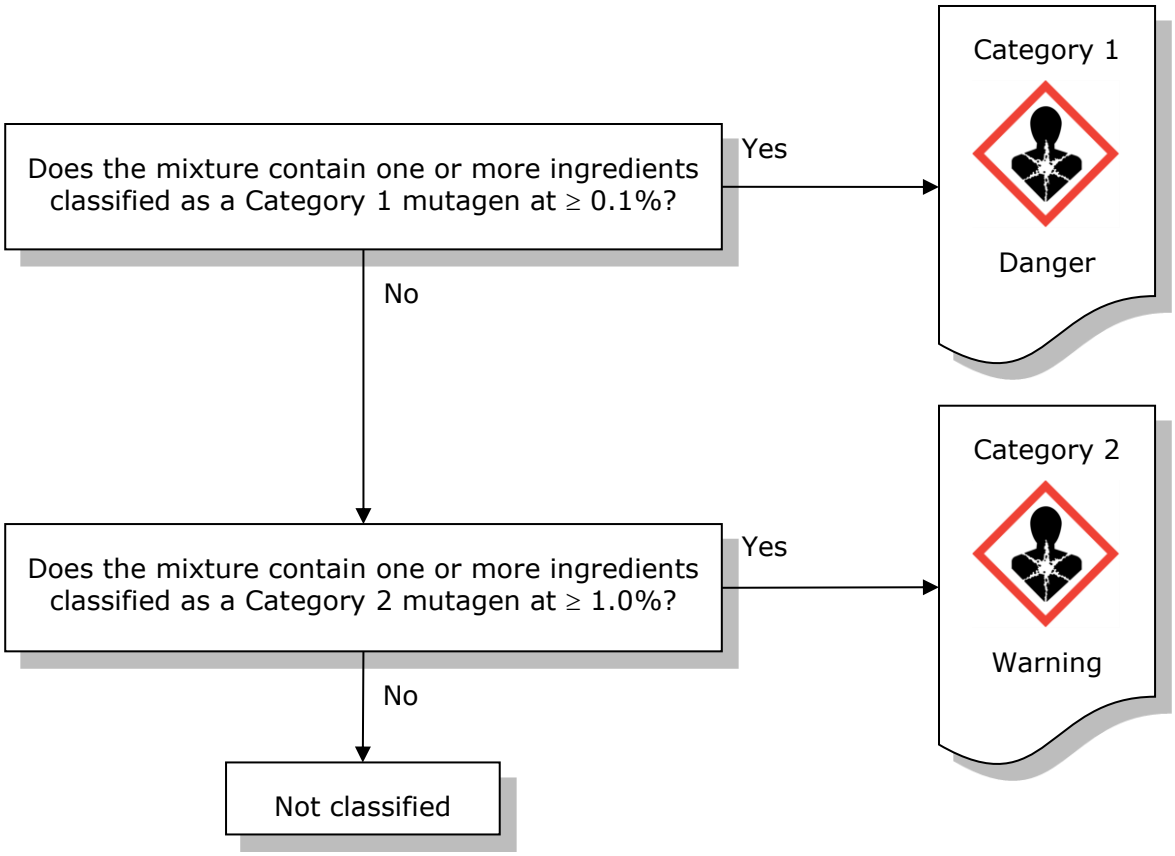
The option to set SCL for germ cell mutagenicity is not considered possible in the process of self-classification as there is no standardized methodical approach available which adequately takes into account all relevant information (see Section 3.5.2.6 of this Guidance).

For germ cell mutagenicity it is reasonable to assume additivity for mutagens, unless there are specific reasons not to do so.

3.5.3.3. Decision logic for classification of mixtures

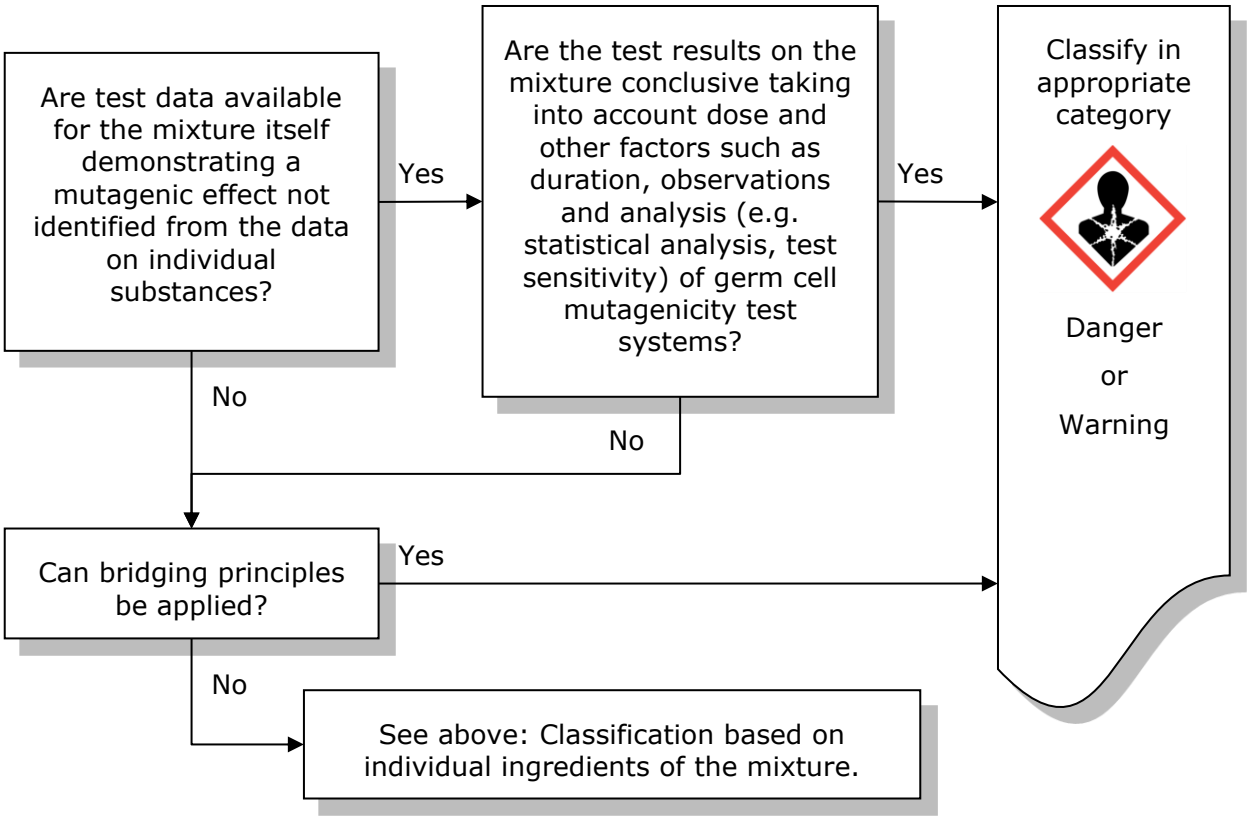
The decision logic which follows is provided as additional guidance. It is strongly recommended that the person responsible for classification study the criteria before and during use of the decision logic. This decision logic deviates (slightly) from the original GHS guidance, to meet CLP requirements.

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 Annex I, 3.5.3.2.1, see also CLP Article 6(3)).


Are test data available for the mixture itself demonstrating a mutagenic effect not identified from the data on individual substances?
Yes
Are the test results on the mixture conclusive taking into account dose and other factors such as duration, observations and analysis (e.g. statistical analysis, test sensitivity) of germ cell mutagenicity test systems?
Yes
Classify in appropriate category
Danger
or
Warning
No
No
Can bridging principles be applied?
Yes
No
See above: Classification based on individual ingredients of the mixture.

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 1* *(Category 1A, 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* *P280*	*P201* *P202* *P280*
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 under the CLP Regulation. However entry 29 of Annex XVII to REACH addresses such substances and mixtures. The packaging of substances with a harmonised classification as

Muta 1A or 1B and that are included in Appendices 3 and 4 of Annex VII of REACH,as well as the packaging of mixtures containing those substances above the concentration limits leading to the classification of the mixture, 'must be marked visibly, legibly and indelibly as follows: "Restricted to professional users".' Derogations from this obligation are outlined in the same provision.

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 Section 3.6.2.3.2.(k) of this Guidance.

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 the Guidance on IR&CSA, 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).

For more about non testing data see Section 3.6.2.3.4 of this Guidance.

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.*

Annex I: *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, 3.6.2.2.3 (see Section 3.6.2.3.1 of this Guidance) and other important factors to consider in CLP Annex I, 3.6.2.2.6 (see Section 3.6.2.3.2 of this Guidance). 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 (CLP Annex I, 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. The Guidance on 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.*

Annex I*: 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.*

Annex I*: 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 CLP Annex I, 3.6.2.2.6 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 (CLP Annex I, 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 (CLP Annex I, 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 single species or several species

The criteria indicate that carcinogenicity in a single animal species (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.

However, as defined under 'sufficient' evidence (CLP Annex I, 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 of this Guidance.

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, a specific hazard statement has been established in CLP, H350i; May cause cancer by inhalation.

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' (CLP Annex I, Table 3.6.3). 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 the Guidance on 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 of this Guidance 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) of this Guidance. 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; Guidance on 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 toxophore) 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 (Guidance on 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. Classification of substances containing CMR constituents

From a compositional and a toxicological point of view the situation for substances containing CMR constituents, additives or impurities is the same as for mixtures containing components classified for these endpoints. For this reason the classification procedure for CMR endpoints that is foreseen by CLP for mixtures containing CMR components, is considered applicable also to substances containing CMR constituents, additives or impurities (see Section 1.1.6.1). As discussed in Section 3.6.3 below, mixtures containing components classified as carcinigenic shall be normally classified using only the relevant available information for the individual substances in the mixture. Further, in cases where the available test data on the mixture itself demonstrate CMR effects which have not been identified from the information on the individual substances, those data shall also be taken into account. For CMR endpoints the lowest incidence possible to detect in the tests is by far unacceptable in humans. Thus a dose as high as possible (such as maximal tolerated dose, MTD dose) is needed to be able to detect CMR hazards. Dilution, as would be the case if mixtures or substances containing CMR constituents were tested, would increase the risk that CMR hazards would not be detected.

According to article 10 (1) substances in other substances and substances in mixtures are treated in the same way regarding the use of GCLs and SCLs.

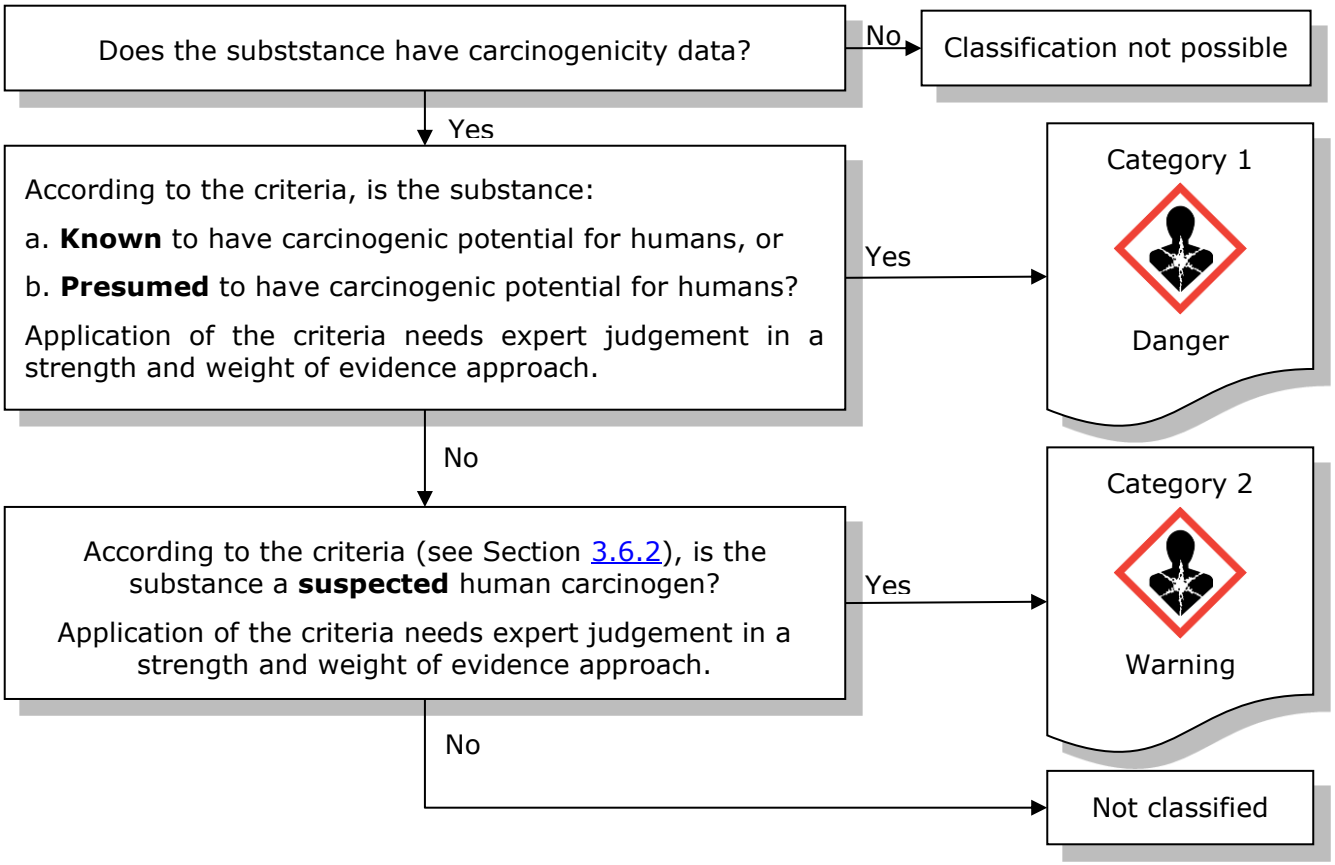
3.6.2.6. Setting of specific concentration limits

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 of this Guidance, 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.

3.6.2.7. 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 on **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 of this Guidance) or based on bridging principles (see Section 3.6.3.1.3 of this Guidance).

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 1 carcinogen		*Category 2 carcinogen*
	Category 1A	*Category 1B*	
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 3.6.2.6 of this Guidance for 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.*

Bridging principles will only be used on a case by case basis (see Section 3.6.3.1 of this guidance). Note that the following bridging principles are not applicable to this hazard class:

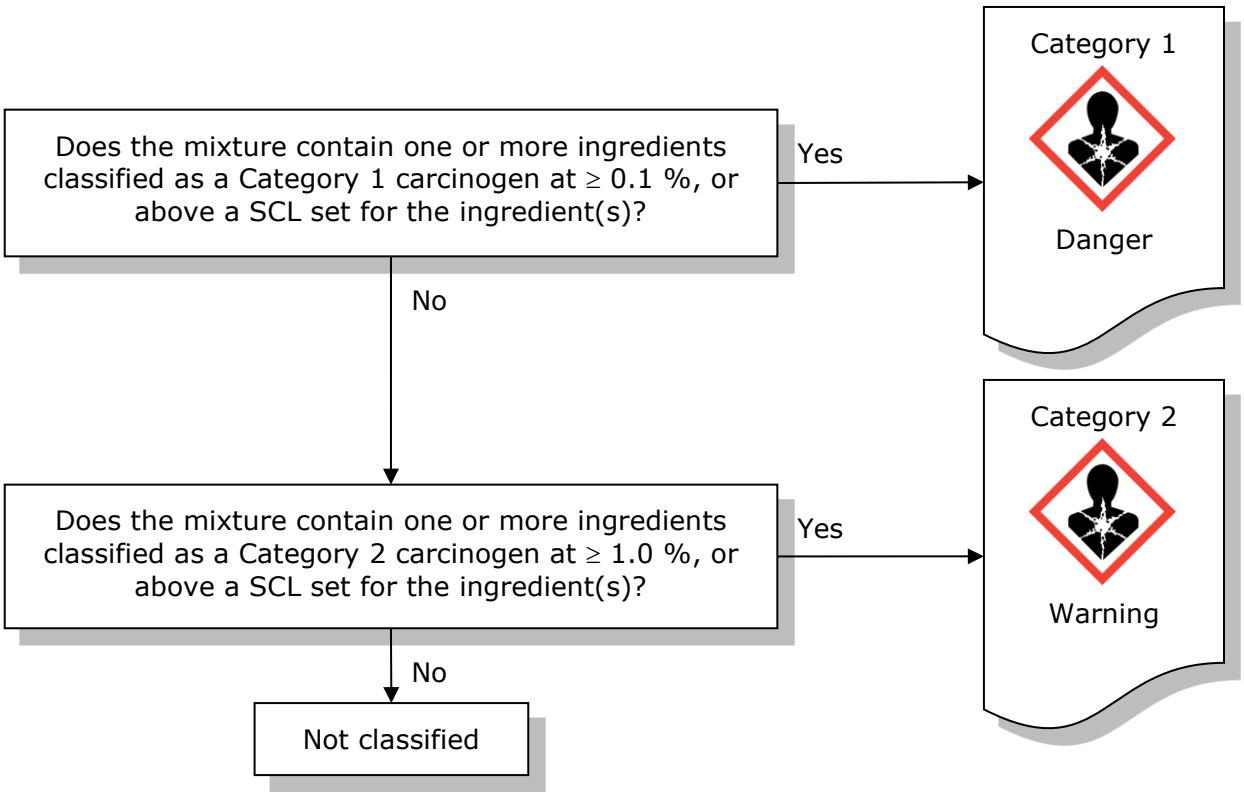
- concentration of highly hazardous mixtures
- interpolation within one hazard category

(see CLP Annex 1, 1.1.3.3 and 1.1.3.4)

3.6.3.2. Decision logic for classification of mixtures

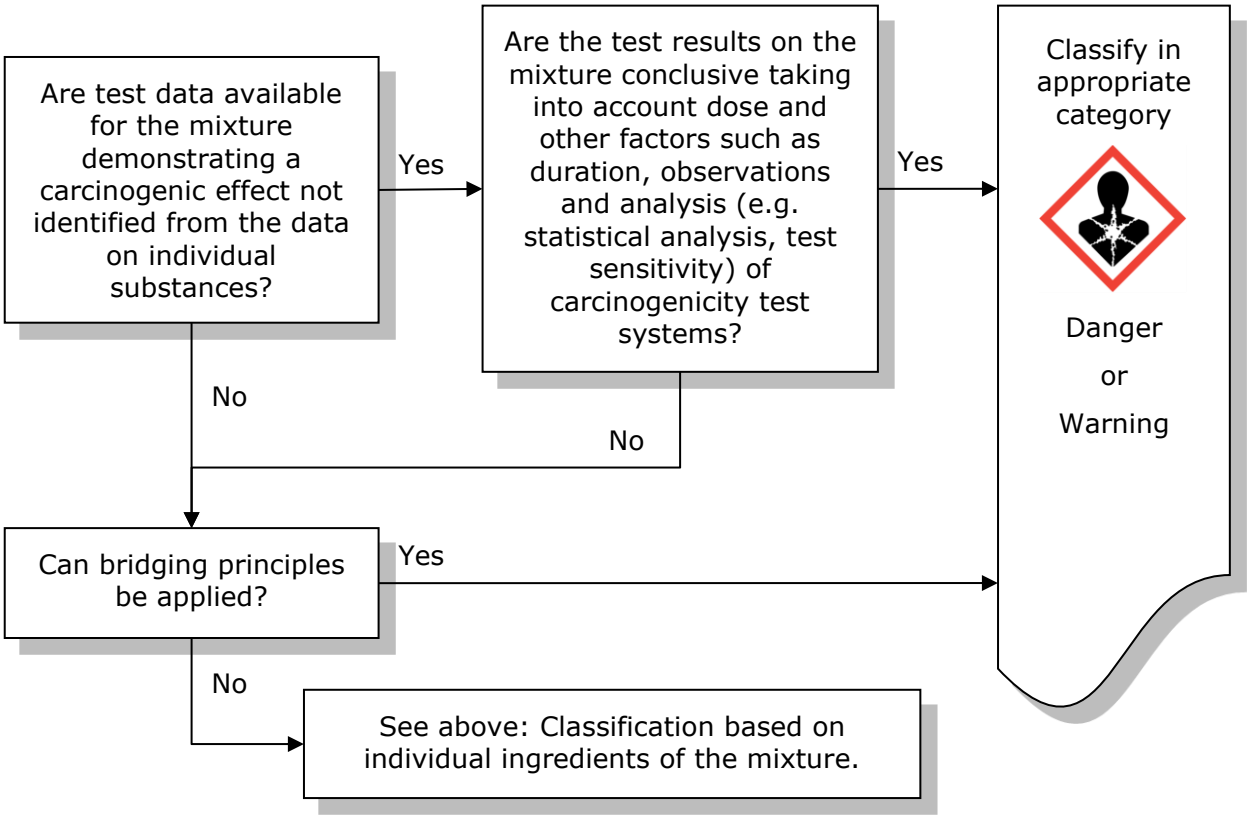
The decision logic which is based on the GHS Guidance is revised to meet CLP requirements. It is strongly recommended that the person responsible for classification, study the criteria for classification before and during use of the decision logic.

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 Annex I, 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.*

Table 3.6.3

Label elements for carcinogenicity

Classification	*Category 1* *(Category 1A, 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 Prevention	*P201* *P202* *P280*	*P201* *P202* *P280*
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 at concentrations warranting classification of the mixture as carcinogenic Category 1A or Category 1B, 'must be marked visibly**,** legibly and indelibly as follows: "Restricted to professional users".' (REACH, Annex XVII, point 28. Derogations from this obligation are outlined in the same provision).

3.6.4.3. 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.

3.6.5. 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.

Annex I: *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*

Annex I*: 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.

Annex I*: 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 (1).

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 in the Guidance on 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 the Guidance on 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*

Category 1A *Category 1B*	*distinguished on the basis of whether the evidence for classification is primarily from human data (Category 1A) or from animal data (Category 1B).* *Known human reproductive toxicant* *The classification of a substance in this Category 1A is largely based on evidence from humans.* *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*

Annex I: ***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.*

Annex I: ***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.*

Annex I: ***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

l. 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.

m. 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 TG 421/422 or the developmental neurotoxicity study OECD TG 426, 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.

n. 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. Classification of substances containing CMR constituents

From a compositional and a toxicological point of view the situation for substances containing CMR constituents, additives or impurities is the same as for mixtures containing components classified for these endpoints. For this reason the classification procedure for CMR endpoints that is foreseen by CLP for mixtures containing CMR components, is considered applicable also to substances containing CMR constituents, additives or impurities (see Section 1.1.6.1). As discussed in Section 3.7.3 below, mixtures containing components classified as germ cell mutagens shall be normally classified using only the relevant available information for the individual substances in the mixture. Further, in cases where the available test data on the mixture itself demonstrate CMR effects which have not been identified from the information on the individual substances, those data shall also be taken into account. For CMR endpoints the lowest incidence possible to detect in the tests is by far unacceptable in humans. Thus a dose as high as possible (such as maximal tolerated dose, MTD dose) is needed to be able to detect CMR hazards. Dilution, as would be the case if mixtures or substances containing CMR constituents were tested, would increase the risk that CMR hazards would not be detected.

According to article 10 (1) substances in other substances and substances in mixtures are treated in the same way regarding the use of GCLs and SCLs.

3.7.2.6. 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.

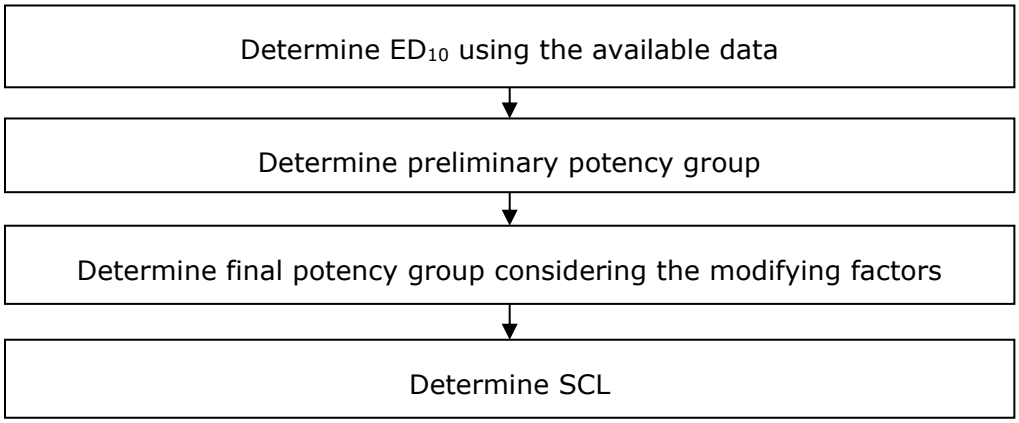
In exceptional circumstances specific concentration limits may be set by the manufacturer, importer or downstream user where he has adequate, reliable and conclusive scientific information that a hazard of a substance classified as hazardous is not evident at a level above the concentrations set for 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.

3.7.2.6.1. 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 3.7.2.6.5. 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 3.6. 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 3.6 Procedure for setting SCL for reproductive toxicity



3.7.2.6.2. 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.

3.7.2.6.3. 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 Section 3.7.2.6.3.2).

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.

3.7.2.6.3.1. 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.

3.7.2.6.3.2. 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 3.10, 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 3.10 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.

3.7.2.6.3.3. 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 3.11, 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 3.11 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	

3.7.2.6.3.4. 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 3.12 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 3.12, 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.

3.7.2.6.3.5. 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 G*uidance 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

3.7.2.6.4. 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 3.13 are used.

Table 3.13 Boundaries of the potency groups[69].

Potency group	Boundaries
High potency group	ED_{10} value ≤ 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 ≥ 400 mg/kg bw/day.

3.7.2.6.5. 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 3.13 above).

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

[69] See Annex VI of this guidance document for more details.

of the modifying factor exceeds the distance of the preliminary ED_{10} 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.

3.7.2.6.5.1. 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.

3.7.2.6.5.2. 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}.

3.7.2.6.5.3. 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.

3.7.2.6.5.4. 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.

3.7.2.6.5.5. 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.

3.7.2.6.5.6. 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.

3.7.2.6.6. 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 3.14 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 [B])
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.

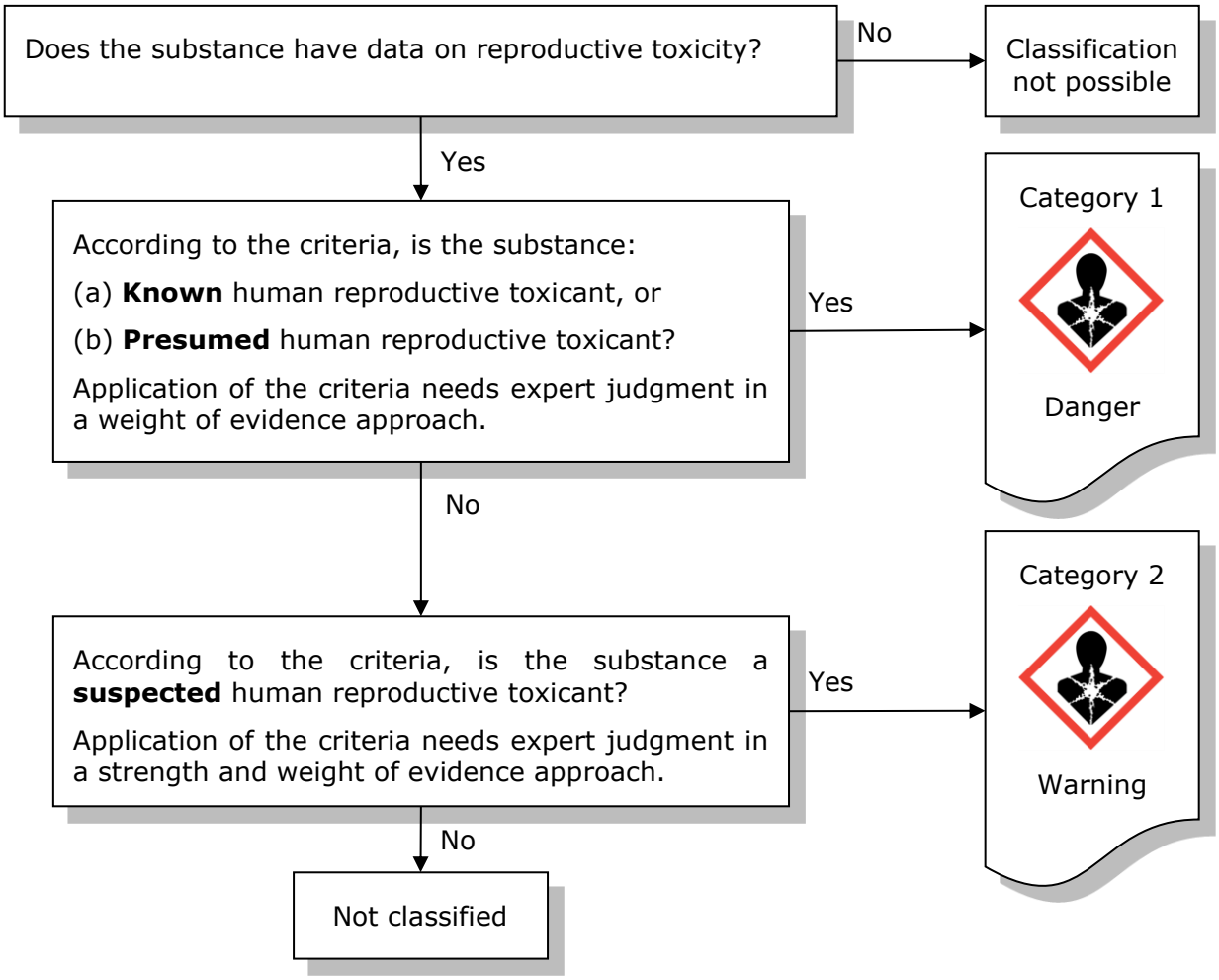
3.7.2.6.6.1. Assigning two SCLs to a substance

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)

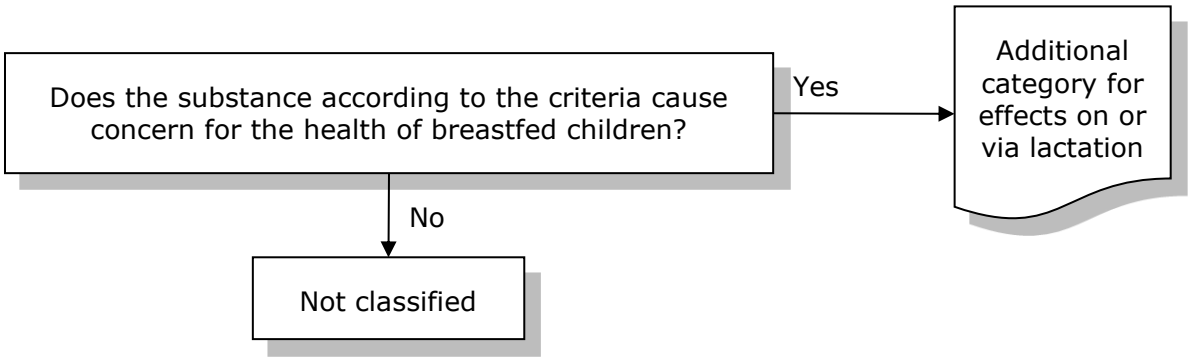
3.7.2.7. Decision logic for classification of substances

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 for mixtures

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 1 reproductive toxicant		*Category 2 reproductive toxicant*	*Additional category for effects on or via lactation*
	Category 1A	*Category 1B*		
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 Table 3.7.2 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 at or 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.*

Annex I: *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.*

Bridging Principles will only be used on a case by case basis (see Section 3.7.3.1 of this guidance). Note that the following bridging principles are not applicable to this hazard class:

- concentration of highly hazardous mixtures
- interpolation within one hazard category

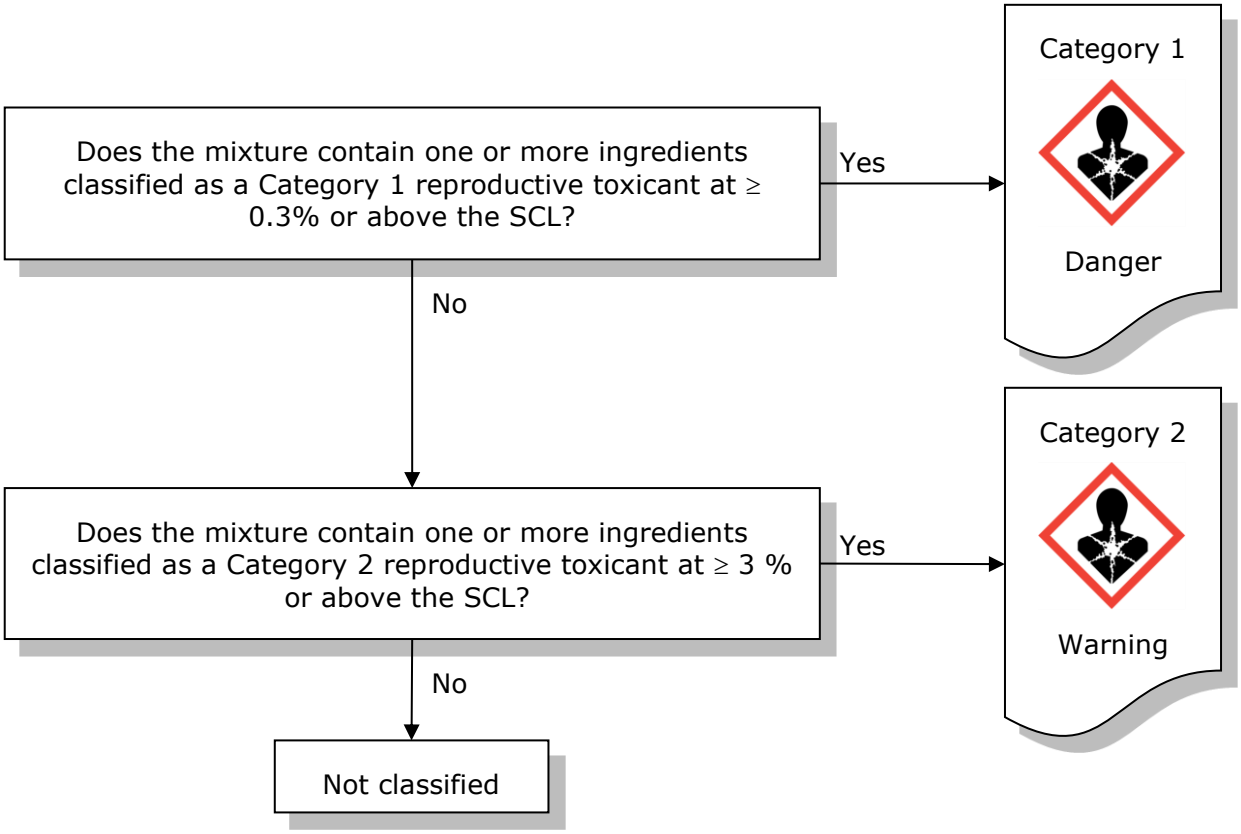
(see CLP Annex 1, 1.1.3.3 and 1.1.3.4)

3.7.3.2. Decision logic for classification of mixtures

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.

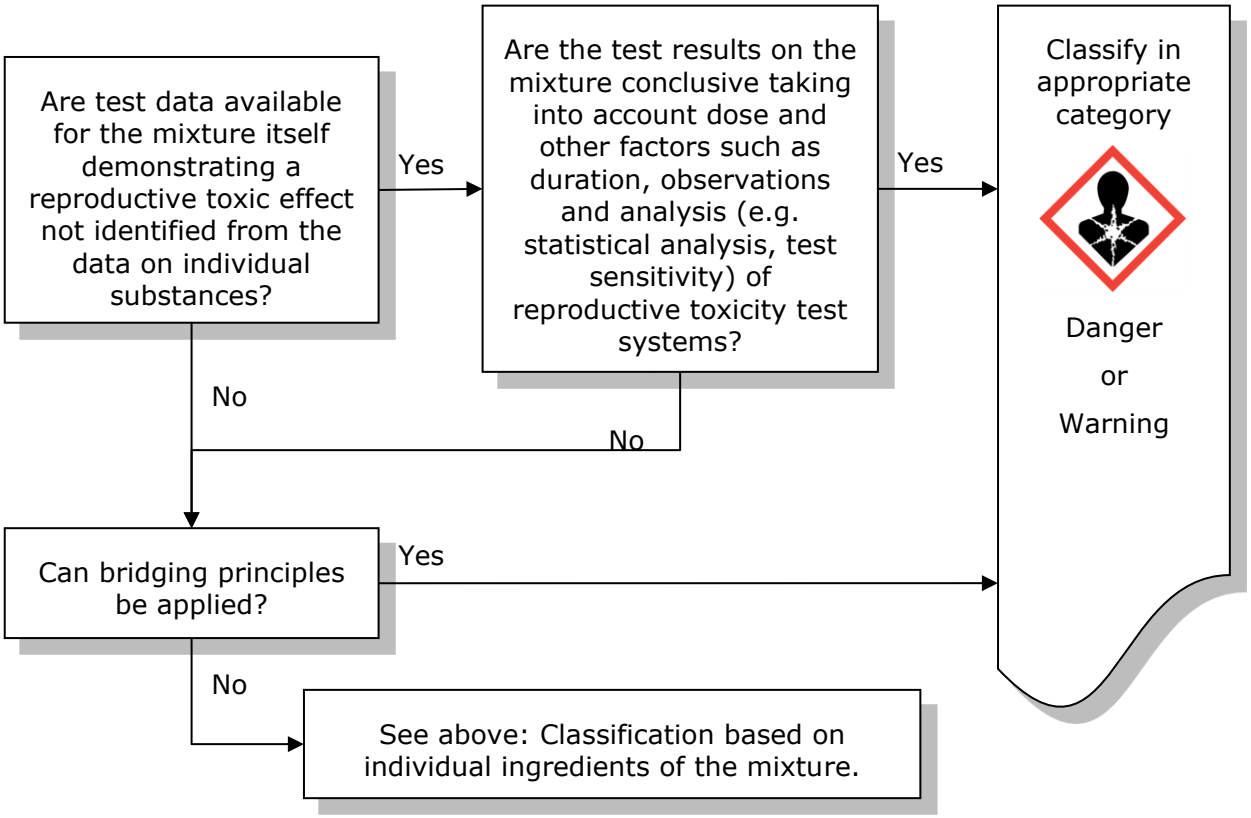
Classification of mixtures for fertility or developmental effects

Classification based on individual ingredients of the mixture



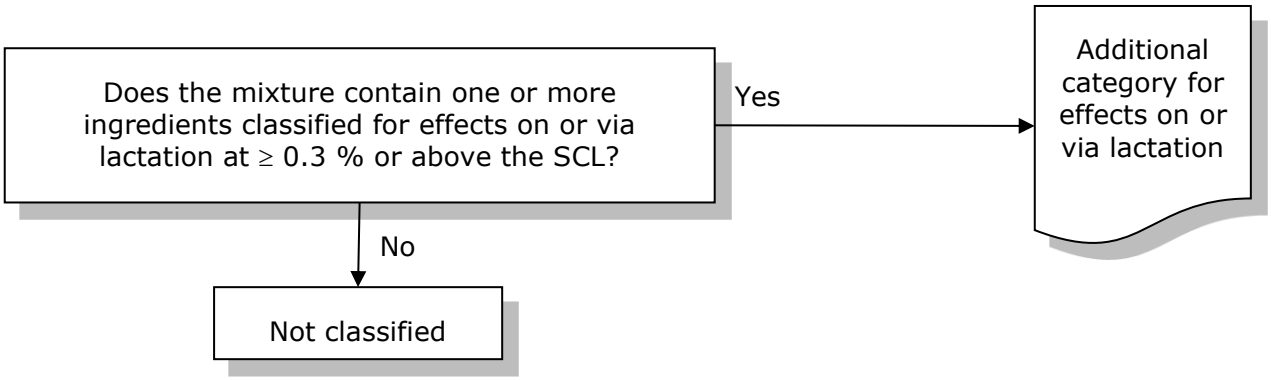
Modified classification on a case-by-case basis

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)).



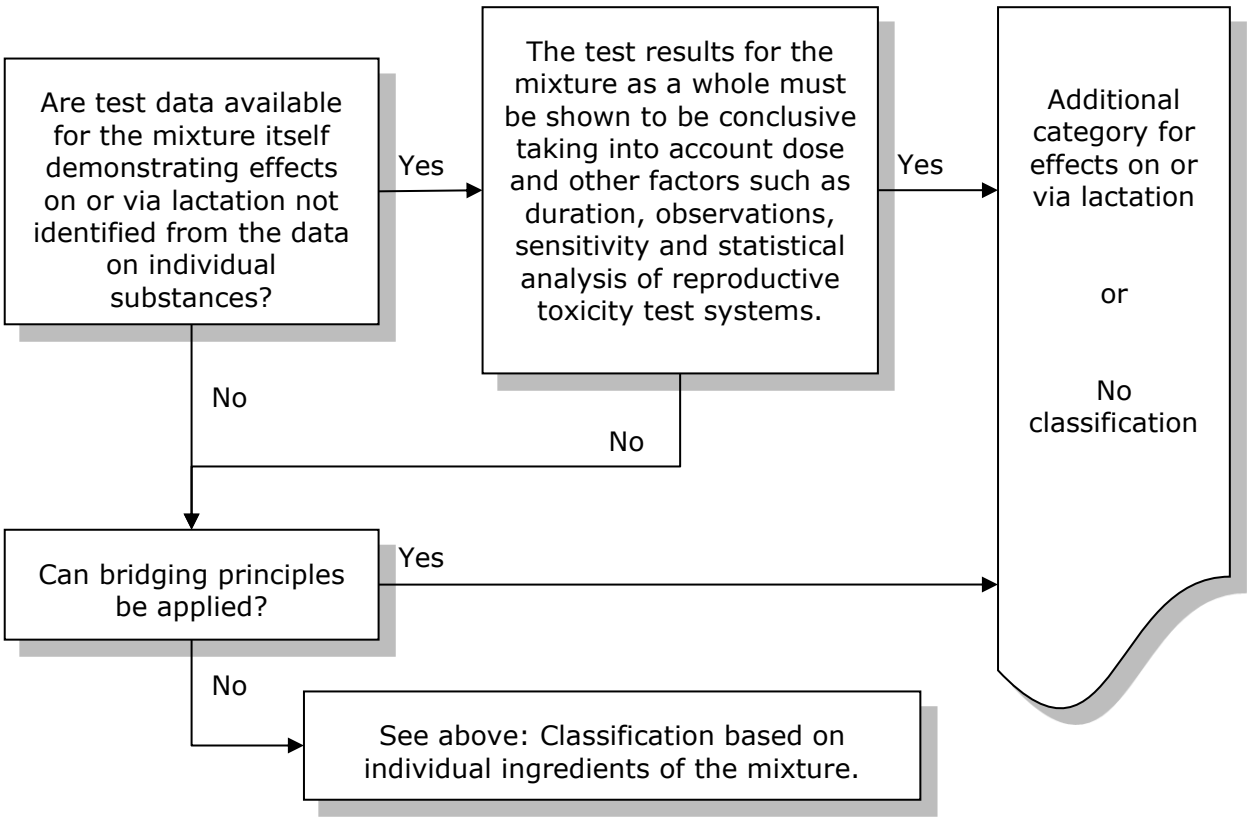
Classification of mixtures for effects via lactation

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 1* *(Category 1A, 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 damage 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)*	*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* *P280*	*P201* *P202* *P280*	*P201* *P260* *P263* *P264* *P270*
Precautionary Statement Response	*P308 + P313*	*P308 + P313*	*P308 + P313*
Precautionary Statement Storage	*P405*	*P405*	
Precautionary Statement Disposal	*P501*	*P501*	

Annex VII: *Note 4 under Table 1.1*

Note 4

Hazard statements H360 and H361 indicate a general concern for;effects on fertility and/or development: "May damage/Suspected of damaging fertility or the unborn child". According to the criteria, the general hazard statement can be replaced by the hazard statement indicating the specific effect of concern in accordance with section 1.1.2.1.2. of Annex VI. When the other differentiation is not mentioned, this is due to evidence proving no such effect, inconclusive data or no data and the obligations in Article 4(3) shall apply for that differentiation.

Annex VI: *1.2.3 Hazard statements for reproductive toxicity*

[…]

According to the criteria, the general hazard statement can be replaced by the hazard statement indicating the specific effect of concern in accordance with section 1.1.2.1.2. When the other differentiation is not mentioned, this is due to evidence proving no such effect, inconclusive data or no data and the obligations in Article 4(3) shall apply for that differentiation.

[…]

Hazard statements H360 and H361 indicate a general concern for effects on fertility and/or development. As shown in CLP Annex I, Table 3.7.3, a substance classified as reproductive toxicant in Category 1A or 1B must be assigned the hazard statements H360 and a substance classified in Category 2 must 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.

The effects of concern should be specified in the hazard statement. Where the effect cannot be specified with respect to fertility or development the general statement must be applied.

When the other differentiation is not mentioned in the CLP Annex VI, this can be due to one of the reasons listed in Note 4 under Table 1.1 in CLP Annex VII (see above). In this case the obligations under Article 4(3) CLP must apply, i.e. classification under Title II shall be carried out for this differentiation.

Self classification must take into account all available relevant data including published RAC documents for Harmonised Classification and Labelling (RAC opinions, background documents and responses to comments as available on ECHA website in section Risk Assessment Committee http://echa.europa.eu).

The resulting different variants of H360 and H361 are shown in the table below, which also provides some examples when they can be assigned.

Table 3.15 Hazard statements for reproductive toxicity: H360 and H361, and their specifications

H No.	Hazard statement
H360	'May damage fertility or the unborn child' *Example: a substance classified in Repr Cat 1 A/B but the effects cannot be specified with respect to fertility and/or developmental toxicity.*
H361	'Suspected of damaging fertility or the unborn child' *Example: a substance classified in Repr Cat 2 but the effects cannot be specified with respect to fertility and/or developmental toxicity.*

H No.	Hazard statement
H360F	'May damage fertility' *Example: a substance classified in Repr Cat 1A/B on the basis of fertility effects. For the effects on developmental toxicity there is evidence providing no such effect, inconclusive data or no data.*
H360D	'May damage the unborn child' *Example: a substance classified in Repr Cat 1A/B on the basis of developmental toxicity. For the effects on fertility there is evidence providing no such effect, inconclusive data or no data.*
H361f	'Suspected of damaging fertility' *Example: a substance classified in Repr Cat 2 on the basis of fertility effects. For the effects on developmental toxicity there is evidence providing no such effect, inconclusive data or no data.*
H361d	'Suspected of damaging the unborn child' *Example: a substance classified in Repr Cat 2 on the basis of developmental toxicity. For the effects on fertility there is evidence providing no such effect, inconclusive data or no 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 which fulfills the criteria for 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 which fulfills the criteria for Repr Cat 2 on the basis of fertility effects.*

According to CLP Annex I, Section 3.7.4.1, the hazard statements must be adapted 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.

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 with harmonised classification for reproductive toxicity Category 1A or Category 1B, and mixtures containing such substances at concentrations warranting classification of the

mixture for reproductive toxicity Category 1A or Category 1B, 'must be marked visibly, legibly and indelibly as follows: "Restricted to professional users".' (REACH Annex XVII, point 30).

3.7.5. Examples

3.7.5.1. Examples of the determination of SCLs

Four examples are given below:

3.7.5.1.1. Example 1

1. Identification

Substance Name:	XXXXXX

2. EU CLP classification

Repro	1B
H	360D

3. ED_{10} in animals

3.1. 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.

3.2. 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

3.3. 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.	
3.4. 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	

3.7.5.1.2. Example 2 (developmental part only)

1. Identification	
Substance Name:	XXXXXX
2. EU CLP classification	
Repro	1B
H	360 FD
3. ED_{10} in animals	

3.1. 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.

3.2. 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

3.3. Determination of the ED_{10} value

ED10 was determined as 33 mg/kg.

Control skeletal malformations is 9%. ED10 rate would be 19%. Interpolation between NOAEL (classification) (12% at 25 mg/kg) and LOAEL (classification) (33% at 50 mg/kg) leads to an ED10 of 33.3 mg/kg bw/day.

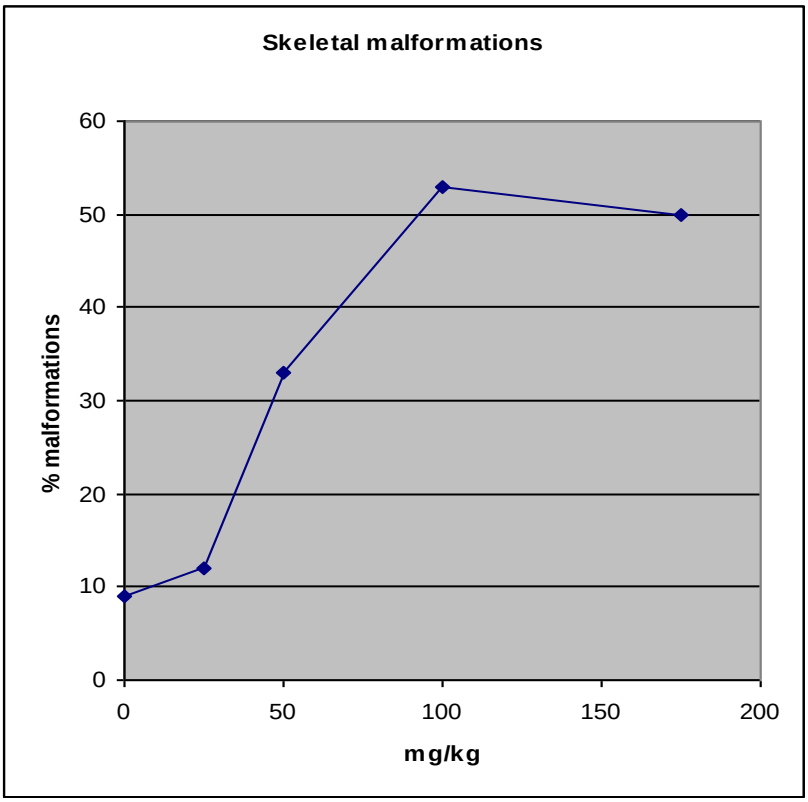
Calculation:

(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.

3.4. 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

3.7.5.1.3. 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

3.1. Brief summary

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.

3.2. Remarks on the study used for the determination of the ED_{10}

Species, strain, sex:	CD(Sprague-Dawley) rats male and female
Study type:	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

3.3. 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.

3.4. 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.
4.4. 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

3.7.5.1.4. Example 4

1. Identification

Substance Name:	XXXXXX

2. EU CLP classification

Repro	2
H	361f

3. ED_{10} in animals

3.1. 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.

3.2. 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

3.3. 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.

3.4. 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 ED_{10} 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

3.8. 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.*

Annex I*: 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.*

Annex I*: 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 Sections 3.8.2.4.3 and 3.8.2.4.2 of this Guidance.

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 (Guidance on IR&CSA, Section 7.2.3.2). For more details see the Guidance on 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, …*

Non-testing data

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 1.4 of this Guidance and in the Guidance on 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 the Guidance on IR&CSA, Section 7.4.3.1.

Testing data

Animal data

The standard tests on acute toxicity are listed in the Guidance on 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 the Guidance on 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 the Guidance on 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).

Annex I: *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 I: *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 I: *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 in Annex 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 Section 3.1 of this Guidance 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 I: *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 (CLP Annex I, 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 could 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 the Guidance on IR&CSA, Section R.7.2.

Annex I: *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 I: *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 I*: 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 of this Guidance. 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 the Guidance on IR&CSA Chapter 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: H2S).

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 of this Guidance and the Guidance on 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 I*: 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 I: *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 I: *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 of this Guidance).

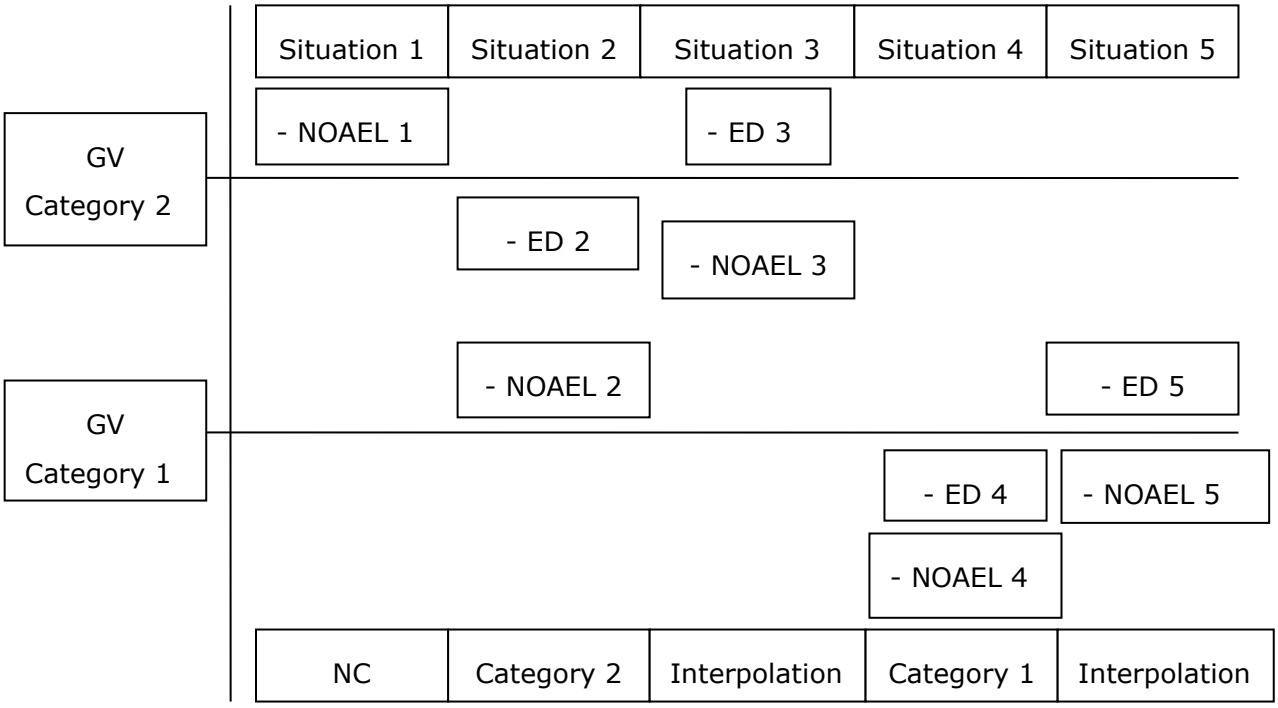
Categories 1 and 2

Generic guidance on data evaluation is presented in the Guidance on IR&CSA, Sections 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 3.7). 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 of this Guidance 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 3.7).

In a case where the ED is above a GV but the NOAEL is below the GV (situations 3 and 5 in Figure 3.7) 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 3.7 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 of this Guidance.

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 the Guidance on IR&CSA 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 = 24,450 x mg/l × 1/MW.

3.8.2.4.5. Weight of evidence

> **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:*
>
> *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 and in the approach described in Section 3.8.2.3 of this Guidance.

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.

3.8.2.5. Decision on classification of substances

Decision on classification for STOT-SE is based on the results of weight of evidence approach described in Section 3.8.2.4.5.

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:

Equation 3.8.2.6.a

$$SCLCat.1 = \frac{ED}{GV1} \times 100\%$$

SCL Cat 1: 0.7 mg/kgbw/300 mg/kgbw x 100%=0.23% --> 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[70] (1, 2 or 5).

Example of determining STOT-SE SCL for a Category 1 substance:

$$= \frac{0.7 mg/kgbw}{300 mg/kgbw} \times 100\%$$ = 0.23% --> 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:

Equation 3.8.2.6.b

$$SCLCat.2 = \frac{ED}{GV2} \times 100\%$$

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:

$$= \frac{0.7 mg/kgbw}{2000 mg/kgbw} \times 100\%$$ = 0.035 --> 0.02% (rounded down)

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 ≥ 0.2% ; Cat 2: 0.02% ≤ 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

[70] 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.

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.

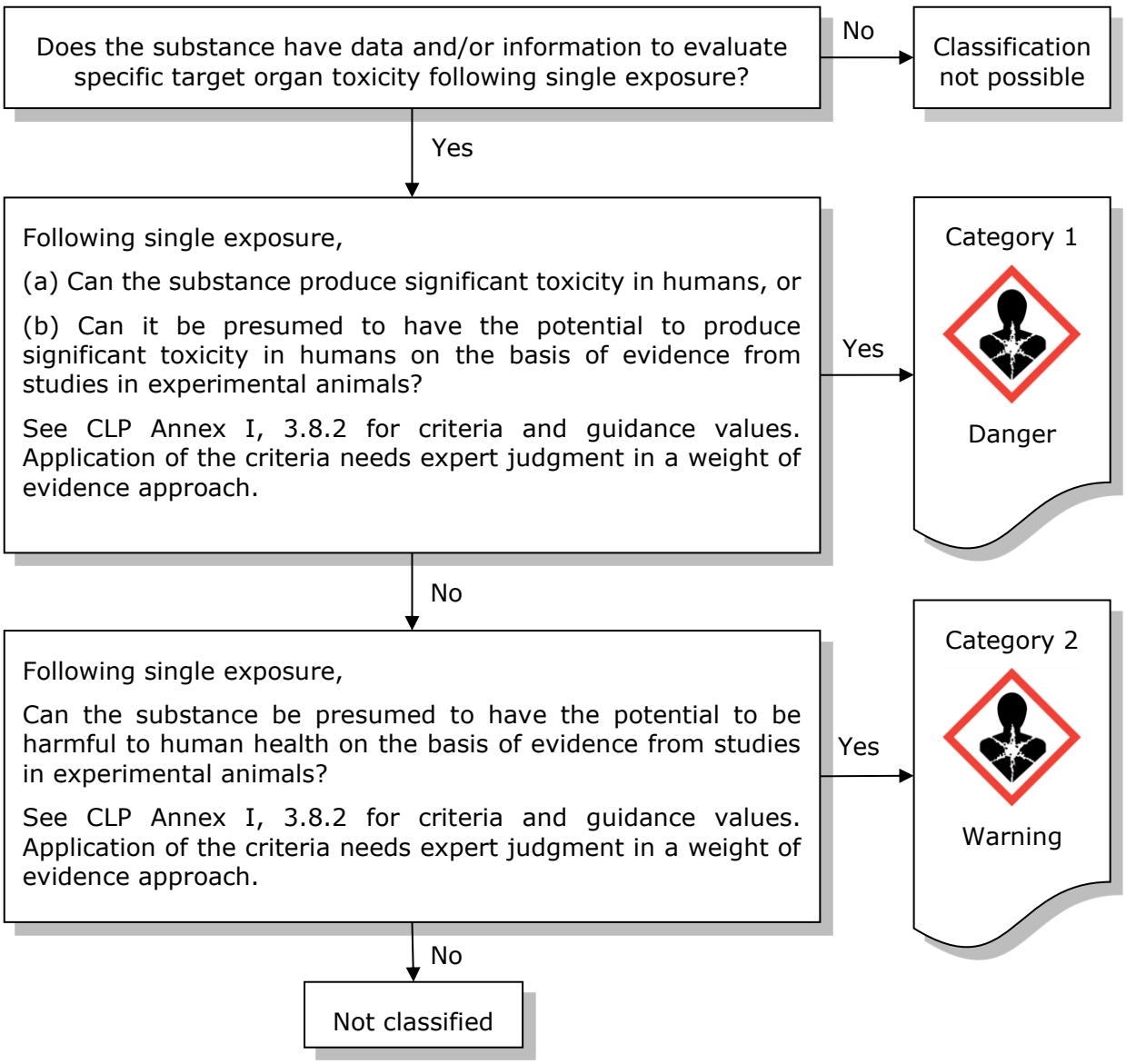
For narcotic effects, the factors to be taken into consideration in order to set lower or higher SCLs are the effective dose/concentration, and in addition for liquids, the volatility (saturated vapour concentration) of the substance.

3.8.2.7. Decision logic for classification of substances

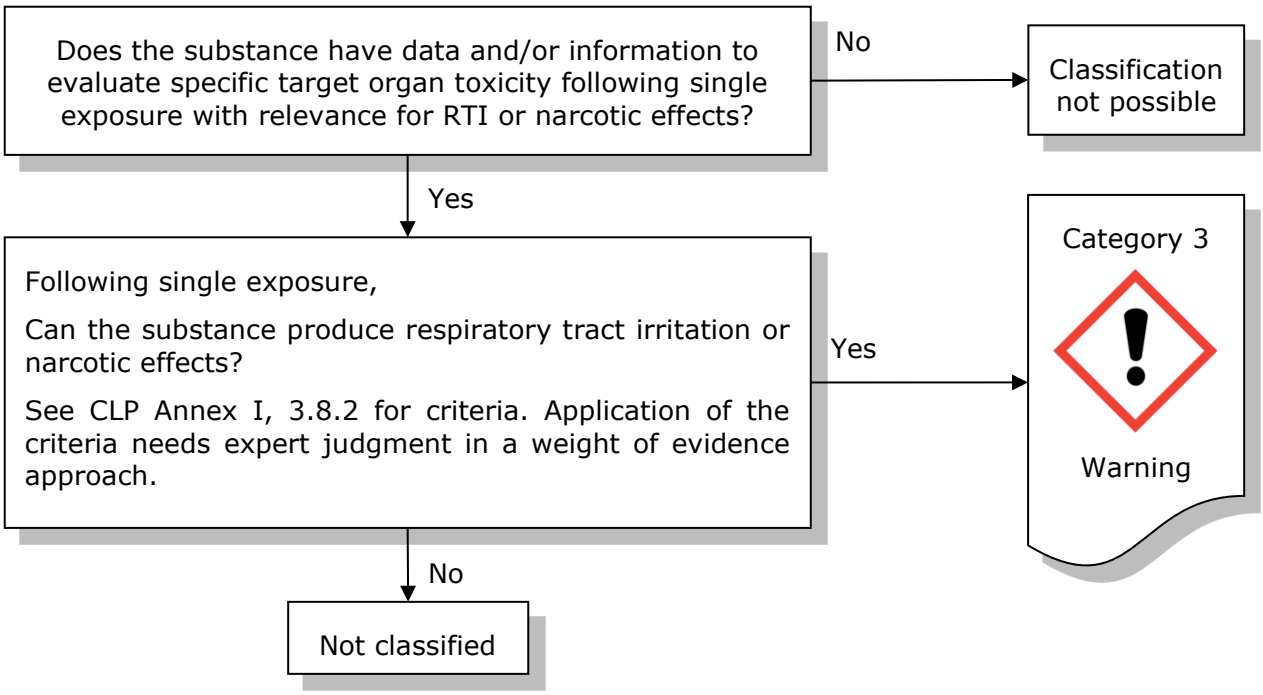
The decision logic is provided as additional guidance. It is strongly recommended that the person responsible for classification study the criteria for classification before and during use of the decision logic.

This decision logic deviates slightly from the original GHS 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 I: ***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 I: ***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 I: ***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.*

In order to apply bridging principles, there needs to be sufficient data on similar tested mixtures as well as the ingredients of the mixture (see Section 1.6.3 of this Guidance).

When the available identified information is inappropriate for the application of the bridging principles then the mixture should be classified using the calculation method or concentration thresholds as described in Sections 3.8.3.2.3, 3.8.3.2.4 and 3.8.3.3 of this Guidance.

3.8.3.2.3. When data are available for all ingredients or only for some ingredients of the mixture

Annex I: ***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 of this Guidance). More information on classification of mixtures into Category 3 is provided below (Section 3.8.3.3 of this Guidance)**.**

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 CLP Annex I, Table 3.8.3), or with a Specific Concentration Limit (see Section 3.8.2.6 of this Guidance) 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 I: *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.* **Annex I*: 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.* **Annex I*: 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. Respiratory tract irritation and narcotic effects are to be evaluated separately in accordance with the criteria given in section 3.8.2.2. When conducting classifications for these hazards, the contribution of each component should be considered additive, unless there is evidence that the effects are not additive.*		

Categories 1 and 2

Each single classified component in a concentration range given in CLP Annex I, 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 should be applied unless there is evidence that the effects are not additive. 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 (CLP Annex I, 3.8.3.2);

b. Classification via the application of bridging principles is not possible since data on a similar mixture was not provided (CLP Annex I, 3.8.3.3.1);

c. Application of CLP Annex I, 3.8.3.4.5 is used for classification. Expert judgement is necessary when applying this paragraph. CLP Annex I, 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 classification of mixtures

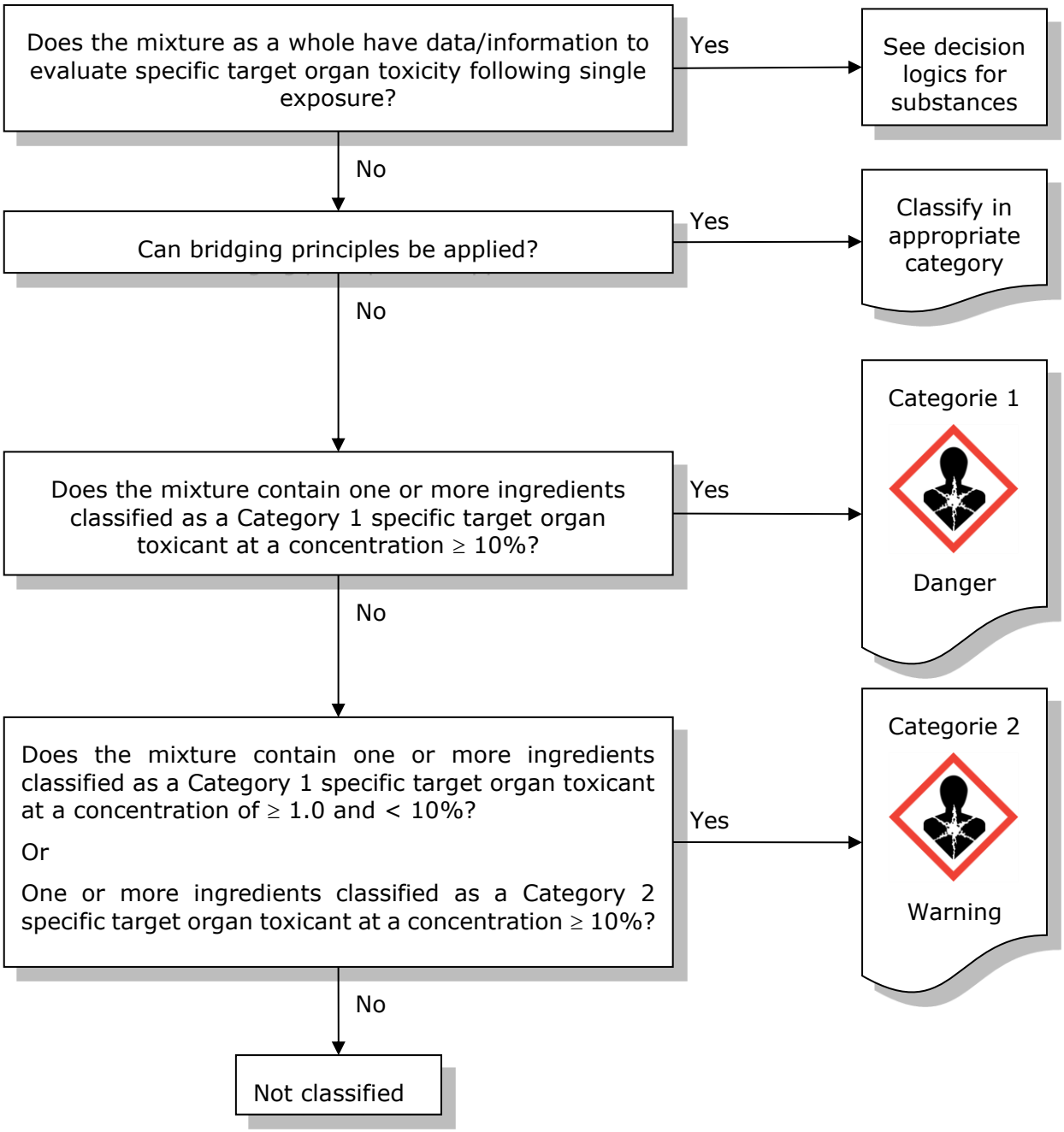
A mixture should be classified either in Category 1 or in Category 2, according to the criteria described above. The corresponding hazard statement (H370 for Category 1 or H371 for Category 2) should be used without specifying the target organs, except if the classification of the mixture is based on 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.

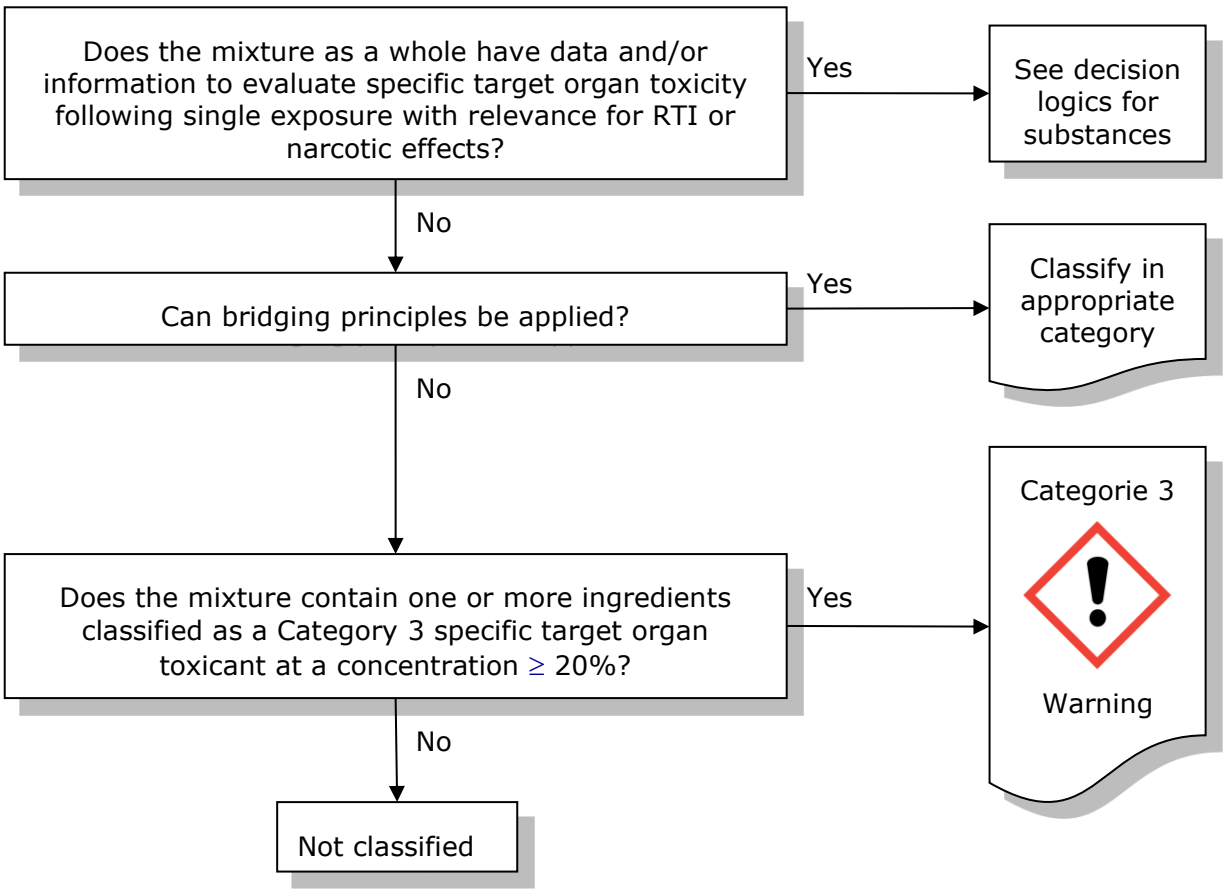
The decision logic is provided as additional guidance. It is strongly recommended that the person responsible for classification study the criteria for classification before and during use of the decision logic.

This decision logic deviates slightly from the original GHS 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 or 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 Response	*P308 + P311* *P321*	*P308 + 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

Annex I: *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 precautionary statements. (As a rule, the supplementary precautionary advice would normally be given for 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. Examples of classification for STOT-SE

3.8.5.1. Examples of substances fulfilling the criteria for classification

3.8.5.1.1. 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 bw) 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	STOT-SE Category 1	The classification criteria for Category 1 are fulfilled: clear human evidence of a specific target organ toxicity effect

	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 bw' (IPCS)		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.		

3.8.5.1.2. 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 bw LD_{50} rat oral 3000 - 3900 mg/kg bw	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.		

3.8.5.1.3. 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		

3.8.5.1.4. Example 4: Toluene

Application	Use of valid animal data		
	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 results in animal experiments
Remarks	Labelling: Pictogram GHS 07; Signal word: Warning; Hazard statement: H336 May cause drowsiness and dizziness		

3.8.5.2. Examples of substances not fulfilling the criteria for classification

3.8.5.2.1. Example 5: ABC

Application	No classification for STOT-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 2,000 mg/kg bw 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 bw. 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

3.8.5.2.2. Example 6: N,N-Dimethylaniline

Application	No classification for STOT-SE in case same effect leading toAcute toxicity classification		
	Test Data	**Classification**	**Rationale**
Available information	Animal data: Acute oral toxicity: LD_{50} values > 1,120-1,300 mg/kg bw 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. 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 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.
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.*

Annex I*: 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.*

Annex I*: 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 the Guidance on 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. (Guidance on 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 has been developed under the OECD HPV chemicals 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 the Guidance on 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' (Guidance on 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 of this Guidance and the Guidance on IR&CSA, Section R.7.5.4.1.

The standard test guidelines are described in the Gudiance on 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 the Guidance on 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(Guidance on 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).*	

⚠ *NOTE: In the Note above (in green box) '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 I: *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 I*: 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 I*: 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 ≤ 100*
Dermal (rat or rabbit)	*mg/kg body weight/day*	*20 < C ≤ 200*
Inhalation (rat) gas	*ppmV/6h/day*	*50 < C ≤ 250*
Inhalation (rat) vapour	*mg/litre/6h/day*	*0,2 < C ≤ 1,0*
Inhalation (rat) dust/mist/fume	*mg/litre/6h/day*	*0,02 < C ≤ 0,2*

Annex I: *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 I: *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 3.16 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 I: *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 or 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 I: *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 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.*

Annex I: ***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.

The Guidance on 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

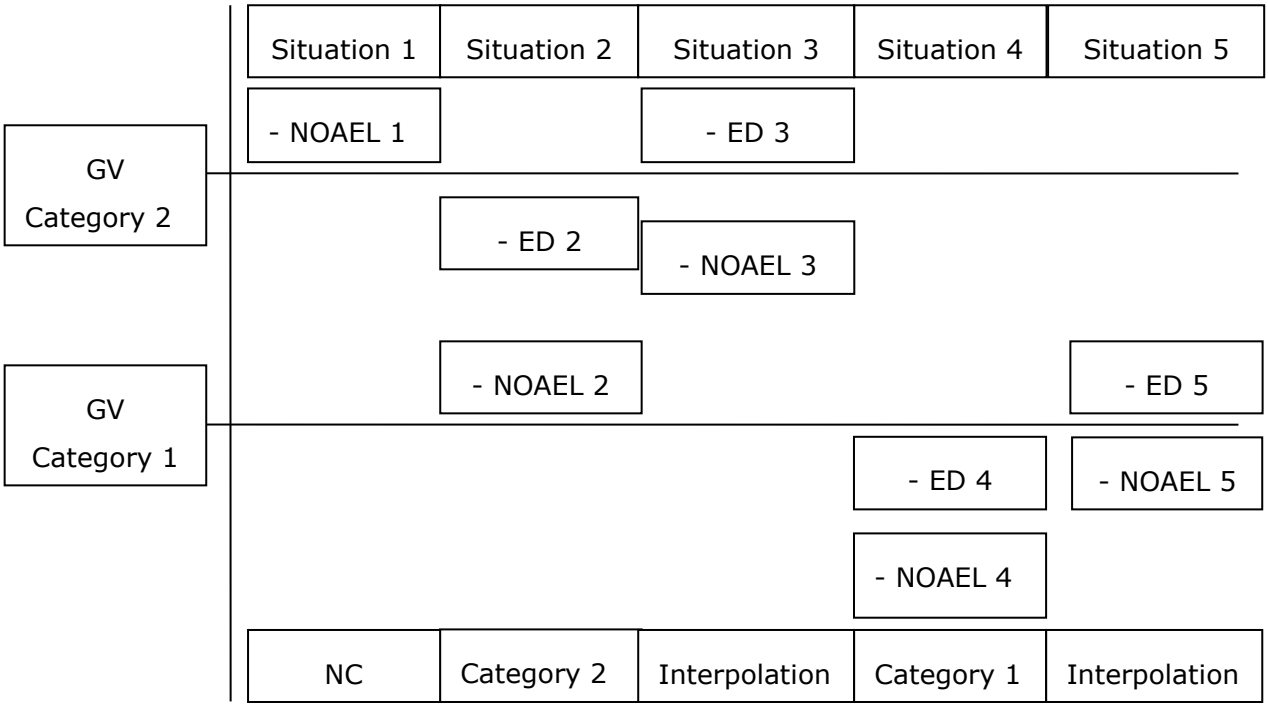
Annex I: ***3.9.2.7.3.*** *Evidence from appropriate studies in experimental animals can furnish much more detail, in the form of clinical observations, haematology, clinical chemistry, and macroscopic and microscopic pathological examination, and this can often reveal hazards that may not be life-threatening 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 Category 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 3.8 below). 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 of this Guidance, 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 3.8).

In a case where the ED is above a GV but the NOAEL is below the GV (situations 3 and 5 Figure 3.8) 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 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 Section 3.9.2.3.4 of this Guidance).

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 (see Section 3.9.2.4 of this Guidance). 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.

3.9.2.3.3. Conversions

The guidance values are giving in mg/kg bw. 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 3.17 and Table 3.18 can be used as 'Approximate relations'. These tables are derived from the following documents: Guidance on 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 3.17 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 3.18 Conversion drinking water

Animal	Weight (kg)	Drinking water 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:

$$\text{mg/kg bw} = \text{ppm/factor}$$

Example:

In a 4 week study rats received the 1000 ppm test substance in feed

Dosage (mg/kg bw): 1000:10= 100 mg/kg bw.

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:

$$mg/l = ppm \times MW \times 1/24{,}450$$

3.9.2.3.4. Weight of evidence

Annex I: *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.*

Annex I*: 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 I: *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.*

Annex I: *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 I: ***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 I: ***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 I: ***3.9.2.8.*** *Effects considered not to support classification for specific target organ toxicity following repeated exposure*

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

(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 then 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.

Hazard statements are provided in Section 3.9.4.1 of this Guidance and can specify the route(s) of exposure according to Table 3.9.2.4.1 below. If only data is available for one route showing that classification is warranted then 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.

Table 3.19 Inclusion of route of exposure in Hazard statement

Route 1	Route 2	Route 3	H-statement H372
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

3.9.2.5. 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 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, (2000) in EU Commission Summary Record of Meeting of the Commission Working Group on C&L of Dangerous Substances ECBI/44/01).

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[71] 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 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: *3.9.2.7.3.*

(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:

[71] 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.

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." (CLP Annex I, 3.9.1.4).

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, EU Commission Meeting of the Commission Working Group on C&L of Dangerous Substances ECBI/27/98 Rev.2).

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 long-term 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, increase in alveolar macrophages following inhalation of insoluble particles that must be cleared from the lungs, or 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 TG 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 often 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 10.1 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 bw 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 (*SCL Cat.1*) can be determined using the following formula:

Equation 3.9.2.6.a

$$SCLCat.1 = \frac{ED}{GV1} \times 100\%$$

SCL Cat 1: 0.12 mg/kg bw**/**10 mg/kg bw 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[72] (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 1 can be determined using the following formula:

Equation 3.9.2.6.b

$$SCLCat.2 = \frac{ED}{GV2} \times 100\%$$

SCL Cat 2: 0.12 mg/kg bw**/**100 mg/kg bw x 100%=0.12% --> 0.1%

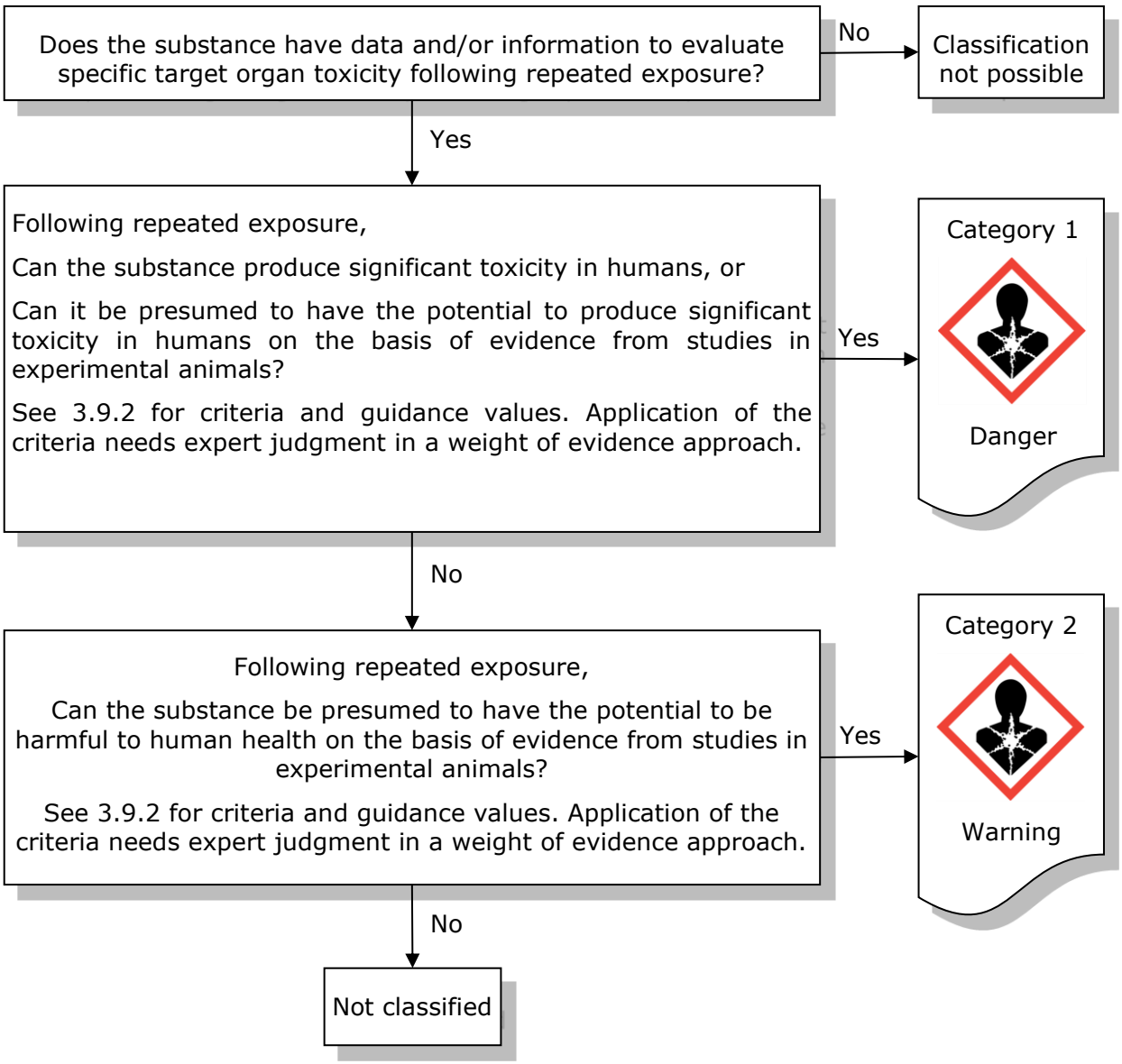
In this formula the ED (effective dose) is the dose inducing specific target organ toxicity and GV2 is the upper guidance value for Category 2 according to CLP Annex I, Table 3.9.3 corrected for the exposure duration. The resulting SCL is rounded down to the nearest preferred values (1, 2 or 5).

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%.

[72] 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.

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 of this Guidance.

3.9.3.2. Classification criteria for mixtures

Annex I: ***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 I: ***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 I: 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.

In order to apply bridging principles, there needs to be sufficient data on similar tested mixtures as well as the ingredients of the mixture (see Section 1.6.3 of this Guidance).

When the available identified information is inappropriate for the application of the bridging principles then the mixture should be classified based on its ingredients as described in Sections 3.9.3.3.2, 3.9.3.3.3 and 3.9.3.4 of this Guidance.

3.9.3.3.2. When data are available for all ingredients or only for some ingredients of the mixture

Annex I: ***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 (see CLP Annex I, Table 3.9.4) or with a specific concentration limit (see also Section 3.9.3.5 of this Guidance) 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 I: *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 I: ***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.*

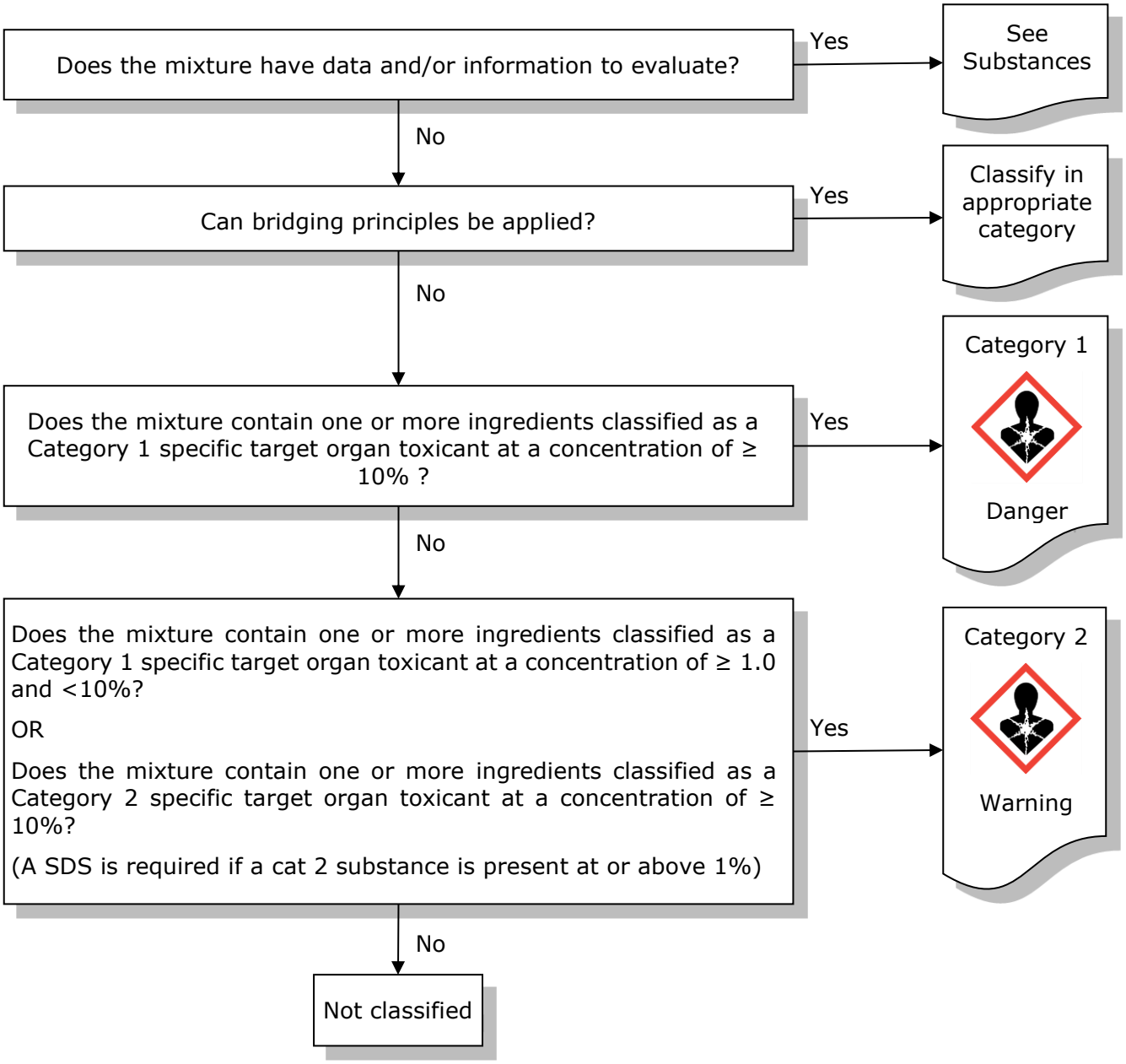
In the case a specific concentration limit has been established for one or more ingredients these SCLs have precedence over the respective generic concentration limit.

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 classification of 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-RE on the 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 I: ***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 Section 3.2 of this Guidance on Skin Corrosion/Irritation).

3.9.5. Examples of classification for STOT-RE

⚠ NOTE: 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).

3.9.5.1. Examples of substances fulfilling the criteria for classification

3.9.5.1.1. 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:

6. Human experience: No information available
7. 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 bw/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 bw/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 < 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 bw/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 bw/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:

- ppm (males 0.2 mg and females 0.4 mg/kg bw/day): No non-neoplastic effects

- 20 ppm (males 1 mg and females 1.6 mg/kg bw/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 bw/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 as a result of the anemia.

Remark:

No effects were observed neither 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 & Labelling:

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 in EU Commission Meeting of the Commission Working Group on C&L of Dangerous Substances ECBI/139/04 Rev.2)

3.9.5.1.2. Example 2: But-2-yn-1,4-diol (EC No 203-788-6; CAS No 110-65-6)

Application of criteria for evaluation/classification and allocation of hazard statements with respect to specific target organs and route of exposure

Available information:

8. Human experience: no information available
9. Animal data:
    - 28d oral study
    - 28d inhalation study
    - Acute oral toxicity: LD_{50} rat 132 (males) and 176 (females) mg/kg bw -> Category 3
    - Acute dermal toxicity: LD_{50} 424 (males) and 983 (females) mg/kg bw-> Category 3
    - Acute inhalation toxicity: LC_{50} rat 0.69 mg/l -> Category 2
    - Corrosivity in animal experiments (Category 1)

STOT-RE oral:

28d rat oral (gavage): doses 0; 1; 10; 50 mg/kg bw/d

- 1 mg/kg bw: NOEL
- 10 mg/kg bw: 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 chemistry
- 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 bw: 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 males and 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 LD_{50} 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 bw moderate but no 'significant/severe' toxicity could be expected; 30 mg/kg bw is the guidance value for Category 1 in a 4 week study according to Haber's rule: 10 mg/kg bw x 3)

STOT-RE inhalation

In a valid 4 week inhalation study (vapour) rats were exposed to 0.5; 5; and 25 mg/m^3/6h/d.

- 0.5 mg/m^3: NOAEC for local effects in the respiratory tract
- mg/m^3: minimal-slight focal squamous metaplasia and inflammation in the larynx
- 25 mg/m^3: minimal-slight focal squamous metaplasia and inflammation in the larynx
- 25 mg/m^3: 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/m^3. It is assumed that the irritation would increase with higher concentrations. The corrosive/irritation potential is covered by the classification as 'corrosive' Category 1, thus no classification as STOT-RE with respect to the inhalation route would result.

<u>Classification & Labelling:</u>

Classification: Category 2 for the oral route is proposed since within the guidance values of 30-300 mg/kg bw 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 bw, 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.

To note: 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. Available at ECHA website: http://echa.europa.eu/documents/10162/49324502-03ba-4005-8800-b2bebf924d2d)

3.9.5.1.3. 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:

- Human experience: No information available
- Animal data:

Key chronic toxicity data (underlined for EU classification)			CLP Repeated Exposure (STOT) classification
Type of study - Effects	**NOAEL ppm (mg/kg bw/d)**	**LOAEL ppm (mg/kg bw/d)**	
mouse, oral 28 days 0, 300, 600, 1200 ppm (M: 0, 51-58, 101-115, 177-226 mg/kg bw/d, F: 0, 59-66, 111-127, 221-281 mg/kg bw/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 bw/d, F: 0, 4, 38, 80 mg/kg bw/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 bw/d (by gavage) (open literature) mortality at 5 (5/25), 10 (7/25) & 25 (8/25) mg/kg bw			No classification is proposed on the basis of this study because the mortality observed in the 3 groups are in contradiction with the other relevant experiments in this species (mortality not dose related, some animals (2/6) already died after 30 days at 5 mg/kg bw)

Key chronic toxicity data (underlined for EU classification)			CLP Repeated Exposure (STOT) classification
Type of study - Effects	**NOAEL ppm (mg/kg bw/d)**	**LOAEL ppm (mg/kg bw/d)**	
rat, oral 2 years 0, 30, 150, 300 ppm (M: 0, 1.46, 7.31, 14.66 mg/kg bw/d, F : 0, 1.8, 8.86, 18.57 mg/kg bw/d) 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 of F at 300 ppm ↑ i. hemorrhages w/i mesenteric lymph nodes at 150 & 300 ppm	30 (M: 1.46, F: 1.8)	150 (M: 7.31, F: 8.86)	Category 2 based on the effects on blood (haemolytic anaemia accompanied by compensatory mechanisms)
rat, oral 80 weeks M: 0, 5, 20, 52 mg/kg bw/d F: 0, 6, 26, 67 mg/kg bw/d (open literature) ataxic syndrom in F at 67 mg/kg bw/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 bw/d, F: 0, 0.1, 1.4, 13.8 mg/kg bw/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

Key chronic toxicity data (underlined for EU classification)			CLP Repeated Exposure (STOT) classification
Type of study - Effects	NOAEL ppm (mg/kg bw/d)	LOAEL ppm (mg/kg bw/d)	
mouse, oral, 97/98 weeks M : 0, 15, 150, 300 ppm (0, 3, 24, 50 mg/kg bw/d) F : 0, 15, 300, 600 ppm (0, 3, 57, 112 mg/kg bw/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 & Labelling:

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.

3.9.5.2. Examples of substances not fulfilling the criteria for classification

3.9.5.2.1. 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 of this Guidance)

Available information:

- Human experience: No information available
- 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.

KEY CHRONIC TOXICITY DATA: SUMMARY OF DATA FOR REPEATED EXPOSURE

For the liver, increases in weight and changes in enzyme activity are seen in rats at exposure levels of 36 mg/kg bw/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 bw/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 bw/day (IRDC 1984). Histopathologically, lesions such as hyperplasia have been observed down to the lowest exposure levels tested (eg. 0.4 mg/kg bw/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 bw/day in a 90-day study (Poon *et al.*, 1995). Inner medullary tubular dilatation was seen at 4 mg/kg bw/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 bw/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 bw/day or more. At 10 mg/kg bw/day the severity of these changes was graded as 'trace', and even at the highest exposure level, 625 mg/kg bw/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 & Labelling:

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 give an idea what are the actual effects around the cut-off values (10-100 mg/kg bw) but probably we could come to the same conclusion, i.e. the effect is not enough to justify the classification in any category.

3.9.5.3. Examples of mixtures fulfilling the criteria for classification

3.9.5.3.1. Example 5

Application of criteria for mixture classification: 'When data are available for the complete mixture' (see Section 3.9.3.3 of this Guidance).

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 & Labelling:

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.

3.9.5.3.2. Example 6

Application of criteria for mixture classification: 'When data are available for all components' (see Section 3.9.3.3 of this Guidance). 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 Category 1
3	54	NC
4	1.5	STOT-RE Category 2

Classification & Labelling:

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 STOT-RE Category 1 ingredient in a concentration of <10%. Therefore the mixture is not classified in STOT-RE Category 1. There is one STOT-RE Category 1 ingredient in a concentration of ≥ 1% and <10%, therefore STOT-RE Category 2 is warranted. The STOT-RE Category 2 ingredient with 1.5% is not taken into account at all, since the concentration is < 10%.

3.9.5.3.3. Example 7

Application of criteria for mixture classification 'When data are available for all components' (Section 3.9.3.3 of this Guidance). Components of a mixture that should be taken into account are listed below together with their concentrations. Generic concentration limits should be used, specific concentration limits should take precedence over generic concentration limits when available, and non-additivity applies.

Available information:

Ingredient	Classification	Concentration (% w/w)	Mixture Classification	Remarks
A	STOT-RE Category 1	0.1		SCL 0.2%
B	STOT-RE Category 1	9		

Classification & Labelling:

Classification of the mixture: STOT-RE 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.

3.9.5.3.4. Example 8

Application of criteria for mixture classification 'When data are available for all components' (Section 3.9.3.3 of this Guidance). Components of a mixture that should be taken into account are listed below together with their concentrations. Generic concentration limits should be used, specific concentration limits should take precedence over generic concentration limits when available, and non-additivity applies.

Available information:

Ingredient	Classification	Concentration (% w/w)	Remarks
A	STOT-RE Category 1	0.3	SCL 0.2%
C	STOT-RE Category 2	9	

Classification & Labelling:

Classification of the mixture: STOT-RE 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.

3.9.5.4. Example of mixtures not fulfilling the criteria for classification

3.9.5.4.1. Example 9

Application of criteria for mixture classification: 'When data are available for all components' (Section 3.9.3.3 of this Guidance); 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 & Labelling:

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 STOT-RE Category 1. Therefore the mixture cannot be classified in STOT-RE Category 1. Though the sum of the STOT-RE 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.

3.9.6. 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)' (Fourth revised edition, 2011, https://www.unece.org/fileadmin/DAM/trans/danger/publi/ghs/ghs_rev04/English/ST-SG-AC10-30-Rev4e.pdf).

The text in part 4, even more so in some of the Annexes to this chapter, is largely based on the text in UN GHS. 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 short-term (acute) and long-term (chronic) 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 (CLP Annex I, part 4) 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 compartment 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. For practical reasons, a limited set of specific properties has been selected through which the short-term (acute) and long-term (chronic) hazards can be best described: acute aquatic toxicity; chronic aquatic toxicity; lack of rapid degradability; and potential for 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 IR&CSA Chapter R.7b and Annex I of this Guidance. 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 (e.g. see Annex I).

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[73]), 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) No 440/2008; OECD TG 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.

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 a 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 (see also section 1.4 of this Guidance).

Information sources

[73] If available, preference is given to EC_{10}, see OECD 2006.

Section R.3.4.1 of IR&CSA Chapter R.3 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 (https://echa.europa.eu/support/guidance).

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: (https://www.echemportal.org/echemportal/)

Further guidance is given in Annex 0 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 (consult the *Guidance for identification and naming of substances under REACH and CLP*, 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 (see section below) 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 take into account 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 section R.4.2.

4.1.3.2.2. Substances difficult to test

For many organic substances, the testing and interpretation of data presents no problems when applying both the relevant Test Methods Regulation (EC) No 440/2008 and/or OECD Test Guidelines and the classification criteria. There are a number of typical interpretational problems, however, that can be attributed to the properties of the substance being studied. These are commonly called 'difficult to test substances':

a. poorly soluble substances: these substances are difficult to test because they present problems in the preparation of a test solution, maintenance of test concentrations and verification of exposure during aquatic toxicity testing. In addition, many available data for such substances have been produced using 'solutions' in excess of the water solubility resulting in major interpretational problems in defining the true L(E)C_{50} or NOEC/EC_x for the purposes of classification. Interpretation of the partitioning behaviour can also be problematic where the poor solubility in water and octanol may be compounded by

insufficient sensitivity in the analytical method. Water solubility may be difficult to determine and is frequently recorded as simply being less than the detection limit, creating problems in interpreting both aquatic toxicity and bioaccumulation studies. In biodegradation studies, poor solubility may result in low bioavailability and thus lower than expected biodegradation rates. The specific test method or the choice of procedures used can thus be of key importance (see also Annex I.4.2);

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 (see also Annex I.4.3);

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 (see also Annex I.4.1);

d. complex or multi-constituent[74] substances: such substances, for example, complex hydrocarbons, or other UVCB[75] 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[76]. 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 (see also Annex I.4.5);

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 (see also Annex I.4.5);

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

g. surface-active substances: such substances can form emulsions in which the bioavailability is difficult to ascertain, even with careful preparation of solutions. Micelle formation can result in an overestimation of the bioavailable fraction even when 'solutions' are apparently formed. This presents significant problems of interpretation in each of the water solubility, partition coefficient, bioaccumulation and aquatic toxicity studies (see also Annex III.3.1);

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;

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[74] Further definitions are provided in the *Guidance for identification and naming of substances under REACH and CLP* (ECHA).

[75] UVCB means Substances of Unknown or Variable composition, Complex reaction products or Biological materials, see Chapter 4.3 of the *Guidance for identification and naming of substances under REACH and CLP*.

[76] 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).

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 *Guidance for identification and naming of substances under REACH and CLP*, 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 23 Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals (OECD, 2019, http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO(2000)6/REV1&docLanguage=En) and also the IR&CSA Chapter R.7b, Appendix 7.8-1 and Annex I to the current Guidance Document.

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).*

Annex I: ***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 and suitable 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 determined 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 or when classifying poorly soluble substances (water solubility e.g. < 1

mg/L CLP Table 4.1.0 note 4), and substances with a specific mode of action inducing effects on reproduction or growth instead of lethality. In the latter cases, there is evidence that acute testing may 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 the current Guidance and in IR&CSA Chapter R.7b, 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.

There are some recently validated in vitro methods available for use as alternative data to determine acute and long-term hazards. Currently, in vitro tests cannot directly substitute in vivo data in terms of one for one replacement for classification purposes. However, in vitro data can already play a role as supporting evidence in a weight of evidence approach and there are ongoing efforts to develop and validate further in vitro methods which may add to our understanding of aquatic toxicity. Although the standard guideline in vivo methods remain the most informative for classification and labelling purposes, all available and relevant information on aquatic toxicity, including non-guideline methods, can be assessed on their own merits and carefully balanced in the overall weight of evidence.

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.*

Annex I: ***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 Annex II.2 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.7b, section R.7.9. The OECD test methods 301A-F (C.4-A to F of the Test Methods Regulation 440/2008), OECD TG 310, or equivalent tests, are commonly used to determine 'ready biodegradability'. Some guidance on the use of (Q)SAR methods for degradability is presented in IR&CSA Chapter R.7b, section 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 when the test material is the multi-constituent substance as a whole. Thus, results of biodegradability tests on complex or multi-constituent substances should be carefully evaluated before use for classification purposes is considered. See Annex II.3.1 for further details.

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.*

Annex I: ***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.*

Annex I: ***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 $\geq 0,5$; 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 10-day window condition may be waived for complex multi-component substances with structurally similar constituents and the pass level applied at 28 days, as discussed in Annex II.2.1.2 to this document). If this is not possible, then the pass level should be evaluated within a 14-day 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 hydrolysis, 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 fulfil 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 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 types of data mentioned above are available, 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 (Q)SARs, 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 I test (OECD TG 301C, 2006 or C.4-E of the Test Methods Regulation 440/2008). In the Closed Bottle test (OECD TG 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).

In all cases, it should be considered that IR&CSA Chapter R.7b, section R.7.9.4 states that "…ready biodegradability tests are intended for pure substances and are generally not applicable for complex compositions containing different types of constituents, like UVCBs". For a UVCB substance, observed biodegradation may indeed represent the biodegradation of only some constituents. In the same document, it is indicated that "it is sometimes relevant to examine the ready biodegradability of mixtures of structurally similar chemicals".

Selection of test systems

As regards section 4.1.2.9.5 (c) in Annex I to CLP ("other convincing scientific evidence available to demonstrate that the substance can be degraded in the aquatic environment to a level > 70 % within a 28-day period"), 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 TG 302A and B, or C.9 and C.12 of the Test Methods Regulation 440/2008) and sewage treatment simulation (OECD TG 303, or C.10 of the Test Methods Regulation 440/2008) tests are not used in this context, due to the high levels of adapted biomass. Anaerobic

degradation tests (OECD TG 311/ISO 11734 and analogous tests) are not suitable because of the specificity of the anaerobic compartments. Also the defined category of 'Enhanced Ready Biodegradation (Screening) Tests' in IR&CSA Chapter R.7b, section R.7.9 are not suitable for use in classification and labelling, as they are designed to promote biodegradation and are not as stringent as OECD TG 301-suite type tests. More specifically, section R.7.9.4.1 explicitly states that "a number of potential enhancements to the ready biodegradation test have been identified. These enhancements have been proposed for the determination of persistence in vPvB/PBT assessment only but are not to be used for Classification and Labelling and quantitative exposure and risk assessment".

Use of SARs and (Q)SARs

The estimation of degradation via SARs and/or (Q)SARs for hydrolysis and biodegradation is a rapidly developing field. The predictions from (Q)SAR models may be considered as contributing to a decision on ready biodegradability or rapid degradation for classification purposes. (Q)SAR 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-ready biodegradability more certainly than ready biodegradability (IR&CSA Chapter R.7b, section R.7.9.4.1). However, (Q)SAR information can be used as a part of expert judgement and WoE practices, for example where very consistent measured and predicted data are available for a structurally analogous compound. More details can be found in IR&CSA Chapter R.7b, section R.7.9.4.1.

General interpretation problems and substances difficult to test

The UN GHS Annex 9 and OECD Guidance 23 (OECD 2019) 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) No 440/2008, OECD TG 305: Bioaccumulation in Fish: Aqueous and Dietary Exposure) or information on the bioaccumulation potential, for organic

substances, may be estimated from the structure of the molecule (see also IR&CSA Chapter R.7b, section R.7.10).

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 and non-surface active 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 (Q)SARs.

Experimentally derived BCF values of high quality are 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 ((Q)SARs) for log K_{ow} may be used in the classification process. If data are available but not validated, expert judgement should be used. (Q)SAR BCF values can be used as part of a WoE approach, but it must be noted that high quality experimental BCF and Log k_{ow} values are always preferred and (Q)SAR BCFs are not considered a one for one substitute (See Annex III.2.2.2 for further details). BCF estimates based on in vitro OECD TGs 319A and B might be considered in a WoE approach for bioaccumulation provided that they fulfil relevant data quality requirements (IR&CSA Chapter R.7b, R.11.4.1.2.10). For ionised organic substances problems may occur, 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 in bioaccumulation testing is provided in the OECD Guidance 23 (OECD 2019).

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 R.4, section R.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 effect value 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 value is available for a given endpoint. In both situations, available information needs to be evaluated carefully. Data deficiency may occur for substances for which there are no reliable data, or only experimental data which is irrelevant 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 rudimentary surrogate and the lowest value is considered to be a cautious approach for defining 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. In case of multiple data points for the same effects endpoint, Guidance R.4 states that "Where there is more than one study for each endpoint, the greatest weight is attached to the studies that are the most relevant and reliable. Sound scientific judgement is an important principle in considering the adequacy, reliability, and relevancy of information and determining the key study".

Conversely, as CLP allows the use of expert judgment in employing non-testing information such as (Q)SARs, 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 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 (Q)SARs 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, also taking into consideration metabolites, reaction products, and 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: '(Q)SARs 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 Klimisch 1 studies in a dataset are given more weight than Klimisch 2 studies or valid (Q)SAR 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 could 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 for the same species and effects endpoint, 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.7b, section 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. However, 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 further guidance.

4.1.3.3. Classification categories and criteria

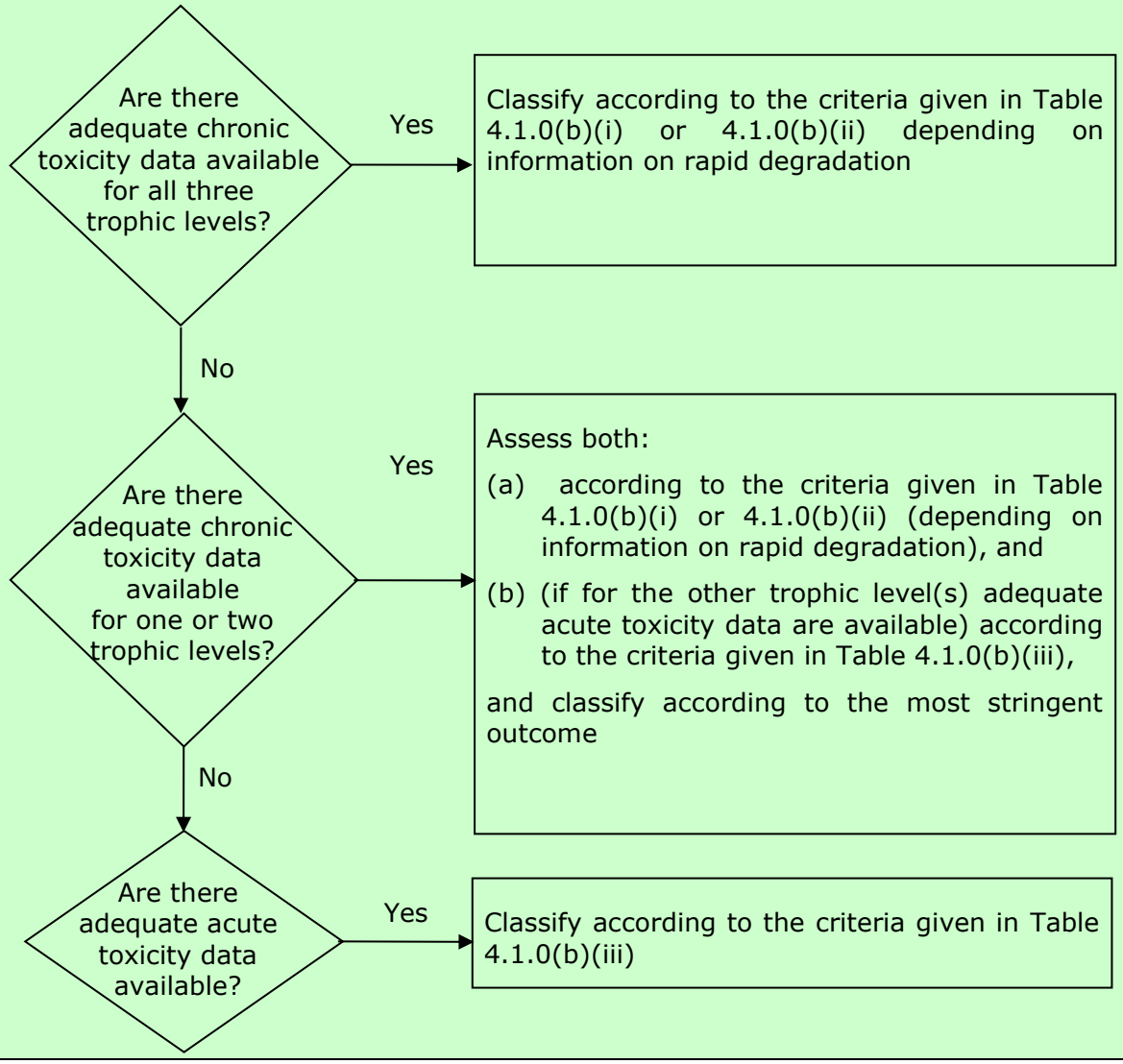
4.1.3.3.1. Outline of the core classification system

Annex I: ***4.1.2.2.*** *The core classification system for substances consists of one short-term (acute) hazard classification category and three long-term (chronic) hazard classification categories. The short-term (acute) and the long-term (chronic) 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 (chronic) 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 (chronic) 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 chronic toxicity of a substance. For the long-term (chronic) 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.*

Chronic toxicity data, where available, are preferred for determining the long-term (chronic) hazard category. 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 dependent on the information on rapid degradation. Chronic toxicity and the degradation properties of the substance should be considered when determining the potential hazard classification. 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.

Since the introduction of chronic aquatic toxicity criteria in ATP 2 to CLP (Table 4.1.0 of Annex I to CLP), chronic toxicity data has become widely available.

Chronic toxicity data (EC_x or NOEC), where available, should be used for long-term hazard classification. However, when assessing the adequacy of available chronic toxicity data, there may be some cases (for example, data poor substances) where the chronic toxicity data do not represent the species that is considered the most sensitive in available short-term toxicity tests. In such cases, the classification should be based on the toxicity data (acute or chronic) that gives the most strict classification (including the M-factor). In the absence of chronic toxicity data, suitable acute toxicity data can be used to determine long-term hazard classification in addition to acute hazard classification (Figure 4.1.1 and Table 4.1.0(b)(iii) of Annex I to CLP).

A review of the existing adequate and 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 $\geq$ 500 or, if absent, the log $K_{ow} \geq 4$) or higher potential longer term exposure (i.e. lack of rapid degradation), it can be used as a suitable surrogate for long-term hazard 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) Short-term (acute) 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 (chronic) 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 EC_x (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 EC_x (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 LC50 (for fish)	*> 1 to ≤ 10 mg/l and/or*
48 hr EC50 (for crustacea)	*> 1 to ≤ 10 mg/l and/or*
72 or 96 hr ErC50 (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 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. 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. 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 be based on parent or degradant data. There may be occasions when a substance tested may degrade to give rise to a more hazardous degradation product under environmental conditions. In these circumstances, the rate of generation of the more hazardous degradation product (i.e.,

quantity produced and time frame) should be considered to assess whether the classification should be based on data for the degradation product. OECD Guidance 23 (OECD 2019) provides useful information on this topic. Further information on unstable substances can be found in Annex I.4.1. There may also be instances where it may be necessary to consider data obtained from mixtures (e.g., formulated products) when assessing hazards to the aquatic environment. In such cases, it is important to understand the aquatic hazard presented by other constituents in order to conduct an accurate assessment of the substance being classified. In all cases, data on the substance being classified (including any relevant degradation products) is clearly preferred over data on mixtures.

4.1.3.3.2. The 'safety net'

Annex I: ***4.1.2.4*** *The system also introduces a "safety net" classification (referred to as 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} ≥ 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 for some poorly soluble substances, which are normally considered as those having a water solubility < 1 mg/L where no acute toxicity is expressed in toxicity tests performed at the solubility limit. If for such a substance, however, the BCF is ≥ 500, or if absent, the log K_{ow} is ≥ 4 (indicating a potential for bioaccumulation) and the substance is also not rapidly degradable, a safety net classification, Chronic 4 is assigned. For these types of substances the exposure duration in short-term toxicity 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.

Another example is that Chronic 4 can also be applied where a concern can be suitably justified for a given species or trophic level (for example, a mechanistic basis for hazard or target organism(s) in the context of a PPP or biocide) and there is insufficient chronic toxicity data for the given species/trophic level to indicate that no classification is warranted. In such a case, the water solubility, rapid degradation, and/or bioaccumulation may strengthen the concern.

Alternatively, with a robust basis for concern they may not be such important elements of the assessment but this is a matter of expert judgement.

The precise definitions of the core elements of this system are described in detail in Annexes I-III to this guidance document. For metals and metal compounds (those relevant for assessment under Annex IV according to Annex IV.1), please see Annexes IV.5.2.2.2 and IV.5.3.2.2.

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 in Article 10 of CLP). Where appropriate, M-factors shall be set for acute and long-term hazard classification separately and are considered an integral part of the classification (Article 10 of CLP). This means that, for such classifications, there will normally be two 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 should be derived using the table below (CLP, Annex I Table 4.1.3) and is dependent on the toxicity band of the substances. For example, a substance with an acute toxicity of 0.005 mg/L requires an acute M-factor of 100 to be assigned. Whereas a chronic toxicity of 0.005 mg/L requires a chronic M-factor of 10 to be assigned for a non-rapidly degradable substance and a chronic M-factor of 1 for a rapidly degradable substance.

Annex I: *Table 4.1.3*

Multiplying factors for highly toxic components of mixtures

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

[a] *Non-rapidly degradable.*

[b] *Rapidly degradable.*

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

For deriving the M-factors of metals and metal compounds (those relevant for assessment under Annex IV according to Annex IV.1), please see Annex IV.5.4.

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, classification starts with an evaluation of the adequacy of the data collected, assessment of the results, and concludes on the endpoints most relevant for environmental hazard classification. Where the assessment shows that criteria for environmental classification are fulfilled, an acute aquatic hazard and/or one category for long-term aquatic hazards should be determined. M-factor(s) should be assigned for classifications as Acute 1 and/or Chronic 1.

List of the examples of 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 (Q)SAR 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 examples below. 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 (Q)SAR 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 TG 210 / Early Life Stage toxicity test, flow-through, GLP
Crustacea	*Daphnia magna*:	1.1 mg/L (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 (i.e., algae/aquatic plants) 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 (i.e., algae/aquatic plants) is between 0.001 and 0.01 mg/L.

Degradation (evidence of rapid degradation):

- 70 % degradation in 28 days (10-d window fulfilled) (i.e., 86% in 28 days, based on dissolved organic carbon (DOC)) 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} ≤ 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 chronic 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 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	Wng
Hazard Statement	H410[77]
Precautionary statement(s)	P273, P391, P501

[77] Note that in accordance with Article 27 of CLP 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 toxicity 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 (i.e., algae/aquatic plants) 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 after 28 days (10d window fulfilled) (i.e. 86% in 28 days, based on dissolved organic carbon (DOC)) 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 log K_{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 chronic 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 chronic 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	Wng
Hazard Statement	H410[78]
Precautionary statement(s)	P273, P391, P501

[78] Note that in accordance with Article 27 of CLP 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 toxicity data available for two trophic levels only; combined set of (Q)SAR 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 (Q)SAR 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})	(Q)SAR, 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 TG 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:		45 % in 28 days	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 moderately soluble. Log K_{ow} 5.75. Based on weight of evidence, valid K_{ow} estimated with (Q)SAR is overruled by valid GLP experimental data.

Note that use of experimental data and (Q)SAR data for estimation log K_{ow} should be carefully considered on a case by case basis. The validity of data may be dependent on the structure of the chemical. See Annex III.2.2 for more details on the use of log K_{ow} data and Annex III.3 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 (Q)SAR data are outweighed by the valid experimental data. Hence, the lowest acute toxicity value of 0.79 mg/L is used for crustacea.

Long-term aquatic toxicity:

- Adequate chronic toxicity data available only for fish and algae/aquatic plants, not for crustacea;
- 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 a high potential for bioaccumulation, which can be used in the 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 chronic 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.

- Based on available chronic toxicity data (Table 4.1.0 (b)(i): lowest long-term aquatic toxicity NOEC ≤ 1 mg/L, not rapidly degradable, hence category Chronic 2;
- Surrogate approach (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	Wng
Hazard Statement	H410[79]
Precautionary statement(s)	P273, P391, P501

[79] Note that in accordance with Article 27 of CLP 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[80]	*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 TG 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	

[80] Some species in this trophic level may be representatives of other taxonomic groups than crustacea *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 crustacea *Procambarus clarkii*;

Note that in general for substances for which multiple toxicity data is available for a taxonomic group (in this case crustacea) 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 chronic 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 crustacea chronic toxicity 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 set for aquatic invertebrates should be considered inadequate.

Degradation (evidence of rapid degradation):

- No data available for this substance. In such cases, 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 the 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} > 0.1 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 chronic 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	Wng
Hazard Statement	H410[81]
Precautionary statement(s)	P273, P391, P501

[81] Note that in accordance with Article 27 of CLP 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:	No data	
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 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 above water solubility for all three trophic levels;
- No other evidence of rapid degradation in the environment.

Labelling elements based on the classification:

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

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

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

Aquatic hazard assessment, conclusions and comments:

Physico-chemical properties:

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

Acute aquatic toxicity:

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

Long-term aquatic toxicity:

- No adequate chronic 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 hydrolytic 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 chronic 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 Annex I section 4.1.2.9.3);
- No evidence of NOEC being above 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.*

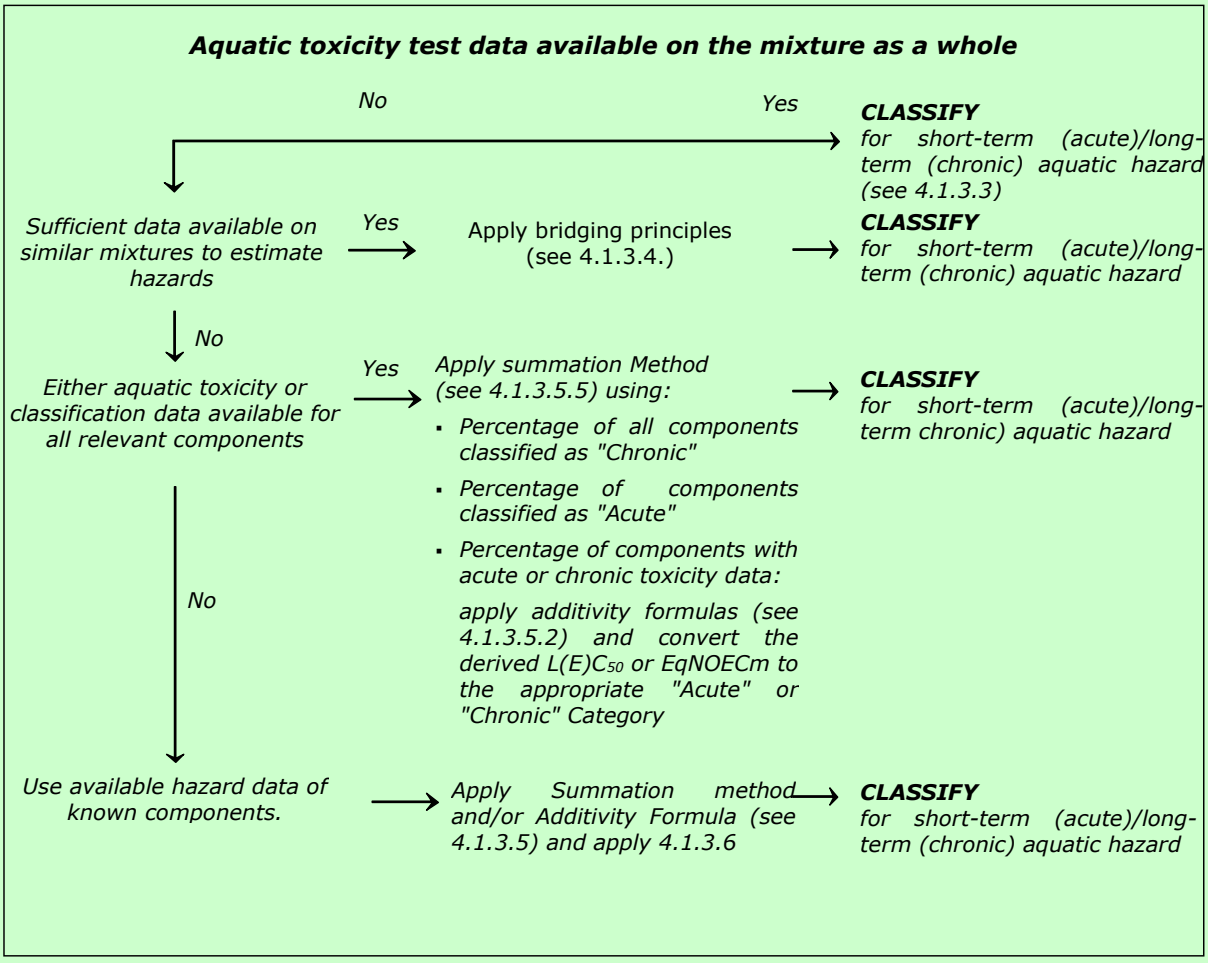
Elements of the tiered approach include:

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 short-term (acute) and long-term (chronic) aquatic environmental hazards



Explanation of Figure 4.1.2:

- Horizontal arrow in first row: 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 section 4.1.3.1 of Annex I to CLP);
    - For the percentage of the other components with acute or chronic toxicity data, the additivity formulas (see section 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.[82]
- 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 short-term (acute) and/or long-term (chronic) 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".*

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

[82] 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 additivity formula will be of limited application.

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 derivation of the correct hazard classification of the final mixture (see also Section 1.6.4 of this guidance document).

Article 11 of CLP 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 section 1.1.2.2.2 (b) of Annex I to CLP. The calculation referred to in (b)(i) of that section, is found in section 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 (chronic) 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 short-term (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 components 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 (ECx or NOEC) available for the mixture as a whole showing ECx(s) or NOEC(s) of the tested mixture > 1 mg/l for normally all trophic levels:

No need to classify for long-term (chronic) 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 section 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 [http://echa.europa.eu/information-on-chemicals/cl-inventory-database]. Where M-factors are not available for the harmonised classification or the SDS there is a general obligation under CLP Art. 10(2) to derive M-factors using available aquatic toxicity data. In cases where 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 short-term (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 short-term (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 (chronic) 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 (chronic) 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 (i.e., no derived classification) 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 crustacea 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 formula.

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 a short-term (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 (chronic) 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: the chronic additivity formula includes a factor of 10 correction for the non-rapidly degradable components to allow equivalent inclusion of not rapidly and rapidly degradable components. Therefore, toxicity values are to be treated as rapidly degradable when deriving a classification. That is, calculated equivalent toxicity values are compared with the criteria in Table 4.1.0 (b)(ii) and M-factors derived from the 'RD' column of Table 4.1.3. Note also 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 formula (see section 4.1.3.5 of Annex I to CLP) and apply section 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 section 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 section 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 formula and 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	Not classified	-	Chronic 3	-	10
Estralamid	Not classified	-	Not classified	-	10
Festralamid	Not classified	-	Not classified	-	66

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 $\times$ M) $\geq$ 25%

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

Long-term aquatic hazard:

Step 1: Classify as Chronic 1 if: $\sum$ (Chronic 1 $\times$ M) $\geq$ 25% (if not, then go to Step 2).

Step 2: Classify as Chronic 2 if: $\sum$ (10 $\times$ Chronic 1 $\times$ M) + $\sum$ (Chronic 2) $\geq$ 25% (if not, then go to Step 3).

Step 3: Classify as Chronic 3 if: $\sum$ (100 $\times$ Chronic 1 $\times$ M) + $\sum$ (10 $\times$ Chronic 2) + $\sum$ (Chronic 3) $\geq$ 25% (if not, then go to Step 4).

Step 4: Classify as Chronic 4 if: $\sum$ (Chronic 1) + $\sum$ (Chronic 2) + $\sum$ (Chronic 3) + $\sum$ (Chronic 4) $\geq$ 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	Resulting Labelling Elements (code)
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 INGREDIENTS 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	Resulting Labelling Elements (code)
GHS Pictogram	GHS09
Signal Word	Wng
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 sensitive 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 $\times$ M) $\geq$ 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	Resulting Labelling Elements (code)
GHS Pictogram	GHS09
Signal Word	Wng
Hazard Statement	H410[83]
Precautionary statement(s)	P273, P391, P501

[83] Note that in accordance with Article 27 of CLP 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, section 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 (0.07 x 10 and 0.1 x 10). Hence - category Chronic 2.

Labelling elements based on the classification:

Element	Resulting Labelling Elements (code)
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:		200 mg/L	1000 mg/L	A.6 / pH: 7.0, non-GLP
Log octanol/water partition coefficient (log K_{ow}):		No data	No data	
Acute (short-term) aquatic toxicity				
Fish:	*Oncorhynchus mykiss*	No data	0.3 mg/L (96 hr LC_{50})	C.1 / static, GLP
Crustacea:	*Daphnia magna*	0.55 mg/L (48 hr EC_{50})	No data	C.2 / static, non-GLP
Algae/aquatic plants: *Scenedesmus subspicatus*		0.37 mg/L (72 hr E_rC_{50})	1.37 mg/L (72 hr E_rC_{50})	C.3 / static, GLP
Long-term aquatic toxicity				
Fish:	*Oncorhynchus mykiss*	0.07 mg/L (28 d NOEC)	1.3 mg/L (28 d NOEC)	OECD 210 / semi-static
Crustacea:	*Daphnia magna*	0.09 mg/L (21 d NOEC)	1.4 mg/L (21 d NOEC)	C.20 / semi-static, GLP

Algae/aquatic plants: *Scenedesmus subspicatus*	0.13 mg/L (72 hr NOEC)	0.53 mg/L (72 hr NOEC)	C.3 / static, GLP
Degradation (evidence of rapid degradation)			
Biotic degradation (% degradation in 28 days (or, if absent, half-life in water (d)):	No data	No data	
Abiotic degradation (Hydrolysis) (half-life (d)):	No data	No data	
Bioaccumulation			
Bioconcentration factor in fish (BCF):	No data	No data	

Long-term hazard 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 Article 4(9) of CLP). 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} 0.37 mg/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*[84]:

$L(E)C_{50m}$ = (50+10) / (50/0.37 mg/L + 10/0.3 mg/L) = 0.36 mg/L

Assign category Acute 1. This means that 60% of this mixture is classified as category Acute 1 and hence, subsequently used in the summation method, the whole mixture is classified as Acute 1.

Long-term aquatic hazard:

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

	Relevant information	Category	C (%)
Component 1	0.07 mg/L (28 d NOEC Fish); No information on degradation. Hence, the substance is considered not rapidly degradable.	Assign Chronic 1, M-factor 1	50 %
Component 2	0.53 mg/L (72 hr NOEC Algae); No information on degradation. Hence, the substance is considered not rapidly degradable.	Assign Chronic 2	10%
Component 3	No data	-	10%
Component 4	Data for basis of classification not available.	Chronic 1	30 %

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*[85] to calculate the combined toxicity for components 1 and 2 (60% of the mixture)

$EqNOEC_m$ = 60 / (50/(0.1 x 0.07) + 10/(0.1 x 1.3)) = 0.008 mg/L for fish

$EqNOEC_m$ = 60 / (50/(0.1 x 0.09)) + 10/(0.1 x 1.4)) = 0.011 mg/L for crustacea

$EqNOEC_m$ = 60 / (50/(0.1 x 0.13) + 10/(0.1 x 0.53)) = 0.015 mg/L for algae

The lowest calculated $EqNOEC_m$ is 0.008 mg/L for fish.

Following the not rapidly degradable correction applied by use of the additivity formula (i.e., a factor of 10 for non-rapidly degradable components), treat the values as those of a rapidly degradable substance by applying point (b) (ii) of Table 4.1.0 of Annex I to CLP. Subsequently, use the 'RD' column of Table 4.1.3. In conclusion, assign category Chronic 1, M-factor 1 to that part of the mixture.

[84] 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.

[85] See also Section 4.1.4.6 of this guidance.

In addition component 4 of the mixture is classified as category Chronic 1 and comprises 30% 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: $\sum$ (Chronic 1 $\times$ M) $\geq$ 25%

$\sum (60 \times 1) + 10 = 70$

Thus, the mixture is classified as category Chronic 1.

Labelling elements based on the classification:

Element	Resulting Labelling Elements (code)
GHS Pictogram	GHS09
Signal Word	Wng
Hazard Statement	H410[86]
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'.

[86] Note that in accordance with Article 27 of CLP, 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.

4.1.5. 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([1]).*

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.*

_____

([1]) 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).

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, 2019)* and also the *Guidance on Labelling and Packaging in accordance with Regulation (EC) No 1272/2008 (ECHA, 2019).*

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:

- Aquatic Acute 1 and/or
- Aquatic Chronic 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:

- Aquatic Acute 1 and/or
- Aquatic 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:

- Aquatic Acute 1

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

- Aquatic 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 in line with Part 1 of Annex III to CLP, where the hazard statement H410 is used on the label due to classification in the long-term hazard category Chronic 1, the hazard statement H400 does not need to appear on the label. Furthermore, where a substance or a mixture is classified both in acute and long-term hazard categories, it is possible to use only hazard statement H410 on the label (see Table 4.1).

Table 4.1 Hazard statement Codes relevant for the hazard class Hazardous to the Aquatic Environment

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[87]	H400; H413	H410
Chronic 1	H410	H410
Chronic 2	H411	H411
Chronic 3	H412	H412
Chronic 4	H413	H413

Precautionary statements

In accordance with Articles 17 and 22 of CLP 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* according to CLP Annex I Table 4.1.4 are:

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

4.1.7. References

ECHA Guidance on information requirements and chemical safety assessment (version 4.0, June 2017), Chapter R7b

OECD 2019: Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals. *Series on Testing and Assessment Number 23 (Second Edition)* ENV/JM/MONO(2000)6/REV1 (http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO(2000)6/REV1&docLanguage=En) (referred here as OECD Guidance 23)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

Guidance for identification and naming of substances under REACH and CLP

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

5. 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[88] should be classified as hazardous to the ozone layer (category 1).

[88] 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 IR&CSA Chapter R.7b, sections R.7.8.3 – R.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 GHS, 2011, fourth revised edition, Section 4.1.1.3:*"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.

According to GHS, 2011, fourth revised edition, Section 4.1.1.3:*"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 (see also Annex 9, para. A9.3.3.2). 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 example tests for potential consideration for classification purposes have been revised or updated. Such revisions may lead to minor modifications of test conditions or even introduction of the potential use of additional effects endpoints depending on the regulatory context. 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 from many sources (e.g., 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 standards; EU standards).

Some general guidance on commonly faced issues with aquatic toxicity testing:

- Evidence should be provided that test concentrations/dose levels and number of concentrations are known and where possible evidence should be provided that concentrations have been maintained throughout the duration of the test. Therefore, mean measured concentrations are preferred over nominal (non-measured) concentrations. If mean measured concentrations are not within ±20% of nominal concentrations, effect values should be related to mean measured concentrations. Where test concentrations remain within ±20% of nominal, mean measured or nominal concentrations can be used, following expert judgement on a case-by-case basis. For flow-through studies the arithmetic mean of measured concentrations should be calculated. For static or semi-static tests the geometric mean of measured concentrations should be calculated (see IR&CSA Chapter R.7b, Appendix R.7.8—1). In some cases where only nominal concentrations are provided, expert judgement may be required to decide whether test concentrations are likely to have been maintained (Note, Nominal testing results on metals or metal compounds (those relevant for assessment under Annex IV according to Annex IV.1) cannot be used for hazard classification as further specified in Annex IV, In contrast, only nominal concentrations (from loading rates) can be used for multi-constituent substances tested using WAF approaches, see Annex I.4.5);
- Some substances, depending on their specific mode of action may produce toxic effects at time points earlier than those typically used in any given test guideline. In such cases, caution should be exercised and evaluation on a case-by-case basis is required. If effect durations less than those indicated in the test guideline are to be accepted for classification purposes, the full test duration should be reported and the respective test guideline validity criteria for that end point must be fulfilled at the time to be used;
- Regarding rapidly degrading substances, studies conducted under flow-through and/or semi-static (usually after 24 hours) conditions are preferred in order to maintain test concentration during the duration of the study. See OECD Guidance 23 (OECD 2019) for further information.
- There are instances where the only data available may lack test details described above. In such cases, expert judgement should be used to determine the suitability of the test for use in classification and the reliability of the endpoint values. For example, there should be enough information to determine whether the test conditions are suitable for the organisms being tested, the viability of the test organisms, demonstration of exposure of the test organisms, a suitable concentration range, and a clear dose response relationship for endpoints of interest. Tests where such information is not available may not be suitable for classification and labelling.

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 size 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 TG 203 (Fish 96 hour LC_{50}) or equivalent should be used for classification.

The Fish Embryo Acute Toxicity (FET) Test (OECD TG 236) was adopted on the 26th July 2013 and its potential to fulfil the REACH information requirement on acute fish toxicity has been the subject of an ECHA commissioned study (May 2015, http://echa.europa.eu/ publications/technical-scientific-reports), which highlighted certain regulatory limitations in its use and thus concluded that the FET test cannot be considered as stand-alone information for addressing the information requirement for acute fish toxicity under the REACH Regulation. Based on current knowledge, ECHA considers that OECD TG 236 might best be used within a Weight of Evidence (WoE) approach together with other independent, adequate, relevant, and reliable sources of information for classification and labelling. However, if the only available information on the fish toxicity of a substance is the FET, the test can be used for classification, even if no other information for weight of evidence is available (https://www.echa.europa.eu/documents/10162/22931011/non_animal_approcches_en.pdf/87ebb68f-2038-f597-fc33-f4003e9e7d7d).

With regards to *in vitro* test methods, as new non-animal alternatives are developed (e.g. the fish cell line assay, OECD TG 249, adopted 2021), it may be possible to use these, as outlined for FET, to assess acute toxicity to fish provided that they fulfil relevant data quality requirements (IR&CSA Chapter R.7b, section R.7.8.4.1).

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. 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. Tests consistent with OECD Test Guideline 210 (Fish Early-life Stage Toxicity Test, FELS), US EPA 850.1500 (the fish life-cycle test), or equivalent can be used in the classification scheme. Currently, other relevant tests include OECD TG 212 (Fish, Short-term Toxicity Test on Embryo and Sac-Fry Stages) and OECD TG 215 (Fish, Juvenile Growth Test).

OECD TG 210 (FELS) is widely accepted as a predictor of chronic toxicity and is used as such for purposes of classification in the harmonised system, particularly as fish early-life stage toxicity data are much more available than fish life cycle or reproduction studies. Technically, the OECD TG 210 is not a 'chronic' test, but a sub-chronic test on sensitive life stages.

However, it is preferred as it is considered to be more sensitive than the OECD TG 212 or OECD TG 215, covering several life stages of the fish from the newly fertilized egg, through hatch to early stages of growth (IR&CSA Chapter R.7b, section R.7.8.4.1). Moreover, the FELS toxicity test is preferable for examining the potential toxic effects of substances which are, for example: expected to cause effects over a longer exposure period, which require a longer exposure period of time to reach steady state (in non flow-through test systems), substances that have a latency of effects, or a longer period to onset of maximum (often sub-lethal) effect. Regarding OECD TG 212, care should be taken when interpreting data from this test to ensure that the test substance is not too lipophilic (e.g. Log K_{ow} > 4), that there is no evidence of endocrine disrupting properties, or other specific modes of action[89]. For further guidance on the use of OECD TG 212 and information on the animal welfare issues related to this test, consult OECD 171 (Fish Toxicity Testing Framework). However, smaller differences in sensitivity between OECD TG 212 and 215 would be expected for chemicals with a non-specific, narcotic mode of action (Kristensen, 1990).

[89] Following amendments to the REACH annexes (Reg (EU) 2022/477 of 24 March 2022) OECD TG 212 has been deleted as a new information requirement due to animal welfare concerns. However, an existing such test can be considered to fulfil the LT toxicity data requirement for fish at Annex IX.

OECD TG 215 measures the growth of juvenile fish over a fixed period of time and it is considered a sensitive indicator of toxicity for the growth endpoint. Although it does not cover all the sensitive points in the fish life cycle, as would normally be required of a chronic toxicity test such as the FELS test, it can be used, for example, when growth inhibition is the most relevant effect endpoint in fish.

Where it has been determined that a substance has endocrine disrupting properties, tests such as the following may be available:

OECD TG 234 (Fish Sexual Development Test adopted on July 28th 2011) is in principle an enhancement of OECD TG 210, where the exposure is continued until the fish are sexually differentiated, i.e. about 60 days post-hatch for Japanese medaka (*Oryzias latipes*), the three-spined stickleback and zebrafish (the exposure period can be shorter or longer for other species that are validated in the future), and endocrine-sensitive endpoints are added. OECD TG 234 currently states that a minimum of three test concentrations should be used, with five test concentrations recommended if the data are to be used for risk assessment. The use of five test concentrations is recommended in order to derive a more precise NOEC/LOEC or ECx value. It should be noted that vitellogenin (VTG) level is affected by exogenous oestrogen stimulation and cannot be used alone for aquatic hazard identification as an endpoint on its own. Rather, it can be used as part of a WoE approach when considered with other data on relevant related effects (e.g., this endpoint in combination with sex ratio endpoint can demonstrate the endocrine mode of action of the test substance).

OECD TG 240 (adopted 28th July 2015) is an extended one generation test using Japanese medaka running until hatching in the F2 generation. This test provides standard long-term toxicity endpoints (hatching and larval survival, growth i.e., length and body weight, etc.) but also has secondary effect endpoints for endocrine disruption. For the latter (vitellogenin etc.) similar considerations as outlined for OECD TG 234 apply.

Regarding OECD TG 204 (Fish, Prolonged Toxicity Test: 14-day Study), OECD has deleted the test guideline on 2nd April 2014. It is noted that, according to the Guidance on Information Requirements and Chemical Safety Assessment (IR&CSA Chapter R.7b, section R.7.8.4.1), "*tests performed according to OECD 204 or similar guidelines cannot be considered suitable long-term tests. They are, in effect, prolonged acute studies with fish mortality as the major endpoint examined*".

I.2.2 Tests with Aquatic Crustacea

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 TG 202 (*Daphnia* acute) or USA-EPA OPPTS 850.1035 (Mysid acute toxicity) or their equivalents should be used for classification.

Although crustacea are the preferred group (*Daphnia magna* being the most common test species), other aquatic invertebrates can be considered on a case-by-case basis. As such, toxicity tests using aquatic insects (e.g., mayfly larvae , chironomids [OECD TG 235]) and molluscs can be acceptable for hazard classification, providing they are relevant and reliable. Where a substance has an intended target invertebrate group (e.g. insecticides), or a group of particular sensitivity, data from such a group or species may be available in addition to crustacea (e.g., daphnids).

I.2.2.2 Chronic testing

Chronic tests with crustacea also generally begin with first instar juveniles and continue through maturation and reproduction. Observational endpoints include time to first brood, number of offspring produced per female, growth, and survival. For daphnids, in particular *Daphnia magna*, 21 days is sufficient for maturation and the production of at least 3 broods, while for mysids 28 days is necessary, and *Ceriodaphnia dubia* produces 3 broods within 7 days (Connors *et al*., 2022). It is recommended that tests consistent with OECD TG 211 (*Daphnia* reproduction), US-EPA 850.1350 (Mysid chronic), ISO 20665 (chronic toxiciy to *Ceriodaphnia dubia*), or their equivalents be used in the classification scheme. Older data according to OECD TG 202 part II could in principle still be available for use pending a thorough assessment.

Data from invertebrate species other than the crustacea mentioned can be used, following the considerations outlined above in Annex I.2.2.1. Concerning the sediment-dwelling larvae of the freshwater dipteran *Chironomus* sp. (OECD TG 218/219), data from such tests can be used provided it can be demonstrated that exposure to the test material is through the water phase and not via sediment. For most substances, uptake from water (bioconcentration, defined as the net result of uptake, transformation, and elimination of a substance in an organism due to waterborne exposure) is believed to be the predominant route of exposure for aquatic organisms. For organic substances and metals, pore water is one of the primary exposure routes for benthic organisms (Di Toro *et al.*, 1991; Ankley *et al.*, 1991). However, for highly lipophilic compounds or other substances that adsorb to particles (e.g. metals), uptake from food or sediment may contribute to the overall exposure, depending on the living and feeding strategy of the exposed organisms. The importance of dietary exposure relative to water exposure as a cause of toxicity is currently not fully understood.

In summary, factors that influence adsorption and thus distribution between sediment and water also influence toxicity to aquatic (pelagic and benthic) species. Generally, the substance must not partition to sediments to any great extent. The low sorption potential of the substance must be demonstrated, and the test design should use the water-spiking method. This may indicate that the organisms are exposed to the substance primarily via the water. When considering the life-stage used in an available test, *Chironomus* spend their most sensitive larval stage (first instar) free swimming in the water phase and will therefore only be exposed via the water in this stage. Other life-stages will involve the sediment so interpretation of results may be less straight-forward. Generally, where sediment is included in the test system, it must be clear what caused the observed toxicity, with regards to the exposure route. Test system equilibrium should favour exposure from the water phase. If it cannot be ruled out that the test organisms were exposed to the substance or metabolites adsorbed to the sediment particle surfaces, the test may not be relevant for classification purposes.

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 TG 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. Annex 2 of OECD TG 201 (Algae) and IR&CSA R.7b report some of the species shown to be generally suitable for the testing and include green algae, diatoms, and cyanobacteria.

The algal growth inhibition test is a short-term test that provides both acute and chronic endpoints. The EC_{50} is treated as an acute value for classification purposes. Classification shall be based on both, the algal growth rate reduction endpoint, E_rC_{50} [= EC_{50} (growth rate)] and NOE_rC [= NOEC (growth rate)] or EC_x value, provided that the control growth is exponential (greater than a factor of 16) (where available, EC_{10} is preferred over NOEC, see 4.1.3.1.1). This endpoint

is preferred because it is not dependent on the test design, whereas the endpoint biomass (growth) inhibition (E_bC_{50}) depends on both, growth rate of the test species as well as test duration and other elements of test design.

In circumstances where the basis of the EC_{50} is not specified and no E_rC_{50} is recorded, classification shall be based on the lowest EC_{50} available. Where the algal toxicity E_rC_{50} 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 TG 221 on *Lemna* and US-EPA 850.4400 (aquatic plant toxicity, *Lemna*) and OECD TG 238/239 (*Myriophyllum spicatum*) should be used. The observational endpoint for *Myriophyllum spicatum* is based on the vegetative growth. Note that for tests using sediment (e.g., OECD TG 239), TG considerations regarding sediment should be followed and exposure should be from the water.

The respective macrophyte TGs are considered to provide both acute and chronic endpoints over the experimental time periods specified.

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 (Q)SARs.

I.3.1 Acute toxicity

Acute toxicity for classification purposes refers to the intrinsic property of a substance to be harmful 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 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 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 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. M-factors are derived using the endpoint value used to derive the hazard category (see Section 3).

I.3.2 Chronic toxicity

Chronic toxicity, for classification purposes, 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 long-term hazard classification, a differentiation is made between rapidly degradable and non-rapidly degradable substances. Substances that rapidly degrade are classified in category Chronic 1 when the chronic toxicity NOEC or EC_x is determined to be ≤ 0.01 mg/L. Rapidly degradable substances with a chronic toxicity NOEC or EC_x between 0.01 and 0.1 mg/L are classified in category Chronic 2. Rapidly degradable substances with a chronic toxicity NOEC or EC_x between 0.1 and 1.0 mg/L are classified in category Chronic 3. Finally, those rapidly degraded 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, based on data or by default (i.e., default applies in cases 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 ≤ 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. Finally, those not rapidly degraded 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 or 2. Note, category Chronic 3 does not apply to non-rapidly degraded substances.

When classifying substances as Chronic 1, it is necessary at the same time to indicate an appropriate M-factor. M-factors are derived using the endpoint value used to derive the hazard category (see Section 3).

In the absence of chronic toxicity data, chronic hazard 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 (see section 4.1.3.3.1), 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 is used directly to determine an appropriate long-term hazard category.

   In cases where chronic toxicity data are available for all three trophic levels, but data are absent for the most acutely sensitive species, the chronic toxicity dataset may not be considered adequate (see Section 4.1.3.3.1). In such cases, it may be appropriate to derive a classification using available acute toxicity data for the most acutely sensitive species following the procedure outlined below (b);

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 toxicity 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 (Figure 4.1.1 and Table 4.1.0(b)(iii) of Annex I to CLP);

c. In order to remove or downgrade a chronic aquatic classification, using chronic toxicity data, it must be demonstrated that the NOEC(s) (or equivalent EC_x) used would be suitable to remove or downgrade 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 or EC_x for the most sensitive species identified by the acute toxicity. Thus, if a long-term hazard classification has been based on a fish acute

LC_{50}, it would generally not be possible to remove or downgrade this classification using a long-term NOEC or EC_x from an invertebrate toxicity test. In this case, the NOEC or EC_x 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 or EC_xs 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 EC_x or equivalent EC_x 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

Three types of exposure conditions are employed in both acute and chronic tests and in both freshwater and saltwater media: static, static-renewal (semi-static), 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 stoichiometric 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

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 rigid rules cannot be applied. The nature of many of the difficulties means 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 that is suitable for use in applying the classification criteria. Metals present their own set of difficulties and are discussed separately (see Annex IV on metals).

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. In cases where loss of test material may occur, actual test concentrations are likely to be less than the nominal or expected test

concentrations and under-represent the actual toxicity. In circumstances where a substance is known to be difficult to test, expert judgement is needed to determine the acceptability of such tests for use in classification. Similarly, caution is also needed when deriving appropriate M-factors.

I.4.1 Unstable substances

While testing procedures which minimise the impacts of instability in the test media should ideally have been deployed, in practice, in certain tests, it can be almost impossible to maintain a constant concentration throughout the test. Common causes of lack of constant exposure concentration during the test include but are not limited to: oxidation, hydrolysis, photodegradation, volatilisation, sorption, and biodegradation. While the latter forms of degradation can be more readily controlled, such controls may be 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 a 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 the 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 guidelines can be considered:

a. where measured data are available for the start and end of the 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 the test are below the analytical detection limit, such concentrations shall be considered to be half of 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 product 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 below the detection limit in purified water. Nevertheless such substances can show toxicity and, where no toxicity is found, expert 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. Here, OECD Guidance 23 (OECD 2019) provides guidance on how to proceed.

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 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 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 below 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 analytically verified/ measured concentrations, the techniques used to achieve the maximum dissolved concentrations must be considered as appropriate.

I.4.3 Other factors contributing to concentration loss

A number of other factors can also contribute to losses of test material from solution and, while some can be avoided by correct study design, interpretation of data where these factors have contributed will 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 K_{oc}/log K_{ow} substances or some substances with a permanent charge (such as some cationic surfactants). 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 due to 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. 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 (UVCBs and multi-constituent substances) (OECD series on testing and assessment Number 23, Guidance Document on Aquatic Toxicity Testing of Difficult to Test Substances and Mixtures) are characterised by a range of chemical structures, covering a wide range of water solubilities and other physico-chemical characteristics. In 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. Whilst taking a constituent based approach may be required for assessing rapid degradability and bioaccumulation, in the absence of adequate whole substance aquatic toxicity data the mixtures approaches (following figure 4.1.2 of CLP) can be followed.

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.

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II ANNEX II: RAPID DEGRADATION

II.1 Introduction

Degradability is one of the important properties of substances that has an 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 which consider 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 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. Therefore, the present section applies only to organic and organometal compounds. A separate section on the classification & labelling (C&L) of metals is provided in Part 4.4.1.5 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 (Q)SAR 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, section 4.1.3.3.1).

II.2 Interpretation of degradability data

Based on the harmonised criteria (CLP I.4.1.2.9), guidance for interpretation of degradation data is presented below.

II.2.1 Ready biodegradability

Ready biodegradability is defined in the OECD Test Guidelines No. 301 methods A-F (OECD 1992), OECD TG 306 (marine water) and OECD TG 310 (OECD 2006). All organic substances that degrade to a level higher than the pass level in a standard OECD ready biodegradability or 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.

Regarding marine data, OECD TG 306 series on Biodegradability in Seawater includes seawater variants of the Closed Bottle Test (OECD 301 D) and of the Modified OECD Screening Test (OECD 301 E). Degradation of substances in seawater has generally been found to be slower than that in freshwater tests inoculated with activated sludge or sewage effluent. This is also confirmed in

the research program conducted in CEFIC LRI ECO11 project, where it was demonstrated that both magnitude and variation in the bacterial diversity were higher in the following order for the different environmental sources: activated sludge > rivers > estuaries > sea water.

OECD test guideline 306 explicitly indicates that results of those tests (shake flask and closed bottle) "*are not to be taken as indications of ready biodegradability, but are to be used specifically for obtaining information about the biodegradability of chemicals in marine environments". Those tests "are not tests for ready biodegradability since no inoculum is added in addition to the micro-organisms already present in the seawater. Neither do the tests simulate the marine environment since nutrients are added and the concentration of test substance is very much higher than would be present in the sea*". However, it is acknowledged that biodegradation in seawater is generally slower. Therefore >60% ThOD or >70% DOC removal in a Biodegradability in Seawater test (OECD 306) obtained after 28 day (Closed Bottle Method) or 60 day (Shake Flask Method) is indicative of potential for ultimate biodegradation in the marine environment and can also be regarded as a piece of evidence that the substance is likely to fulfil the criteria for ready biodegradability. For example, a positive OECD TG 306 test is regarded as an indication of rapid degradation for classification and labelling. However, if the ratio of inoculum to substrate in the test system is enhanced by increasing the concentration of micro-organisms as it has been proposed recently in Ott *et al*. (2020), this also increases the degradation potential. In this case the test system does not resemble a pelagic water body anymore and is thus less stringent. This has consequences for interpretation of the so produced degradation data with respect to conclusion on ready biodegradation behaviour as such enhancements will render the test unsuitable for assessing ready biodegradability (rapid degradation) under CLP.

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 inoculum 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 (e.g., OECD TG 209), 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 Chapter R.7b, section R7.8.18. 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 of the onset of biodegradation. This is not in line with the OECD TG 301 in which the 10-day time window applies to the OECD ready biodegradability tests except the MITI I test (OECD TG 301C). Furthermore, in the Closed Bottle test (OECD TG 301D), a 14-day window may be used instead when measurements have not been made after ten days or are not possible due to experimental design. However, occasionally only limited information is available for 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 10-day time window is available. This should, however, only be accepted for existing experimental studies and test results where the 10-day window does not apply or is not available. Tests following current test guidelines should allow assessment of the 10-day window, where appropriate.

Where there is sufficient justification, the 10-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 stereoisomers, 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 10-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 do not fulfil the criteria for classification as hazardous to the aquatic environment.

The fulfilment of criterion (c) of paragraph 4.1.2.9.5 of CLP (other convincing scientific evidence) 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 in the context of rapid degradation 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 (e.g., OECD TG 309). However simulation test data from other environmental compartments could be considered as well (e.g., OECD TG 308), but such data require in general more scientific judgement before use.

II.2.3.1 Aquatic simulation tests

Aquatic simulation tests (e.g. Aerobic Mineralisation in Surface Water – Simulation Biodegradation Test, OECD TG 309) 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, with 12 °C being the average surface water temperature in the EU (see Table R.16-8 in IR&CSA Chapter R.16 "Environmental exposure estimation"), that can be considered under CLP;

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, although detection of an anthropogenic substance in groundwater could be an indication that the substance is not rapidly degradable. 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 TG 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 TG 303 (Simulation Test - Aerobic Sewage Treatment -- A: Activated Sludge Units; B: Biofilms) and OECD TG 314 B (Simulation Tests to Assess the Biodegradability of Chemicals Discharged in Wastewater) cannot be used for assessing the degradation in the aquatic environment, for classification purposes. 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 wastewater 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 comparable 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 in the absence of aquatic degradation data 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 (e.g., OECD TG 311) cannot be used to decide whether a substance should be regarded as rapidly degradable for classification purposes, because the aqueous phase of the aquatic environment is generally regarded as the aerobic compartment where the aquatic organisms, such as those of relevance for aquatic hazard classification, are found.

II.2.3.8 Hydrolysis

Data on hydrolysis e.g. OECD TG 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 TG 316 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 adequate information be available for a thorough evaluation based on photochemical degradation.

II.2.3.10 Estimation of degradation

Hydrolysis: Certain (Q)SARs 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 (Q)SARs 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.7b, section R.7.9.3.1).

Biodegradation: In general, no quantitative estimation method ((Q)SAR) 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.7b, section R.7.9.3.1.

In general, a (Q)SAR prediction that the substance is not rapidly degradable is considered a better justification 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. Apart from the substance's physical-chemical properties, volatilisation from the aquatic environment is also 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 refer to single substances. However, complex substances also need to be considered for classification and labelling and these are normally considered as single substances in a regulatory context. Some complex substances such as multi-constituent substances of natural origin, chemicals that are produced or extracted from mineral oil or plant material, etc., are highly complex with a high number of constituents, many of which may be unidentified. The constituents of a complex substance can be highly varied and possess a wide range of physical-chemical

properties important for aquatic degradation assessment (e.g., water solubility, Log k_{ow}, adsorption characteristics, and volatility). Therefore, it may not be possible to make a degradation assessment using a test on the whole complex substance and data on known constituents will need to be considered to assess the whole substance. Occasionally, complex substances may be 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. Occasionally, a borderline degradation is found because some of the individual constituents may be rapidly degradable and others may not be rapidly degradable. As above, this requires a 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 (OECD TG 301 suite and 310) recommend 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 TG 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-day 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

Where data from more than one experimental degradation study are available for the same substance, there is a possibility that the results may be conflicting. The IR&CSA Chapter R.7b, section R.7.9.4.1 indicates that ready biodegradability tests may sometime fail because of the stringent test conditions, positive test results should generally supersede negative test results in cases where good quality experimental studies are presented. However, when conflicting test results are reported, possible differences in the test conditions and design should be investigated. In particular the origin of the inoculum should be examined in order to verify whether or not there are differences in the adaptation of the inoculum which may explain the differences in the results (OECD, 2006b). Also, differing results always have to be assessed considering the test conditions, substance properties and reliability of the data. Good data reliability depends on the test method applied, statistical robustness of the study and its reporting which in turn depend on several factors, e.g. number of replicates, and number of controls.

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. This is especially likely in the Modified MITI (I) test (OECD TG 301C) and the Manometric Respirometry test (OECD Test Guideline 301F) where high concentrations (100 mg/L) are prescribed, compared to the low test substance concentrations 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.7b, section R.7.8.14) or by assessing whether there is evidence of inhibition of intrinsic respiration in the ready biodegradability test (e.g., lower respiration in the test item vessel compared to the blank inoculum may be indicative of an inhibitory effect).

Volatile substances should only be tested in closed systems, such 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 can provide a range of half-lives for various 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 conservative half-life, 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 waters (e.g.,

OECD TG 309) are preferred relative to aquatic sediment or soil simulation test data for 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:

c. 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 10-day window condition may be waived for complex multi-component substances and the pass level applied at 28 days, as discussed in II.2.1.2). If this is not possible, then the pass level should be evaluated within a 14-day time window if possible, or after the end of the test; or

d. 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

e. The substance is demonstrated to be primarily degraded biotically or abiotically e.g. via hydrolysis, 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 fulfil 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 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 (Q)SARs, 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

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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 Chapter R.7c, section 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 Chapter R.7c, section 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. IR&CSA Chapter R.7a, section 7.1.8 gives guidance on n-octanol/water partition coefficient and IR&CSA Chapter R.7c, section 7.10.4 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, section 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 IR&CSA Chapter R.7c, section.

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 ((Q)SARs). Guidance for interpretation of such data is given in IR&CSA Chapter R.7c, sections 7.10.4 and 7.10.5. Guidance is also given on ionised chemicals and other classes that need special attention (see Annex 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).

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 IR&CSA Chapter R.7c, section 7.10.4. BCF results of 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.

Different test guidelines for the experimental determination of bioconcentration in fish have been documented and adopted, the most generally applied being the OECD TG 305 (OECD, 2012; C.13 in Test Methods Regulation 440/2008 is a corresponding test). 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 relate to experimental considerations, 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.

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 OECD TG 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 Chapter R.7c, section 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 measurements in water and fish samples. The BCF from radio-labelled studies should, preferentially, be based on the parent compound. If these are unavailable, for classification purposes, the BCF based on total radio-labelled residues can be used. If the BCF, in terms of radio-labelled residues, is ≥ 1000, the identification and quantification of degradation products documented to be ≥ 10 % of total residues in fish tissues at steady state, are strongly recommended. This is because 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 represents both the parent substance and takes account of the radio labelled part of the metabolites (i.e., the BCF represents the whole undegraded molecule). Thus, 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. Also, for some substances it is the metabolite which is the most toxic or which has the highest bioconcentration potential. Therefore, 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).

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. As these concepts are of limited applicability to metals and metal compounds (relevant for assessment for assessment under Annex IV according to Annex IV.1), please see Annex IV.4 for more information.

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 Relationship ((Q)SAR) results for log K_{ow} may be used in the classification process. Such (Q)SAR results may be used without modification to the agreed criteria when they meet the validity criteria indicated in IR&CSA Chapter R.6. These requirements include, among others, the use of a scientifically valid model and that the substance falls within its applicability domain. For substances like strong acids and bases, substances which react with the eluent, or surface-active substances, a (Q)SAR 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}. For ionisable substances, measurements should be taken on 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. Similarly, (Q)SAR estimates should be based on the non-ionised structure. 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.

III.2.2.1 Experimental determination of K_{ow}

For experimental determination of K_{ow} values, several different methods are described in standard guidelines. IR&CSA Chapter R.7a, section 7.1.8.3 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 (Q)SARs for determination of log K_{ow} and BCF

Numerous (Q)SARs have been and continue to be developed for the estimation of K_{ow} and BCF. When an estimated K_{ow} value is found, the estimation method has to be taken into account. Further guidance is also provided in IR&CSA Chapter R.7a, section 7.1.8.4. (Q)SARs can also be used to derive BCF values. However, as CLP (I.4.1.2.8) clearly prefers experimental BCF data and experimental log K_{ow} data where available, (Q)SAR BCF data can only be considered as part of a broader WoE approach. As for other endpoints derived using (Q)SARs, careful attention should be paid to the validity of the result as further detailed in IR&CSA Chapter R.6. It should be noted that due to the wording of CLP (I.4.1.2.8), (Q)SAR BCF data cannot be used as a one for one substitute for experimental BCF or log K_{ow} data. Furthermore, following the weighting of data described above (Q)SAR BCFs derived using as input experimental data (e.g., log K_{ow} and intrinsic clearance data from OECD TG 319A and B) should generally be given greater weight than those where the log K_{ow} and other source data is calculated. Examples of freely available (Q)SAR software programs that include models for the prediction of log K_{ow} and BCF are EPISuite (https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface), OECD (Q)SAR Toolbox (https://qsartoolbox.org/) and VEGA (https://www.vegahub.eu/).

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 Chapter R.7c, mainly in Appendix R.7.10-3.

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 uptake. 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, e.g., water solubility. 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 Chapter R.7c, section 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 (Q)SAR estimations of log K_{ow} (see Annex 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 IR&CSA Chapter R.7c, Appendix R.7.10-3.

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 Chapter R.7c, section 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 Chapter R.11).

III.3.4 Surface-active substances (surfactants)

Surfactants consist of a non-polar, 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 IR&CSA Chapter R.7c, Appendix R.7.10-3 for further guidance.

Measured (experimentally derived) BCF values on surfactants show that BCF tends to increase with increasing alkyl chain length and be dependent on 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 shake-flask 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 IR&CSA Chapter R.7c, Appendix R.7.10-3.

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 ≥ 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, 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 (IR&CSA Chapter R.7c, section R.7.10.4.6).

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 ≥ 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, (Q)SAR 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 Chapter R.7c, gives guidance on read-across and categories in section R.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. A conclusion on (the potential for) bioaccumulation is required under CLP and a conclusion should always be presented. In the event that available data is genuinely equivocal,

a conclusion of 'inconclusive' may be acceptable but a positive/negative conclusion is clearly preferred. For metals and metal compounds (relevant for assessment under Annex IV according to Annex IV.1), please see Annex IV.4.

Experimentally derived BCF values of high quality are ultimately preferred for classification purposes. BCF results from poor or questionable quality studies should preferably 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. As discussed in III.2.2.2, BCF (Q)SARs cannot be placed in the decision scheme due to the considerations expressed in CLP (I.4.1.2.8) but can be used as part of a WoE assessment.

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 experimental data of high quality are available, validated Quantitative Structure Activity Relationships ((Q)SARs) for log K_{ow} may be used in the classification process. Such validated (Q)SARs 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 (Q)SAR estimated value of $K_{ow,}$ or an estimate based on individual *n*-octanol and water solubilities could be provided instead of an analytical determination of K_{ow}.

If data are available but not validated, expert judgement should be used. Attempts to reach a conclusion should be made with all available data under a weight of evidence approach, where possible.

As mentioned in the first paragraph above, whether or not a substance has a potential for bioaccumulation 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 has a potential for bioaccumulation in the aquatic environment*

→ BCF < 500: *The substance does not have a potential for bioaccumulation in the aquatic environment*

Valid/high quality experimentally determined BCF value → NO:

→ Valid/high quality experimentally determined log K_{ow} value → YES:

→ log K_{ow} ≥ 4: *The substance has a potential for bioaccumulation in the aquatic environment*

→log K_{ow} < 4: *The substance does not have a potential for bioaccumulation in the aquatic environment*

Valid/high quality experimentally determined BCF value → NO:

Valid/high quality experimentally determined log K_{ow} value → NO:

Use of validated (Q)SAR for estimating a log K_{ow} value → YES:

→ log K_{ow} ≥ 4: *The substance has a potential for bioaccumulation in the aquatic environment*

→ log K_{ow} < 4: *The substance does not have a potential for bioaccumulation in the aquatic environment*

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 part 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 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 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.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/EC_x 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[90]). 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 4.1.3.2.4 of this document) is also applicable to metals.

The term adequacy covers here both the **reliability** *(*inherent quality of a test relating to test methodology and the way that the performance and results of a test are described) and the **relevance** *(*extent to which a test is appropriate to be used for the derivation of an ecotoxicity reference value) of the available ecotoxicity data.

Under the reliability criteria, metal specific considerations include the description of some abiotic parameters in the test conditions for enabling the consideration of the bioavailable metal concentration and free metal ion concentration:

- **Description of the physical test conditions**: further to the general parameters (O_2, T°, pH, …) abiotic parameters such as dissolved organic carbon (DOC), hardness, alkalinity of the water that govern the speciation and hence the metal bioavailability is required. A proper description of culture conditions related to the level of essential metals is required to avoid artefacts due to acclimatisation/adaptation (see also below);
- **Description of test materials and methods**: to calculate the free metal ion concentration with speciation models the concentrations of dissolved major ions and cations like Al, Fe, Mg, Ca… are required;
- **Concentration-effect relationship; hormesis**: sometimes an increased performance in growth or reproduction is seen at low metal doses that exceed the control values, referred to as hormesis. Such effects can be important especially for major trace nutrients such as

[90] 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.

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 Chapter R.7c, section R.7.13.1).

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 endpoints (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 TG 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 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 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 Annex IV.2.1 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[91] 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[92] 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).

[91] 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.

[92] The standard protocol in Annex 10 to UN GHS presently only foresees a long-term loading rate of 1 mg/l and lower loading rates may not even be practically feasible for each case. While TDp testing at lower loading rates is in principle the best way forward it is technically often not feasible for the lower chronic loading rates. Extensive experience with the T/D protocol demonstrated that reliable predictions can be made for other loading rates. In order to make maximal use of existing Transformation Dissolution data, the 28 days results for the lower chronic loading rates (0,1 and 0,01 mg/l) can therefore be derived by extrapolation from TDp evidence from other loading rates. Such read-across should be justified on a case by case basis and supported by reliable information on the T/D at different loading rates, *e.g*. over 7 and/or 28 days. It should be noted that the relationship between loading rate and dissolved metal concentration may well not be linear. Therefore, extrapolation of T/D data to lower loadings should preferably be made by using the equations of section A10.6.1 of the UN-Annex 10 transformation dissolution protocol or alternatively by extrapolating in a precautionary way.

The UN announced to change/update Annex 10 in the near future to bring it better in line with the chronic classification strategy an aim that is already anticipated in this guidance note for the CLP.

IV.2.3 Comparison of aquatic toxicity data and solubility data

A decision on whether or not the substance is classified will be made by comparing aquatic toxicity data and solubility data. Depending on the available data two approaches can be followed.

1. When only a **limited dataset** is available existing data should be taken together irrespective of whether the toxicity and dissolution data are at the same pH and the lowest data point should give the basis for classification (this should be used as the default approach). This default approach may lead to the lowest toxicity data point compared with the highest Transformation Dissolution result each derived at different pH levels used for the purpose of classification.
2. When a more **extensive toxicity/dissolution dataset** is available, a split of the acute and chronic ecotoxicity reference values can be performed according to their pH used during T/D test. The worst case classification entry across pHs should be used based on comparing TDp data with relevant ecotox data across the pH range. Meaning that toxicity data and transformation data are in this case always compared at the same pH.

This split of the effects data into pH classes would apply in an equal way to the acute and the long-term effects data sets.

IV.3 Assessment of environmental transformation

Environmental transformation of one species of a metal to another species of the same metal does not constitute 'degradation' as applied to organic compounds and may increase or decrease the availability and bioavailability of the toxic species. In addition naturally occurring geochemical processes can partition metal ions from the water column while also other processes may remove metal ions from the water column (e.g. by precipitation and speciation). Data on water column residence time, transformation in the aquatic environment, and 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 Annex 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 multiple lines of evidence that could be considered 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 in speciation to species which are considerably less soluble than that of the metal compound being considered.

Some caution is recommended; see Annex IV.1 of this document, the 5th and 6th paragraph.

⚠ Comment by ECHA: Two workshops were held on the issue, in 2012 and 2019. The 2012 workshop defined " types of metals in respect to Rapid Removal (RR) mechanisms: 1) metals that methylate and are by default not considered as rapidly transformed (e.g., Hg), 2) metals that quickly hydrolyse and form different products that quickly precipitate in the water column (Al and Fe) for which the new species can be considered as rapidly transforming and 3) metals for which the key question is 'irreversibility' (i.e., binding to a non-bioavailable form under a range of environmental conditions). A second workshop (WS) was held in June 2019 to discuss the issue of Rapid Removal (RR) for type 3 metals. The conclusion of the WS was that at this stage neither RR nor the extended T/D protocol (T/Dp-E) were suitable for use under CLP (CA_68_2019) and that metals shall only be assessed on a case-by-case basis evaluating the available evidence. This conclusion was brought to CARACAL 32, which agreed with the conclusion (CA_101_2019). Consequently, neither RR nor the T/Dp-E are considered

suitable for use under CLP without further technical advancements of the science and case by case data sets. Instead, environmental transformation as described in IV.3 shall be used for classification and labelling. Annex IV example D provides a practical example, taking both chemical transformation and potential removal mechanisms into account.

IV.4 Bioaccumulation

While log K_{ow} is a good predictor of BCF for certain types of organic compounds e.g. non-polar 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 $ERV_{compound}$ = acute ERV of the metal compound = acute ERV of metal ion x (Molecular weight of metal compound /atomic weight of the metal).

Chronic $ERV_{compound}$ = 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. 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.

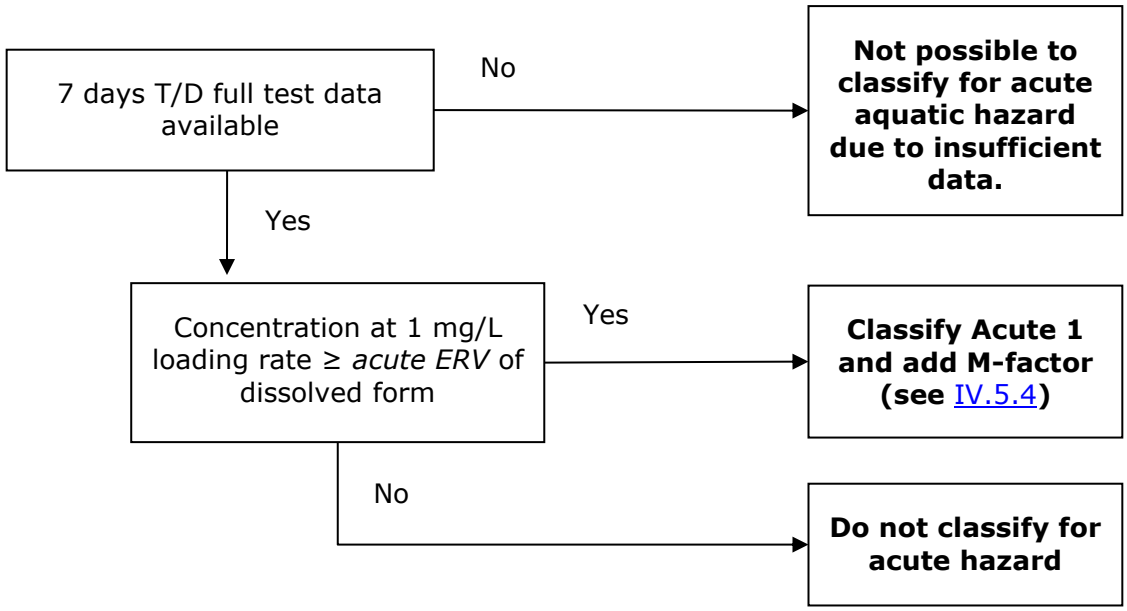
Where the acute ERV for the metal ions of concern is less than or equal to 1 mg/L consideration must be given to the data available on the rate and extent to which these ions can be generated from the metal. Such rate and extend data, to be valid and useable should have been generated using the Transformation/Dissolution 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. 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 Figure IV. 2 and IV. 3.

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 Annex IV.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:

a. **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

b. **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

c. **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. 2 Classification strategy for determining long-term aquatic hazard for metals

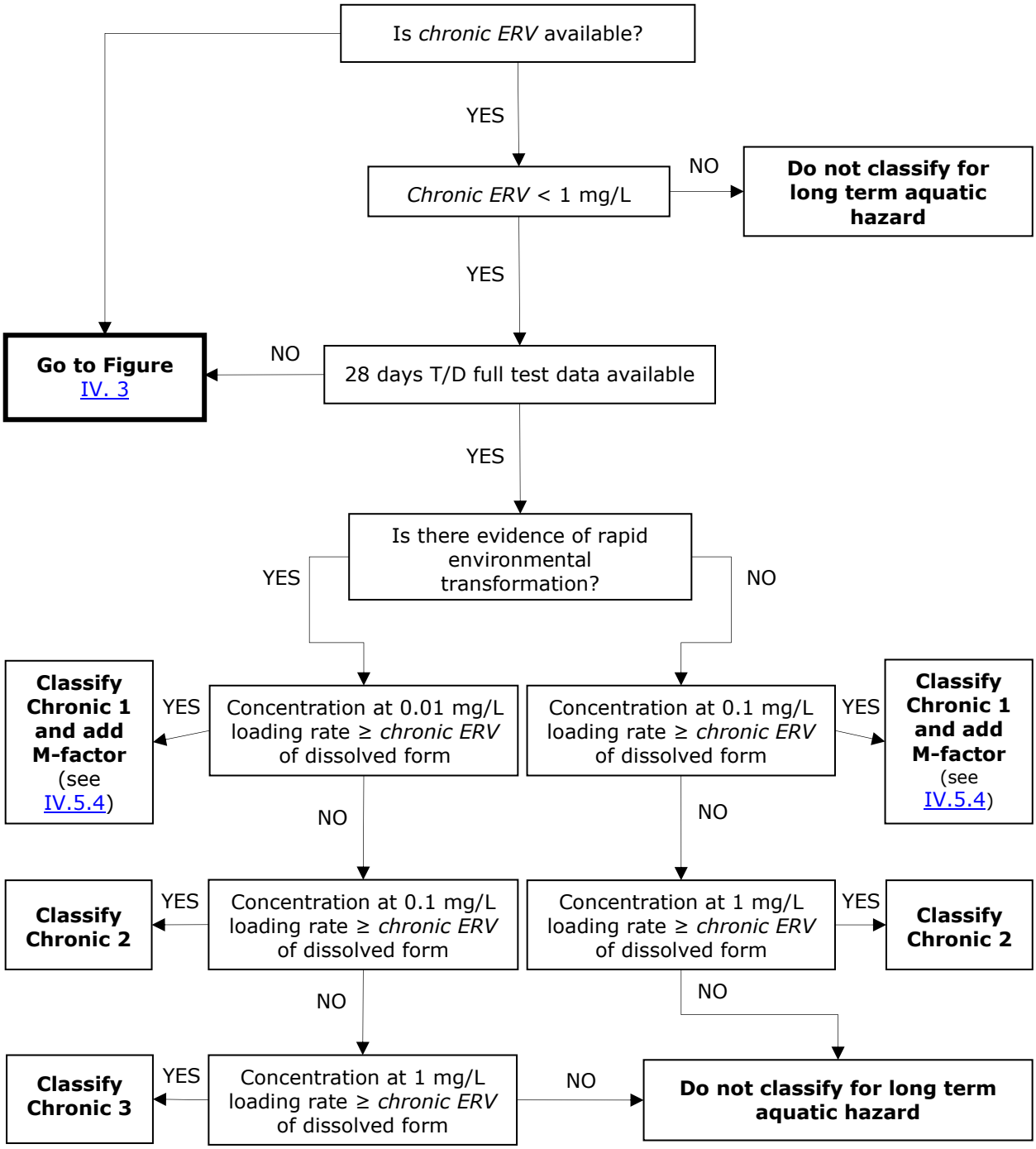
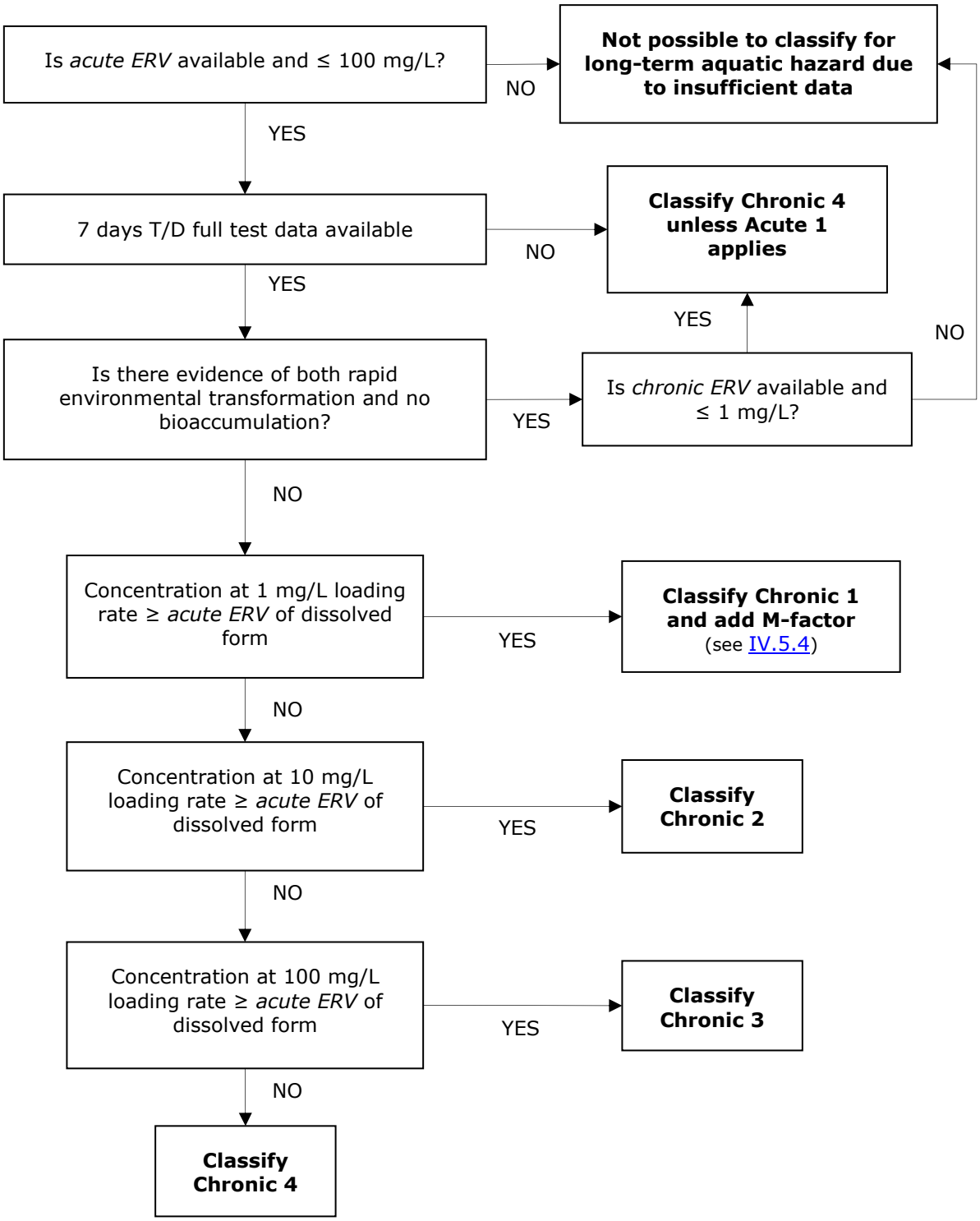


Figure IV. 3 Classification strategy for determining long-term aquatic hazard for metals in absence of appropriate chronic toxicity reference and/or T/Dp data



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. 4.

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

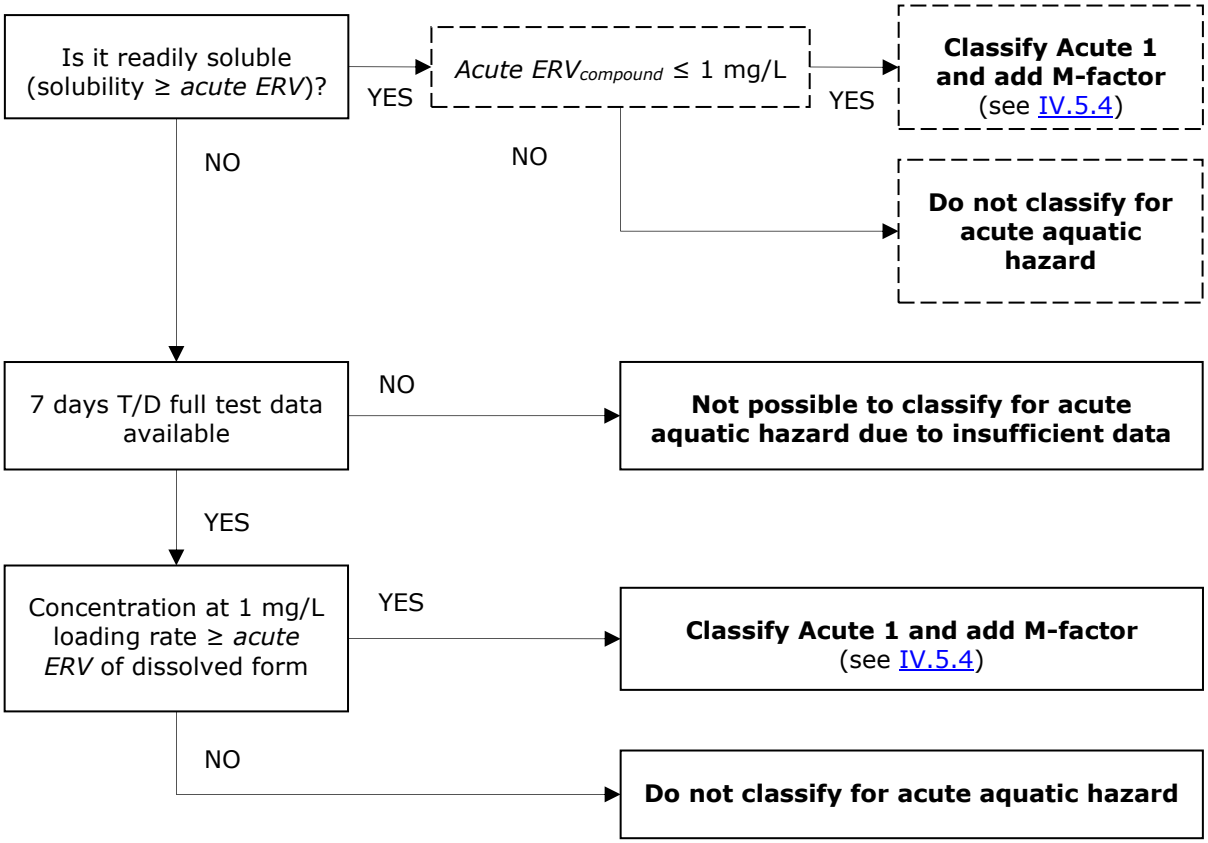
Classify the metal compound as ***Category Acute 1*** if the acute $ERV_{compound} \leq 1$ mg/L, an M-factor must also be established as part of this classification (see IV.5.4).

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. 4 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 Figure IV. 5 and IV. 6.

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$_{compound}$ ≤ 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$_{compound}$ > 0.1mg/L and ≤ 1 mg/L.

If there is *evidence* of rapid environmental transformation:

a. **Classify** the metal compound as ***Category Chronic 1*** if the chronic ERV$_{compound}$ ≤ 0.01 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$_{compound}$ > 0.01mg/L and ≤ 0.1 mg/L; or

c. **Classify** the metal compound as ***Category Chronic 3*** if the chronic ERV$_{compound}$ > 0.1mg/L and ≤ 1 mg/L.

Poorly soluble metal compounds

Where *the chronic ERV* for the metal ions of concern is greater than 1 mg/L, the metals need not be considered further in the classification scheme.

Where the chronic ERV$_{\mathbf{compound}}$ 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 Annex IV.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:

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 0.01 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

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 0.1 mg/L is greater than or equal to the chronic ERV; or

c. **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 Annex IV.3 and IV.4), *readily soluble metal compounds* are classified as:

a. **Category Chronic 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); or

b. **Category Chronic 2** if the acute $ERV_{compound} > 1$mg/L and ≤ 10 mg/L; or

c. **Category Chronic 3** if the acute $ERV_{compound} > 10$mg/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 Classification strategy for determining long-term aquatic hazard for metal compounds

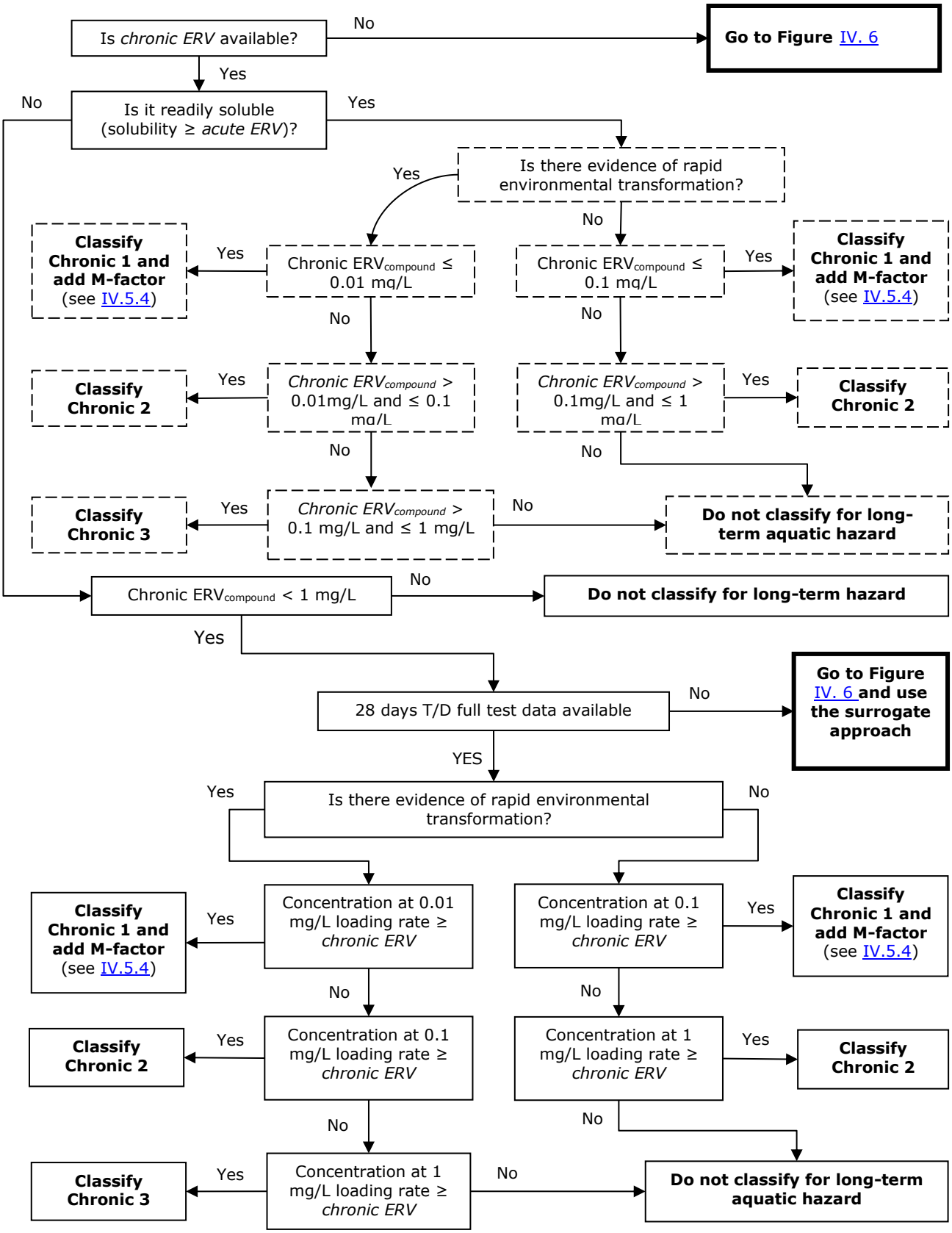
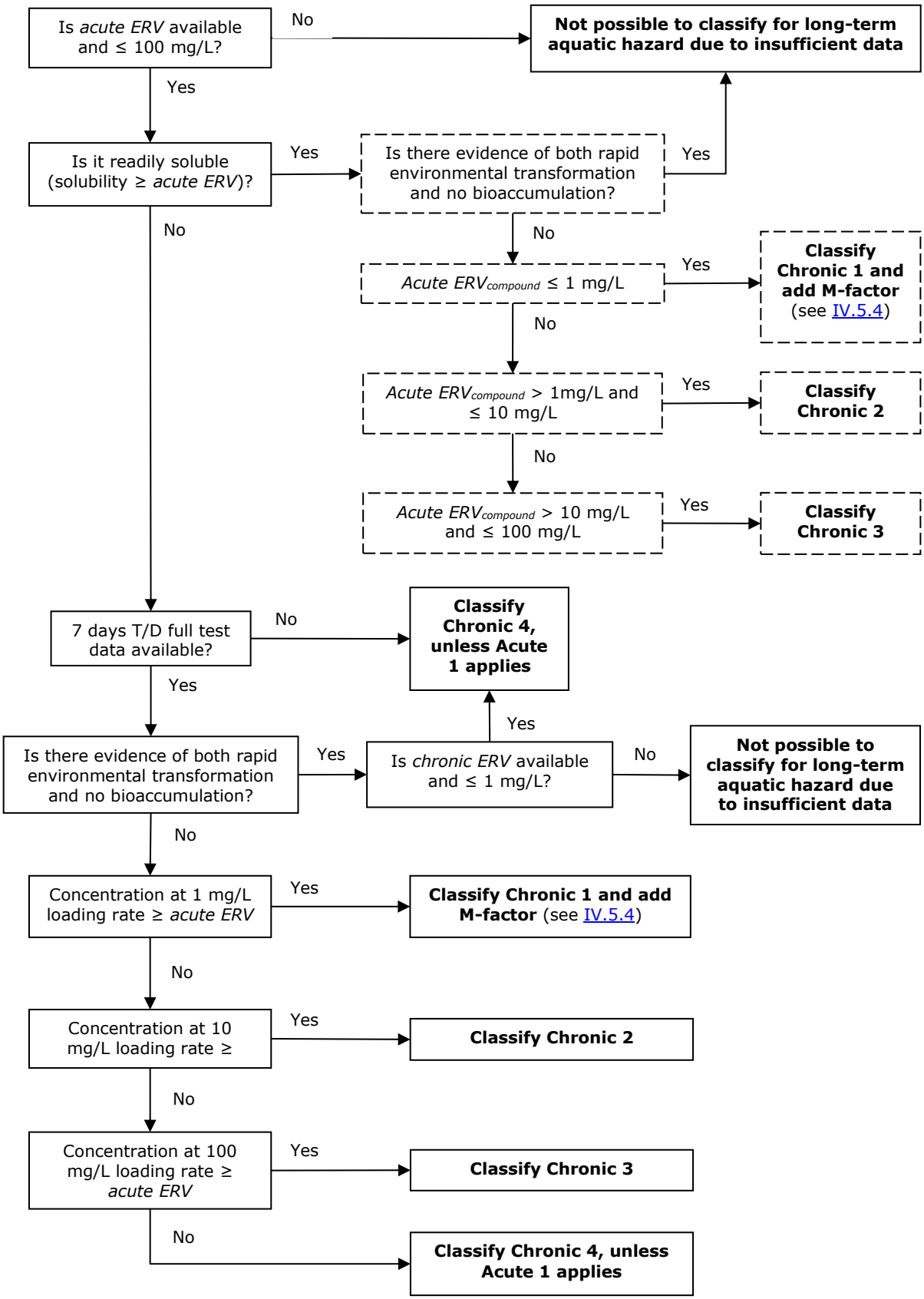


Figure IV. 6 Classification strategy for determining long-term aquatic hazard for metal compounds in absence of appropriate chronic toxicity reference and/or T/Dp data



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 Article 10(4) of CLP.

For *soluble metal compounds* M-factors are applied as for organic substances (see Table IV. 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 (7 d at a loading of 1 mg/L or 28 d at the loading used to determine classification as Chronic 1, i.e., 0.1 or 0.01 mg/L, depending on rapid/no-rapid transformation) and the ERV of the dissolved metal ion taking the considerations mentioned in IV.2.3 into account. If this ratio is:

- below 10 then an M-factor of 1 should be applied;
- 10 and < 100 then the M-factor would be 10;
- 100 and < 1000 then the M-factor would be 100.

Continue in factor 10 intervals.

Table IV. 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 categories 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 considered as mixtures for the purpose of classification and labelling (Article 2(27) of CLP), although due to their (eco)toxicity profile differing from that of their constituents, they may require special consideration. 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 (e.g. the rate and extend of metals release from pure metals are different from the ones from alloys). The rate and extend to which the ingredients 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.

IV.7.1 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[93]		
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[94]		
Fish: *Danio rerio*	24 µg/L (28 d NOEC) at pH 6	OECD 210 / 28 d flow-through, non-GLP
Marine Fish	87 µg/L (28 d NOEC) at pH 8	OECD 210 /28 d flow through, GLP)
	1414 µg/L (28 d EC_{10})	OECD 210 /28 d flow through, GLP)

[93] Tests performed with readily soluble salts such as metal sulphates and metal chlorides.

[94] Tests performed with readily soluble salts such as metal sulphates and metal chlorides.

Crustacea:	*Daphnia magna*	37 µg/L (21 d EC_{10}) at pH 7.8 8.6 µg/L (21 d NOEC) at pH 6.4	C.20. / semi-static, GLP C.20./semi-static non-GLP
	Marine decapoda	1612 µg/L (21 d NOEC)	Non-standard test
Algae/aquatic plants:	*Scenedesmus subspicatus*	21.6 µg/L (72 h NOEC) at pH 8 8.7 µg/L (72 h NOEC) at pH 6.2	C.3. / static, GLP C.3. / static, non-GLP
Degradation (evidence of rapid degradation)			
Rapid 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 toxicity 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).[95]
- Marine toxicity data are not included in the chronic ERV assessment given far less sensitive as freshwater 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	Wng
Hazard Statement	H400, H410 → H410[96]
Precautionary statement(s)	P273, P391, P501

[95] 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.

[96] In accordance with Article 27 of CLP, 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.

IV.7.2 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

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 at 0.01 mg/L loading	pH 6: no data available pH 8: no data available pH 6: 9 µg/L pH 8: <1 (DL)	Metals TDp, non-GLP Metals TDp, non-GLP Metals TDp, non-GLP Metals TDp, non-GLP
MWT of the metal ion versus compound		
MWT of the metal ion versus compound	60 / 91	
Acute aquatic toxicity of metal ion[97]		
Fish: *Oncorhynchus mykiss*	186 µg/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

[97] Tests performed with readily soluble salts such as metal sulphates and metal chlorides.

Chronic aquatic toxicity[98]		
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 µg/L (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 fails 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

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:

[98] Tests performed with readily soluble salts such as metal sulphates and metal chlorides.

- 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. According to Annex IV.5.4 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	Wng
Hazard Statement	H410
Precautionary statement(s)	P273, P391, P501

IV.7.3 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 at 10 mg/L loading at 100 mg/L loading	pH 6 : 1.7 µg/L (.) pH 8 : 3 µg/L pH 6 : 24 µg/L pH 8 : 29 µg/L pH 6 : 340 µg/L pH 8 : 280 µg/L	Metals TDp, non-GLP
28 d TDp test at 1 mg/L loading at 0.1 mg/L loading at 0.01 mg/L loading	pH 6: 2.3 µg/L pH 8: 3.5 µg/L no measured data available no measured data available	Metals TDp, non-GLP
MWT of the metal		
MWT of the metal	59	
Acute aquatic toxicity of metal ion[99]		
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

[99] Tests performed with readily soluble salts such as metal sulphates and metal chlorides.

Algae/aquatic plants: *Pseudokirchneriella subcapitata*	Data sets available for the 2 pH ends but less sensitive than crustacean at high pH end and most sensitive endpoint at low end. Most sensitive value (96 h EC_{10}) at the low pH range: 120 µg metal ion/l	C.3. / static, GLP And non-GLP C.26. / static, non-GLP
Chronic aquatic toxicity[100]		
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: (EC_{10} 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 EC_{50} 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***

[100] Tests performed with readily soluble salts such as metal sulphates and metal chlorides.

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
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[101] 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 ***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 (CMe(aq)) = -5.144 + 1.0229log(Ameas), whereby

$C_{me(aq)}$ = total dissolved concentration of metal (mg/L)

[101] The finest representative metal powder should be used for TDp testing.

A_{meas} = initial surface area loading (mm^2/l) [equals (measured specific surface area, *SA*, in m^2/g) × (substance mass loading in g/l) X 10], where *SA* was measured with the BET nitrogen adsorption-desorption technique.

An equal approach can be followed for the lower pH level.

- Measured and estimated transformation dissolution data for the *metal powder* are listed in the table below

Loading (mg metal ion/l)	Measured or *calculated*	pH*	Highest dissolution (mg metal/L)	Reference toxicity value (mg metal/L)	Dissolution > toxicity reference value?
1	Measured	low	0.0023	0.020	No
1	Measured	high	0.0035	0.0024	Yes
0.1	Estimated	Low	0.00023	0.020	No
0.1	Estimated	High	0.00035	0.0024	No

* pH value at which dissolution testing was conducted and similar to the pH for the acute toxicity reference value

- The release after 28 days at the 1 mg/L loading for the higher pH level slightly exceeds the chronic ERV, while no such effect is noted at pH 6 mainly due to the lower sensitivity of the species.

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

Acute (short-term) aquatic hazard:

- for the powder form: no acute hazard classification
- for the massive form: no acute hazard classification

Long-term aquatic hazard:

- for the powder form: category Chronic 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 powder form:

Element	Code
GHS Pictogram	GHS09
Signal Word	none
Hazard Statement	H411
Precautionary statement(s)	P273, P391, P501

Labelling elements based on the classification for the massive form: none

Element	Code
GHS Pictogram	none
Signal Word	none
Hazard Statement	none
Precautionary statement(s)	none

IV.7.3.1 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 hazard 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 hazard 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 TG 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 long-term 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***.

IV.7.4 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, $Ksp = 1.6 \times 10^{-14}$) this in turn undergoes further oxidation to form metal hydroxide ($MeOH_3$) which is highly insoluble ($Ksp = 1 \times 10^{-36}$). 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. 2 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* *Lepomis macrochirus*	96h 96h	Survival Survival	21.8 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
$MeCl_3.6H_2O$	*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. 3 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/guidance-documents/guidance-on-reach
OECD Series on Testing and Assessment	OECD	http://www.oecd.org/document/30/0,3746,en_2649_34377_1916638_1_1_1_1,00.html
EU Test Method Regulation 440/2008	EC	http://eur-lex.europa.eu/lexuriserv/lexuriserv.do?uri=celex:32008r0440:en:not
OECD test guidelines	OECD	http://www.oecd.org/env/ehs/testing/oecdguidelinesforthetestingofchemicals.htm l
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

VI.1 Executive summary

Regulation (EC) No 1272/2008 on the classification, labelling and packaging of substances and mixtures (the 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 the 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.

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 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 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 following SCLs 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[B])
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.

VI.2 Introduction

VI.2.1 General description of the classification system for reprotoxic substances and mixtures

The CLP Regulation contains rules for the classification of substances and mixtures. In CLP Annex I, 3.7.2.1.1 Table 3.7.1 (a), the criteria are given for the classification of substances as reprotoxicants in one of the following categories:

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.*

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. The 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 in 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 must 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.

VI.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.

VI.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 an 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, potency is defined as the dose at which a 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 three 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.

VI.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[102], LOAEL[103], 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 VI. 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.

VI.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. For

[102] NOAEL means No Observed Adverse Effect Level.

[103] LOAEL means Lowest Observed Adverse Effect Level.

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 VI. 2). 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 VI. 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 VI. 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 VI. 2**Error! Reference source not found.**). 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 VI. 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 deviation	Lowest value	Highest value	Potency 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 Table VI. 1 and Table VI. 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 VI. 1 is mainly due to the absence of an ED_{10} for some very potent substances.

VI.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 six parameters for potency is less than a factor of four. This is small compared to the difference in potency between substances for each parameter of up to 30,000 (Table VI. 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 VI. 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 (classification)	70	24	7	0.032	940	29375
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 VI. 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 VI. 4).

Table VI. 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 Table VI. 3 and Table VI. 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 VI. 3 is due to the absence of an ED_{10} for some very potent substances.

VI.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 can 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 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.

VI.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 below). It should be noted that several of the elements may be interrelated.

VI.3.1 Boundaries of the potency groups

Table VI. 5 Boundaries of the potency groups

Potency group	Boundaries
High potency group	ED_{10} value ≤ 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 ≥ 400 mg/kg bw/day.

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 IV.4 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 3.7.2.6.5).

VI.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:

VI.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.

VI.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.

VI.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.

VI.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 (CLP Annex I 3.8.2.1.10.4 and CLP Annex I 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, (CLP Annex I Table 3.1.1: see section 3.1.2.2 of this Guidance) or guidance values (CLP Annex I Table 3.8.2 – see section 3.8.2.2.1 of this Guidance and Annex I Table 3.9.2 and 3.9.3- see section 3.9.2.2 of this Guidance) 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.

VI.5 Potency groups and specific concentration limits

VI.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.

VI.5.1.1 General considerations on potency groups

VI.5.1.1.1 Legal requirements

According to the second subparagraph of CLP Article 10(1):

> **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):

> **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.

VI.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.

VI.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 VI. 5) 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 VI. 6 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.

VI.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.

VI.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 VI. 6 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 VI. 6 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
	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 VI. 6 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 agreed that volatility was not considered a modifying factor and thus, the ED_{10} distribution changes as shown in Table VI. 7. 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 VI. 7 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 Table VI.

6 and Table VI. 7 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.

VI.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 VI. 8.

Table VI. 8 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[B])
Group 2 medium potency	$ED_{10} \geq 4$ mg/kg bw/day, and ≤ 400 mg/kg bw/day	0.3% (GCL)	$ED_{10} \geq 4$ mg/kg bw/day, and ≤ 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).

VI.5.2 Assigning SCLs

The SCL or GCL for each substance can be determined using the final potency group of the substance using Table VI. 6.

VI.6 References

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VII ANNEX VII: RELATION BETWEEN TRANSPORT AND CLP CLASSIFICATION REGARDING PHYSICAL HAZARDS

Table VII. 1 on physical hazards only, provided in this annex, contains additional information on transport classifications in relation to CLP classifications that could be of added value. However, these comparisons have certain restrictions with regard to their applicability. In particular, the area of applicability of the transport regulation is different from the CLP Regulation (ADR 49 countries, IMDG-Code, ICAO-TI international regulations). Therefore, the table should be used as reference for deriving CLP classifications and not vice versa.

The transport classification of named substances or mixtures in the transport regulations reflects the transport conditions and therefore were not adapted to take into account the GHS criteria. The transport classifications may be based on experience or certain events that are specific to transport. The transport classification of named substances or mixtures is legally binding for transport and should not be used to derive a CLP classification without an expert review.

The transport regulations include the concept of precedence of hazards which guarantees that information on the most dangerous hazards is communicated with precedence. 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 in the transport classification are allocated and noted under the respective UN-Number (giving information on subsidiary risks, appropriate packaging and transport conditions).

It needs to be noted that a substance may have more than one entry in the Dangerous Goods List. These are usually within the same class, but transport conditions are different because of different severity of the hazard for different concentrations of this substance.

The following table refers only to physical hazards, as health hazards are not harmonised regarding cut-off values, and/or allowed methods.

Tabel VII. 1 Relation between transport and CLP classifications regarding physical hazards

⚠ (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	A correspondence only applies to the

	2 Liquefied gas. 3 Refrigerated liquefied gas 4 Dissolved gas 5 Aerosol dispensers, Class 2.1 Class 2.2 6 Other articles containing gas under pressure 7 Non-pressurised gases subject to special requirements 8 Chemicals under pressure*** 9 Adsorbed gas	Gaseous Gaseous Gaseous Not relevant (Articles) Gaseous Gaseous Not relevant Gaseous	 Aerosols Flammable gases Oxidising gases	Liquefied gas. Refrigerated liquefied gas Dissolved gas Category 1 Category 2 Category 3 Category 1 Category 1	form in which the gas is transported. If it is used in a different form, then the classification has to be amended. Matching criteria with 2.5. Note: Gases may be packaged in other forms such as "chemical under pressure" or "adsorbed gases" that are not considered in the GHS/CLP. The transport classification does not differentiate between Aerosols Category 1 and 2 (both are classified as class 2.1)
Class 3	Packing group I Packing group II Packing group III	Liquid Liquid Liquid	Flammable liquid Flammable liquid Flammable liquid	Category 1 Category 2 Category 3	
Class 4.1	Types B-F	Solid or liquid	Self-reactive substances	Types B-F	

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

(*) Substances and articles (except aerosols and chemicals under pressure) of Class 2 are assigned to one of the following transport groups according to their hazardous properties, as follows: A asphyxiant, O oxidising, F flammable, T toxic, TF toxic, flammable, TC toxic corrosive, TO toxic, oxidising, TFC toxic, flammable, corrosive, TOC toxic, oxidising, corrosive

(**) Aerosols are assigned to one of the following transport groups according to their hazardous properties, as follows: A asphyxiant, O oxidising, F flammable, T toxic, C corrosive, CO corrosive, oxidising, FC flammable, corrosive, TF toxic, flammable, TC toxic corrosive, TO toxic, oxidising, TFC toxic, flammable, corrosive, TOC toxic, oxidising, corrosive

(***) Chemicals under pressure are assigned to one of the following transport groups according to their hazardous properties, as follows: A asphyxiant, F flammable, T toxic, C corrosive, FC flammable, corrosive, TF toxic, flammable

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