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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 5.0
July 2017

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Guidance on the Application of CLP Criteria

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 The update includes the following: • Revision of Part 1, by eliminating and amending out of date information and restructuring the text in order to reflect the Guidance update.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

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.

Table of Contents

Table of Tables

Table of Figures

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

[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
TG	Test Guideline
TGD	Technical Guidance Document
TM	Test Method as listed in the Test Methods Regulation
Test Methods Regulation	Regulation (EC) No 440/2008 laying down test methods pursuant to the REACH Regulation[12]
TOPKAT	Mathematical (Q)SAR model for prediction of skin corrosion/irritation
UDP	Uridine 5'-diphosphate
UDPG	Uridine diphosphate glucuronyl
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

[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
	(http://www.unece.org/trans/danger/publi/ghs/ghs_welcome_e.html)
UNSCETDG (or SCETDG)	United Nations SubCommittee of Experts on the Transport of Dangerous Goods (http://www.unece.org/trans/danger/danger.htm)
US-FHSA	United States Federal Hazardous Substance Act - 40 Code of Federal Regulations 1500.41
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.

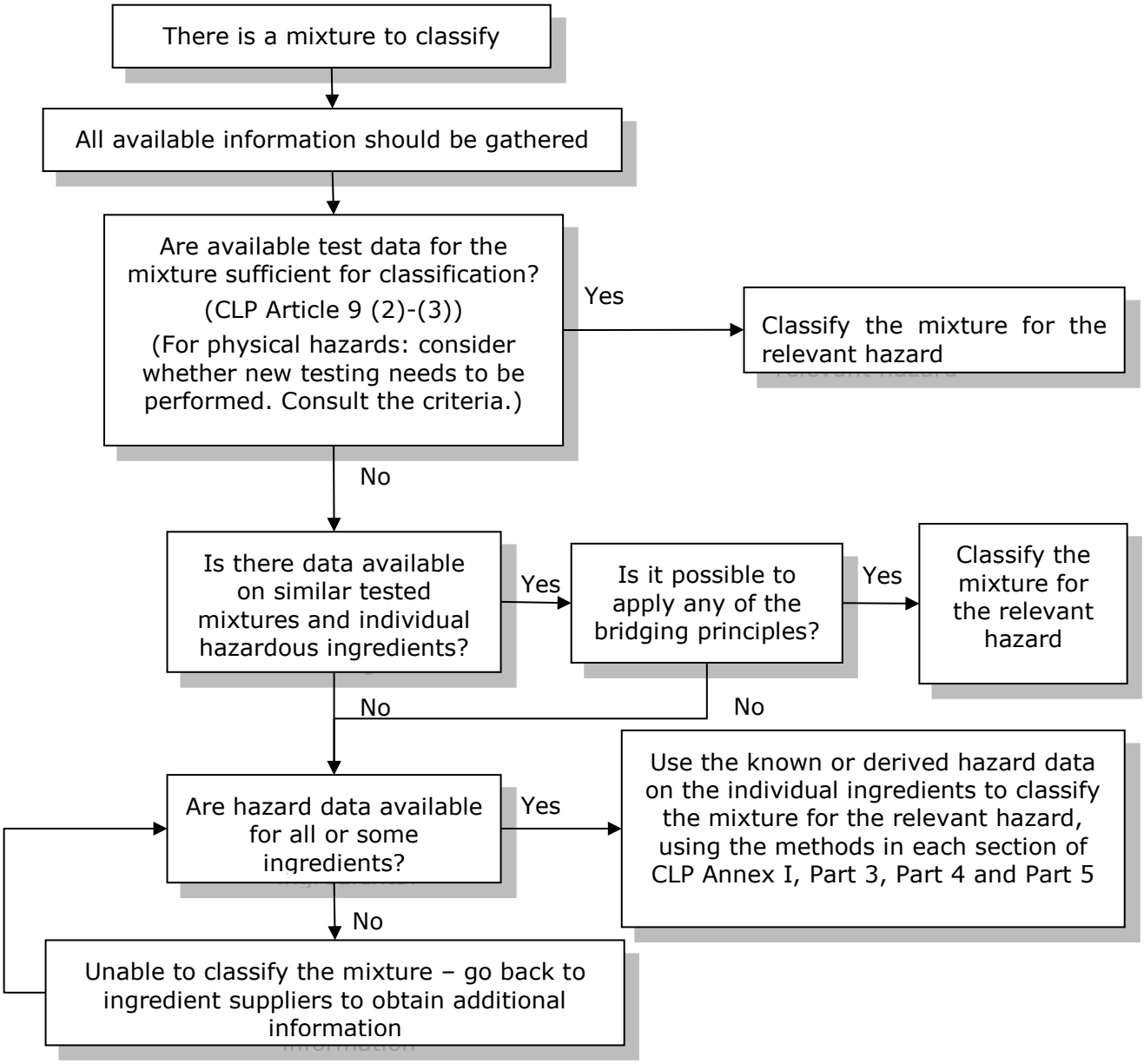
Useful sources for such information are the SDS from the supplier of the substance or the mixture, and the C&L Inventory provided by ECHA, which also includes the harmonised classifications of substances listed in Annex VI to CLP. Also data from registration dossiers are a valuable source of information.

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.

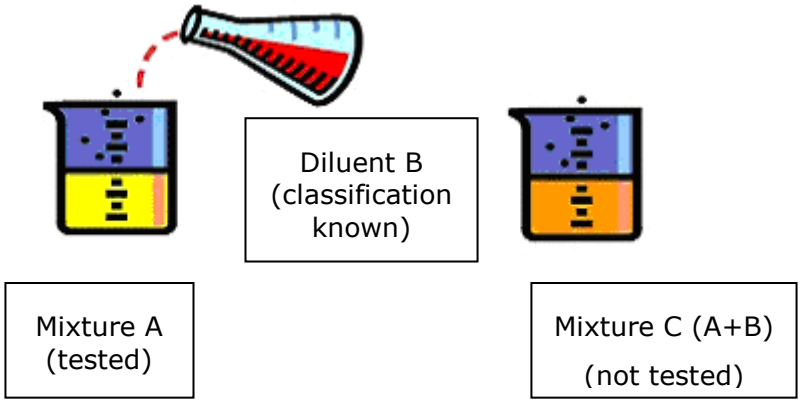
It is necessary to consult Annex I of CLP, Part 3 for health hazards and Part 4 for environmental hazards, before undertaking any of these assessments.

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

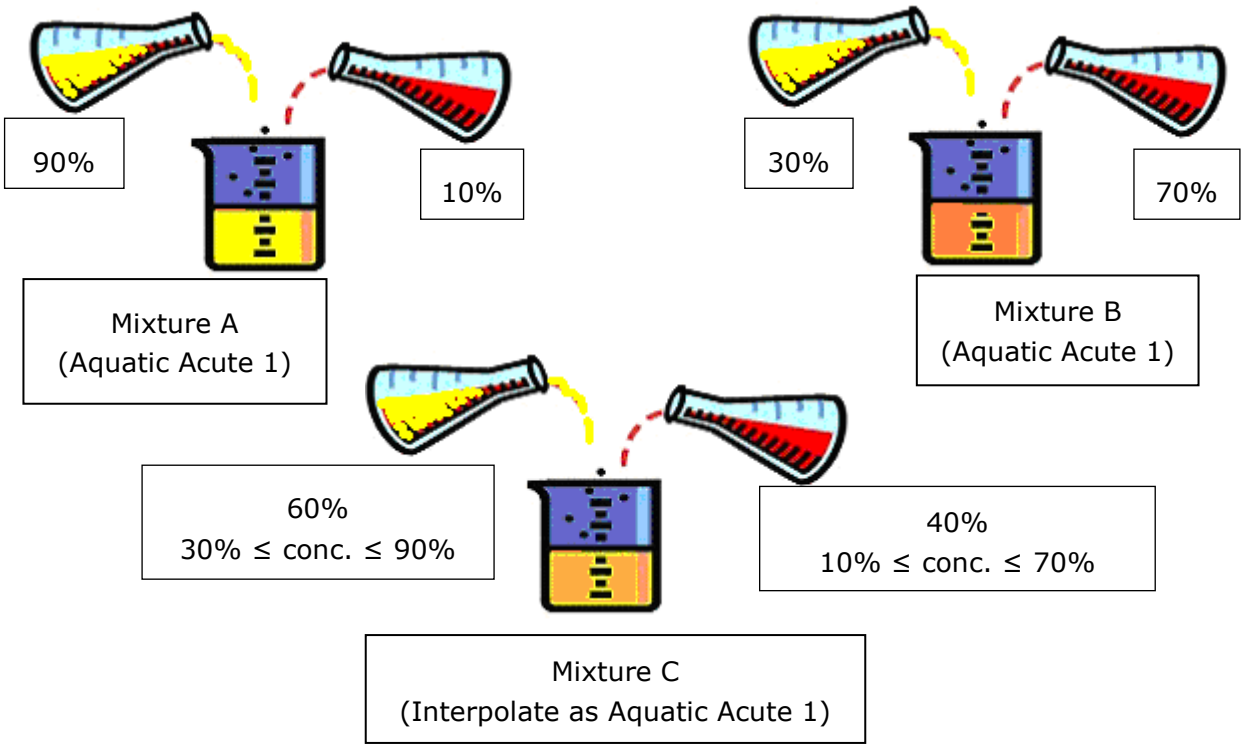
Where a tested mixture is already classified in the highest hazard category or sub-category, an untested mixture which contains a higher concentration of those ingredient substances that are in that category or sub-category should also be classified in the highest hazard category or sub-category (CLP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

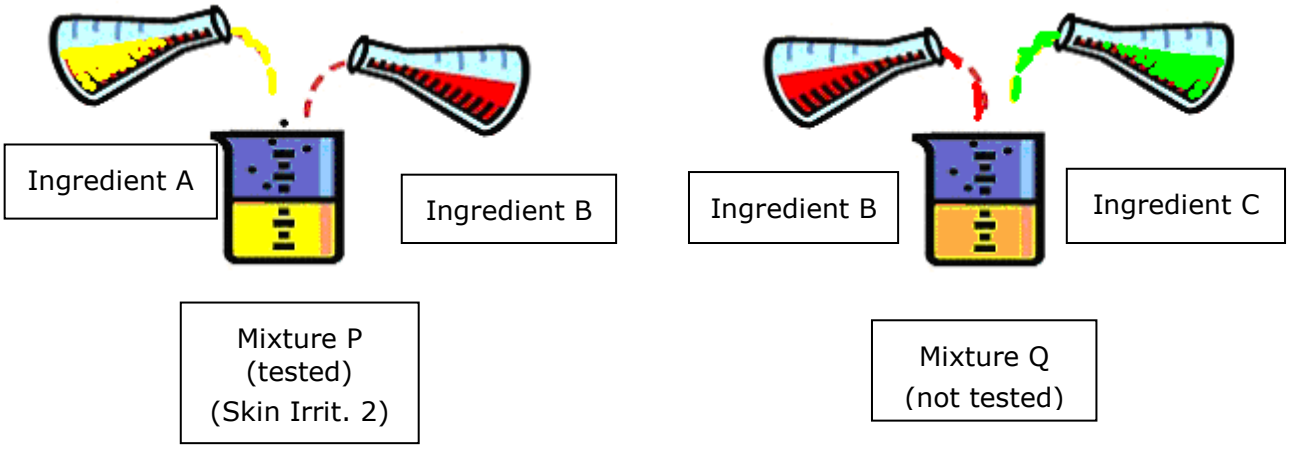
Figure 1.3 Application of the bridging principle: interpolation for determining the aquatic acute hazard classification of a mixture



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:

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

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.

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[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:

$$C_xH_yO_z + \left[x + \left(\frac{y}{4}\right) - \left(\frac{z}{2}\right)\right]O_2 \rightarrow xCO_2 + \left(\frac{y}{2}\right)H_2O$$

Using the formula:

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.

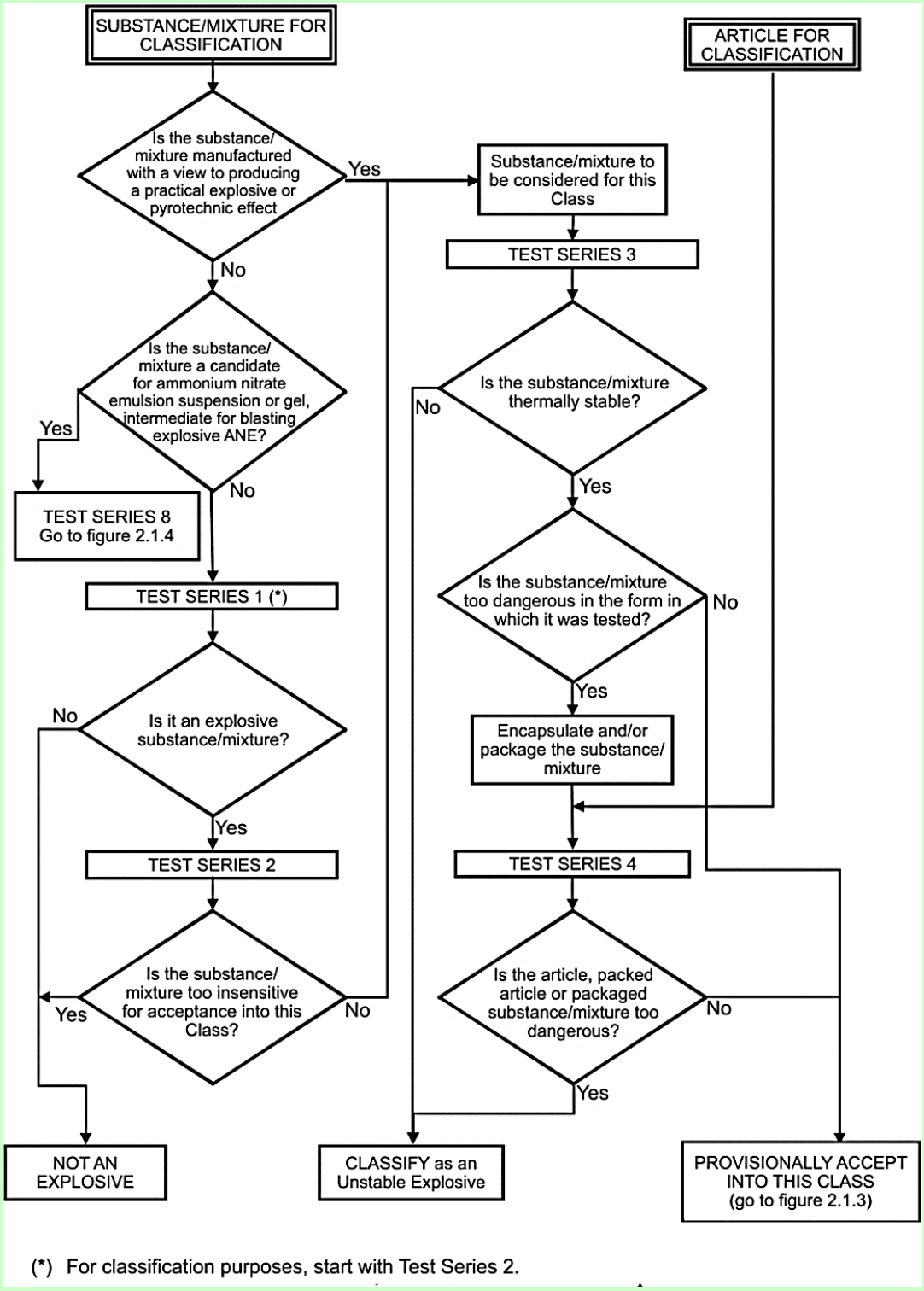
2.1.4.5.1. Acceptance procedure

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

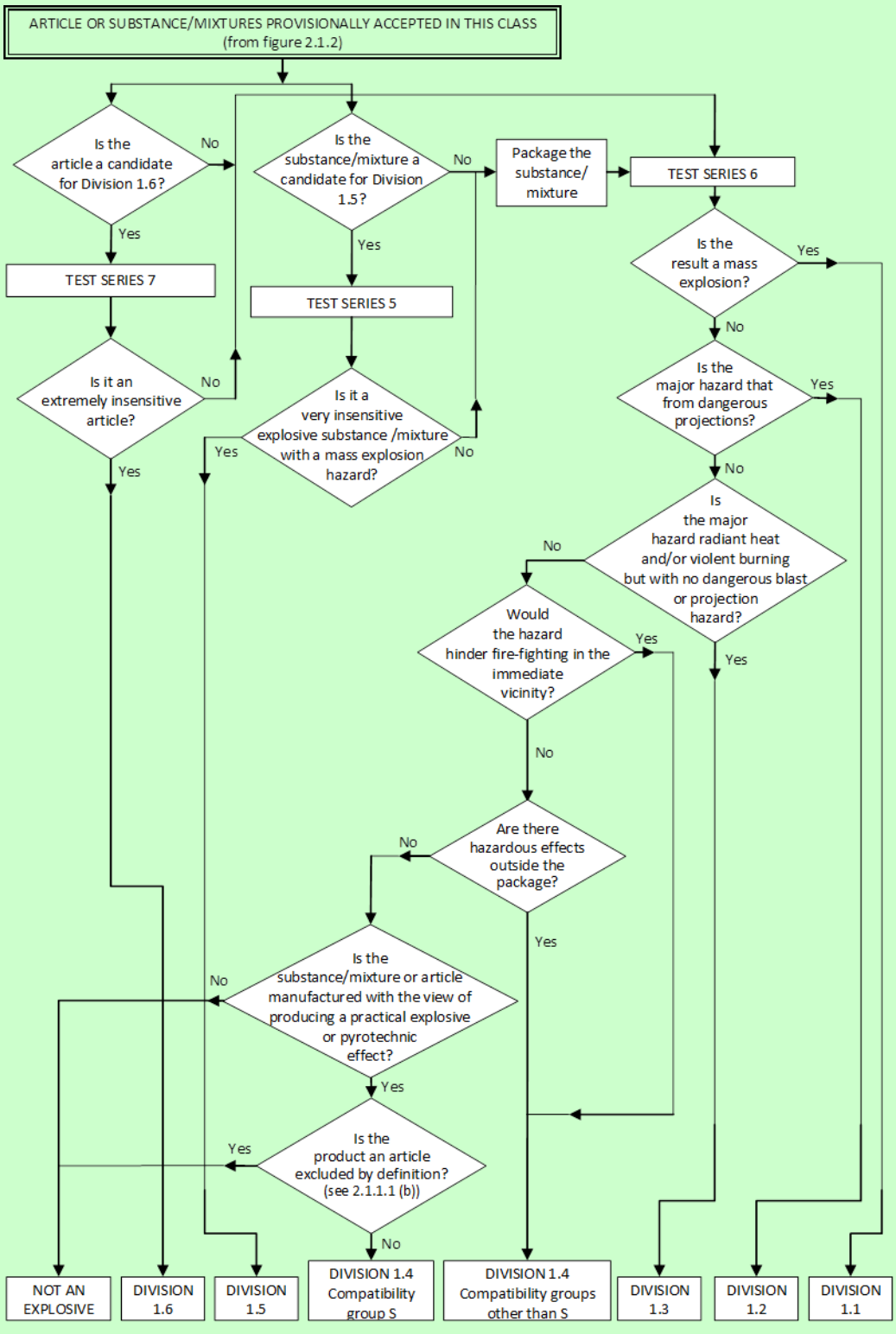
to the results of the tests to which the substance, mixture or article, as offered for supply and use, has been subjected. Other test results, and data gathered from accidents which have occurred, may also be taken into account.

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);

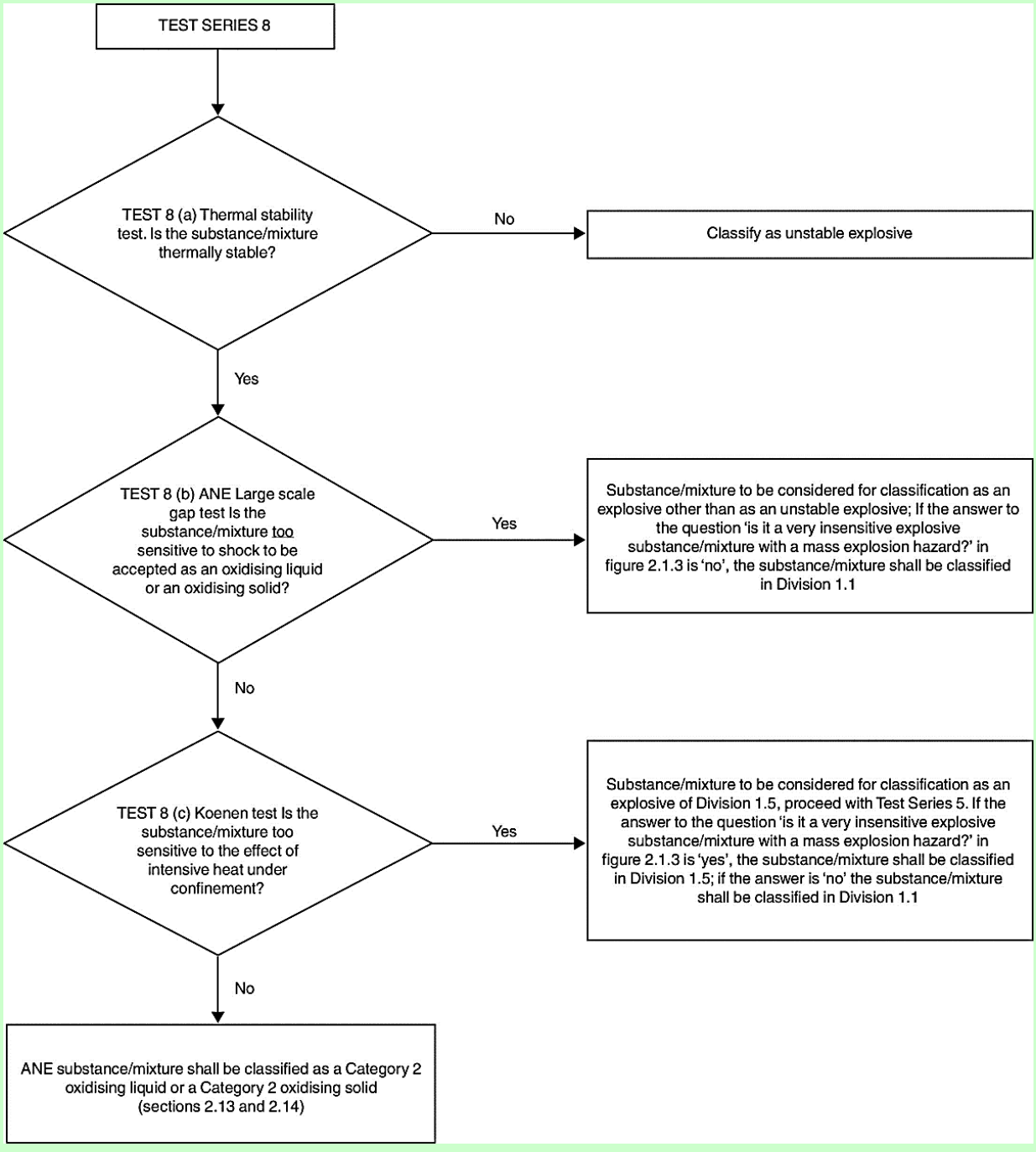
Type 8 (b): a shock test to determine sensitivity to intense shock (ANE gap test); and

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 2.2.4.4.1

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

where:

Equation 2.2.4.4.2

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

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 2.2.4.4.2, 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 2.2.4.4.1 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

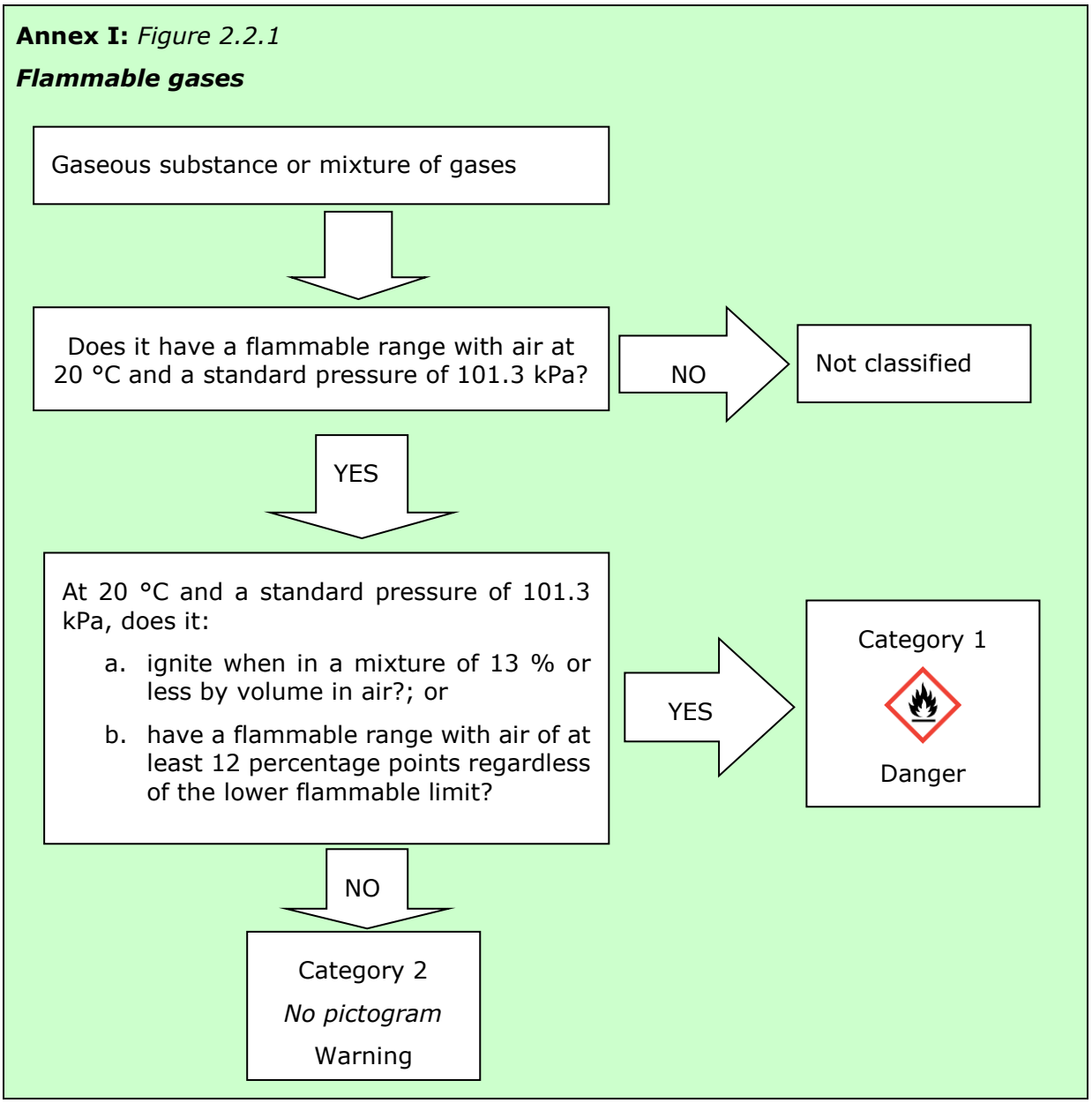
Classification of flammable gases is laid down in the following flow-charts which are applicable according to CLP.

⚠ 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*

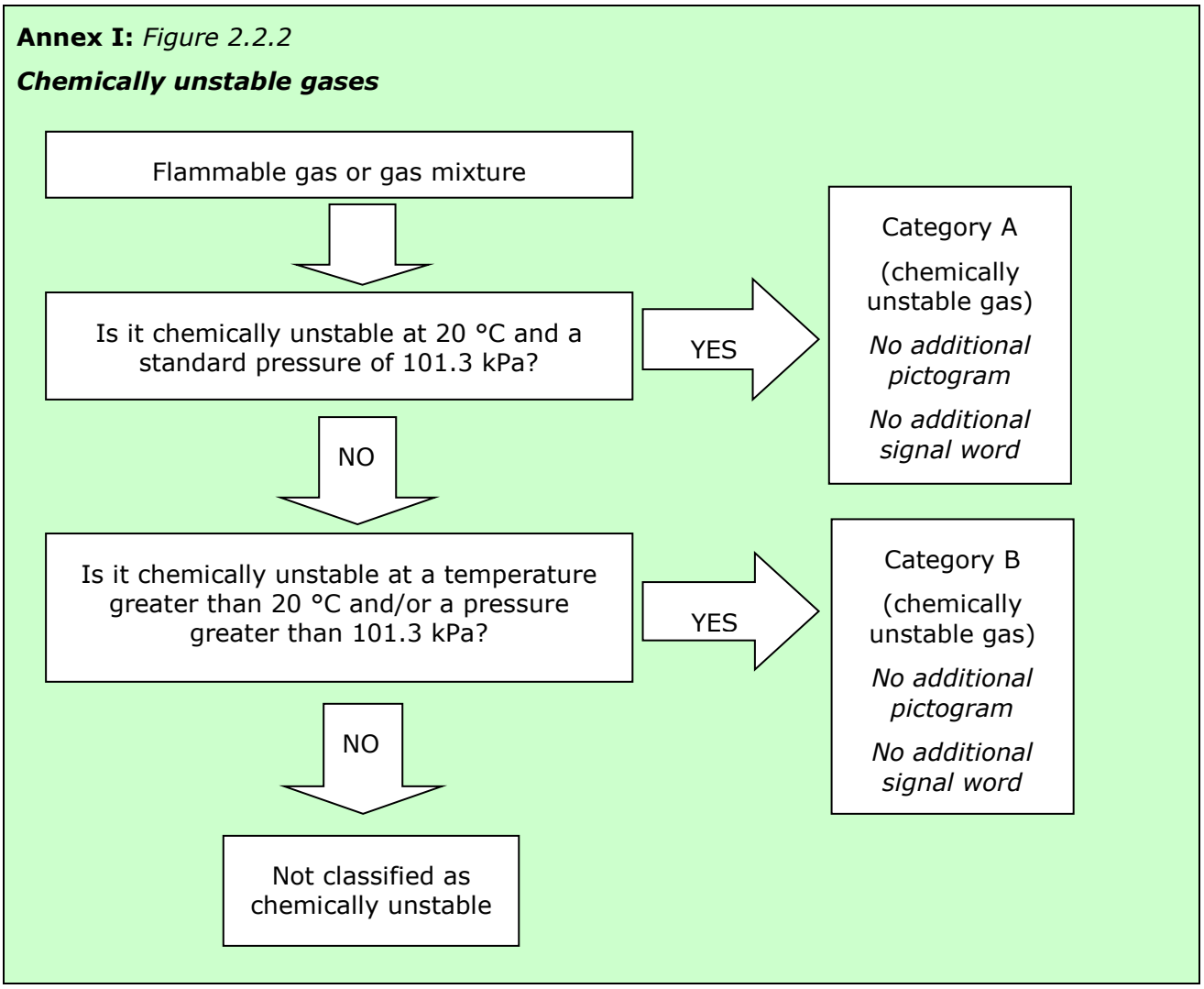
Flammable gases



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 2.2.4.4.2

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

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

***Step 4:* Calculate the flammability of the gas mixture according to** Equation 2.2.4.4.1

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

***Step 5*: Compare the outcome to the criterion in** Equation 2.2.4.4.1

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

AEROSOL

Does it contain ≤ 1% flammable components (by mass) and does it have a heat of combustion < 20 kJ/g?

YES

Category 3

No pictogram

Warning

NO

Does it contain ≥ 85% flammable components (by mass) and does it have a heat of combustion ≥ 30 kJ/g?

YES

Category 1

Danger

NO

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

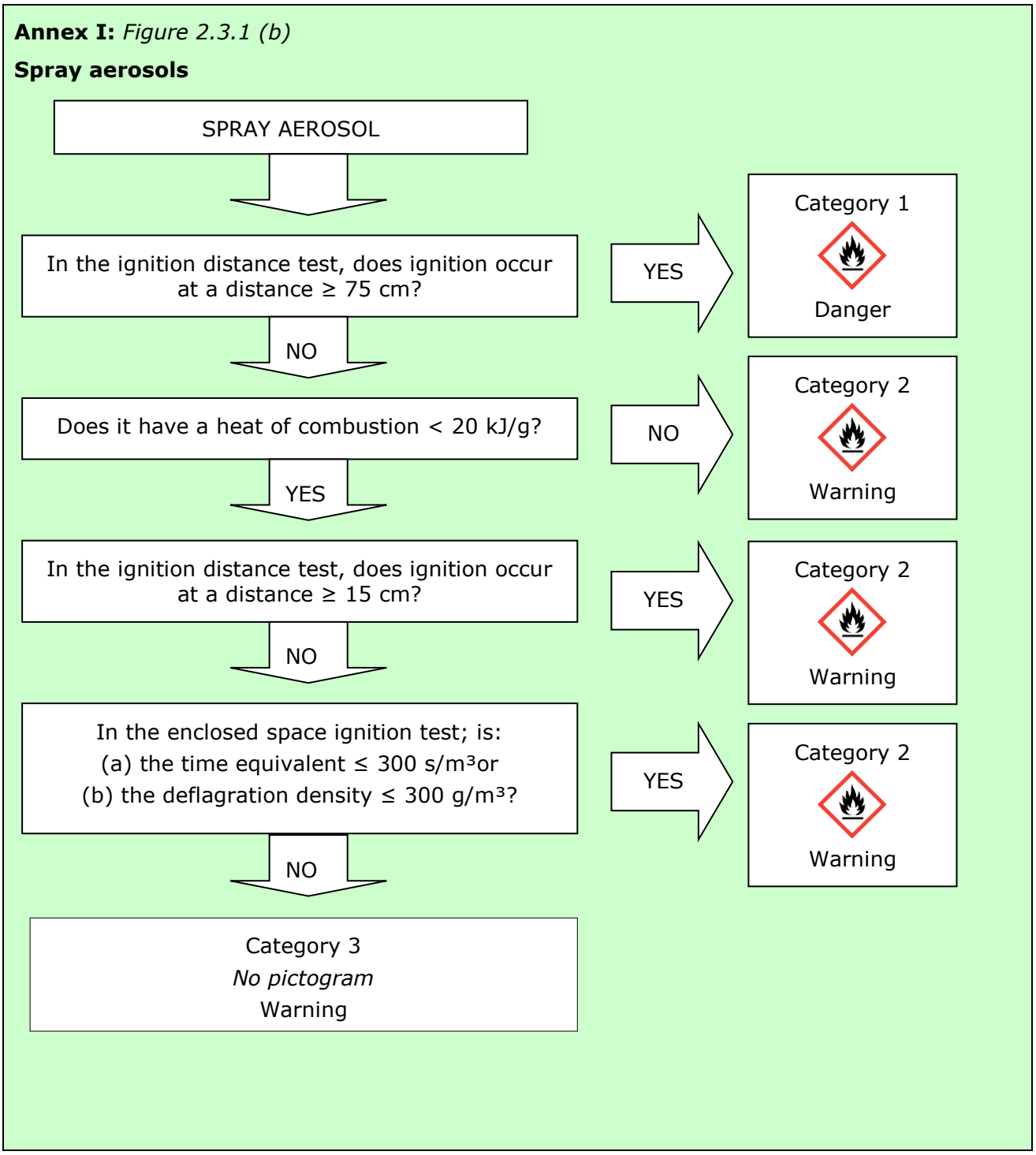
For foam aerosols, go to decision logic 2.3.1(c)'

'

2.3.4.3.2. Decision logic for spray aerosols

Annex I: *Figure 2.3.1 (b)*

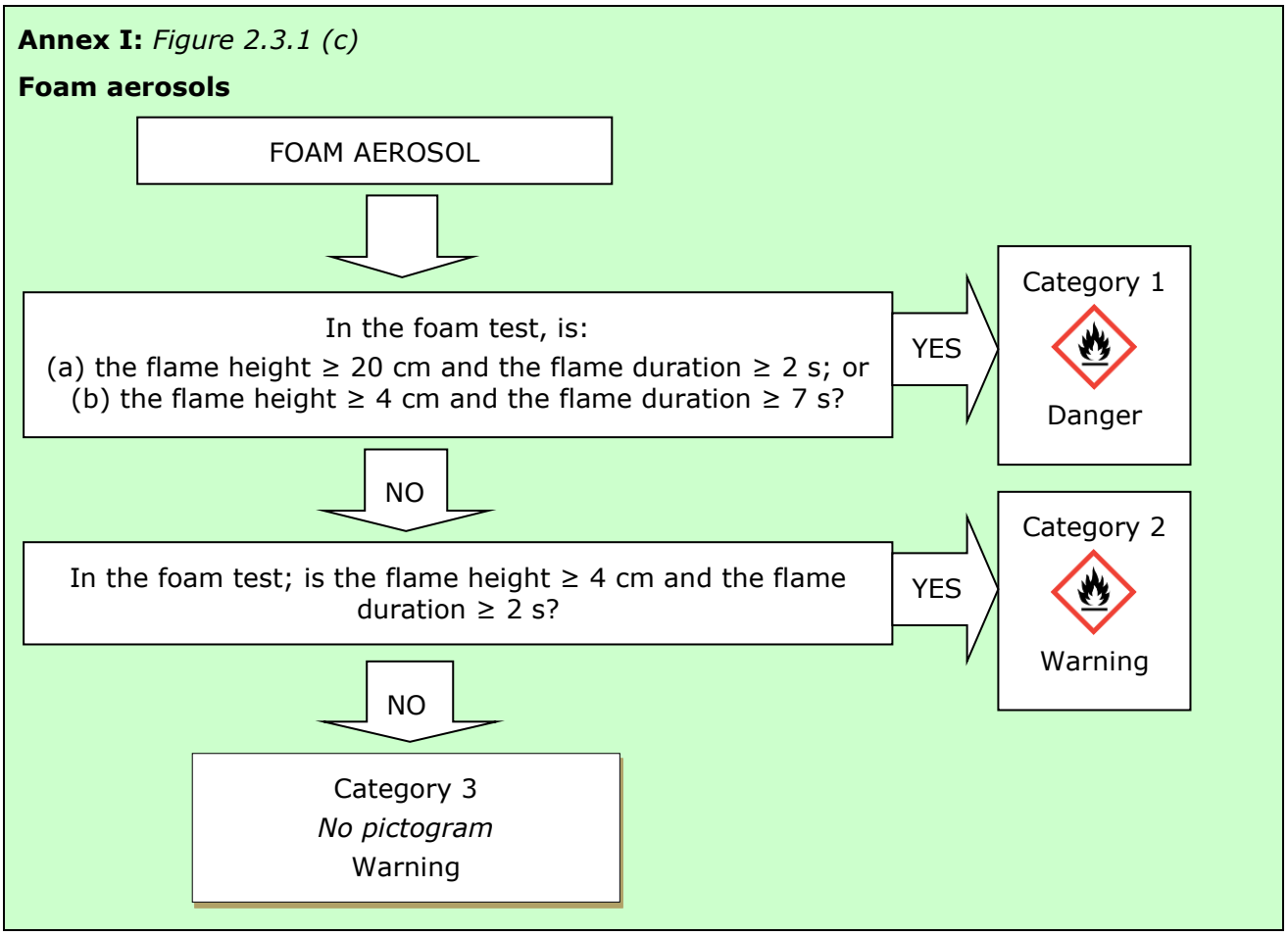
Spray aerosols



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 2.4.4.4.1

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

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

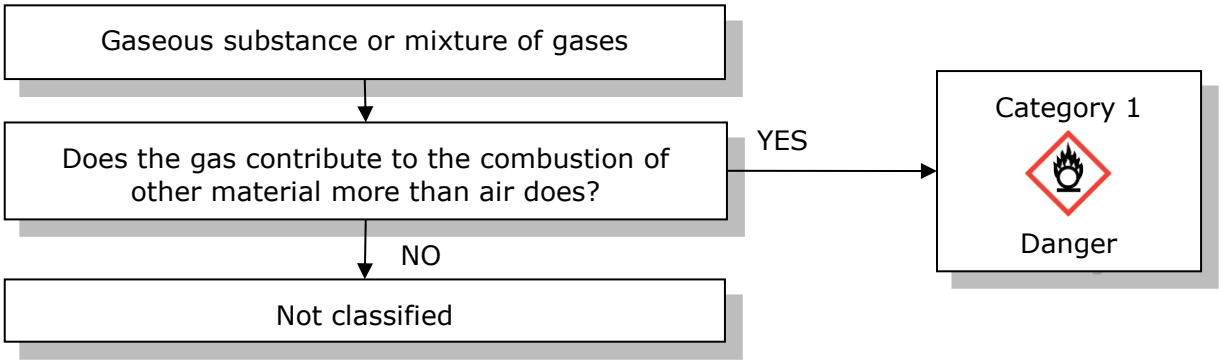
For mixtures containing both flammable and oxidising components, special calculation methods are described in ISO 10156 as amended.

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 2.4.4.4.1

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

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.

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

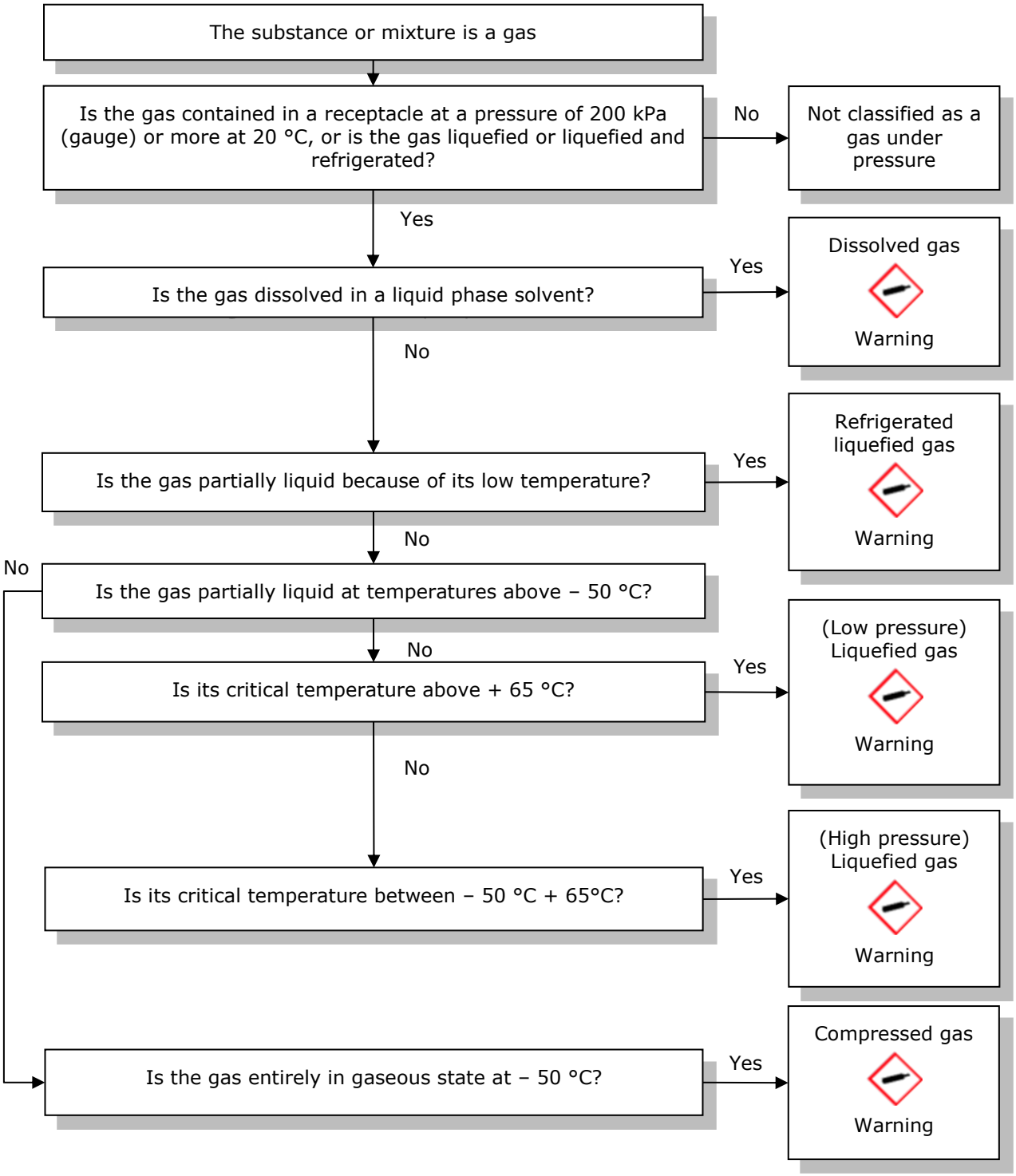
where x_i is the molar concentration of component *i* and T_{Crit_i} is the critical temperature (in °C or in K) of the component *i*.

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.

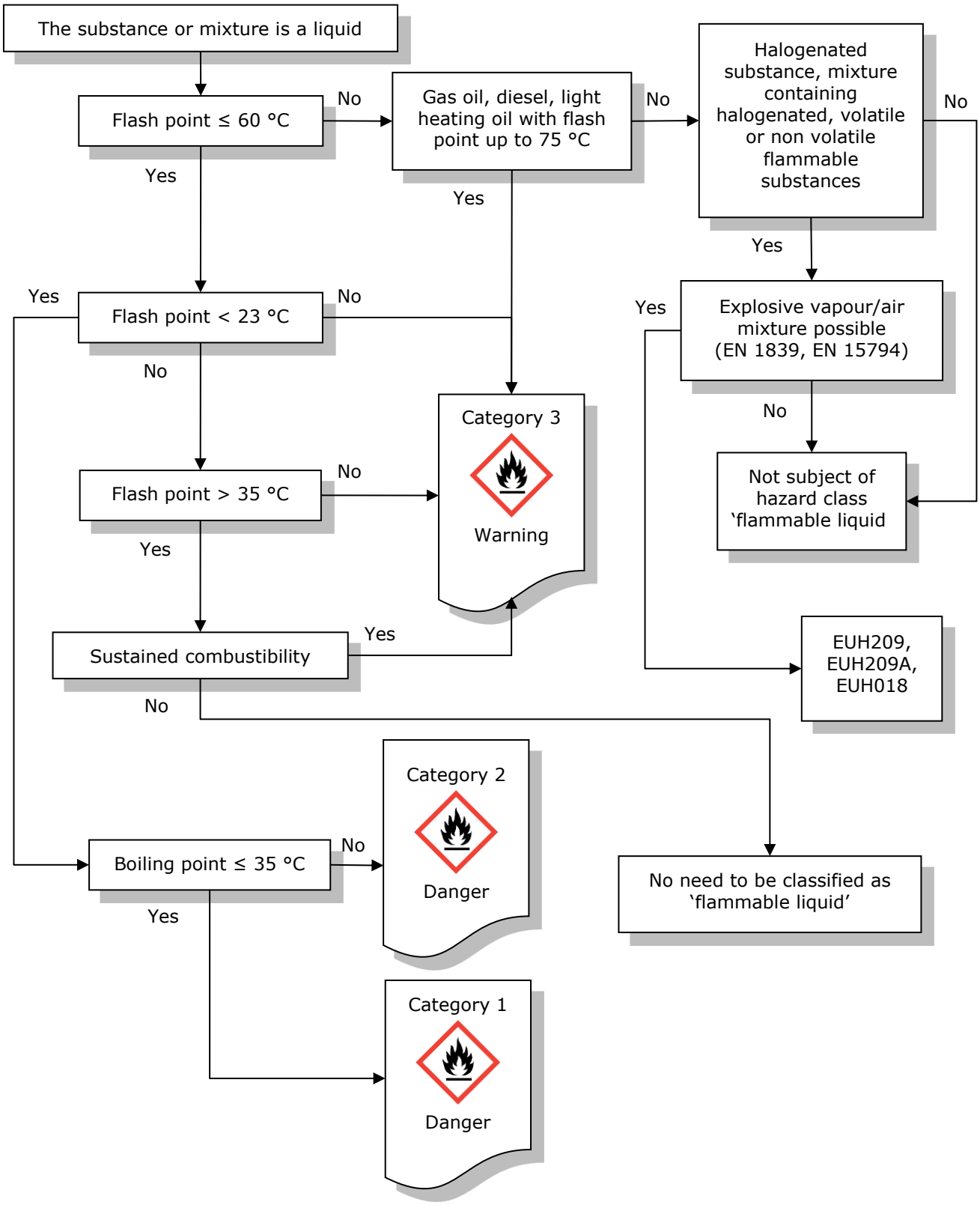
According to the criteria either Category 1, Category 2 or Category 3, including the relevant hazard statement and signal word, have to be assigned (see Section 2.6.5). In case the criteria for EUH018, EUH209 or EUH209A are met, the liquid has to be labelled with the respective supplemental hazard statement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

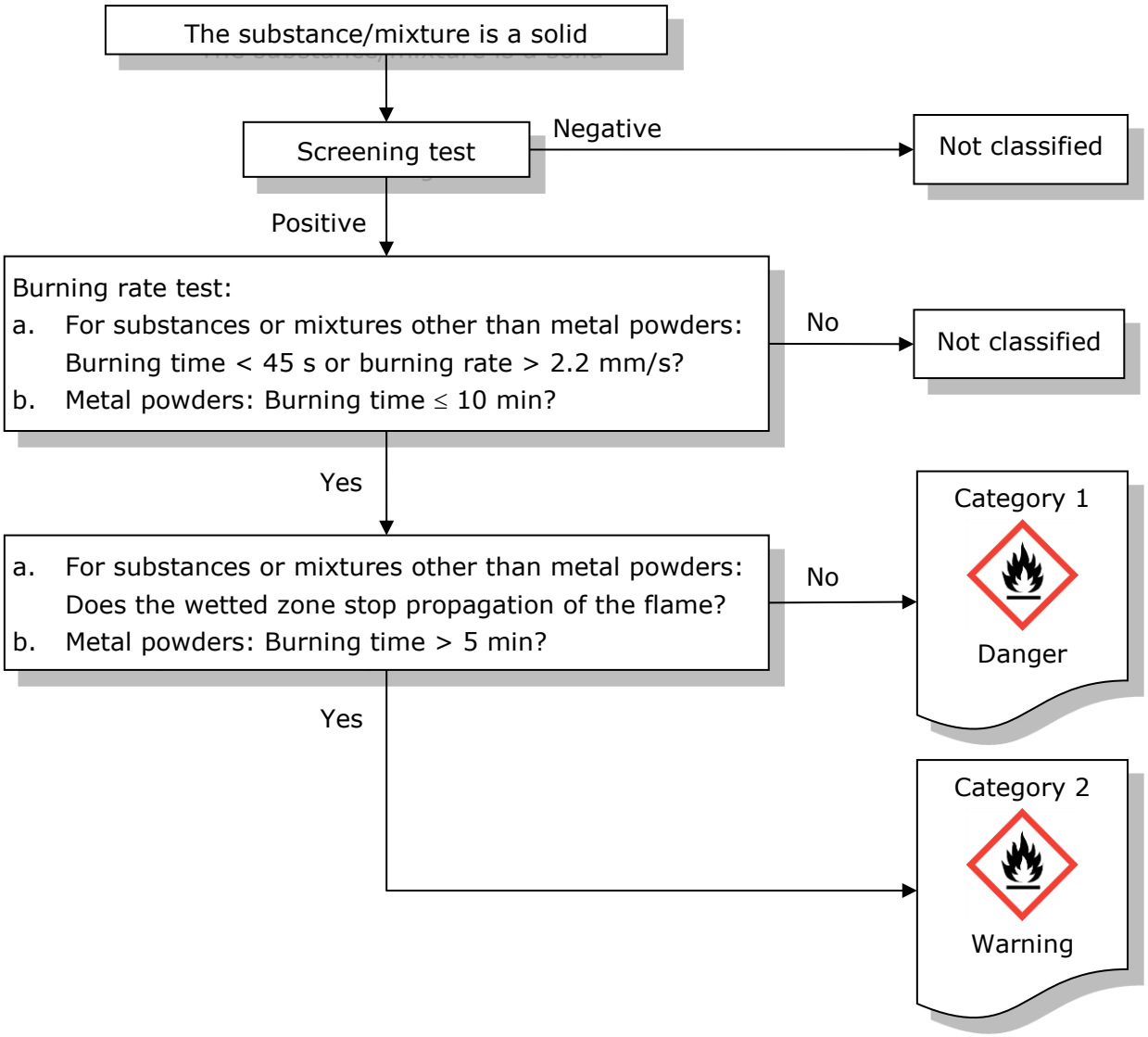
For safety reasons, it is advisable to test for explosive and self-reactive properties first and to rule out pyrophoric behaviour before performing this test. The classification test is described in Part III, Sub-section 33.2.1.4.3.2 of the UN-MTC. The sample should be tested in its commercially relevant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

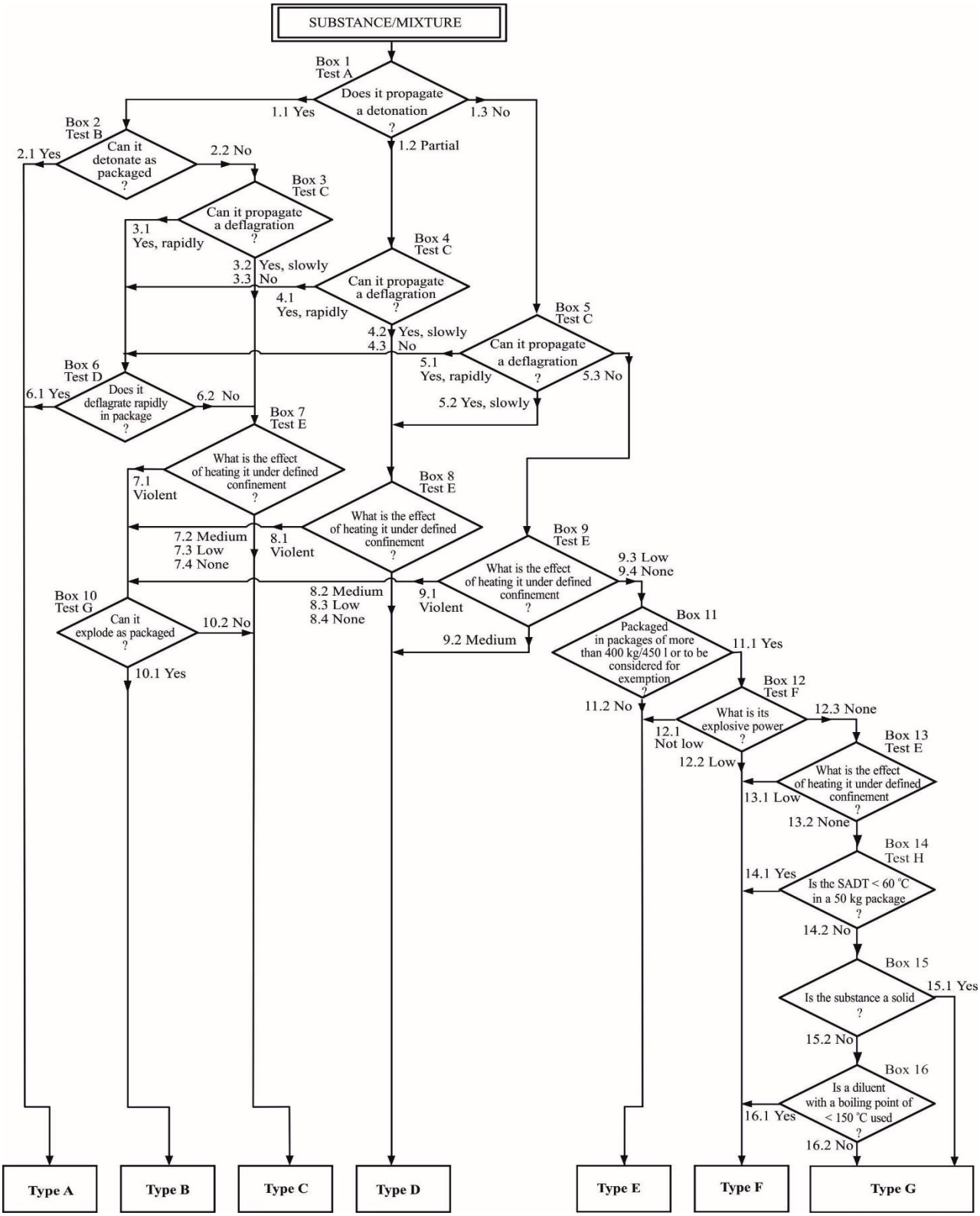
Please note that polymerising substances do not fulfil the criteria for classification as self-reactives. However, there are on-going discussions at the UNSCEGHS on this subject.

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:

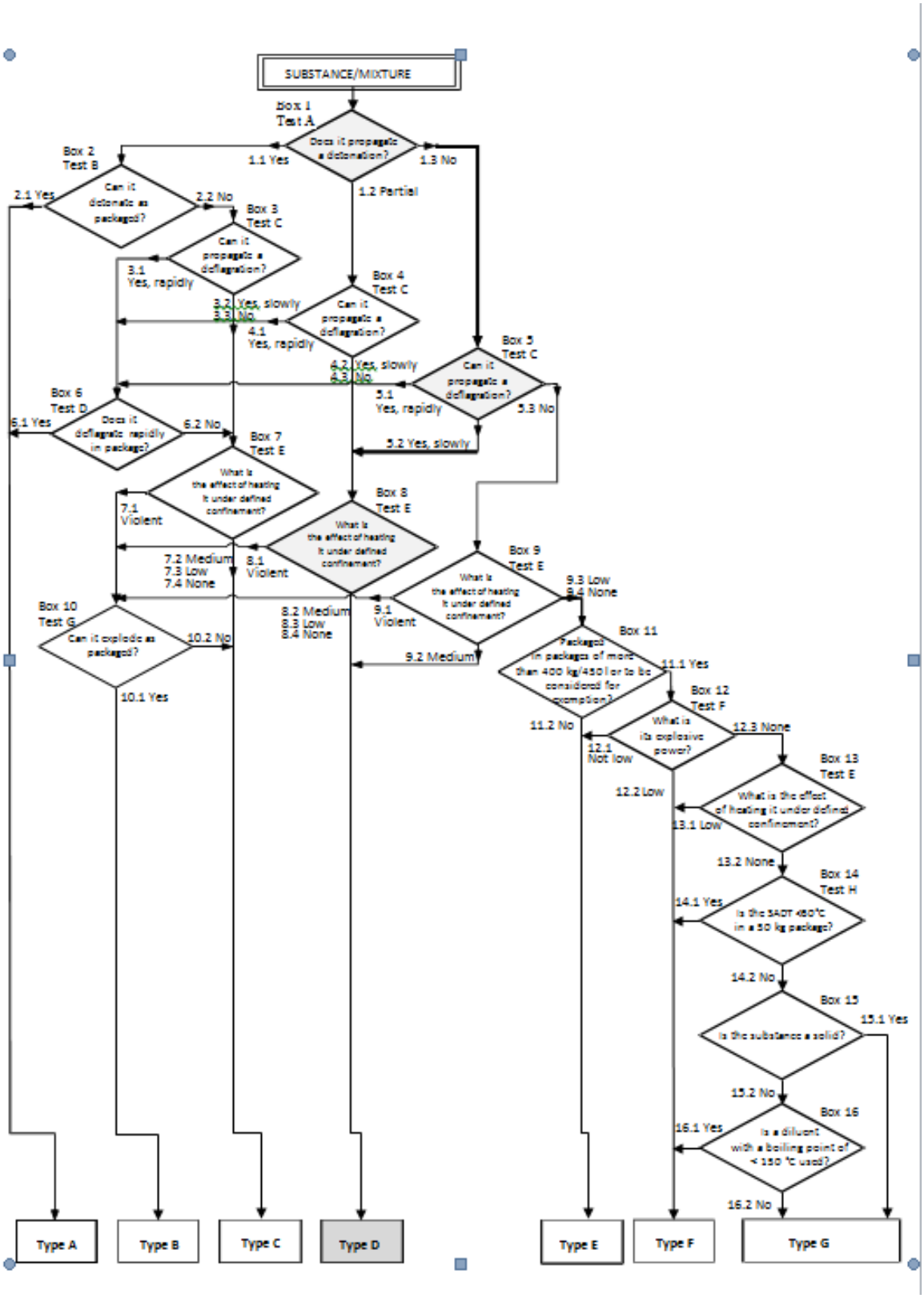
CLASSIFICATION TEST RESULTS	
1. Name of the self-reactive substance or mixture:	NP
2. General data	
2.1. Composition	NP, technically pure
2.2. Molecular formula	n.a.
2.3. Physical form	solid, fine powder
2.4. Colour	brown
2.5. Density (apparent)	460 kg/m^3
3. Detonation (test series A)	
Box 1 of the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

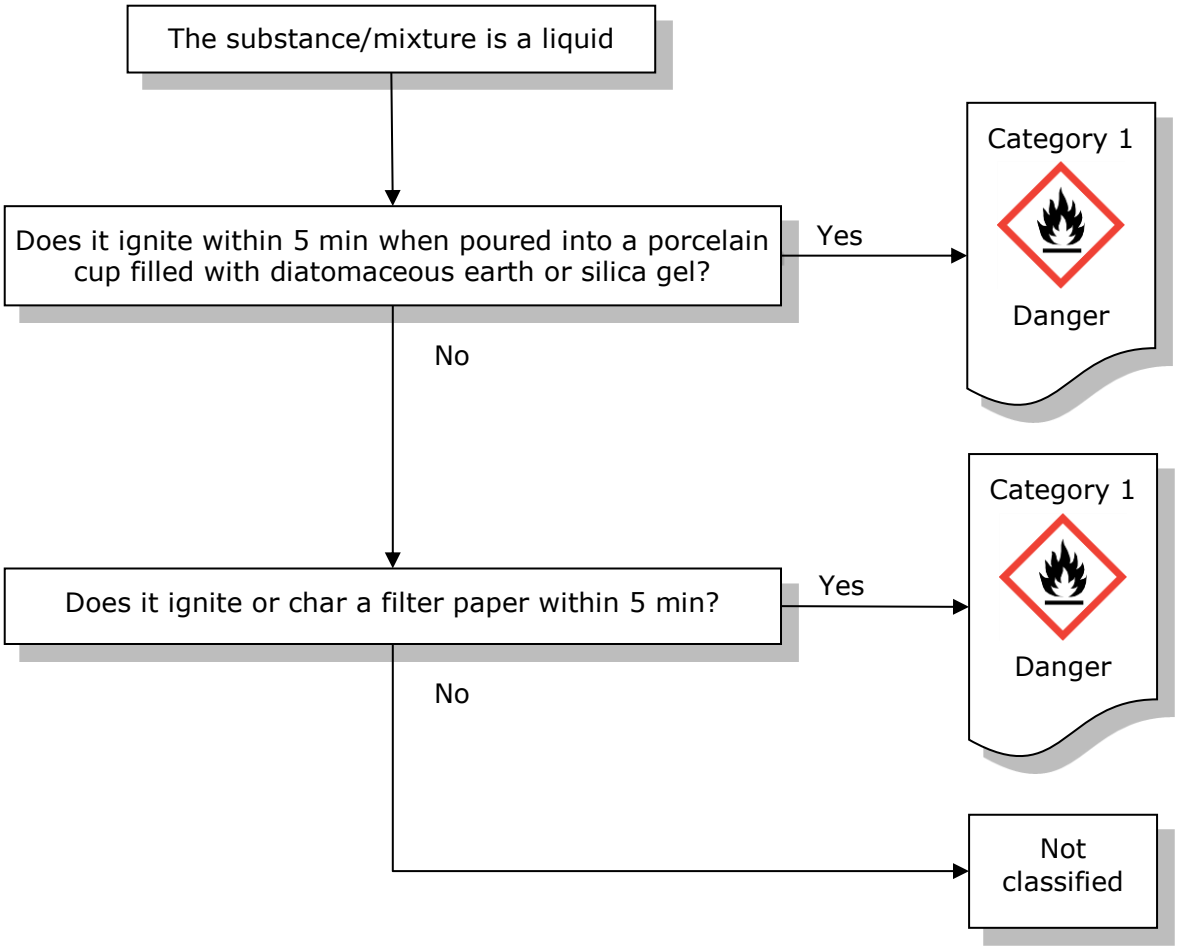
2.9.4.5. Decision logic

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.

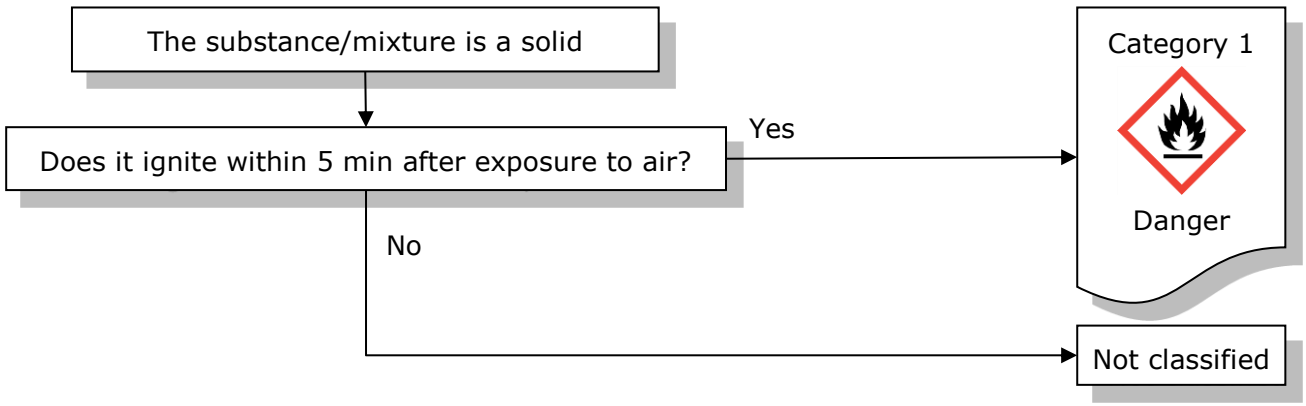
2.10.4.5. Decision logic

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.

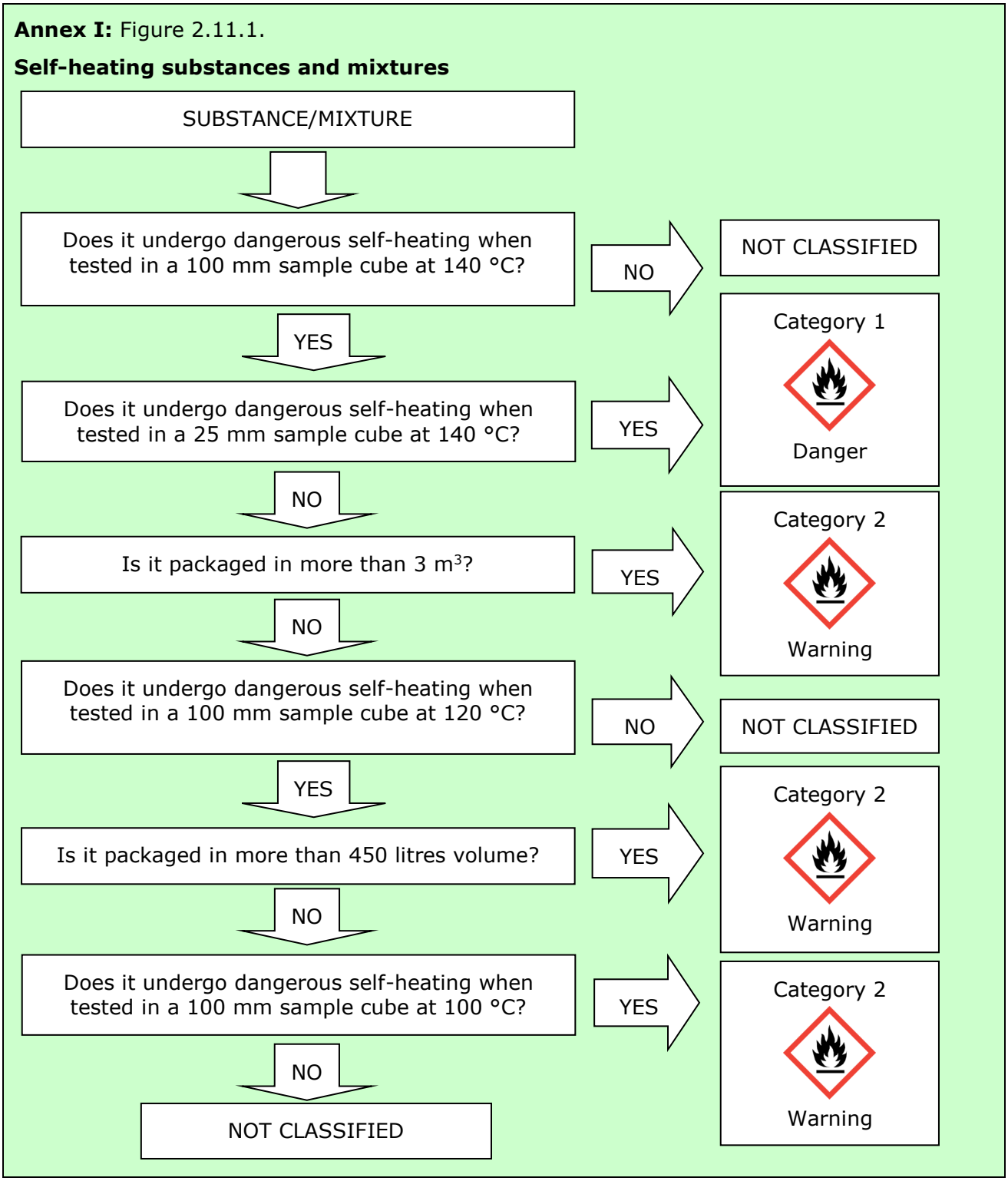
2.11.4.5. Decision logic

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):

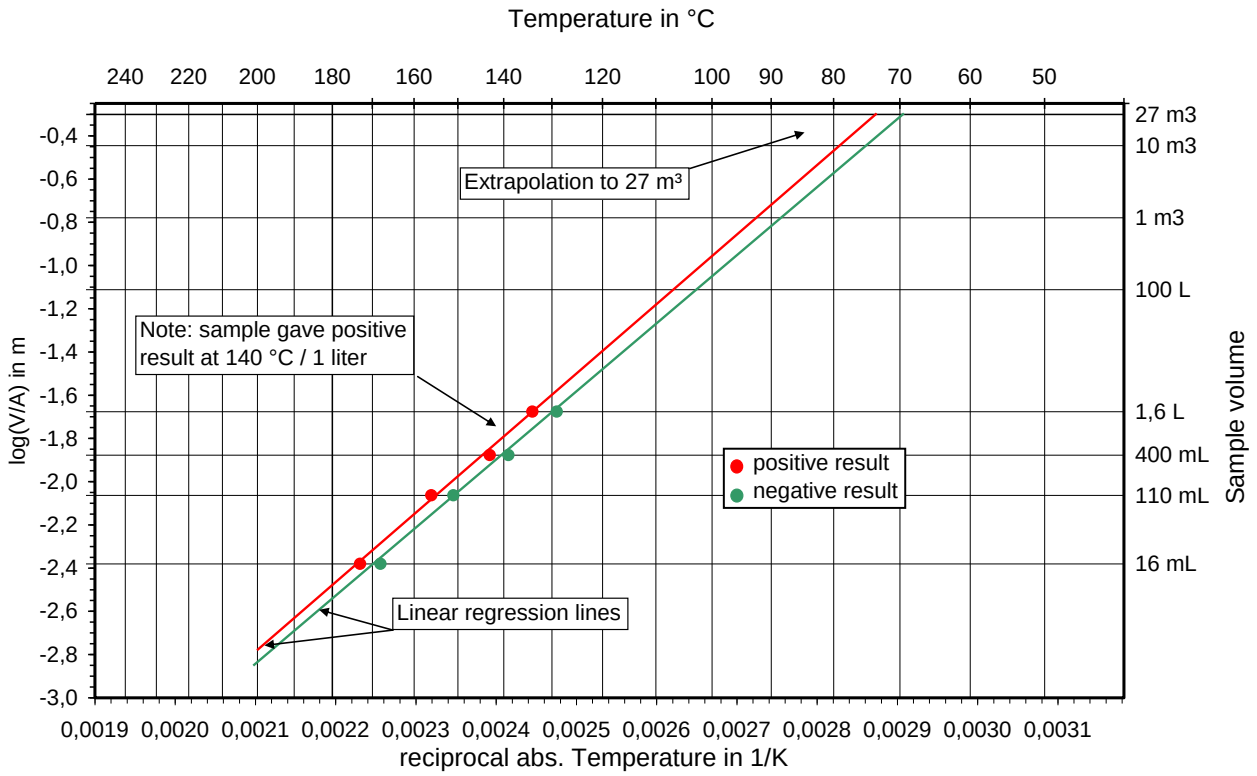
- Substances and mixtures with a temperature of spontaneous combustion higher than 50 °C for a volume of 27 m³ must not be classified as a self-heating substance or mixture.

- 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.

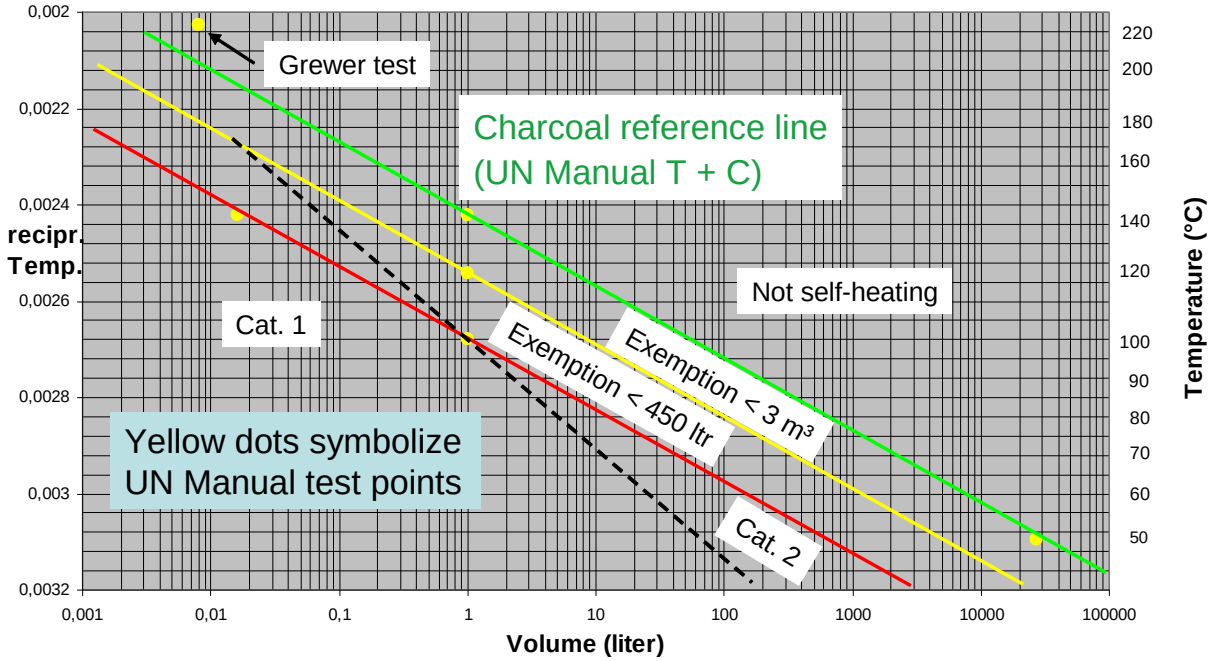
Scientific background

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.

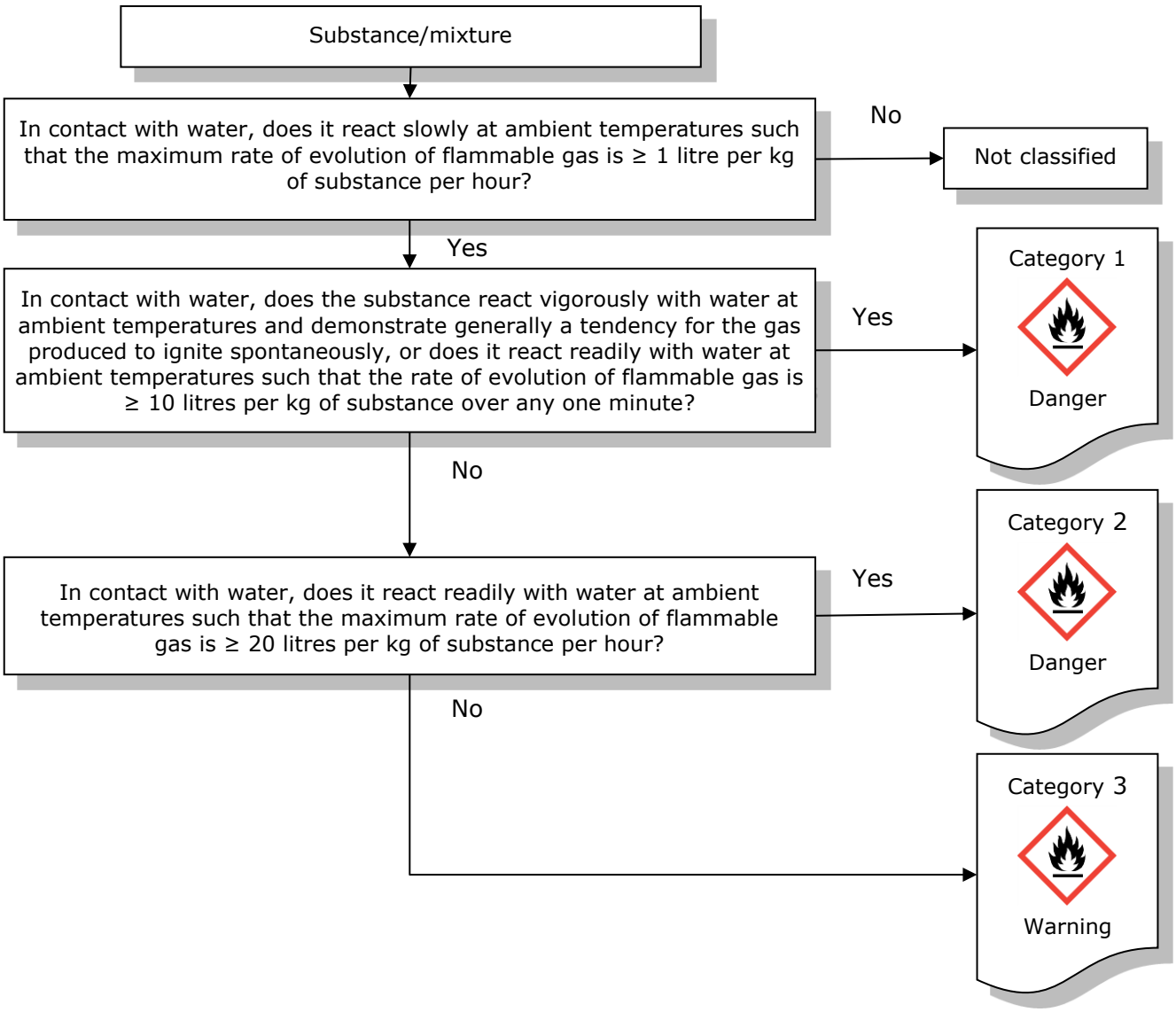
The assignment to the respective hazard class/category will further determine the technical means to be taken to avoid dangerous events which, in combination with other safety characteristics such as i) explosion limits, ii) flash points (applicable only for liquids) or iii) self-ignition temperature,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

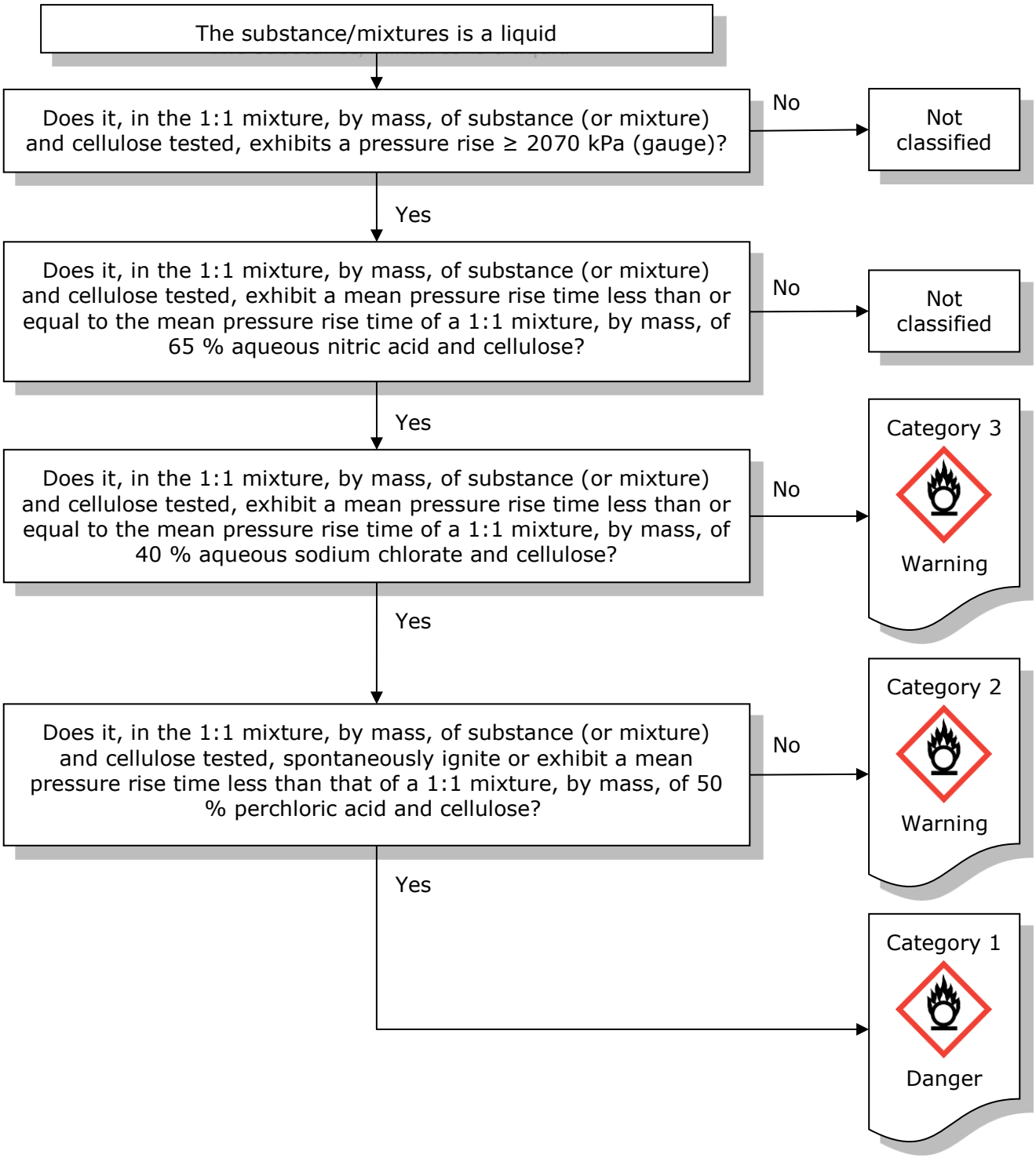
The test methods for oxidising liquids are designed to give a final decision regarding their classification. Apart from testing, also experience in the handling and use of substances or mixtures which shows them to be oxidising is an important additional factor in considering classification in this hazard 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.

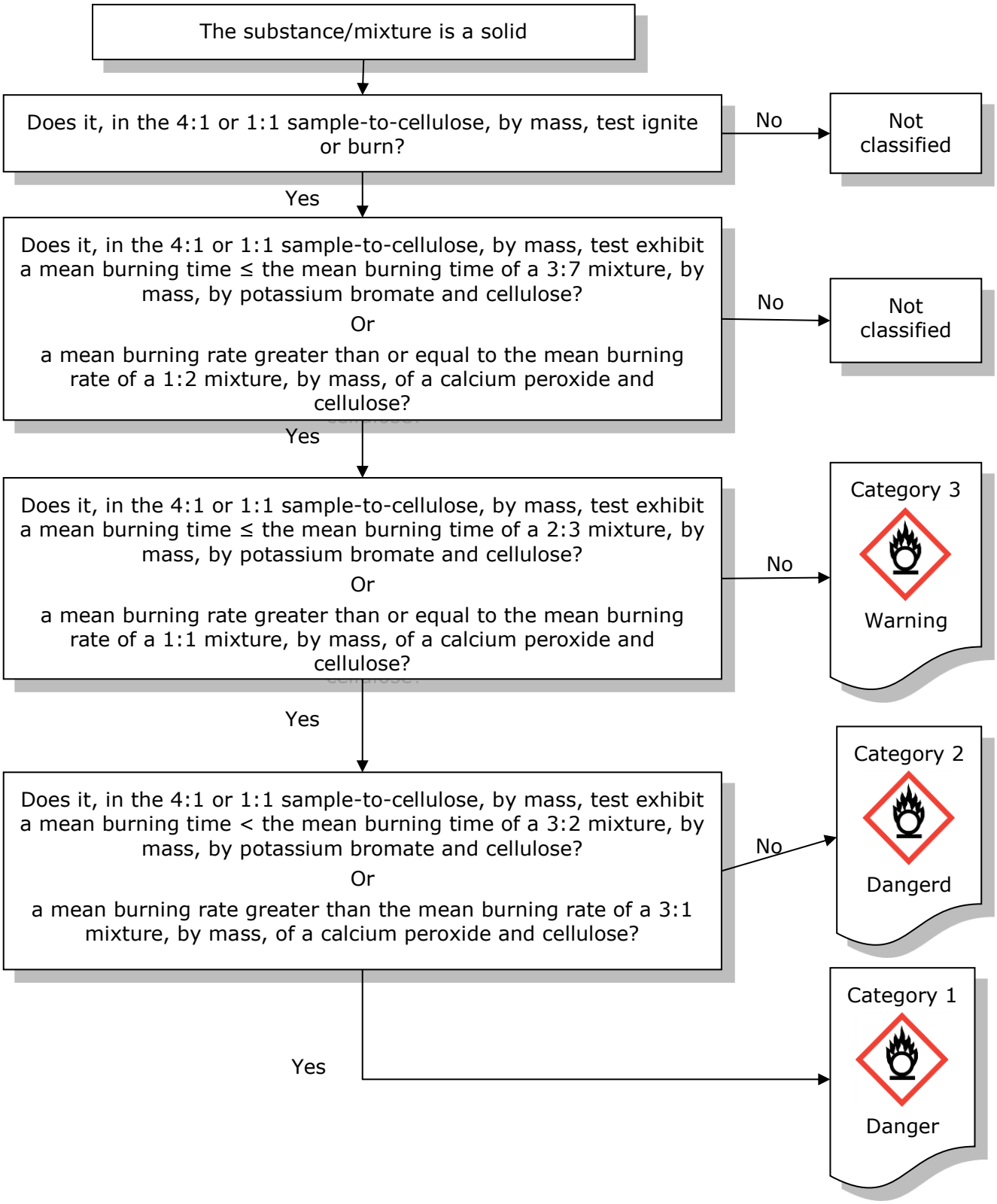
2.14.4.4. Decision logic

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.

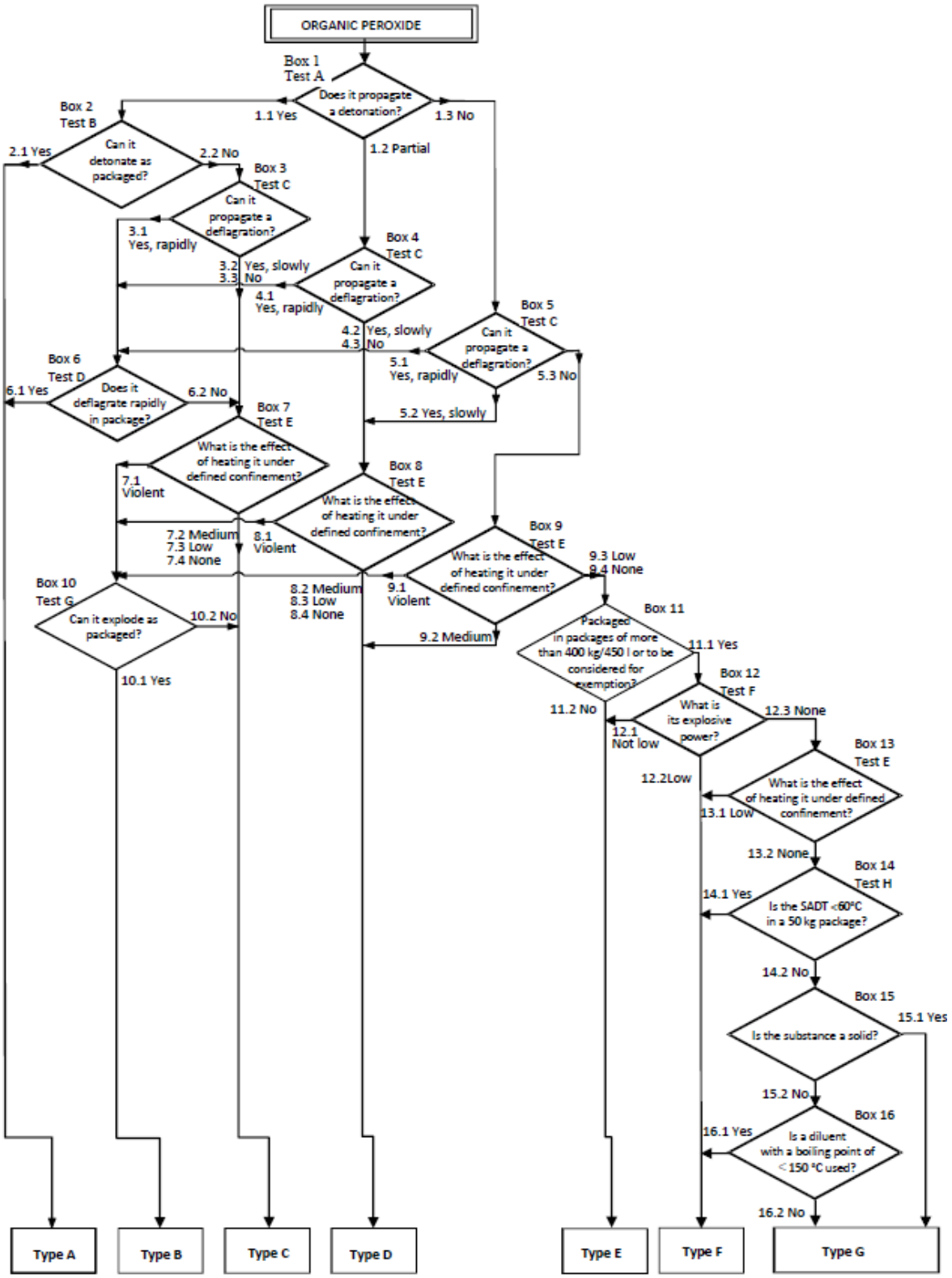
Formulated commercial organic peroxides are classified according to their SADT.

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

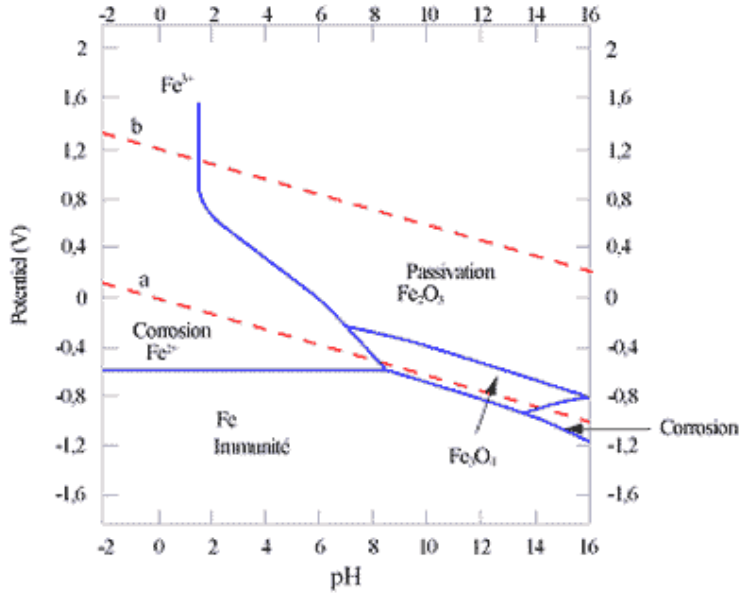
The criteria for 'Corrosive to metals' are found in Annex I, Section 2.16 of CLP and are identical to those in Chapter 2.16 of GHS.

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

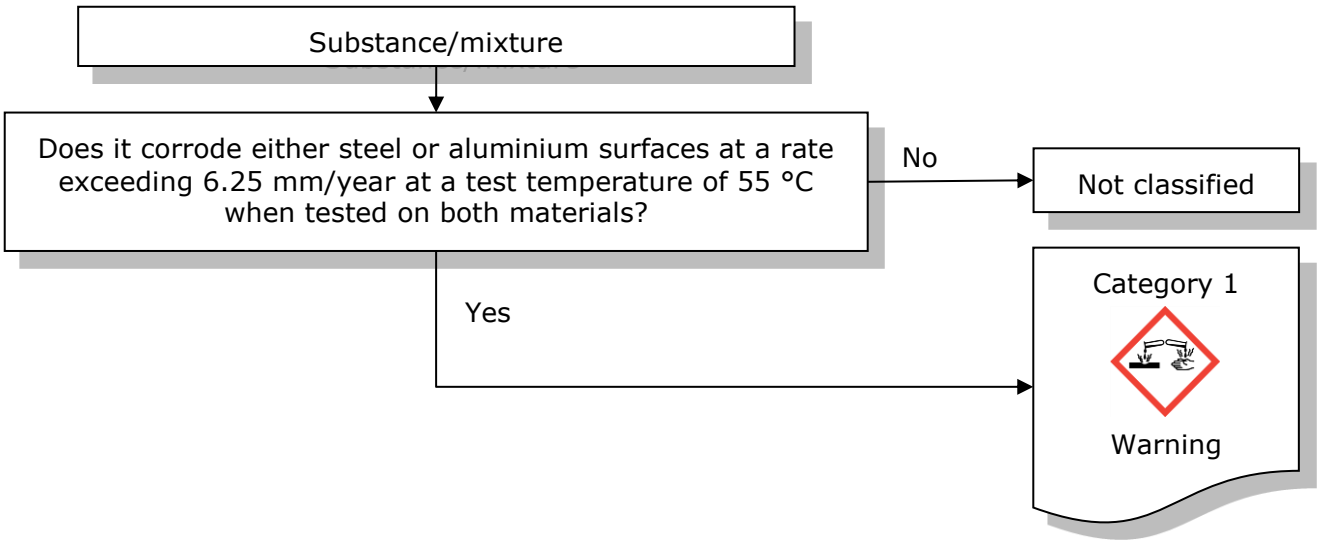
Figure 2.16 Example of testing equipment available on the market to perform UN Test C.1

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;

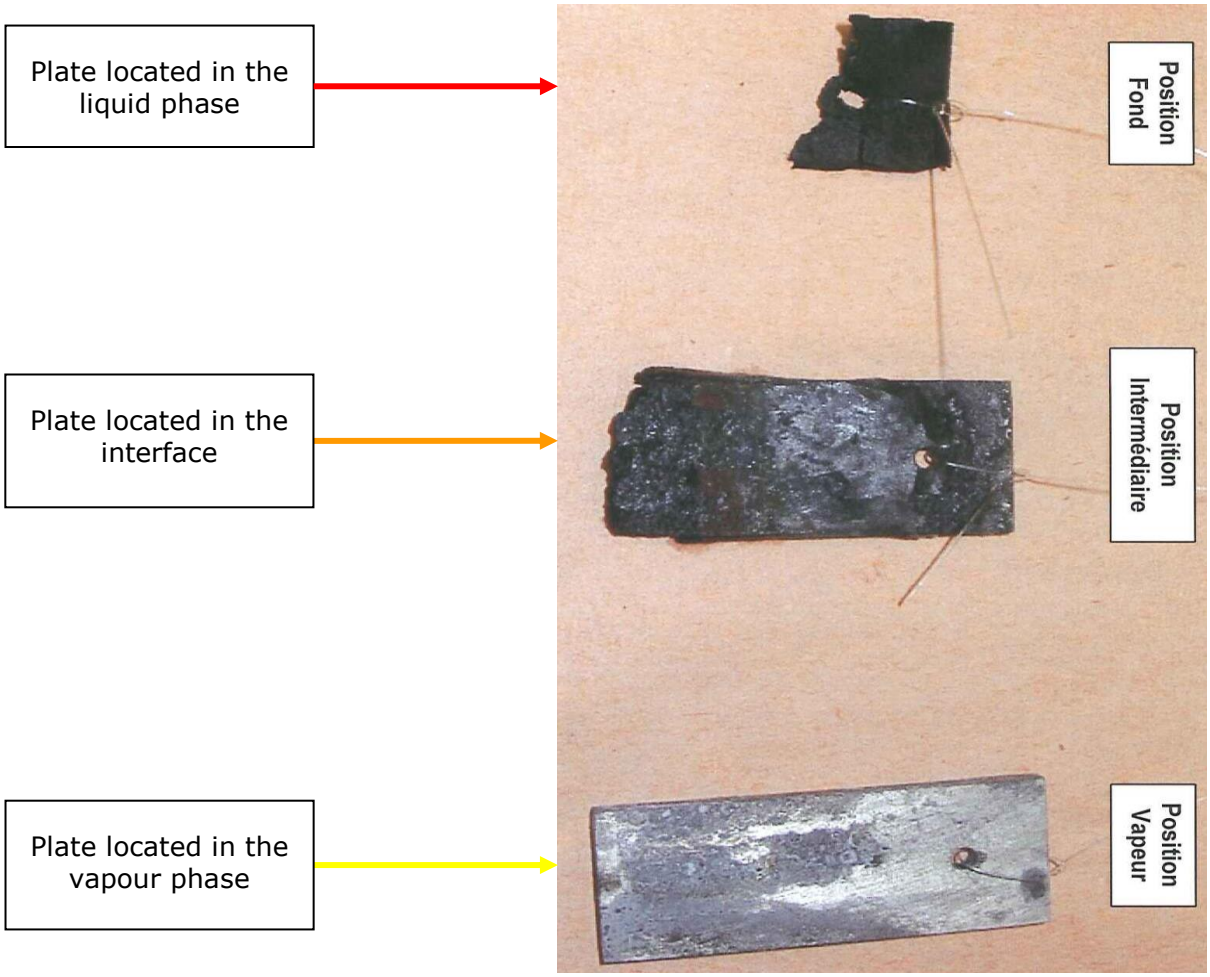
'Not corroded' means corrosion resistant in the sense of UN Test C.1;

'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.

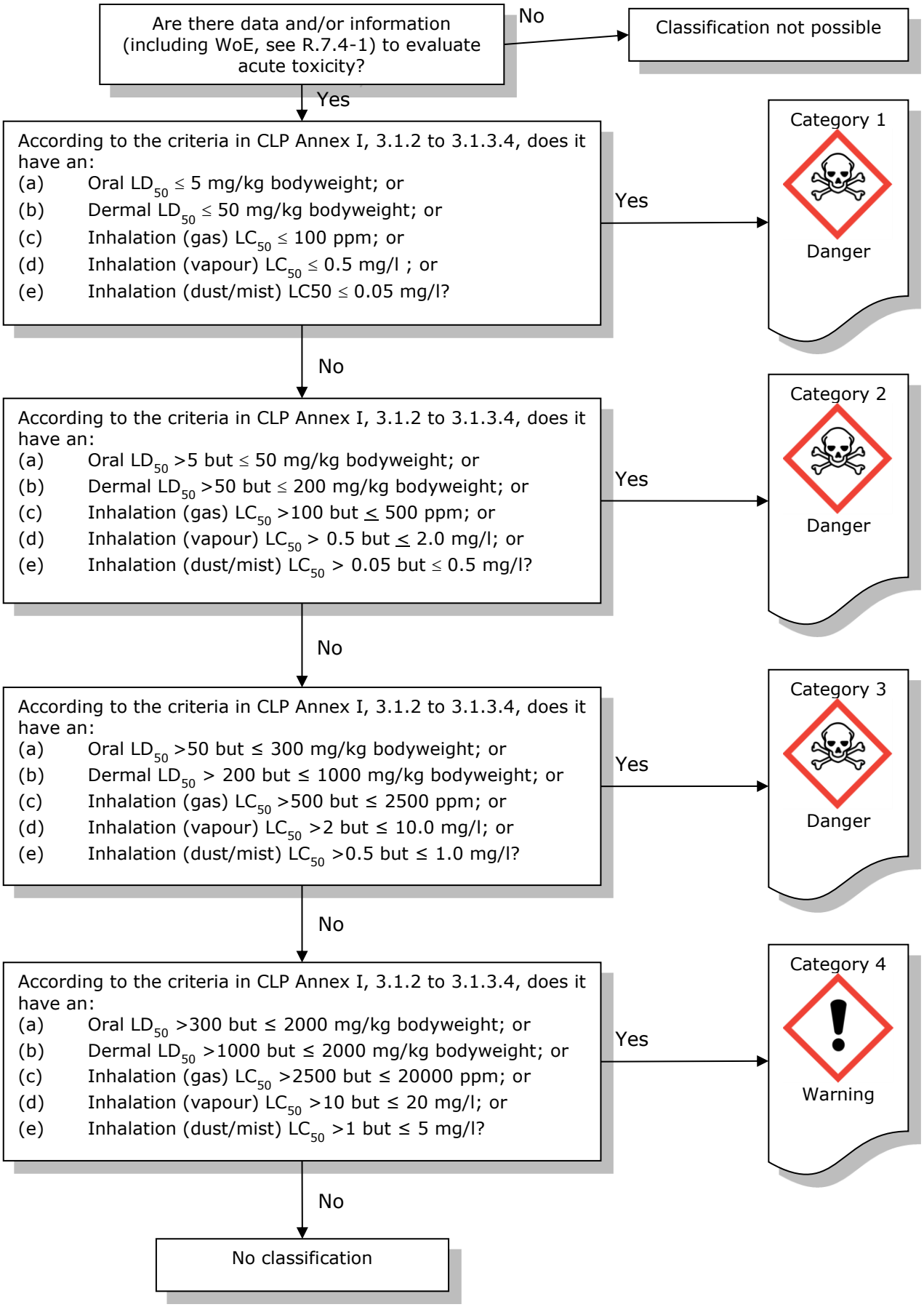
3.1.2.5. Setting of specific concentration limits

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:*

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

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

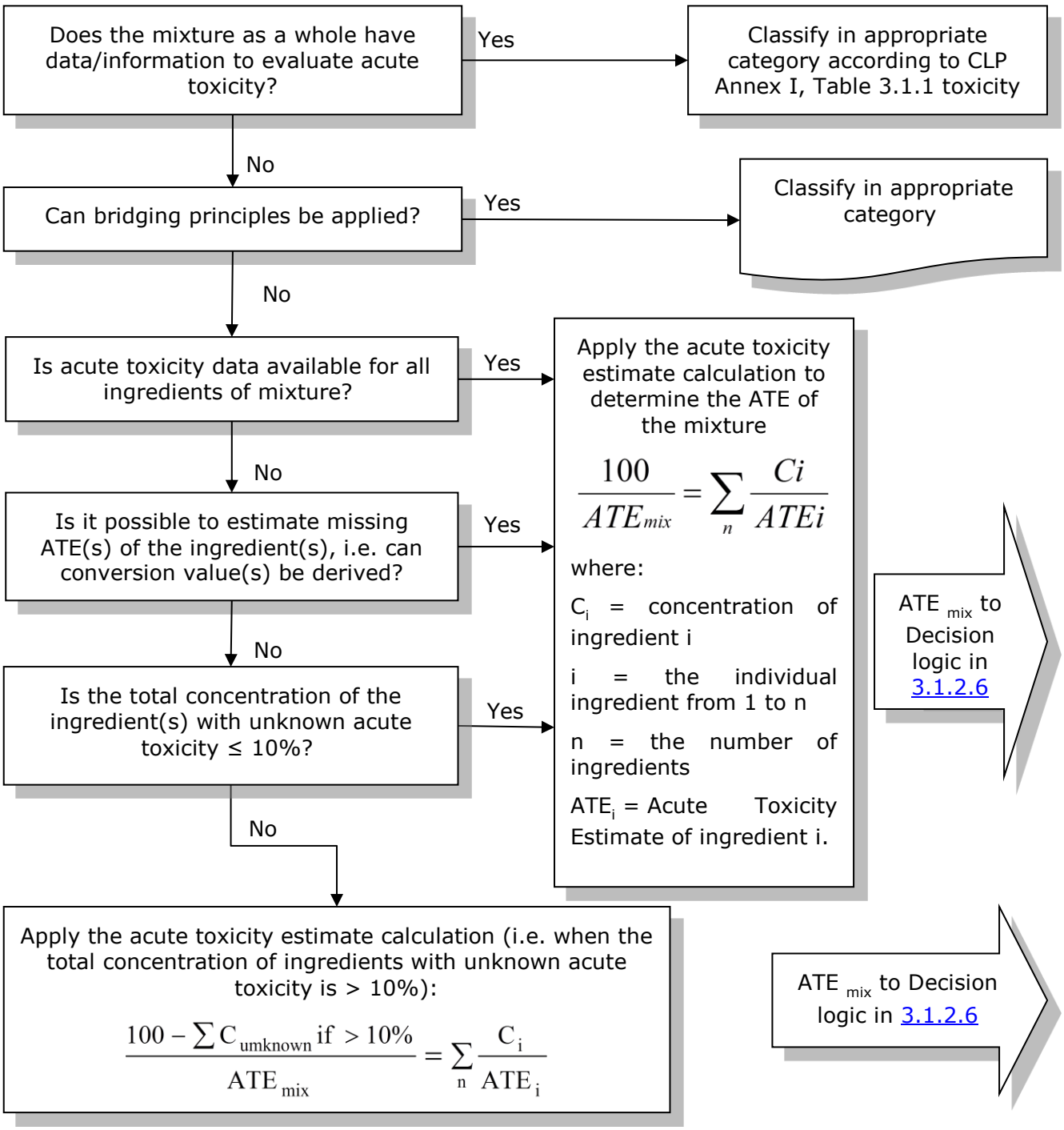
Generic concentration limits as such are not applicable for acute toxicity classification; therefore specific concentration limits are also not applicable (see Section 3.1.2.5 of this Guidance). Nevertheless, according to CLP Annex VI, 1.2.1 the classification for entries with the reference * in the 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.
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
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.

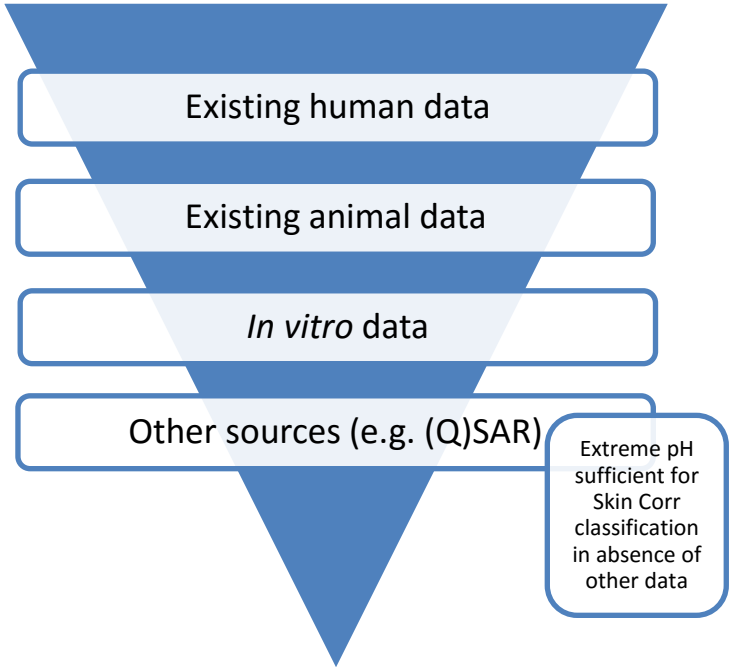
A weight of evidence determination means that all available and scientifically justified information bearing on the determination of hazard is considered together, such as physico-chemical parameters (e.g., pH, reserve alkalinity/acidity), information from the application of the category approach (grouping, 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.

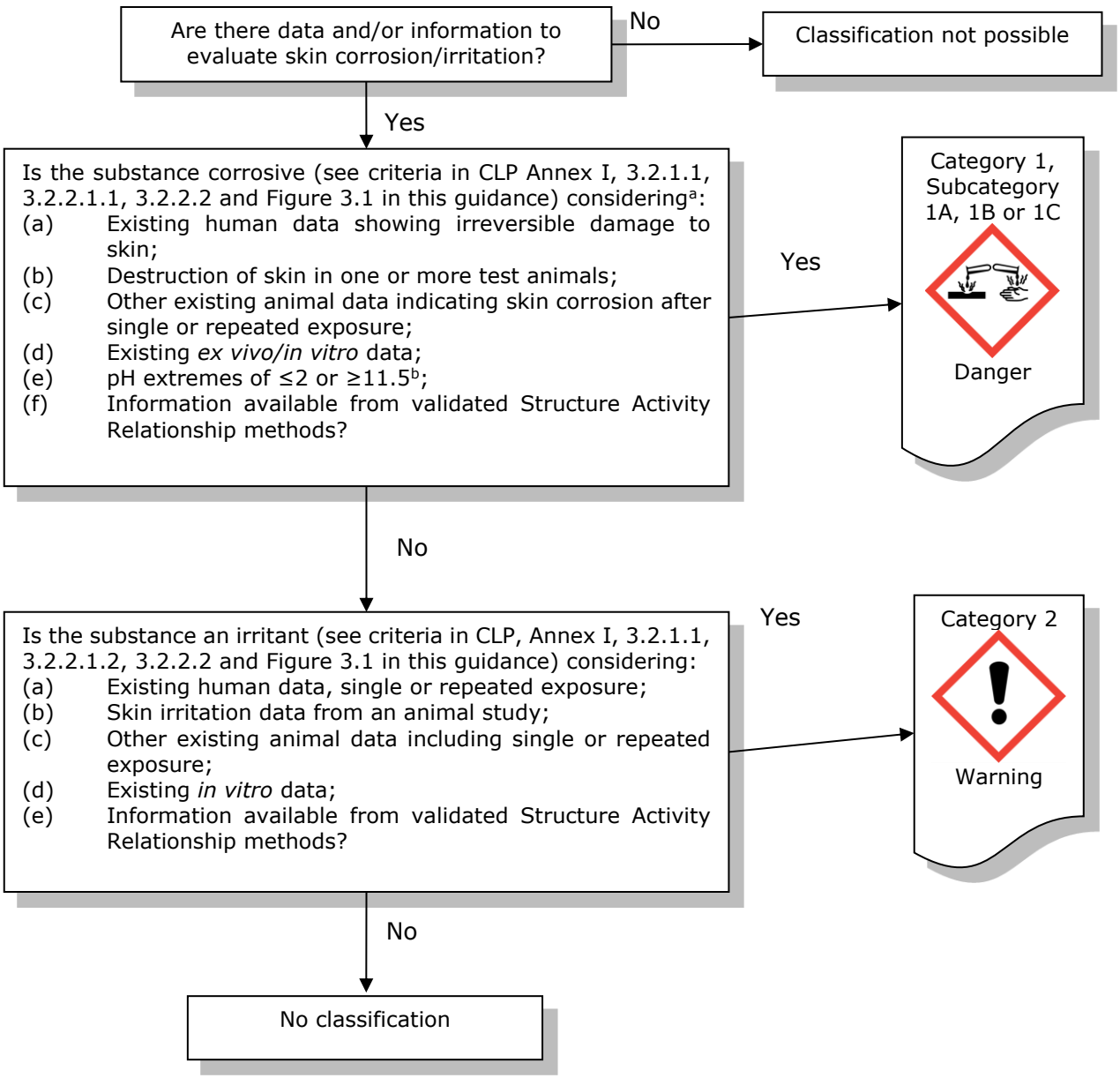
always be available, for mixtures containing substances already classified for skin corrosion/irritation, making it possible to identify the hazard for the mixture by using the GCLs (Article 9(4), CLP).

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%

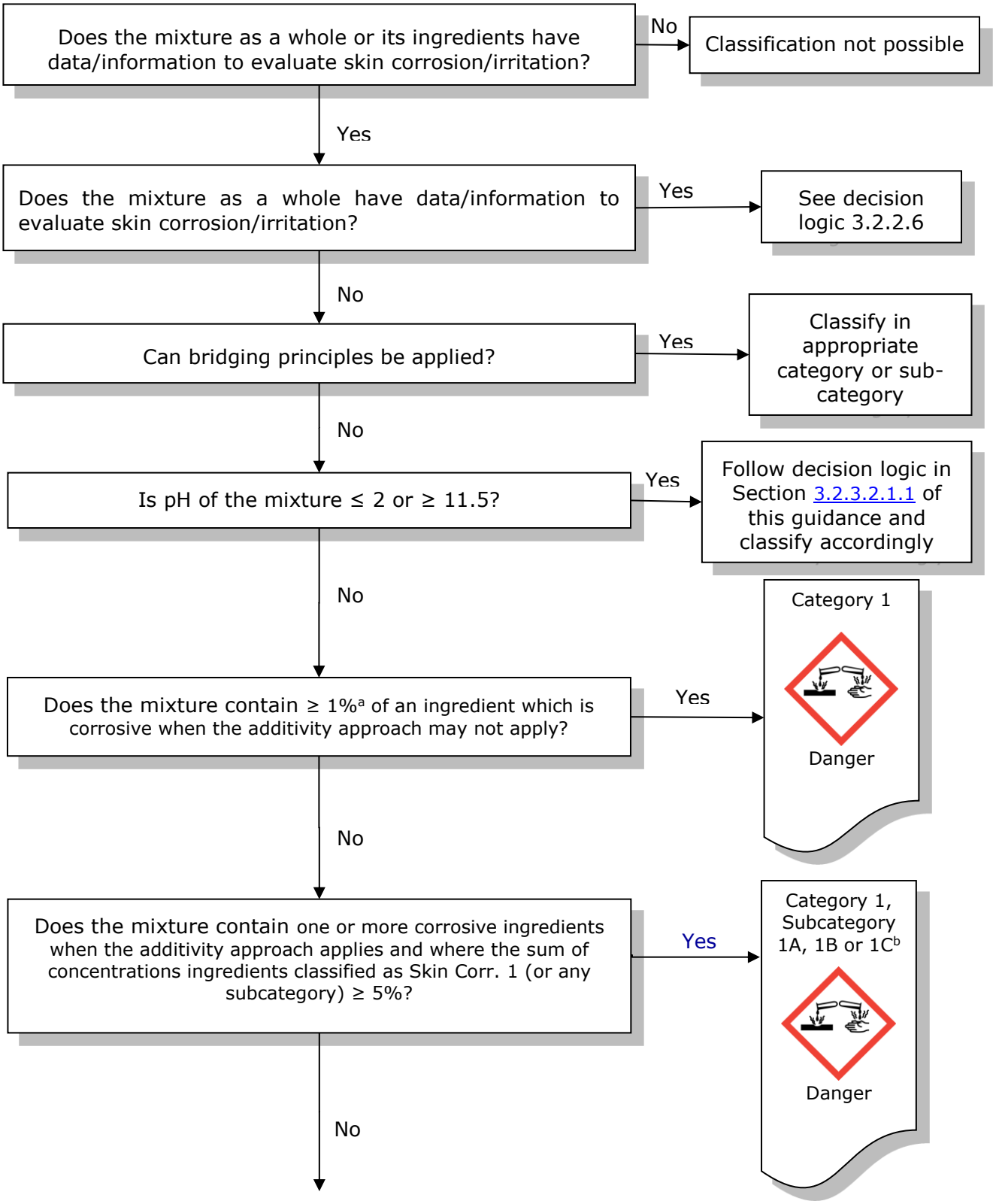
(10 x Skin corrosion Sub-Category 1A, 1B, 1C or Category 1) + Skin irritation Category 2		≥ 10%
Note *The sum of all ingredients of a mixture classified as Skin Corrosion Sub-Category 1A, 1B or 1C respectively, shall each be ≥ 5% respectively in order to classify the mixture as either Skin Corrosion 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 %.*		

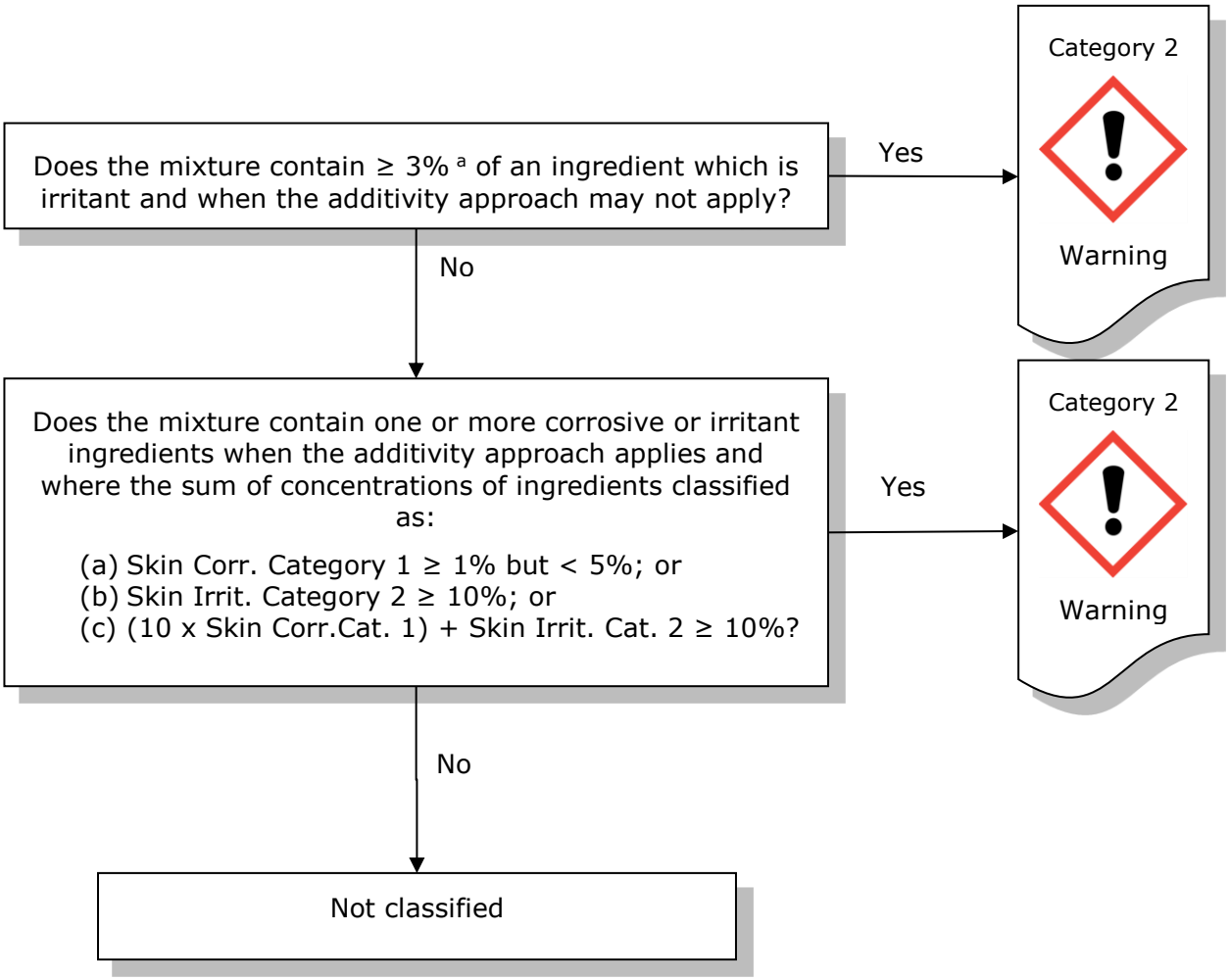
3.2.3.3.2. When the additivity approach is not applicable

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

[58] The German Federal Institute for Risk Assessment (BfR) has developed a Decision Support System (DSS) to assess certain hazardous properties of pure chemicals.

Microphysiometer (CM)[59] test, Isolated Rabbit Eye (IRE) test and the Hen's Egg Test on Chorio-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

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[59] A draft OECD TG available at http://www.oecd.org/env/ehs/testing/DRAFT%20Cytosensor%20TG%20(V9)%2021%20Dec%2012_clean.pdf.

[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.

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 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:

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

b. 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:

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

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

d. 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.

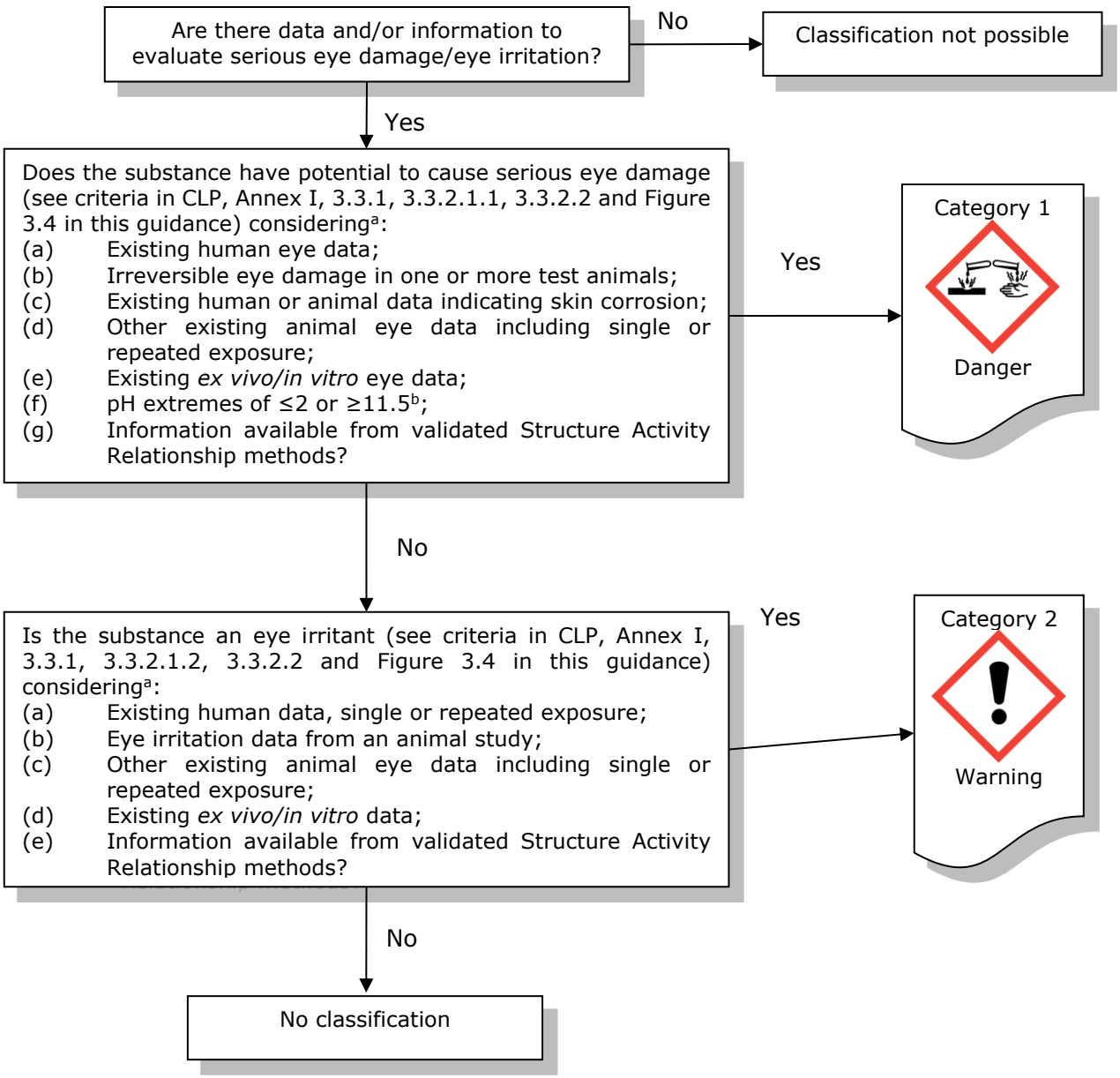
which provide adequate reliability of data, are possible. The GCLs must be applied for the classification of a mixture on the basis of its ingredient substances classified as causing serious eye damage or as an eye irritant, if there are no already existing specific data justifying an SCL which is lower 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

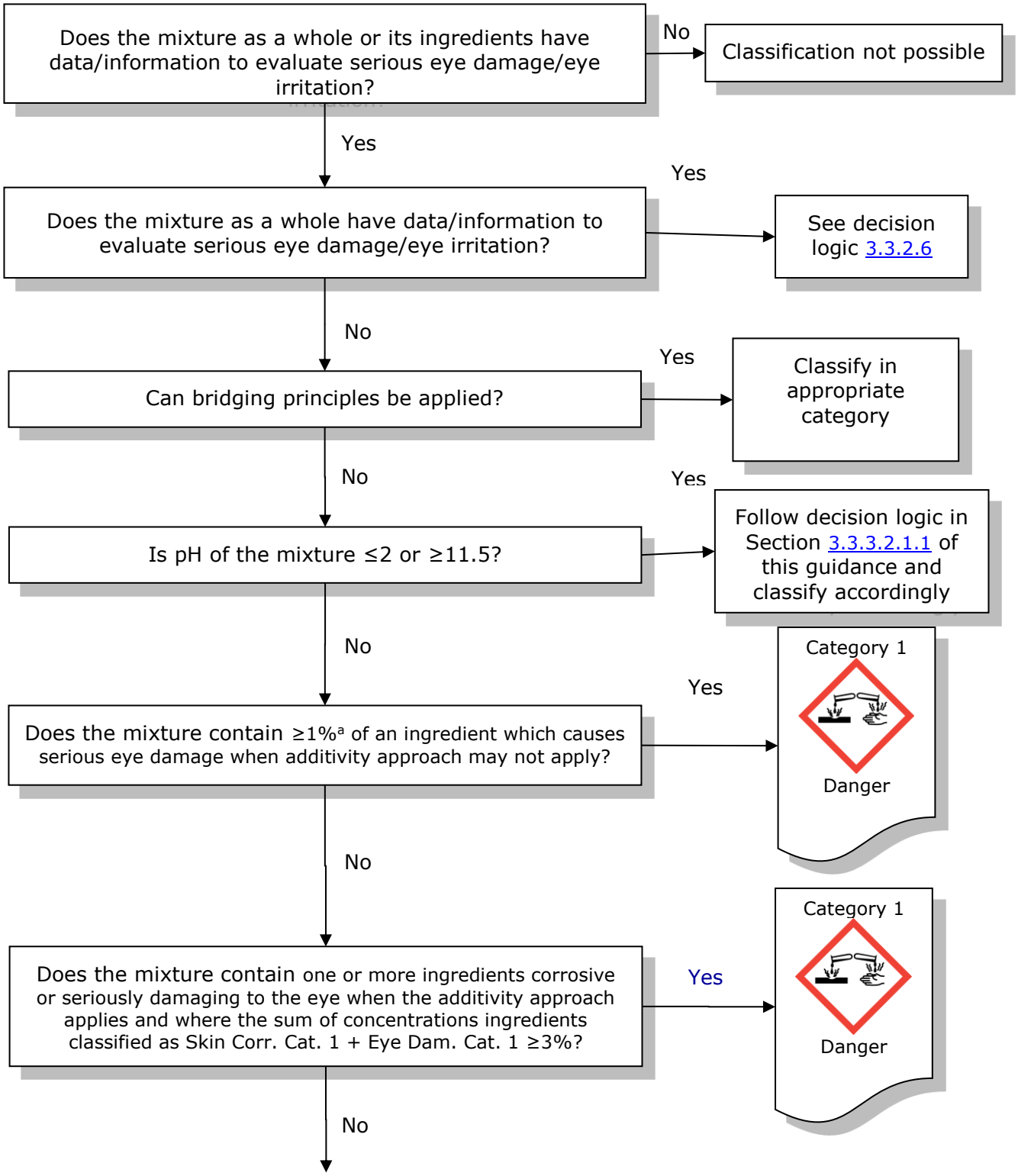
Annex I: *Table 3.3.4*

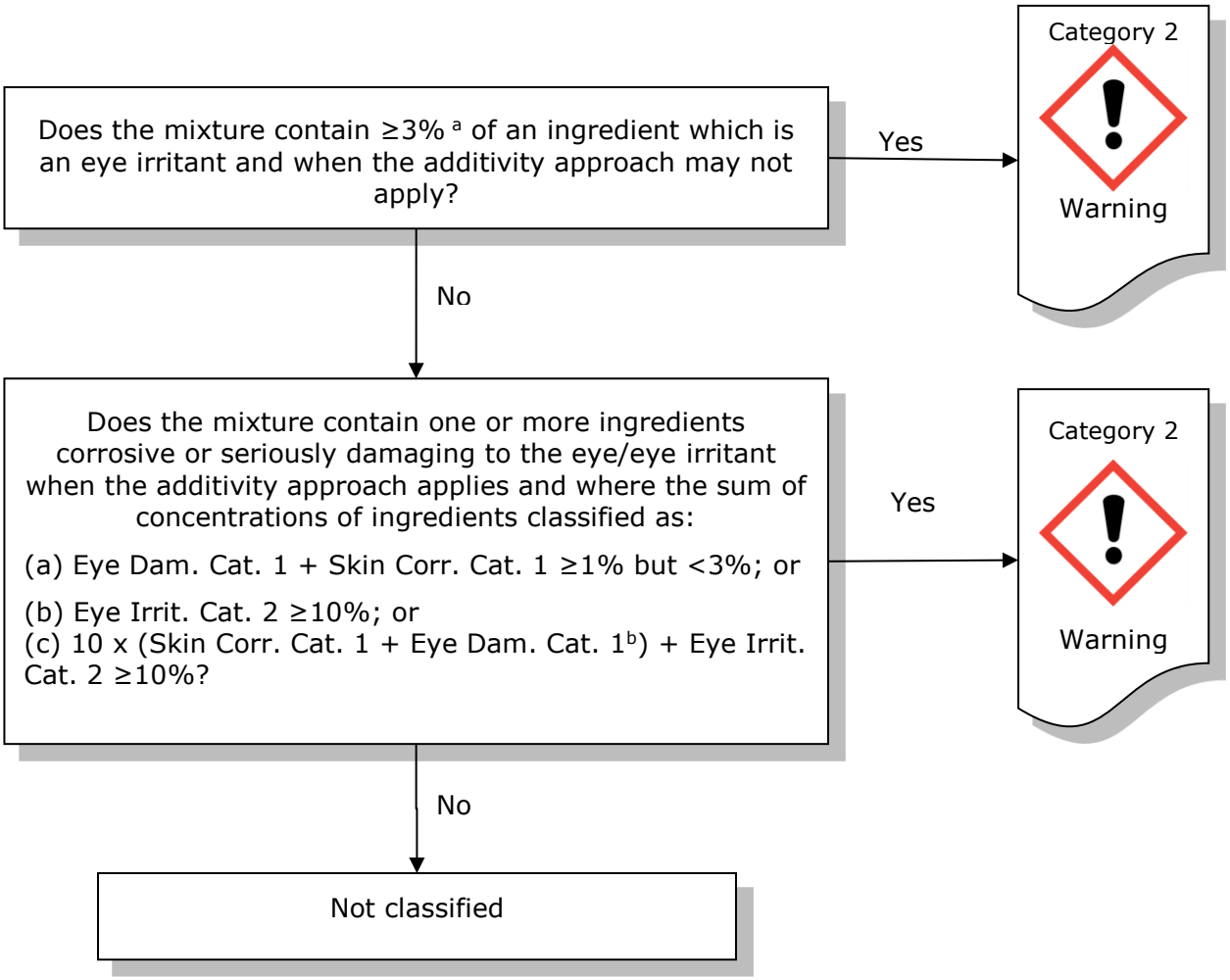
Generic concentration limits of ingredients of a mixture as serious eye damage (Category 1) or eye irritation (Category 2), where the additivity approach does not apply

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	Yes	
		Ø 24/48/72 h animal 1 is 3					
2	2	2	2	1	0	No	
		Ø 24/48/72 h animal 2 is 1.7					
3	2	3	2	2	0	Yes	
		Ø 24/48/72 h animal 3 is 2.3					

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	no	yes
		Ø 24/48/72h = 2.7							
2	1	2	2	3	1	1	0	no	yes
		Ø 24/48/72h = 2.3							
3	1	2	3	3	2	1	0	no	yes
		Ø 24/48/72h = 2.7							
4	1	2	4	4	2	1	0	yes	yes
		Ø 24/48/72h = 3.3							

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 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. 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

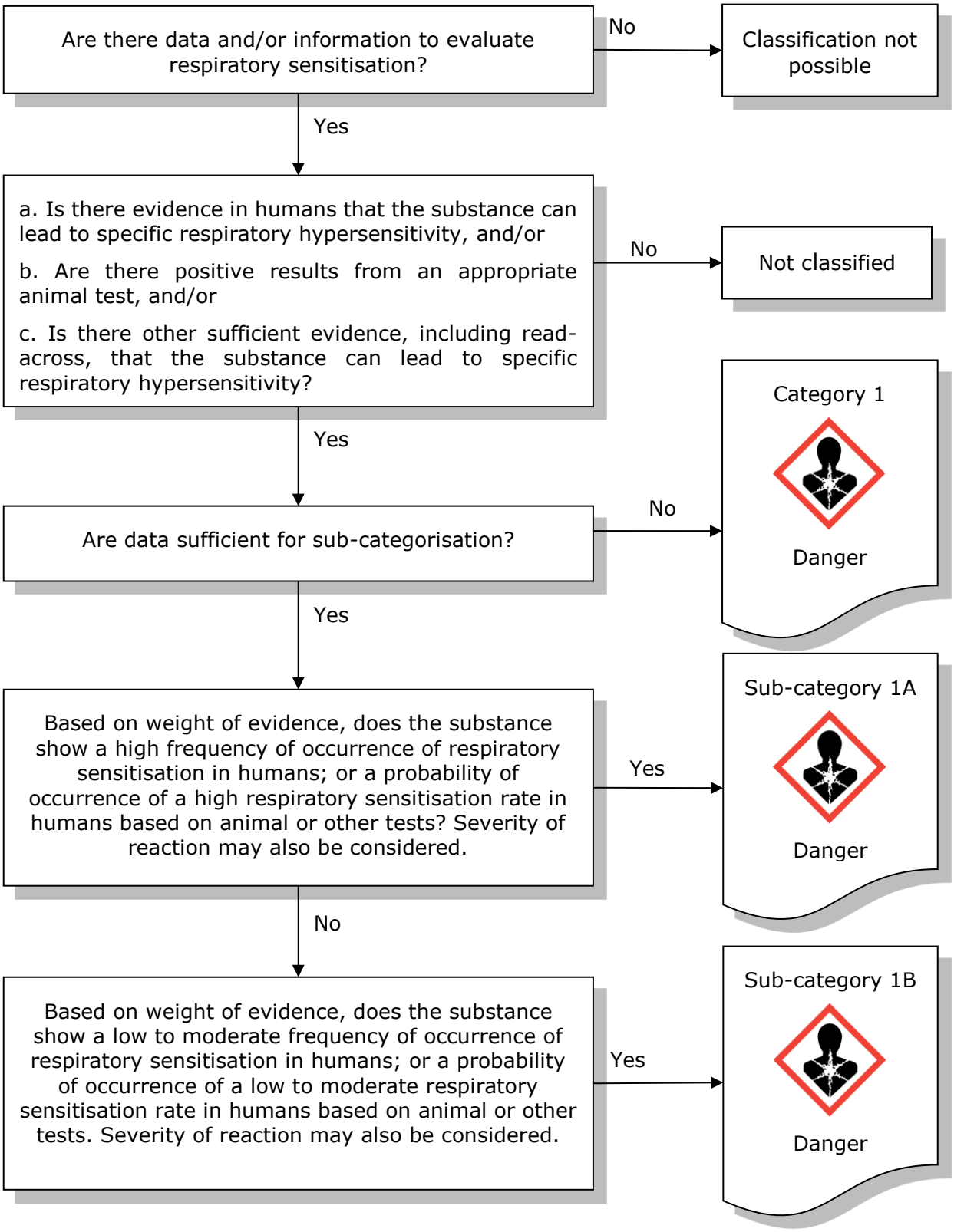
According to CLP Annex I, Section 3.4.2.1.1.4 substances fulfilling the criteria for respiratory sensitisation will be classified as such in Category 1 (and in Sub-category 1A or 1B when sufficient data are available),

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.

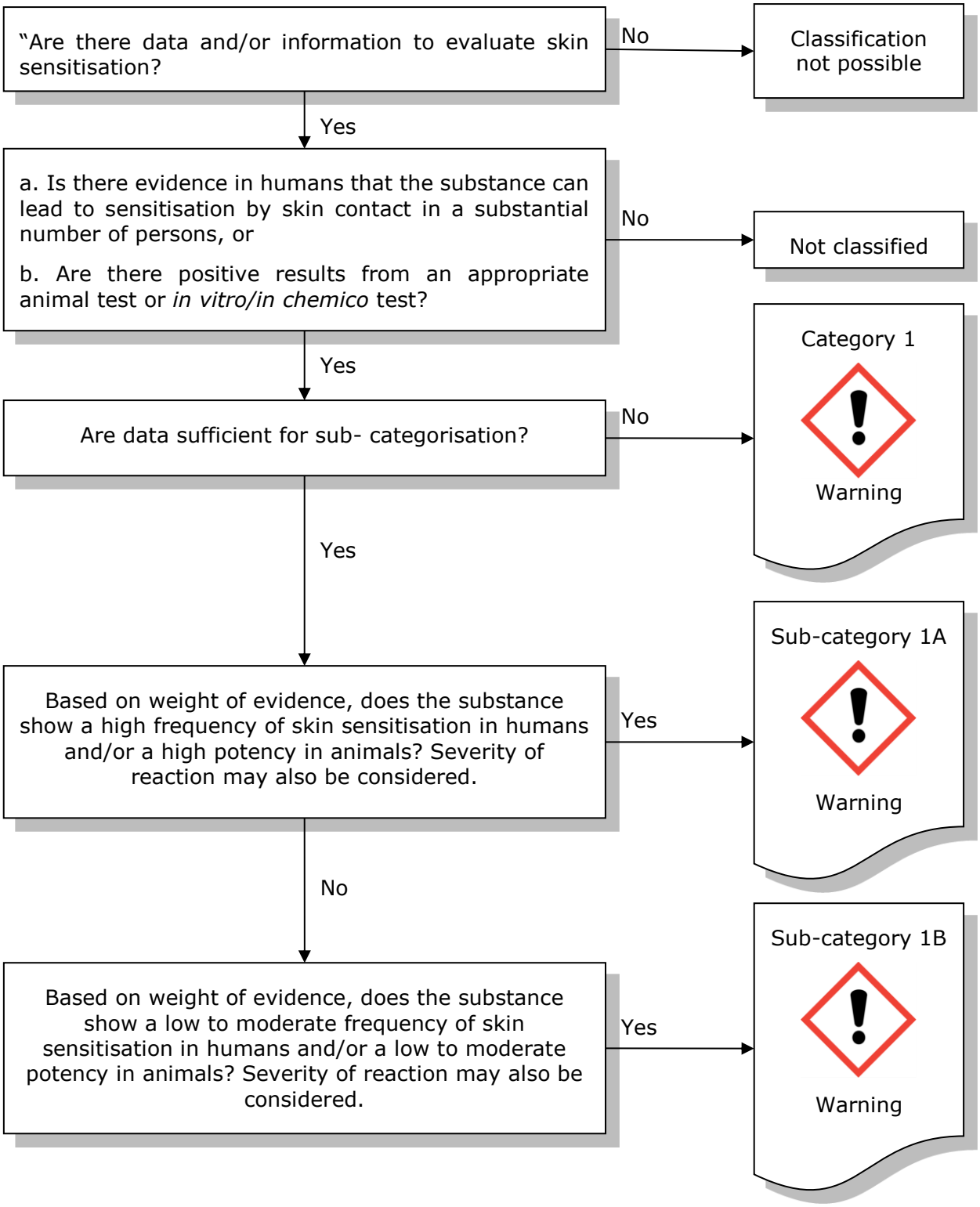
The concentration limits for skin sensitisers categorised according to their sensitisation potency in Table 3.9 are based on the recommendations from an EU expert group on skin sensitisation (Basketter *et al*., 2005a).

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.