Guidance to Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of substances and mixtures

Extracts of the document for update:

- Corrections to Part 1 – General Principles for Classification p. 30-74
- Update of Part 3 - Health Hazards p. 88-316
- Inclusion of new Annex VI p. 325-348

Note that the numbering and headlines of the sections that are not revised are displayed in this document, to retain the original numbering of the sections as shown in the original Guidance. This will facilitate the comparison of the revised parts with the original.
This document is the Guidance on the Application of the CLP Criteria. It is a comprehensive technical and scientific document on the application of Regulation (EC) No 1272/2008 on the classification, labelling and packaging of substances and mixtures (CLP), which will replace the Dangerous Substance Directive 67/548/EEC (DSD) and the Dangerous Preparations Directive 1999/45/EC (DPD) in a staggered way. CLP is based on the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) and is implementing the provisions of the GHS within the EU. The objective of this document is to provide detailed guidance on the application of the CLP criteria for physical, health and environmental hazards. The guidance is developed to assist primarily manufacturers or importers applying classification and labelling criteria and it also includes practical examples. It is also assumed to be the guidance on classification and labelling for Competent Authorities in the Member States (MS CA), for the Commission services and 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 DG ENTR. The final guidance was handed over to ECHA in summer 2009.

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

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

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

1 PART 1: GENERAL PRINCIPLES FOR CLASSIFICATION

1.1 INTRODUCTION

1.1.1 The objective of the guidance document

1.1.2 Background

1.1.3 Hazard classification

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

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

1.1.6 What information is needed for classification

1.1.6.1 Information for the classification of substances

1.1.6.2 Data for the classification of mixtures

1.1.7 Data evaluation and reaching a decision on classification

1.1.8 Updating of hazard classifications

1.1.9 The interface between hazard classification and hazard communication

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

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

1.1.12 Relation of classification to other EU legislation

1.1.12.1 REACH

1.1.12.2 Plant Protection Products and Biocides

1.1.12.3 Transport legislation

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’

1.2.2 The term ‘reasonably expected use’ in relation to hazard classification

1.2.3 The term ‘form or physical state’ in relation to hazard classification

1.2.3.1 Physical hazards

1.2.3.2 Human health hazards

1.2.3.3 Environmental hazards

1.3 SPECIFIC CASES REQUIRING FURTHER EVALUATION – LACK OF BIOAVAILABILITY

1.3.1 Definition

1.3.2 Bioavailability

1.3.2.1 Human health hazards

1.3.2.2 Environmental hazards

1.3.2.3 Other types of hazards

1.3.3 Specific cases requiring further evaluation – lack of bioavailability in physical mixtures
1.4 USE OF SUBSTANCE CATEGORISATION (READ ACROSS AND GROUPING) AND (Q)SAR(S) FOR CLASSIFICATION AND LABELLING

1.4.1 (Q)SAR

1.4.2 Grouping

1.4.3 Read across

1.5 SPECIFIC CONCENTRATION LIMITS AND M-FACTORS

1.5.1 Specific concentration limits

1.5.2 Multiplying factors (M-factors)

1.6 MIXTURES

1.6.1 How to classify a mixture

FIGURE 1.6.1 HOW TO CLASSIFY A MIXTURE

1.6.2 Classification for physical hazards

1.6.3 Health and environmental hazards

1.6.3.1 Classification derived using data on the mixture itself

1.6.3.2 Bridging principles

1.6.3.2.1 Dilution

1.6.3.2.2 Batching

1.6.3.2.3 Concentration of highly hazardous mixtures

1.6.3.2.5 Substantially similar mixtures

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

1.6.3.3 Aerosols (some health hazards only)

1.6.3.4 Classification based on calculation or concentration thresholds

1.6.4 Classification of mixtures in mixtures

ACUTE TOXICITY

SKIN CORROSION/IRRITATION

SERIOUS EYE DAMAGE/EYE IRRITATION

SKIN SENSITISATION

TABLE 1.6.4.1(A) INGREDIENTS IN MIXTURE A

TABLE 1.6.4.1(B) INGREDIENT 'FRAGRANCE MIXTURE'
ACUTE TOXICITY ........................................................................................................... ERROR! BOOKMARK NOT DEFINED.

SKIN CORROSION/IRRITATION ............................................................................ ERROR! BOOKMARK NOT DEFINED.

SERIOUS EYE DAMAGE/EYE IRRITATION ...................................................... ERROR! BOOKMARK NOT DEFINED.

RESPIRATORY SENSITISATION ......................................................................... ERROR! BOOKMARK NOT DEFINED.

STOT ......................................................................................................................... ERROR! BOOKMARK NOT DEFINED.

TABLE 1.6.4.2(A) INGREDIENTS IN MIXTURE B .................................................. ERROR! BOOKMARK NOT DEFINED.

TABLE 1.6.4.2(B) INGREDIENT ' BASE POWDER ' ............................................. ERROR! BOOKMARK NOT DEFINED.

1.7 THE APPLICATION OF ANNEX VII .................................................................. ERROR! BOOKMARK NOT DEFINED.

1.7.1 Introduction ...................................................................................................... Error! Bookmark not defined.

1.7.2 Use of Annex VII translation tables ......................................................... Error! Bookmark not defined.

1.7.2.1 Applicability of the Annex VII translation tables ...... Error! Bookmark not defined.

TABLE 1.7.2.1(B) ADDITIONAL INFORMATION USING TRANSPORT CLASSIFICATIONS ERROR! BOOKMARK NOT DEFINED.

1.7.3 Additional considerations for re-classification due to changes in the classification criteria ............................................................................................................. Error! Bookmark not defined.

2 PART 2: PHYSICAL HAZARDS ............................................................................. ERROR! BOOKMARK NOT DEFINED.

2.1 INTRODUCTION ................................................................................................. ERROR! BOOKMARK NOT DEFINED.

2.1.1 General remarks about the prerequisites of classification and testing Error! Bookmark not defined.

2.1.2 Safety ............................................................................................................ Error! Bookmark not defined.

2.1.3 General conditions for testing .................................................................... Error! Bookmark not defined.

2.1.4 Physical state ............................................................................................... Error! Bookmark not defined.

2.1.5 Quality .......................................................................................................... Error! Bookmark not defined.

2.2 EXPLOSIVES ................................................................................................... ERROR! BOOKMARK NOT DEFINED.

2.2.1 Introduction ...................................................................................................... Error! Bookmark not defined.

2.2.2 Definitions and general considerations for the classification of explosives Error! Bookmark not defined.

2.2.3 Classification of substances, mixtures or articles as explosives Error! Bookmark not defined.

2.2.3.1 Identification of hazard information ....................................................... Error! Bookmark not defined.

2.2.3.2 Screening procedures and waiving of testing...................................... Error! Bookmark not defined.

2.2.3.3 Classification criteria .............................................................................. Error! Bookmark not defined.

2.2.3.4 Testing and evaluation of hazard information ................................ Error! Bookmark not defined.

2.2.3.5 Classification procedure and decision logics ...................................... Error! Bookmark not defined.

2.2.3.5.1 Acceptance procedure ................................................................. Error! Bookmark not defined.

2.2.3.5.2 Assignment procedure to a division .............................................. Error! Bookmark not defined.

2.2.4 Hazard communication for explosives ....................................................... Error! Bookmark not defined.

2.2.4.1 Pictograms, signal words, hazard statements and precautionary statements Error! Bookmark not defined.

2.2.4.2 Additional labelling provisions............................................................ Error! Bookmark not defined.

2.2.5 Re-classification of substances and mixtures classified as explosive according to DSD or already classified for transport .......................................................... Error! Bookmark not defined.

2.2.5.1 Re-classification of substances and mixtures classified in accordance with DSD ................................................................................................................ Error! Bookmark not defined.

2.2.5.2 Relation to transport classification ...................................................... Error! Bookmark not defined.

2.2.6 Examples of classification for explosives ................................................... Error! Bookmark not defined.

2.2.6.1 Example of substances and mixtures fulfilling the classification criteria Error! Bookmark not defined.
2.3 FLAMMABLE GASES............................................................................... ERROR! BOOKMARK NOT DEFINED.
2.3.1 Introduction .............................................................................. Error! Bookmark not defined.
2.3.2 Definitions and general considerations for the classification of flammable gases Error! Bookmark not defined.
2.3.3 Relation to other physical hazards .............................................. Error! Bookmark not defined.
2.3.4 Classification of substances and mixtures as flammable gases Error! Bookmark not defined.
  2.3.4.1 Identification of hazard information...................................... Error! Bookmark not defined.
  2.3.4.2 Screening procedures and waiving of testing for gas mixtures Error! Bookmark not defined.
  2.3.4.3 Classification criteria ............................................................. Error! Bookmark not defined.
  2.3.4.4 Testing and evaluation of hazard information .............. Error! Bookmark not defined.
  2.3.4.5 Pictograms, signal words, hazard statements and precautionary statements Error! Bookmark not defined.
  2.3.4.6 Additional labelling provisions....................... Error! Bookmark not defined.
2.3.5 Re-classification of substances and mixtures classified as flammable gases according
to DSD or already classified for transport------------------------ Error! Bookmark not defined.
  2.3.5.1 Re-classification of substances and mixtures classified in accordance with
  DSD........................................................................................................ Error! Bookmark not defined.
  2.3.5.2 Relation to transport classification .................................... Error! Bookmark not defined.
2.3.6 Example of classification for flammable gases........................... Error! Bookmark not defined.
2.4 FLAMMABLE AEROSOLS ................................................................. ERROR! BOOKMARK NOT DEFINED.
2.4.1 Introduction .............................................................................. Error! Bookmark not defined.
2.4.2 Definitions and general considerations for the classification of flammable aerosols Error! Bookmark not defined.
2.4.3 Classification of flammable aerosols ............................................ Error! Bookmark not defined.
  2.4.3.1 Classification criteria ............................................................. Error! Bookmark not defined.
  2.4.3.2 Testing and evaluation of hazard information .............. Error! Bookmark not defined.
  2.4.3.3 Decision logic .......................................................... Error! Bookmark not defined.
2.4.4 Hazard communication for flammable aerosols ....................... Error! Bookmark not defined.
  2.4.4.1 Pictograms, signal words, hazard statements and precautionary statements Error! Bookmark not defined.
  2.4.4.2 Additional labelling provisions....................... Error! Bookmark not defined.
2.4.5 Re-classification of flammable aerosols according to DSD ...... Error! Bookmark not defined.
2.4.6 Examples of classification for flammable aerosols..................... Error! Bookmark not defined.
2.4.6.1 EXAMPLES OF AEROSOLS FULFILLING THE CLASSIFICATION CRITERIA Error! Bookmark not defined.
  2.4.6.2 Examples of aerosols not fulfilling the classification criteria Error! Bookmark not defined.
2.5 OXIDISING GASES................................................................................. ERROR! BOOKMARK NOT DEFINED.
2.5.1 Introduction .............................................................................. Error! Bookmark not defined.
2.5.2 Definitions and general considerations for the classification of oxidising gases Error! Bookmark not defined.
2.5.3 Classification of substances and mixtures as oxidising gases ... Error! Bookmark not defined.
  2.5.3.1 Identification of hazard information...................................... Error! Bookmark not defined.
  2.5.3.2 Screening procedures and waiving of testing.............. Error! Bookmark not defined.
  2.5.3.3 Classification criteria ............................................................. Error! Bookmark not defined.
  2.5.3.4 Testing and evaluation of hazard information .............. Error! Bookmark not defined.
2.5.4 Hazard communication for oxidising gases......................... Error! Bookmark not defined.
  2.5.4.1 Pictograms, signal words, hazard statements and precautionary statements Error! Bookmark not defined.
2.5.5 Re-classification of substances and mixtures classified as oxidising gases according to
DSD or already classified for transport------------------------ Error! Bookmark not defined.
  2.5.5.1 Re-classification of substances and mixtures classified in accordance with
  DSD........................................................................................................ Error! Bookmark not defined.
  2.5.5.2 Relation to transport classification .................................... Error! Bookmark not defined.
Guidance to Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of substances and mixtures

2.7 FLAMMABLE LIQUIDS

2.7.4 IDENTIFICATION OF HAZARD INFORMATION

2.7.4.1 Screening procedures and waiving of testing

2.7.4.2 Flash point

2.7.4.3 Classification criteria

2.7.4.4 Testing and evaluation of hazard information

2.7.4.5 Decision logic

2.7.5 Hazard communication for flammable liquids

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

2.7.7 Examples of classification for flammable liquids

2.8 FLAMMABLE SOLIDS

2.8.4.1 IDENTIFICATION OF HAZARD INFORMATION

2.8.4.2 Screening procedures and waiving of testing
2.8.4.3 Classification criteria ................................................. Error! Bookmark not defined.
2.8.4.4 Testing and evaluation of hazard information .... Error! Bookmark not defined.

2.8.4.5 DECISION LOGIC .................................................. ERROR! BOOKMARK NOT DEFINED.
2.8.5 Hazard communication for flammable solids ............ Error! Bookmark not defined.
2.8.5.1 Pictograms, signal words, hazard statements and precautionary statements Error! Bookmark not defined.
2.8.6 Re-classification of substances and mixtures classified as flammable solids according
to DSD or already classified for transport ..................... Error! Bookmark not defined.
2.8.6.1 Re-classification of substances and mixtures classified in accordance with
DSD ............................................................................. Error! Bookmark not defined.
2.8.6.2 Relation to transport classification ......................... Error! Bookmark not defined.
2.8.7 Examples of classification for flammable solids ........ Error! Bookmark not defined.
2.8.7.1 Example of substances and mixtures fulfilling the classification criteria Error! Bookmark not defined.
2.8.7.2 Examples of substances and mixtures not fulfilling the classification criteria Error! Bookmark not defined.

2.9 SELF-REACTIVE SUBSTANCES ............................................. ERROR! BOOKMARK NOT DEFINED.
2.9.1 Introduction ............................................................. Error! Bookmark not defined.
2.9.2 Definitions and general considerations for the classification of self-reactives Error! Bookmark not defined.
2.9.3 Classification of substances and mixtures as self-reactive .... Error! Bookmark not defined.
2.9.3.1 Identification of hazard information ................................ Error! Bookmark not defined.
2.9.3.2 Classification criteria ............................................. Error! Bookmark not defined.
2.9.3.3 Testing and evaluation of hazard information .......... Error! Bookmark not defined.
2.9.3.3.1 Thermal stability tests and temperature control Error! Bookmark not defined.
2.9.3.3.2 Additional testing .............................................. Error! Bookmark not defined.
2.9.3.3.3 Additional classification considerations... Error! Bookmark not defined.
2.9.3.4 Decision logic ..................................................... Error! Bookmark not defined.
2.9.4 Hazard communication for self-reactives .................. Error! Bookmark not defined.
2.9.4.1 Pictograms, signal words, hazard statements and precautionary statements Error! Bookmark not defined.
2.9.5 Re-classification of substances and mixtures classified as self-reactives according to
DSD or already classified for transport ......................... Error! Bookmark not defined.
2.9.5.1 Re-classification of substances and mixtures classified in accordance with
DSD ............................................................................. Error! Bookmark not defined.
2.9.5.2 Relation to transport classification ......................... Error! Bookmark not defined.
2.9.6 Examples of classification for self-reactives ............. Error! Bookmark not defined.
2.9.6.1 Examples of substances and mixtures fulfilling the classification criteria Error! Bookmark not defined.

2.10 PYROPHORIC LIQUIDS AND SOLIDS ..................................... ERROR! BOOKMARK NOT DEFINED.
2.10.1 Introduction ............................................................. Error! Bookmark not defined.
2.10.2 Definitions and general considerations for the classification pyrophoric liquids and
solids ............................................................................. Error! Bookmark not defined.
2.10.3 Relation to other physical hazards ........................... Error! Bookmark not defined.
2.10.4 Classification of substances and mixtures as pyrophoric liquids and solids Error! Bookmark not defined.
2.10.4.1 Identification of hazard information ...................... Error! Bookmark not defined.
2.10.4.2 Screening procedures and waiving of testing .......... Error! Bookmark not defined.
2.10.4.3 Classification criteria ............................................. Error! Bookmark not defined.
2.10.4.4 Testing and evaluation of hazard information ........ Error! Bookmark not defined.
2.10.4.5 Decision logic ..................................................... Error! Bookmark not defined.
2.10.5 Hazard communication for pyrophoric liquids and solids ...... Error! Bookmark not defined.
2.10.5.1 Pictograms, signal words, hazard statements and precautionary statements Error! Bookmark not defined.
2.10.6 Re-classification of substances and mixtures classified as pyrophoric liquids and
solids according to DSD or already classified for transport ...... Error! Bookmark not defined.
2.11 SELF-HEATING SUBSTANCES AND MIXTURES

2.11.1 Introduction

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

2.11.3 Relation to other physical hazards

2.11.4 Classification of self-heating substances and mixtures

2.11.4.1 Identification of hazard information

2.11.4.2 Screening procedures and waiving of testing

2.11.4.3 Classification criteria

2.11.4.4 Testing and evaluation of hazard information

2.11.4.5 Decision logic

2.11.4.6 Exemption

2.11.5 Hazard communication for self-heating substances and mixtures

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

2.11.7 Examples of classification for self-heating substances and mixtures

2.11.8 References

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

2.12.1 Introduction

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

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

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

2.12.5 Decision logic

2.12.6 Screening procedures and waiving of testing

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

2.12.8 References
Guidance to Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of substances and mixtures

2.12.4.2 Additional labelling provisions............................... Error! Bookmark not defined.
2.12.5 Re-classification of substances and mixtures which, in contact with water, emit flammable gases according to DSD or already classified for transport Error! Bookmark not defined.
2.12.5.1 Re-classification of substances and mixtures classified in accordance with DSD .................................................. Error! Bookmark not defined.
2.12.5.1.1 Differences in classification and labelling Error! Bookmark not defined.
2.12.5.1.2 Differences in the test procedures .......... Error! Bookmark not defined.
2.12.5.2 Relation to transport classification ...................... Error! Bookmark not defined.
2.12.6 Examples of classification for substances and mixtures which, in contact with water, emit flammable gases............................................ Error! Bookmark not defined.
2.12.6.1 Example of a substance fulfilling the classification criteria Error! Bookmark not defined.
2.12.6.2 Example of a substance not fulfilling the classification criteria Error! Bookmark not defined.
2.12.7 References................................................................ Error! Bookmark not defined.

2.13 OXIDISING LIQUIDS AND OXIDISING SOLIDS ..................... ERROR! BOOKMARK NOT DEFINED.
2.13.1 Introduction ................................................................ Error! Bookmark not defined.
2.13.2 Definitions and general considerations for the classification of oxidising liquids and oxidising solids........................................... Error! Bookmark not defined.
2.13.3 Classification of substances and mixtures as oxidising liquids and oxidising solids Error! Bookmark not defined.

2.13.3.1 IDENTIFICATION OF HAZARD INFORMATION ............ ERROR! BOOKMARK NOT DEFINED.
2.13.3.1.1 Non-testing data .............................................. Error! Bookmark not defined.
2.13.3.2 Classification criteria ............................................ Error! Bookmark not defined.
2.13.3.2.1 General ......................................................... Error! Bookmark not defined.
2.13.3.2.2 Oxidising liquids ............................................ Error! Bookmark not defined.
2.13.3.2.3 Oxidising solids ............................................. Error! Bookmark not defined.
2.13.3.3 Testing and evaluation of hazard information .......... Error! Bookmark not defined.
2.13.3.4 Decision logic ..................................................... Error! Bookmark not defined.

2.13.3.4.1 DECISION LOGIC 2.13 FOR OXIDISING LIQUIDS .......... ERROR! BOOKMARK NOT DEFINED.
2.13.3.5 Pictograms, signal words, hazard statements and precautionary statements Error! Bookmark not defined.

2.13.4 Re-classification of substances and mixtures classified as oxidising liquids and oxidising solids according to DSD or already classified for transport Error! Bookmark not defined.
2.13.4.1 Re-classification of substances and mixtures classified in accordance with DSD .................................................. Error! Bookmark not defined.
2.13.4.1.1 Liquids ......................................................... Error! Bookmark not defined.
2.13.4.1.2 Solids .......................................................... Error! Bookmark not defined.
2.13.4.2 Relation to transport classification ...................... Error! Bookmark not defined.

2.13.5 Examples of classification for oxidising liquids and oxidising solids Error! Bookmark not defined.
2.13.5.1 Examples of substances and mixtures fulfilling the classification criteria Error! Bookmark not defined.
2.13.5.1.1 Liquids ......................................................... Error! Bookmark not defined.
2.13.5.1.2 Solids .......................................................... Error! Bookmark not defined.
2.13.5.2 Examples of substances and mixtures not fulfilling the classification criteria Error! Bookmark not defined.

2.13.5.2.1 Liquids ......................................................... Error! Bookmark not defined.
2.13.5.2.2 Solids .......................................................... Error! Bookmark not defined.

2.13.6 Reference ................................................................ Error! Bookmark not defined.

2.14 ORGANIC PEROXIDES .................................................... ERROR! BOOKMARK NOT DEFINED.
2.14.1 Introduction ................................................................ Error! Bookmark not defined.
2.14.2 Definitions and general considerations for the classification of organic peroxides Error! Bookmark not defined.
2.14.3 Relation to other physical hazards ............................... Error! Bookmark not defined.
2.14.4 Classification of substances and mixtures as organic peroxides

2.14.4.1 Identification of hazard information

2.14.4.2 Classification criteria

2.14.4.3 Testing and evaluation of hazard information

2.14.5 Hazard communication for organic peroxides

2.14.6 Re-classification of substances and mixtures classified as organic peroxides according to DSD or already classified according to transport

2.14.7 Examples of classification for organic peroxides

2.15 CORROSIVE TO METALS

2.15.1 Introduction

2.15.2 Definitions and general considerations for the classification of substances and mixtures corrosive to metals

2.15.3 Classification of substances and mixtures as corrosive to metals

2.15.4 Hazard communication for substances and mixtures corrosive to metals

2.15.5 Re-classification of substances and mixtures classified as corrosive to metals according to DSD

2.15.6 Examples of classification for substances and mixtures corrosive to metals

3 HEALTH HAZARDS

3.1 ACUTE TOXICITY

3.1.1 Definitions and general considerations for acute toxicity

3.1.2 Classification of substances for acute toxicity

3.1.2.1 Identification of hazard information

3.1.2.2 Classification criteria

3.1.2.3 Evaluation of hazard information
3.1.2.3.1 Evaluation of human data
3.1.2.3.2 Evaluation of non-human data
3.1.2.3.3 Weight of evidence
3.1.2.4 Decision on classification
3.1.2.5 Setting of specific concentration limits
3.1.2.6 Decision logic
3.1.3 Classification of mixtures for acute toxicity
3.1.3.1 General considerations for classification
3.1.3.2 Identification of hazard information
3.1.3.3 Classification criteria
3.1.3.4 When data are not available for all components
3.1.3.5 Components that should be taken into account for the purpose of classification
3.1.3.6 Generic concentration limits for substances triggering classification of mixtures
3.1.3.7 Decision on classification
3.1.3.8 Decision logic
3.1.4 Hazard communication in form of labelling for acute toxicity
3.1.4.1 Pictograms, signal words, hazard statements and precautionary statements
3.1.4.2 Additional labelling provisions
3.1.5 Re-classification of substances and mixtures classified for acute toxicity according to DSD and DPD
3.1.5.1 Is direct “translation” of classification and labelling possible?
3.1.5.2 Re-evaluation of data
3.1.6 Examples of classification for acute toxicity
3.1.6.1 Examples of substances fulfilling the criteria for classification
3.1.6.2 Examples of substances not fulfilling the criteria for classification
3.1.6.3 Examples of mixtures fulfilling the criteria for classification
3.1.6.4 Examples of mixtures not fulfilling the criteria for classification
3.1.6.5 Components that should be taken into account for the purpose of classification
3.1.6.6 Weight of evidence
3.1.6.7 Setting of specific concentration limits
3.1.6.8 Decision logic
3.1.6.9 Decision on classification
3.1.6.10 Additional labelling provisions
3.1.6.11 Pictograms, signal words, hazard statements and precautionary statements
3.1.6.12 Additional labelling provisions
3.1.6.13 Re-classification of substances and mixtures classified for acute toxicity according to DSD and DPD
3.1.6.14 Is direct “translation” of classification and labelling possible?
3.1.6.15 Re-evaluation of data
3.1.6.16 Examples of classification for acute toxicity
3.1.6.17 Examples of substances fulfilling the criteria for classification
3.1.6.18 Examples of substances not fulfilling the criteria for classification
3.1.6.19 Examples of mixtures fulfilling the criteria for classification
3.1.6.20 Examples of mixtures not fulfilling the criteria for classification
3.1.6.21 Additional labelling provisions
3.1.6.22 Pictograms, signal words, hazard statements and precautionary statements
3.1.6.23 Additional labelling provisions
3.1.6.24 Re-classification of substances and mixtures classified for acute toxicity according to DSD and DPD
3.1.6.25 Is direct “translation” of classification and labelling possible?
3.1.6.26 Re-evaluation of data
3.1.7 References

3.2 SKIN CORROSION/IRRITATION
3.2.1 Definitions for classification for skin corrosion/irritation
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

3.2.2.1.2 Identification of non human data

3.2.1.2.1 Consideration of physico-chemical properties

3.2.2.2 NON-TESTING METHODS: (Q)SARS AND EXPERT SYSTEMS

3.2.2.2.1 TESTING-METHODS: PH AND ACID/ALKALINE RESERVE

3.2.2.2.2 TESTING METHODS: IN VITRO METHODS

3.2.2.2.3 TESTING METHODS: IN VIVO DATA

3.2.2.2.4 Classification of mixtures for skin corrosion/irritation

3.2.2.2.5 Evaluation of hazard information

3.2.2.2.6 Evaluation of human data

3.2.2.2.7 Evaluation of non human data

3.2.2.2.8 In vitro data

3.2.2.2.9 In vivo data

3.2.2.3 Decision on classification

3.2.2.3.1 Identification of hazard information

3.2.2.3.2 Classification criteria

3.2.2.3.3 Weight of evidence

3.2.2.3.4 Setting of specific concentration limits

3.2.2.3.5 Decision logic for classification of mixtures

3.2.2.3.6 Decision logic for classification of substances

3.2.2.3.7 Additional labelling provisions

3.2.2.4 Testing methods: PH and acid/alkaline reserve

3.2.2.5 Setting of specific concentration limits

3.2.2.6 Examples of classification for skin corrosion/irritation

3.2.2.7 TESTING METHODS: (Q)SARS AND EXPERT SYSTEMS

3.2.2.8 NON-TESTING METHODS: PH AND ACID/ALKALINE RESERVE

3.2.2.9 TESTING METHODS: IN VITRO METHODS

3.2.2.10 TESTING METHODS: IN VIVO DATA

3.2.2.11 Classification of mixtures for skin corrosion/irritation

3.2.2.12 Evaluation of hazard information

3.2.2.13 Evaluation of human data

3.2.2.14 Evaluation of non human data

3.2.2.15 In vitro data

3.2.2.16 In vivo data

3.2.3 Classification of mixtures for skin corrosion/irritation

3.2.3.1 Identification of hazard information

3.2.3.2 Classification criteria

3.2.3.3 Weight of evidence

3.2.3.4 Decision logic for classification of mixtures

3.2.3.5 Decision logic for classification of substances

3.2.3.6 Additional labelling provisions

3.2.3.7 Generic concentration limits for substances triggering classification of mixtures

3.2.3.8 The additivity approach is applicable

3.2.3.9 The additivity approach is not applicable

3.2.3.10 Decision on classification

3.2.3.11 Hazard communication in form of labelling for skin corrosion/irritation

3.2.3.12 Re-classification of substances and mixtures classified for skin corrosion/irritation according to DSD and DPD

3.2.3.13 Is direct “translation” of classification and labelling possible?

3.2.3.14 Re-evaluation of data

3.2.3.15 Examples of classification for skin corrosion/irritation

3.2.3.16 Examples of substances fulfilling the criteria for classification

3.2.3.17 Example 1: Standard test according to OECD TG 404 with three animals

3.2.3.18 Example 2: Standard test according to OECD TG 404 with three animals

3.2.3.19 Example 3: Standard test according to OECD TG 404 with three animals

3.2.3.20 Example 4: Standard test according to OECD TG 404 with three animals

3.2.3.21 Example 5: Standard test according to OECD TG 404 with three animals

3.2.3.22 Example 6: Standard test according to OECD TG 404 with three animals

3.2.3.23 Example 7: Standard test according to OECD TG 404 with three animals

3.2.3.24 Example 8: Standard test according to OECD TG 404 with three animals

3.2.3.25 Example 9: Standard test according to OECD TG 404 with three animals
3.3.4 Hazard communication in form of labelling for serious eye damage/eye irritation

3.3.4.1 Hazard classification

3.3.4.1.1 Hazard class

3.3.4.1.2 Hazard statement

3.3.4.1.3 Pictograms

3.3.4.1.4 Additional information

3.3.4.2 Hazard communication in form of material safety data sheet

3.3.4.2.1 General information

3.3.4.2.2 Hazard classification

3.3.4.2.3 Hazard statements

3.3.4.2.4 Pictograms

3.3.4.2.5 Additional information

3.3.4.3 Hazard communication in form of training

3.3.4.3.1 General information

3.3.4.3.2 Hazard classification

3.3.4.3.3 Hazard statements

3.3.4.3.4 Pictograms

3.3.4.3.5 Additional information

3.3.4.4 Other hazard communication methods

3.3.4.4.1 General information

3.3.4.4.2 Hazard classification

3.3.4.4.3 Hazard statements

3.3.4.4.4 Pictograms

3.3.4.4.5 Additional information

3.3.4.5 Guidance on the decision logic for the classification of mixtures for serious eye damage/eye irritation

3.3.4.5.1 General information

3.3.4.5.2 Decision logic

3.3.4.5.3 Examples of mixtures fulfilling the criteria for classification

3.3.4.5.4 Examples of mixtures not fulfilling the criteria for classification

3.3.4.6 Additional information

3.3.4.6.1 General information

3.3.4.6.2 Hazard classification

3.3.4.6.3 Hazard statements

3.3.4.6.4 Pictograms

3.3.4.6.5 Additional information
3.4.4 Hazard communication for respiratory or skin sensitisation

3.4.4.1 Pictograms, signal words, hazard statements and precautionary statements

3.4.4.2 Additional labelling provisions
3.5.4 Re-classification of substances and mixtures classified for respiratory or skin sensitisation according to DSD and DPD

3.5.4.1 Is direct “translation” of classification and labelling possible?”

3.5.4.2 Re-evaluation of the skin sensitisation data

3.5.6 Examples of classification for skin sensitisation

3.5.6.1 Example of substance fulfilling the criteria for classification for skin sensitisation

3.5.6.2 Example of substances or mixtures not fulfilling the criteria for classification for skin sensitisation

3.5.6.2.1 Example 1

3.5.6.2.2 Example 6

3.6 CARCINOGENICITY

3.6.1 Definitions and general considerations for classification for carcinogenicity

3.6.2 Classification of substances for carcinogenicity

3.6.2.1 Identification of hazard information

3.6.2.2 Classification criteria for substances

3.6.2.3 Evaluation of hazard information

3.6.2.3.1 Specific considerations for classification

3.6.2.3.2 Evaluation of non human data

3.6.2.3.3 Evaluation of human data

3.6.2.3.4 Identification of human data

3.6.2.3.5 Identification of non human data

3.6.2.4 Decision on classification

3.6.2.5 Setting of specific concentration limits

3.6.2.6 Decision logic for mixtures

3.6.2.7 Additional labelling provisions

3.6.2.8 Pictograms, signal words, hazard statements and precautionary statements

3.6.3 Hazard communication in form of labelling for germ cell mutagenicity

3.6.3.1 Pictograms, signal words, hazard statements and precautionary statements

3.6.3.2 Additional labelling provisions

3.6.3.3 Decision logic for mixtures

3.6.3.4 Setting of specific concentration limits

3.6.3.5 Decision on classification

3.6.3.6 Evaluation of non human data

3.6.3.7 Evaluation of human data

3.6.3.8 Identification of human data

3.6.3.9 Identification of non human data

3.6.3.10 Identification of hazard information

3.6.3.11 Classification criteria for substances

3.6.3.12 Classification criteria for mixtures

3.6.3.13 When data are available for the complete mixture

3.6.3.14 When data are not available for the complete mixture: bridging principles

3.6.3.15 Generic concentration limits for substances triggering classification of mixtures

3.6.3.16 Decision logic for mixtures

3.6.3.17 Setting of specific concentration limits

3.6.3.18 Decision on classification

3.6.3.19 Evaluation of non human data

3.6.3.20 Evaluation of human data

3.6.3.21 Identification of non human data

3.6.3.22 Identification of human data

3.6.3.23 Identification of hazard information

3.7 References
Guidance to Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of substances and mixtures

3.7 REPRODUCTIVE TOXICITY

3.7.1 Definitions and general considerations for reproductive toxicity

3.7.1.1 Special considerations on effects on or via lactation.

3.7.2 Classification of substances for reproductive toxicity

3.7.2.1 Identification of hazard information

3.7.2.1.1 Identification of human data

3.7.2.1.2 Identification of non human data

3.7.2.2 Classification criteria

3.7.2.2.1 Classification in the presence of parental toxicity

3.7.2.3 Evaluation of hazard information

3.7.2.3.1 Use of data from standard repeat dose tests

3.7.2.3.2 Study design

3.7.2.4 Decision on classification

3.7.2.5 Setting of specific concentration limits

3.7.2.6 Decision logic

3.7.3 Classification of mixtures for reproductive toxicity

3.7.3.1 Classification criteria

3.7.3.1.1 When data are available for the individual ingredients

3.7.3.1.2 When data are available for the complete mixture

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

3.7.3.2 Decision logic

3.7.3.3 When data are available for the complete mixture: bridging principles

3.7.4 Hazard communication in form of labelling for reproductive toxicity

3.7.4.1 Pictograms, signal words, hazard statements and precautionary statements

3.7.4.2 Additional considerations for classification

3.7.4.3 Setting of specific concentration limits

3.7.4.4 Decision logic

3.7.4.5 Decision on classification

3.7.4.6 Additional labelling provisions

3.7.4.7 Pictograms, signal words, hazard statements and precautionary statements

3.7.5 Re-classification of substances and mixtures classified for carcinogenicity according to DSD and DPD

3.7.6 Examples of classification for carcinogenicity

3.7.7 References

3.6.2.3.2 Additional considerations for classification

3.6.2.3.3 Consideration of mutagenicity

3.6.2.3.4 Non testing data

3.6.2.4 Decision on classification

3.6.2.5 Setting of specific concentration limits

3.6.2.6 Decision logic for classification of substances

3.6.3 Classification of mixtures for carcinogenicity

3.6.3.1 Classification criteria for mixtures

3.6.3.1.1 When data are available for all ingredients or only for some ingredients

3.6.3.1.2 When data are available for the complete mixture

3.6.3.1.3 When data are not available for the complete mixture: bridging principles

3.6.3.2 Decision logic for classification of mixtures

3.6.4 Hazard communication in form of labelling for carcinogenicity

3.6.4.1 Pictograms, signal words, hazard statements and precautionary statements

3.6.4.2 Additional labelling provisions

3.6.5 Re-classification of substances and mixtures classified for carcinogenicity

3.6.6 Examples of classification for carcinogenicity

3.6.7 References

3.5.3.1.1 When data are available for all ingredients or only for some ingredients

3.5.3.1.2 When data are available for the complete mixture

3.5.3.1.3 When data are not available for the complete mixture: bridging principles

3.5.3.2 Decision logic

3.5.3.3 When data are available for the complete mixture: bridging principles

3.5.3.4 Decision logic for classification of mixtures

3.5.3.5 Decision on classification

3.5.3.6 Additional labelling provisions

3.5.3.7 Pictograms, signal words, hazard statements and precautionary statements

3.5.4 Re-classification of substances and mixtures classified for carcinogenicity

3.5.5 Setting of specific concentration limits

3.5.6 Decision logic

3.5.7 Decision on classification

3.5.8 Additional labelling provisions

3.5.9 Pictograms, signal words, hazard statements and precautionary statements

3.4.2 Additional labelling provisions

3.4.3 Re-classification of substances and mixtures classified for carcinogenicity

3.4.4 Setting of specific concentration limits

3.4.5 Decision logic

3.4.6 Decision on classification

3.4.7 Additional labelling provisions

3.4.8 Pictograms, signal words, hazard statements and precautionary statements

3.3.2 Additional labelling provisions

3.3.3 Re-classification of substances and mixtures classified for carcinogenicity

3.3.4 Setting of specific concentration limits

3.3.5 Decision logic

3.3.6 Decision on classification

3.3.7 Additional labelling provisions

3.3.8 Pictograms, signal words, hazard statements and precautionary statements

3.2.2 Additional labelling provisions

3.2.3 Re-classification of substances and mixtures classified for carcinogenicity

3.2.4 Setting of specific concentration limits

3.2.5 Decision logic

3.2.6 Decision on classification

3.2.7 Additional labelling provisions

3.2.8 Pictograms, signal words, hazard statements and precautionary statements

3.1.2 Additional labelling provisions

3.1.3 Re-classification of substances and mixtures classified for carcinogenicity

3.1.4 Setting of specific concentration limits

3.1.5 Decision logic

3.1.6 Decision on classification

3.1.7 Additional labelling provisions

3.1.8 Pictograms, signal words, hazard statements and precautionary statements

3.0.2 Additional labelling provisions

3.0.3 Re-classification of substances and mixtures classified for carcinogenicity

3.0.4 Setting of specific concentration limits

3.0.5 Decision logic

3.0.6 Decision on classification

3.0.7 Additional labelling provisions

3.0.8 Pictograms, signal words, hazard statements and precautionary statements
3.8 SPECIFIC TARGET ORGAN TOXICITY – SINGLE EXPOSURE (STOT-SE)

3.8.1 Definitions and general considerations for STOT-SE...

3.8.2 Classification of substances for STOT-SE...

3.8.2.1 Identification of hazard information...

3.8.2.1.1 Identification of human data...

3.8.2.1.2 Identification of non human data...

3.8.2.2 CLASSIFICATION CRITERIA FOR CATEGORIES 1 AND 2...

3.8.2.2.1 Guidance values...

3.8.2.3 CLASSIFICATION CRITERIA FOR CATEGORY 3: TRANSIENT TARGET ORGAN EFFECTS...

3.8.2.4 Evaluation of hazard information on STOT-SE for substances...

3.8.2.4.1 Evaluation of human data...

3.8.2.4.2 Evaluation of non human data...

3.8.2.4.3 Evaluation of non-testing and *in vitro* data...

3.8.2.4.4 Conversions...

3.8.2.4.5 Weight of evidence...

3.8.2.5 Decision on classification of substances...

3.8.2.6 Setting of specific concentration limits for STOT-SE...

3.8.2.7 Decision logic...

3.8.3 Classification of mixtures for STOT-SE...

3.8.3.1 Identification of hazard information...

3.8.3.2 Classification criteria for mixtures...

3.8.3.2.1 When data are available for the complete mixture...

3.8.3.2.2 When data are not available for the complete mixture: bridging principles...

3.8.3.2.3 When data are available for all components or only for some components of the mixture...

3.8.3.2.4 Components of a mixture that should be taken into account for the purpose of classification...

3.8.3.3 Generic concentration limits for substances triggering classification of mixtures for STOT-SE...

3.8.3.4 Decision logic for mixtures...

3.8.4 Hazard communication in form of labelling for STOT-SE...

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

3.8.4.2 Additional labelling provisions...

3.8.4.3 Is direct “translation” of Classification and Labelling possible for STOT-SE substances?...

3.8.4.4 Re-evaluation of the STOT-SE data...

3.8.5 Examples of classification for STOT-SE...

3.8.5.1 Examples of substances fulfilling the criteria for classification...

3.8.5.1.1 Example 1: Methanol...

3.8.5.1.2 Example 2: Tricresyl phosphate...

3.8.5.1.3 Example 3: Sulfur dioxide...

3.8.5.1.4 Example 4: Toluene...

3.8.5.2 Examples of substances not fulfilling the criteria for classification...

3.8.5.2.1 Example 5: ABC...
3.8.5.2.2  Example 6: N,N-Dimethylaniline......... Error! Bookmark not defined.

3.9  SPECIFIC TARGET ORGAN TOXICITY – REPEATED EXPOSURE (STOT-RE)

3.9.1  Definitions and general considerations for STOT-RE ............... Error! Bookmark not defined.

3.9.2  Classification of substances for STOT-RE ........................ Error! Bookmark not defined.

3.9.2.1  Identification of hazard information ............................... Error! Bookmark not defined.

3.9.2.1.1  Identification of human data .................................. Error! Bookmark not defined.

3.9.2.1.2  Identification of non human data ............................... Error! Bookmark not defined.

3.9.2.2  Classification criteria for substances ............................. Error! Bookmark not defined.

3.9.2.3  Evaluation of hazard information ................................. Error! Bookmark not defined.

3.9.2.3.1  Evaluation of human data .................................. Error! Bookmark not defined.

3.9.2.3.2  Evaluation of non human data ............................... Error! Bookmark not defined.

3.9.2.3.3  Conversions ......................................................... Error! Bookmark not defined.

3.9.2.3.4  Weight of evidence ........................................ Error! Bookmark not defined.

3.9.2.4  Decision on classification ........................................ Error! Bookmark not defined.

3.9.2.5  Additional considerations ....................................... Error! Bookmark not defined.

3.9.2.5.1  Irritating/corrosive substances ............................... Error! Bookmark not defined.

3.9.2.5.2  Hemotoxicity ......................................................... Error! Bookmark not defined.

3.9.2.5.3  Mechanisms not relevant to humans (CLP Annex I, 3.9.2.8.1. (e)) Error! Bookmark not defined.

3.9.2.5.4  Adaptive responses (CLP Annex I, 3.9.2.8.1. (d)) Error! Bookmark not defined.

3.9.2.5.5  Post-observation periods in 28 day and 90 day studies Error! Bookmark not defined.

3.9.2.6  Setting of specific concentration limits ...................... Error! Bookmark not defined.

3.9.2.7  Decision logic for classification of substances ................. Error! Bookmark not defined.

3.9.3  Classification of mixtures for STOT-RE .......................... Error! Bookmark not defined.

3.9.3.1  Identification of hazard information ............................... Error! Bookmark not defined.

3.9.3.2  Classification criteria for mixtures ............................. Error! Bookmark not defined.

3.9.3.3  When data are available for the complete mixture .......... Error! Bookmark not defined.

3.9.3.3.1  When data are not available for the complete mixture: bridging principles ................................................. Error! Bookmark not defined.

3.9.3.3.2  When data are available for all components or only for some components of the mixture ..................... Error! Bookmark not defined.

3.9.3.3.3  Components of a mixture that should be taken into account for the purpose of classification ................................................. Error! Bookmark not defined.

3.9.3.4  Generic concentration limits for substances triggering classification of mixtures ......................................................... Error! Bookmark not defined.

3.9.3.5  Decision logic for mixtures ....................................... Error! Bookmark not defined.

3.9.4  Hazard communication in form of labelling for STOT RE .......... Error! Bookmark not defined.

3.9.4.1  Pictograms, signal words, hazard statements and precautionary statements Error! Bookmark not defined.

3.9.4.2  Additional labelling provisions ..................................... Error! Bookmark not defined.

3.9.5  Re-classification of substances and mixtures classified for STOT-RE according to DSD and DPD ......................................................... Error! Bookmark not defined.

3.9.5.1  Is direct “translation” of classification and labelling possible for STOT-RE substances? ......................................................... Error! Bookmark not defined.

3.9.5.2  Re-evaluation of the STOT-RE data ................................ Error! Bookmark not defined.

3.9.6  Examples of classification for STOT-RE .............................. Error! Bookmark not defined.

3.9.6.1  Examples of substances fulfilling the criteria for classification Error! Bookmark not defined.

3.9.6.1.1  Example 1: Hydroxylamine / Hydroxylamonium salts (CAS no. 7803-49-8) ......................................................... Error! Bookmark not defined.

3.9.6.1.2  Example 3: XYZ ........................................ Error! Bookmark not defined.

3.9.6.2  Examples of substances not fulfilling the criteria for classification Error! Bookmark not defined.

3.9.6.2.1  Example 4: MCCPs (Medium Chain Chlorinated Paraffins) = Alkanes, C_{14-17}, Chloro- (EC No 287-477-0; CAS No 85535-85-9) Error! Bookmark not defined.
4.1 HAZARDOUS TO THE AQUATIC ENVIRONMENT ..............................................

4.1.1 Introduction ........................................................................

4.1.2 Scope .............................................................................

4.1.3 Classification of substances hazardous to the aquatic environment ..............................................

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

4.1.3.1.1 Substance properties used for classification ..............................................

4.1.3.1.2 Information sources and data availability ..............................................

4.1.3.2 Evaluation of available information ..............................................

4.1.3.2.1 General considerations ..............................................

4.1.3.2.2 Substances difficult to test ..............................................

4.1.3.2.3 Interpretation of data for aquatic toxicity, degradation and bioaccumulation ..............................................

4.1.3.2.3.1 Aquatic toxicity ..............................................

4.1.3.2.3.2 Degradation ..............................................

4.1.3.2.3.3 Bioaccumulation ..............................................

4.1.3.2.4 Using weight of evidence in evaluations in the context of C&LError! Bookmark not defined.

4.1.3.2.4.1 General aspects of weight of evidence ..............................................

4.1.3.2.4.2 Guidance on WoE for data deficient substances ..............................................

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

4.1.3.2.4.4 Outliers ..............................................

4.1.3.2.4.5 Weight of evidence in degradation ..............................................

4.1.3.2.4.6 Weight of evidence in bioaccumulation ..............................................

4.1.3.3 Classification categories and criteria ..............................................

4.1.3.3.1 The “safety net” ..............................................

4.1.3.3.2 Setting an M-factor for highly toxic substances ..............................................

4.1.3.4 Decision on classification: examples for substances ..............................................

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

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

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

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

4.1.3.4.5 Example E: “Safety net” classification category Chronic 4Error! Bookmark not defined.
4.1.4.6 Example F: Substance difficult to test, toxicity above level of water solubility. 

4.1.4 Classification of mixtures hazardous to the aquatic environment

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

4.1.4.2 Information requirements.

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

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

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

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

4.1.4.7 Decision on classification: examples for mixtures.

Example A: When classification data is available for some or all components of a mixture: straight-forward application of the summation method.

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

Example B2: When toxicity data on the mixture as a whole are available for some but not for all three trophic levels: classification based on test data for the mixture.

Example C: When no data is available on the mixture or on its components, but test data is available on a similar tested mixture: Use of the Bridging Principles – Dilution with water.

Example D: When only test data is available for some components of the mixture: Use of the additivity formula and summation method.

4.1.5 Metal and metal compounds.

4.1.6 Hazard communication for hazards to the aquatic environment.

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

4.1.8 References.

5.1 HAZARDOUS TO THE OZONE LAYER.

ANNEXES.
Guidance to Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of substances and mixtures

I.2.3.2 Tests with aquatic macrophytes

I.3 Aquatic toxicity concepts

I.3.1 Acute toxicity

I.3.2 Chronic toxicity

I.3.3 Exposure regimes

I.3.4 Test media for algae and Lemma

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

I.4 Substances which are difficult to test

I.4.1 Unstable substances

I.4.2 Poorly soluble substances

I.4.3 Other factors contributing to concentration loss

I.4.4 Perturbation of the test media

I.4.5 Complex substances

I.5 References

II ANNEX II: RAPID DEGRADATION

II.1 Introduction

II.2 Interpretation of degradability data

II.2.1 Ready biodegradability

II.2.1.1 Concentration of test substance

II.2.1.2 Time window

II.2.2 BOD₅/COD

II.2.3 Other convincing scientific evidence

II.2.3.1 Aquatic simulation tests

II.2.3.2 Field investigations

II.2.3.3 Monitoring data

II.2.3.4 Inherent and Enhanced Ready Biodegradability tests

II.2.3.5 Sewage treatment plant simulation tests

II.2.3.6 Soil and sediment degradation data

II.2.3.7 Anaerobic degradation data

II.2.3.8 Hydrolysis

II.2.3.9 Photochemical degradation

II.2.3.10 Estimation of degradation

II.2.3.11 Volatilisation

II.2.4 No degradation data available

II.3 General interpretation problems

II.3.1 Complex substances

II.3.2 Availability of the substance

II.3.3 Test duration less than 28 days

II.3.4 Primary biodegradation

II.3.5 Conflicting results from screening tests

II.3.6 Variation in simulation test data

II.4 Decision scheme

II.5 References

III ANNEX III: BIOACCUMULATION

III.1 Introduction

III.2 Interpretation of bioconcentration data

III.2.1 Bioconcentration factor (BCF)

III.2.1.1 BCF in different test species

III.2.1.2 Use of radio-labelled substances
III.2.2 Octanol-water-partitioning coefficient ($K_{ow}$)..............Error! Bookmark not defined.
III.2.2.1 Experimental determination of $K_{ow}$ ............Error! Bookmark not defined.
III.2.2.2 Use of QSARs for determination of $log K_{ow}$ Error! Bookmark not defined.
III.2.2.3 Biomagnification factor.........................................Error! Bookmark not defined.
III.3 Chemical classes that need special attention with respect to BCF and $K_{ow}$ valuesError! Bookmark not defined.
III.3.1 Substances difficult to test ..................................................Error! Bookmark not defined.
III.3.2 Poorly soluble and complex substances ...............Error! Bookmark not defined.
III.3.3 High molecular weight substances ...................... Error! Bookmark not defined.
III.3.4 Surface-active substances (surfactants)............... Error! Bookmark not defined.
III.3.4.1 Octanol-water-partition coefficient ($K_{ow}$) Error! Bookmark not defined.
III.4 Conflicting data and lack of data ..............................................Error! Bookmark not defined.
III.4.1 Conflicting BCF data .......................................................Error! Bookmark not defined.
III.4.2 Conflicting $log K_{ow}$ data ..............................................Error! Bookmark not defined.
III.4.3 Expert judgement .......................................................Error! Bookmark not defined.
III.5 Decision scheme ..............................................................Error! Bookmark not defined.
III.6 References............................................................................Error! Bookmark not defined.

IV ANNEX IV: METALS AND INORGANIC METAL COMPOUNDS Error! Bookmark not defined.
IV.1 Introduction ........................................................................Error! Bookmark not defined.
IV.2 Application of aquatic toxicity data and solubility data for classification Error! Bookmark not defined.
IV.2.1 Interpretation of aquatic toxicity data.................Error! Bookmark not defined.
IV.2.1.2 Metal complexation and speciation ..............Error! Bookmark not defined.
IV.2.2 Interpretation of solubility data .....................................Error! Bookmark not defined.
IV.2.2.1 Assessment of existing data ..................................Error! Bookmark not defined.
IV.2.2.2 Screening T/D test for assessing solubility of metal compounds Error! Bookmark not defined.
IV.2.2.3 Full T/D test for assessing solubility of metals and metal compounds.................Error! Bookmark not defined.
IV.2.3 Comparison of aquatic toxicity data and solubility data Error! Bookmark not defined.
IV.3 Assessment of environmental transformation .................Error! Bookmark not defined.
IV.4 Bioaccumulation ................................................................Error! Bookmark not defined.
IV.5 Classification strategies for metals and metal compounds ....Error! Bookmark not defined.
IV.5.1 Introduction..............................................................Error! Bookmark not defined.
IV.5.2 Classification strategies for metals .................Error! Bookmark not defined.
IV.5.2.1 Classification strategy for determining acute aquatic hazard for metals........................................Error! Bookmark not defined.
IV.5.2.2 Classification strategy for determining long-term aquatic hazard for metals ........................................Error! Bookmark not defined.
IV.5.2.2.1 Approach based on available chronic toxicity reference data..................................................Error! Bookmark not defined.
IV.5.2.2.2 The surrogate approach ........................................Error! Bookmark not defined.
IV.5.3 Classification strategies for metal compounds............Error! Bookmark not defined.
IV.5.3.1 Classification strategies for determining acute aquatic hazard for metal compounds .................Error! Bookmark not defined.
IV.5.3.2 Classification strategy for determining long-term aquatic hazard for metal compounds ..........Error! Bookmark not defined.
IV.5.3.2.1 Approach based on available chronic toxicity reference data..................................................Error! Bookmark not defined.
IV.5.3.2.2 The surrogate approach ........................................Error! Bookmark not defined.
IV.5.4 Particle size and surface area ..............................................Error! Bookmark not defined.
IV.5.5 Classification of mixtures of metals and metal compounds Error! Bookmark not defined.
IV.5.5.1 Classification of alloys and complex metal containing materials Error! Bookmark not defined.
IV.5.5.2 M-factor application for metal mixtures and alloys Error! Bookmark not defined.
IV.6 References

IV.7 Decision on classification: examples for metals and metal compounds

Example B: poorly soluble metal compound with acute and chronic toxicity data, Transformation Dissolution data at 7 days (low loading rate) and 28 days (low, medium and high loading rates) and evidence of rapid removal from the water column.

Example C: Poorly soluble metal compound with acute and chronic toxicity data equal to example B, transformation/dissolution data at 7 days (low loading rate) and at 28 days (only low and medium loading rates) and no evidence of rapid removal from the water column.

Example D: metal in powder and massive form with acute and chronic toxicity data and Transformation/Dissolution data at 7 days (low, medium and high loading rates) and at 28 days (only the high loading rate) and evidence of rapid removal from the water column.

Explanatory note to Example D - Critical Surface Area (CSA) approach.


Comment [U1]: This comes from the expert group dealing with the update of the guidance on the aquatic classification.

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

VI ANNEX VI: BACKGROUND DOCUMENT TO THE GUIDANCE FOR SETTING SPECIFIC CONCENTRATION LIMITS FOR SUBSTANCES CLASSIFIED FOR REPRODUCTIVE TOXICITY ACCORDING TO REGULATION (EC) NO 1272/2008

24
I LIST OF ABBREVIATIONS

ADN Accord européen relatif au transport international des marchandises dangereuses par voie de navigation intérieure (European Agreement concerning the International Carriage of Dangerous Goods by Inland Waterways)\(^2\)

ADR Accord européen relatif au transport international des marchandises dangereuses par route (European Agreement concerning the International Carriage of Dangerous Goods by Road)\(^3\)

ANE Ammonium Nitrate Emulsion

ASTM American Society for the Testing of Materials

ATE Acute Toxicity Estimate

BAM Bundesanstalt für Materialforschung und -prüfung (Federal Institute for Materials Research and Testing)

BCF Bioconcentration Factor

BCOP Bovine Corneal Opacity and Permeability test

BfR German Federal Institute for Risk Assessment

BfR DSS Decision support system by the German Federal Institute for Risk Assessment

BP Boiling point

bw Body weight

C&L Classification and Labelling

CA Competent Authority

cATpE Converted Acute Toxicity point Estimate

CLP Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures\(^4\)

CNS Central Nervous System

CSA Chemical Safety Assessment

CSR Chemical Safety Report

DIN Deutsche Industrie Norm (German Industry Standard)

DNA Deoxyribonucleic Acid

DOC Dissolved Organic Carbon

DPD Directive 1999/45/EC on the classification and labelling of Dangerous Preparations\(^5\)

DSD Directive 67/548/EEC on the classification and labelling of Dangerous Substances\(^6\)

---

\(^2\) European Agreement concerning the International Carriage of Dangerous Goods by Inland Waterways, concluded at Geneva on 26 May 2000, as amended

\(^3\) European Agreement concerning the International Carriage of Dangerous Goods by Road, concluded at Geneva on 30 September 1957, as amended


EC3 Effective Concentration inducing a stimulation index of 3 in the LLNA test
ECB European Chemicals Bureau

The formerly known European Chemicals Bureau (ECB) was part of the Institute for Health and Consumer Protection (IHCP), which is one of the seven scientific institutes in the European Commission's Joint Research Centre (JRC). Its mission was to provide scientific and technical support to the conception, development, implementation and monitoring of EU policies on chemicals and consumer products. (http://ecb.jrc.ec.europa.eu/)

ECVAM European Centre for the Validation of Alternative Methods (http://ecvam.jrc.it/)
ED Effective Dose
ESAC ECVAM Scientific Advisory Committee (http://ecvam.jrc.it/)
f/F Female
FP Flash point
GCL General Concentration Limits
GHS Globally Harmonised System of Classification and Labelling of Chemicals
GJIC Gap junction intercellular communication
GLP Good Laboratory Practice
GnRH Gonadotropin-releasing hormone
GPMT Guinea Pig Maximisation Test
GV Guidance Value
Hb Haemoglobin
HET-CAM Hen's Egg Test on Chorio-allantoic Membrane
HS Hazard statement
HSM Human skin model
Ht Hematocrit
IARC International Agency for Research on Cancer (http://www.iarc.fr/)
IATA(DGR) International Air Transport Association (Dangerous Goods Regulations Manual)
IBC Intermediate Bulk Container
ICAO TI International Civil Aviation Organization (Technical Instructions for the Safe Transport of Dangerous Goods by Air)
ICE Isolated Chicken Eye
IEC International Electrotechnical Commission (http://www.iec.ch/)
IMDG International Maritime Dangerous Goods Code

Guidance on Identification and Naming of Substances under REACH, ECHA, 2007


<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPCS</td>
<td>International Programme on Chemical Safety (joint programme of WHO, ILO and UNEP)</td>
</tr>
<tr>
<td>INS</td>
<td>Guidance on Identification and Naming of Substances under REACH, ECHA, 2007</td>
</tr>
<tr>
<td>INS</td>
<td>Integrated Testing Strategy</td>
</tr>
<tr>
<td>LD₅₀/LC₅₀</td>
<td>Median (50%) lethal dose/concentration</td>
</tr>
<tr>
<td>LLNA</td>
<td>Local Lymph Node Assay</td>
</tr>
<tr>
<td>LO (A) EL/C</td>
<td>Lowest Observed (Adverse) Effect Level/Concentration</td>
</tr>
<tr>
<td>LVET</td>
<td>Volume Eye Test</td>
</tr>
<tr>
<td>m/M</td>
<td>Male</td>
</tr>
<tr>
<td>MetHB</td>
<td>Methaemoglobinemia</td>
</tr>
<tr>
<td>MetHb</td>
<td>Methaemoglobin</td>
</tr>
<tr>
<td>MP</td>
<td>Melting Point</td>
</tr>
<tr>
<td>MTD</td>
<td>Maximal Tolerated Dose</td>
</tr>
<tr>
<td>MW</td>
<td>Molecular weight</td>
</tr>
<tr>
<td>n.a.</td>
<td>Not available</td>
</tr>
<tr>
<td>NC</td>
<td>No Classification</td>
</tr>
<tr>
<td>NE</td>
<td>Narcotic effect(s)</td>
</tr>
<tr>
<td>NO(A)EC</td>
<td>No Observed (Adverse) Effect Concentration</td>
</tr>
<tr>
<td>NO(A)EL</td>
<td>No Observed (Adverse) Effect Level</td>
</tr>
<tr>
<td>ODS</td>
<td>Ozone Depleting Substances</td>
</tr>
<tr>
<td>ODP</td>
<td>Ozone Depleting Potential</td>
</tr>
<tr>
<td>OECD</td>
<td>Organisation for Economic Co-operation and Development</td>
</tr>
<tr>
<td>OECD TG</td>
<td>OECD Test Guideline</td>
</tr>
</tbody>
</table>

The OECD Guidelines for the Testing of Chemicals are a collection of the most relevant internationally agreed test methods used by government, industry and

---

independent laboratories to determine the safety of chemicals and chemical preparations, including pesticides and industrial chemicals. All Test Guidelines are available at the OECD homepage:
http://www.oecd.org/document/40/0,3343,en_2649_34377_37051368_1_1_1_1,00.html

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>OP</td>
<td>Oxidising Power</td>
</tr>
<tr>
<td>P statement (or PS)</td>
<td>Precautionary statement</td>
</tr>
<tr>
<td>PB/PK</td>
<td>Physiologically-based pharmacokinetic</td>
</tr>
<tr>
<td>PC</td>
<td>Physico-chemical</td>
</tr>
<tr>
<td>PPARα</td>
<td>Peroxisome proliferator-activated receptor-alpha</td>
</tr>
<tr>
<td>PS (or P statement)</td>
<td>Precautionary statement</td>
</tr>
<tr>
<td>(Q)SAR</td>
<td>(Quantitative) Structure Activity Relationship</td>
</tr>
<tr>
<td>RID</td>
<td>Règlement concernant le transport international ferroviaire de marchandises dangereuses (Regulations concerning the International Carriage of Dangerous Goods by Rail) (^10)</td>
</tr>
<tr>
<td>RIP</td>
<td>REACH Implementation Project</td>
</tr>
<tr>
<td>RTDG</td>
<td>Regulations on the Transport of Dangerous Goods. Generic term that covers all modal transport regulations (ADR, RID, ADN, IMDG and ITDG)</td>
</tr>
<tr>
<td>RTI</td>
<td>Respiratory tract irritation</td>
</tr>
<tr>
<td>SADT</td>
<td>Self-Accelerating Decomposition Temperature</td>
</tr>
<tr>
<td>SCEGHS (or UNSCEGHS)</td>
<td>Sub-Committee of Experts on the Globally Harmonised System (<a href="http://www.unece.org/trans/danger/publi/ghs/ghs_welcome_e.html">http://www.unece.org/trans/danger/publi/ghs/ghs_welcome_e.html</a>)</td>
</tr>
<tr>
<td>SCETDG (or UNSCETDG)</td>
<td>Sub-Committee of Experts on the Transport of Dangerous Goods (<a href="http://www.unece.org/trans/danger/danger.htm">http://www.unece.org/trans/danger/danger.htm</a>)</td>
</tr>
<tr>
<td>SCL</td>
<td>Specific Concentration Limit</td>
</tr>
<tr>
<td>SDS</td>
<td>Safety Data Sheet</td>
</tr>
<tr>
<td>SIFT</td>
<td>Skin integrity function test</td>
</tr>
<tr>
<td>SSD</td>
<td>Species Sensitivity Distribution</td>
</tr>
<tr>
<td>STOT-SE</td>
<td>Specific Target Organ Toxicity - Single Exposure</td>
</tr>
<tr>
<td>STOT-RE</td>
<td>Specific Target Organ Toxicity - Repeated Exposure</td>
</tr>
<tr>
<td>SVC</td>
<td>Saturated Vapour Concentration</td>
</tr>
</tbody>
</table>


\(^10\) 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.
T25: The daily dose (in mg per kg bodyweight) inducing a tumour incidence of 25% upon lifetime exposure

T95: Inhalation chamber equilibrium (attained at the time t95)

TER: Transcutaneous electrical resistance

TG: Test Guideline

TGD: Technical Guidance Document

TM: Test Method as listed in the Test Methods Regulation

Test Methods Regulation: Regulation (EC) No 440/2008 laying down test methods pursuant to the REACH Regulation

TOPKAT: Mathematical (Q)SAR model for prediction of skin corrosion/irritation

UDP: Uridine 5'-diphosphate

UDPG: Uridine diphosphate glucuronyl

UGT: UDP-glucuronyltransferase

UN: United Nations


VDI: Verein Deutscher Ingenieure (The Association of German Engineers)

VP: Vapour Pressure

WAF: Water Accommodated Fraction

WoE: Weight of Evidence

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

---

1  PART 1: GENERAL PRINCIPLES FOR CLASSIFICATION AND LABELLING

4  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, hereafter referred to as CLP.

CLP amends the Dangerous Substance Directive 67/548/EEC (DSD), the Dangerous Preparations Directive 1999/45/EC (DPD) and Regulation (EC) No 1907/2006 (REACH), and will replace DSD and DPD from 1 June 2015. CLP is based on the Globally Harmonised System of Classification and Labelling of Chemicals (UN GHS 2007) and is implementing the provisions of the GHS within the EU, without lowering the protection of human health and the environment, compared to the classification, labelling and packaging system in DSD and DPD.

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

Given that many provisions under REACH are linked to classification, the implementation of REACH and CLP is interlinked and should be planned and applied in tandem. Further advice on the implementation of CLP is available in the Agency’s Introductory Guidance on the CLP Regulation.

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

---


1.1.2 Background

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

The EU has had a comprehensive system for the classification and labelling of dangerous substances and mixtures for over 40 years, mainly DSD and DPD. In addition, the Safety Data Sheet (SDS) Directive 91/155/EEC\(^\text{16}\) required suppliers to provide more detailed information for professional users. These directives contributed to a single market in chemicals in the EU, based on a high level of protection of human health and the environment.

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

The GHS criteria for classifying hazardous substances were developed taking into account existing systems for hazard classification, such as the EU supply and use system, the Canadian and US Pesticide systems, GESAMP\(^\text{17}\) hazard evaluation procedure, IMO\(^\text{18}\) Scheme for Marine Pollutants, the European Road and Rail Transport Scheme (RID/ADR), and the US Land Transport. These systems include supply and subsequent use of chemicals, the sea transport of chemical substances as well as transport of chemical substances by road and rail. The harmonised criteria are therefore intended to identify hazardous chemicals in a common way for use throughout all these systems.

The GHS provides a basis for an internationally uniform information system on hazardous substances and mixtures. It provides harmonised criteria for classification and hazard communication measures for different target audiences, including consumers, workers and emergency responders, and in transport. It follows a “building block” approach to enable jurisdictions to adopt the system according to the needs of their law and the various target audiences.

The GHS was agreed by the UN Committee of Experts on the Transport of Dangerous Goods and the Globally Harmonized System of Classification and Labelling of Chemicals (CETDG/GHS). It was formally approved by the UN Economic and Social Council (UN ECOSOC) in 2003 and published in 2003 after a decade of negotiations. It is updated biennially.

1.1.3 Hazard classification

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


\(^{17}\) Group of Experts on the Scientific Aspects of Marine Environmental Protection

\(^{18}\) International Maritime Organisation
Guidance to Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of substances and mixtures

32

− identification and examination of relevant information regarding the potential hazards of a substance or mixture;

− comparison of the information (data) with the classification criteria; and

− decision on whether the substance or mixture shall be classified as hazardous in relation to the hazard classes or differentiations provided in CLP Annex I, and the degree of hazard, where appropriate.

Preliminary information on identification and review of relevant data is provided in section 1.1.7 of this guidance document, while further guidance is provided in Part B of the ECHA Guidance document on Information Requirements and Chemical Safety Assessment (IR/CSA, sections R.2 to R.4).

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

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

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

Until 1 December 2010:

Substances and mixtures shall be classified, labelled and packaged in accordance with DSD and DPD, respectively. They may also be classified, labelled and packaged in accordance with CLP. In that case they shall not be labelled and packaged according to DSD or DPD. When a substance or mixture is classified, labelled and packaged according to CLP the classification information according to both systems shall be provided in SDS.

From 1 December 2010 to 1 June 2015:

Substances shall be classified, labelled and packaged in accordance with CLP, but also classified in accordance with DSD in order to allow these classifications to be used in the classifications of mixtures. Classifications in accordance with both systems shall be included in SDS, but classifications in accordance with DSD shall not appear on the label.

Mixtures shall be classified, labelled and packaged in accordance with DPD. They may also be classified, labelled and packaged in accordance with CLP. In that case they shall not be labelled and packaged according to DPD. When a mixture is classified, labelled and packaged according to CLP the classification information according to both systems shall be provided in SDS.

From 1 June 2015:

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

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

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

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

However, a number of substances and mixtures are exempted from the classification requirements:

– radioactive substances and mixtures (Directive 96/29/Euroatom19);
– certain substances and mixtures which are subject to customs supervision;
– non-isolated intermediates;
– certain substances and mixtures for scientific research and development;
– waste (Directive 2006/12/EC20); and
– certain substances or mixtures in the finished state, intended for the final user:
  – medicinal products (Directive 2001/83/EC21),
  – veterinary medicinal products (Directive 2001/82/EC22),
  – cosmetic products (Directive 76/768/EEC23),
  – medical devices as defined in Directive 90/385/EEC24 (active implantable medical devices) and 93/42/EEC25 (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/EEC26), and
  – food or feeding stuffs as defined in (Regulation 178/200227), including when they are used as food additives (Directive 89/107/EEC28), flavouring in

Guidance to Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of substances and mixtures

foodstuffs (Directive 88/388/EEC and Decision 1999/217/EC\textsuperscript{29}), as an additive in feeding stuff within the scope of Regulation (EC) 1831/2003\textsuperscript{30} and in animal nutrition within the scope of Directive 82/471/EEC\textsuperscript{31}. 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, as noted above the criteria for classification are intended to be the same in the two systems. Thus, a substance or mixture classified in a hazard class which is common to both CLP and the transport legislation will normally be classified the same in both systems. However, the transport classifications do not include all of the GHS categories, so the absence of a transport classification does not mean the substance or mixture should not be classified under CLP.

### 1.1.6 What information is needed for classification

#### 1.1.6.1 Information for the classification of substances

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

CLP does not require new testing for the purpose of classification for health or environmental hazards; testing for physical hazards is required unless adequate and reliable information is already available. 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 Regulation (EC) No 1107/2009\textsuperscript{32} (plant protection products) and Directive 98/8/EC (biocidal products)\textsuperscript{34}, or from various non-Community programmes.

Finally, the supplier may decide to conduct new testing in order to fill data gaps, provided that he has exhausted all other means of generating information. Testing on animals must be

---

avoided wherever possible and alternative methods (including in vitro testing, the use of (Q)SARs, read-across and/or category approaches) must always be considered first, provided they are sufficiently adequate and reliable.

If, for the purpose of CLP, it is required or decided to generate new data, certain test methods and quality conditions must be met. Studies must be conducted in accordance with the EU test methods (Regulation 440/2008) or other international test methods validated according to international procedures such as those of the OECD. For physical hazards new tests shall be carried out (at least from January 2014) in compliance with relevant recognised quality system or by laboratories complying with a relevant recognised standard, and for health and environmental hazards in compliance with the principles of Good Laboratory Practice (GLP). Animal tests must comply with the Directive 86/609/EEC. Tests on non-human primates are prohibited for the purposes of CLP. Tests on humans shall not be performed for the purpose of CLP. However, existing data obtained from other sources, such as accident records and epidemiological and clinical studies, can be used.

### 1.1.6.2 Data for the classification of mixtures

For mixtures, classification for physical hazards should normally be based on the results of tests carried out on the mixtures themselves.

When considering health and environmental hazards, the classification can be based on available information (including test data) on the mixtures themselves, except when classifying for e.g. CMR effects or for the evaluation in relation to the bioaccumulation and degradation properties within the “hazardous to the aquatic environment” hazard class referred to in sections 4.1.2.8 and 4.1.2.9 of Annex I to CLP. In these cases classification of the mixtures is normally based on the information on the substances. If no test data are available on the mixtures themselves, such data should not normally be generated; rather, all available information on the ingredients of the mixture should be used to derive a classification. Only when the manufacturer, importer or downstream user has exhausted all other means of generating information, new tests may be performed.

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

### 1.1.7 Data evaluation and reaching a decision on classification

#### 1.1.7.1 Classification of substances

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

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

1.1.7.2 Influence of impurities, additives or individual constituents on 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\^{37} substances. The classification of such impurities, additives or individual constituents may influence the classification of the substance, in addition to the other hazardous properties.

1.1.8 Updating of hazard classifications

Updating of classifications may be necessary, if new information is obtained or if the criteria in CLP are amended. When manufacturers, importers or downstream users become aware of new information or an amendment to CLP or when a change is introduced in a mixture, they must reconsider the classification of the substance or mixture (but note that a downstream user can rely on the classification from his supplier, provided he shares the new information with that supplier to allow him to meet the requirements).

1.1.9 The interface between hazard classification and hazard communication

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

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

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

\footnote{\textsuperscript{37} Substance of Unknown or Variable composition from complex reaction or biological materials. see IR/CSA guidance.}
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 Community level, while mixtures must always be self-classified (except for pesticidal and biocidal products where the Member State Competent Authorities (CAs) decide on the classification as part of the national authorisation scheme).

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, but where some but not all hazard classes or differentiations within hazard classes have been harmonised, the remainder should be self-classified to complete the classification.

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

Substances regulated under the Biocidal Products Directive 98/8/EC 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 MS CAs only. However, in general proposals for harmonised classification for a particular substance to be added to Annex VI to CLP can be made by both MS CAs and by manufacturers, importers and downstream users. Only MS CAs can propose a revision of an existing harmonised classification and labelling.

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

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

Under DSD, as a rule all hazards were evaluated for a substance and ending up in harmonised classifications for all hazards relevant for that substance. Only a few substances (such as complex coal- and oil-derived substances) were exempted from this 'complete' classification.

Under CLP the harmonised classifications will be partial and in most cases only cover the hazard classes of particular concern (i.e. CMR and respiratory sensitisation) or any other hazard classes where the need for action at Community level for other hazard classes is justified for the substance.

---

40 M-factors are used to derive by the summation method the classification of a mixture in which the substance for which the M-factor has been established is present. For further guidance on how to establish and use M-factors, see sections 4.1.3.2 and 4.1.4.5, respectively.
1.1.11 The Classification and Labelling Inventory (C&L Inventory)

Manufacturers and importers are required to notify the Agency of the classification and labelling of hazardous substance(s) placed on the market and of substances which are placed on the market and subject to registration in accordance with the REACH Regulation. The Agency will then include the information in a classification and labelling inventory in form of a database. Substances placed on the market on or after 1 December 2010 require notification within one month after their placing on the market. However, substances placed on the market before 1 December 2010 may be notified before that date. There is no need to notify the substance if the same information has already been submitted as part of a registration under REACH, as the classification and labelling, when part of the registration package, will automatically be added to the C&L Inventory. Further guidance on what should be included in a notification and how to do it is available on the ECHA website http://echa.europa.eu/clp/inventory_notification_en.asp.

The Agency shall make certain information from the C&L Inventory publicly available on its website, including the substance name, the classification, labelling and any relevant specific concentration limit or M-factor(s). It will be indicated if there is a harmonised classification for the entry, or if it is an agreed entry between manufacturers or importers. While multiple notifications of the same substance may be made by different manufacturers or importers, with the potential for differences in the classifications notified, over time this should provide the stimulus for suppliers to liaise in order to agree on a single entry.

1.1.12 Relation of classification to other EU legislation

A network of EU legislation relies on classification in one way or the other (see section 23 of the Introductory Guidance on the CLP Regulation for a detailed list of the laws concerned). This downstream legislation includes laws protecting consumers and workers, as well as rules on biocides, pesticides and waste. Therefore, the consequences of classification are greater than just a hazard label or an SDS in that it also has a direct effect on the management of associated risks.

1.1.12.1 REACH

Classification plays a key role in REACH; it must be included in the registration dossier for a substance and it triggers certain provisions such as the performance of an exposure assessment and risk characterisation as part of the CSA and the obligation to provide an SDS. Classification of a substance as mutagenic, carcinogenic or toxic to reproduction (CMR) may also lead to restrictions and the need to apply for authorisations.

1.1.12.2 Plant Protection Products and Biocides

Pursuant to Recital 47 of the CLP Regulation, Directive 91/414/EEC on plant protection products and Directive 98/8/EC on biocidal products “shall remain fully applicable to any product within their scope.” For example, there are separate provisions for updating labels for such substances and mixtures in these acts, and their suppliers must apply these provisions instead of the CLP rules, see also CLP Article 30(3). Nevertheless, active substances as well as the plant protection or biocidal products containing them shall be classified in accordance with CLP by the applicable deadlines and also carry the relevant CLP labelling elements.

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).

The transport classification of a substance could be a source of information for the classification and labelling of substances or mixture under CLP, especially for physical hazards.

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

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

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

Article 5 (1)
The information shall relate to the forms or physical states in which the substance is placed on the market and in which it can reasonably be expected to be used.

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

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

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

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

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

1.3.2.2.2 Hazard classification incorporates … identification of relevant data regarding the hazards of a substance or mixture …”

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

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

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

Reasonably expected use of a substance is as follows:
Guidance to Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of substances and mixtures

Any process, including production, handling, maintenance, storage, transport or disposal.

All technical operations/manufacturing activities like e.g. spraying, filing, and sawing

Any putative consumer contact through e.g. do-it-yourself or household chemicals.

All professional and non-professional uses including reasonably foreseeable misuse, but not abuse such as criminal or suicidal uses.

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

1.2.3 The term ‘form or physical state’ in relation to hazard classification

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

1.2.3.1 Physical hazards

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

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

General considerations

The form of a substance or mixture as placed on the market might be such that it is not possible to test it in this form, e.g. if it is in the form of tablets or pellets. In such circumstances, the physical hazards of the substance or mixture shall be considered for classification especially if they are friable and produce secondary effects due to abrasion or crushing during supply and use. If phase separation does occur, the hazardous properties of the most hazardous phase of the substance or mixture shall be communicated.

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

Specific requirements of certain test methods

Some test methods for the classification of physical hazards have specific requirements regarding the form/particle size of the sample to be tested. In these cases, the specific requirements of the test methods prevail. Examples of tests which have specific requirements regarding the form/particle size of the sample to be tested include those used to determine the
classification of explosives and of substances which in contact with water emit flammable gases.
In other test methods, there are no specific requirements regarding the particle size but it is stated explicitly that the particle size may have a significant effect on the test result. Therefore, these properties should be mentioned in the test report (i.e. testing of oxidising solids). Moreover, particle size is crucial for several other classes such as explosives, flammable solids, self-reactive substance, pyrophoric solids, self-heating substances, solid organic peroxides and substances which, in contact with water, emit flammable gases.

1.2.3.2 Human health hazards
Also for human health, different forms (e.g. particle sizes, coating) or physical states may result in different hazardous properties of a substance or mixture in use. However, due to test complexity, not every form or physical state can be tested for each health hazard. In general, testing should be performed on the smallest available particle size and the default approach is to test for different routes of exposure (oral, dermal, inhalation). Again, due to test complexity, mostly the data for only one exposure route are available.
In general, the assumption is made that the testing conditions of valid animal assays reflect the hazards to man and these data shall be used for classification. Moreover, it is assumed that classification for human health hazards takes into account all the potential hazards which are likely to be faced for all forms or physical states in which the substance is placed on the market and can reasonably be expected to be used. It is assumed that it comprises putative accidental exposures. This approach generally, but not necessarily comprehensively, covers the whole range of intrinsic properties of a substance or mixture: in some cases, substances or mixtures have to be transformed into specific forms not mirroring 'real-life' exposures in order that an animal test can be performed. As a consequence, the results of such tests may have to be evaluated taking into account any limitations due to the fact that the specific form of the tested substance or mixture does not or not perfectly represent that to which human exposure may occur during intended, known or reasonably expected use. Such evaluation has to be performed according to the state of the scientific and technical knowledge. The burden of proof is on the person placing a substance or mixture on the market.

1.2.3.3 Environmental hazards
The environmental hazard classification is principally concerned with the aquatic environment and the basis of the identification of hazard is the aquatic toxicity of the substance or mixture, and information on the degradation and bioaccumulation behaviour.
The system of classification is designed to ensure that a single classification applies to a substance. In general it takes no account of the specific form since this can vary and is not intrinsic to the substance. The form in which the substance is placed on the market is taken into account when deciding what label to apply and various derogations from labelling exist, e.g. the metals in the massive form. In the massive form the hazard may not be present and the substance need not be labelled. The SDS will, however, indicate the classification and intrinsic hazardous properties to warn the user that subsequent transformation of the substance may produce the hazardous form.
For aquatic hazard classification, organic substances are generally tested in the dissolved form. Exceptions to this approach include complex, multi-component substances and metals and their compounds. Examples of alternative approaches include the use of Water Accommodated Fractions (WAF) for complex, multi-component substances where the toxicity cut-off is related to the loading, and a test strategy for metals and their compounds in
which the specific form (i.e. particle size) used for testing is standardised and forms or physical states are not further taken into account.

1.3 SPECIFIC CASES REQUIRING FURTHER EVALUATION – LACK OF BIOAVAILABILITY

1.3.1 Definition

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

1.3.2 Bioavailability

Article 12
Specific cases requiring further evaluation

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

[...]

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

[...]

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

In general terms, for a substance or mixture to have an effect on a biological or environmental system, there must be some degree of bioavailability. Therefore, it follows that a substance or mixture need not be classified when it can be shown by conclusive experimental data from internationally acceptable test methods, e.g. from Council Regulation (EC) No 440/2008, that the substance or mixture is not biologically available (UN GHS 1.3.2.4.5.1). A non bioavailable substance may, however, react with the media to transform to soluble available forms. The rate and extent at which this process, known as "transformation" for the purposes of the classification guidance, takes place can vary extensively between different substances, and can be an important factor in determining the appropriate hazard category (see Annex IV, section IV.1 of this document).

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

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

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

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

Information on bioavailability is usually obtained from adequate, reliable, and conclusive toxicokinetic studies for all relevant routes of exposure and all relevant forms or physical states where the substance and/or metabolite(s) of the substance have been quantified in body fluids and/or target organs. It should be noted that concluding that there is lack of or reduced bioavailability has a high burden of evidence and needs to be supported by robust data and expert evaluation.

Bioavailability of a substance or a mixture is normally assumed if there are in vitro studies available which show the solubility of a substance or mixture in body fluids or artificial simulated body fluids. Furthermore, conclusions on bioavailability of a substance or a mixture may be based on considerations of the physical properties of a substance or derived from Structural Activity Relationships (SAR). In certain exceptional circumstances it may be possible that a substance on its own or in a mixture can be considered to be non-bioavailable, based on either appropriate in vitro data, e.g. from skin absorption models, SAR considerations or considering the physical properties of a substance, if the respective requirements described above have been taken into account in an adequate analysis.

1.3.2.2 Environmental hazards

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

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

In general, there are no specific environmental test methods developed to measure biological availability of substances or mixtures. This aspect is built into the testing methodology for toxicity and if adverse effects are identified the substance should be classified accordingly.

Substances which lack bioavailability would not be absorbed by the exposed organisms and therefore due to lack of toxic effects these substances would not be classified, unless they are known to degrade or transform to hazardous products. For example see the strategy for metals classification in Annex IV to this document.

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

| Article 5(1) | Manufacturers, importers and downstream users of a substance shall identify the relevant available information for the purposes of determining whether the substance entails a physical, health or environmental hazard as set out in Annex I, and, in particular, the following:
| … |
| (c) any other information generated in accordance with section 1 of Annex XI to Regulation (EC) No 1907/2006; |

| Article 6(1) | Manufacturers, importers and downstream users of a mixture shall identify the relevant available information on the mixture itself or the substances contained in it for the purposes of determining whether the mixture entails a physical, health or environmental hazard as set out in Annex I, and, in particular, the following:
| … |
| (c) any other information generated in accordance with section 1 of Annex XI to Regulation (EC) No 1907/2006 for the mixture itself or the substances contained in it; |

Section 1 of Annex XI to REACH provides a list of data that can be used instead of testing when standard data are missing. Annex XI of REACH specifies the conditions under which results of (Q)SARs, read across and grouping may be used for the classification of substances. Annex XI of REACH, states that results of (Q)SARs may be used instead of testing when the (Q)SAR models have been scientifically validated, “the substance falls within the applicability domain”, the "results are adequate for the purpose of classification and labelling" and “adequate and reliable documentation of the applied method is provided”.

Results generated by read across and grouping may according to the same principles be used for classification and labelling if they are "adequate for classification and labelling", “have adequate and reliable coverage of the key parameters addressed in the corresponding test method”, “cover an exposure duration comparable to or longer than the corresponding test method”, and “adequate and reliable documentation of the applied method” is provided. A weight of evidence approach has to be used where the criteria cannot be applied directly to the available data according to CLP Article 9(3). This approach is further worked out in CLP Annex I, 1.1.1.

No specific guidance is given in REACH, Annex XI on when a result obtained with one of the methods is “adequate for the purpose of classification and labelling”. However, it is
important to note that most of the criteria for classification are directly related to specific test methods. Thus, the adequacy of results of (Q)SARs, read across and grouping should be evaluated against the criteria taking into account that normally the individual method attempts to estimate the same hazard as the criterion. Nevertheless, when grouping, read across and (Q)SARs are being used alone or as a part of the basis for classification, it is normally necessary to do so employing weight of evidence and expert judgement to decide on the classification.

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

### Annex 1: 1.1.1.3

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

IR/CSA, section 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, section R.7.

In general, read-across, grouping and use of (Q)SARs as the sole information elements to obtain data on basic physical-chemical properties is not recommended, since reliable data should normally be available or is easily obtainable through testing. However, there may occasionally be practical problems with testing of substances for physical-chemical properties, especially for UVCBs where the properties may be dependent on the variable composition. Therefore, the appropriateness of using read-across, categorisation and (Q)SARs for physical-chemical assessment should be considered on a case by case basis. Given the availability of extensive guidance only a brief overview of each approach is presented below. For classification of mixtures see section 1.6 of this document.

### 1.4.1 (Q)SAR

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

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

Extensive guidance on the use of (Q)SARs for hazard identification is given in IR/CSA, section R.6.1. Guidance on the use of (Q)SARs for classification and labelling according to DSD is also given in IR/CSA, section 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, section R.6.2. Annex XI to REACH opens the possibility of evaluating substances not on a one-by-one basis, but by grouping substances in categories. A substance category is a group of substances whose physico-chemical, human health, environmental and/or environmental fate properties are expected to be similar or to follow a regular pattern as a result of structural similarity.

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

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

1.4.3 Read across

Read across is the use of hazard specific information for one substance (“source”) to predict the same hazard for another substance (“target”), which is considered to have similar physico-chemical environmental fate and/or (eco)toxicological properties. This can be based on structural similarity (e.g., (Q)SAR), bioavailability, bioaccessibility, or known physical-chemical properties such as water solubility. In principle, read-across can be applied to characterise physico-chemical properties, environmental fate, human health effects and ecotoxicity. For certain substances without test data the formation of common significant metabolites or information with those of tested substances or information from precursors may be valuable information (IR/CSA, section R.6.2.5.2 and OECD 2004). For any hazard class, read-across may be performed in a qualitative or quantitative manner. Extensive guidance on the use of read across is given in IR/CSA, section 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, section R.6.2.5. This is because the concept of substance categories has traditionally been widely used for hazard classification and to some extent also for risk assessment.

1.5 SPECIFIC CONCENTRATION LIMITS AND M-FACTORS

1.5.1 Specific concentration limits

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

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

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

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

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

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

The procedure of derivation of SCLs is different for every health hazard class and therefore guidance on how to set SCLs is provided in the respective sections of this document.

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

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

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

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

An overview of guidance available is also illustrated by Table 1.5.1 below.

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

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

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

<table>
<thead>
<tr>
<th>Hazard class</th>
<th>Category</th>
<th>Lower SCL than GCL</th>
<th>Higher SCLs than GCL (in exceptional circumstances)</th>
<th>Guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute toxicity</td>
<td>all</td>
<td>not applicable</td>
<td>not applicable</td>
<td>not necessary</td>
</tr>
<tr>
<td>Skin corrosion/irritation</td>
<td>all</td>
<td>yes</td>
<td>yes</td>
<td>available in section 3.2</td>
</tr>
<tr>
<td>Serious eye damage/eye irritation</td>
<td>all</td>
<td>yes</td>
<td>yes</td>
<td>available in section 3.3</td>
</tr>
<tr>
<td>Respiratory sensitisation</td>
<td>1</td>
<td>yes</td>
<td>no</td>
<td>available in section 3.4</td>
</tr>
<tr>
<td>Skin sensitisation</td>
<td>1</td>
<td>yes</td>
<td>yes</td>
<td>available in section 3.4</td>
</tr>
<tr>
<td>Germ cell mutagenicity</td>
<td>all</td>
<td>no</td>
<td>no</td>
<td>currently not possible</td>
</tr>
<tr>
<td>Carcinogenicity</td>
<td>all</td>
<td>yes</td>
<td>yes</td>
<td>available in section 3.6</td>
</tr>
<tr>
<td>Reproductive toxicity</td>
<td>all</td>
<td>yes</td>
<td>yes</td>
<td>available in section 3.7 and in Annex VI</td>
</tr>
<tr>
<td>STOT-SE</td>
<td>1</td>
<td>yes</td>
<td>no</td>
<td>available in section 3.8</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>no</td>
<td>no</td>
<td>see section 3.8</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>yes</td>
<td>yes</td>
<td>available in section 3.8</td>
</tr>
<tr>
<td>STOT-RE</td>
<td>1</td>
<td>yes</td>
<td>no</td>
<td>available in section 3.9</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>no</td>
<td>no</td>
<td>see section 3.9</td>
</tr>
<tr>
<td>Aspiration hazard</td>
<td>1</td>
<td>not applicable</td>
<td>not applicable</td>
<td>not necessary</td>
</tr>
</tbody>
</table>

1.5.2 Multiplying factors (M-factors)

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

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

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

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

For further guidance on how to establish the M-factor, see section 4.1.3.3 of this document. M-factors should have been established in accordance with CLP Article 10 and be available in the C&L Inventory.

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

1.6 MIXTURES

1.6.1 How to classify a mixture

The classification of mixtures under CLP is for the same hazards as for substances. As a general rule and as is the case with substances, available data on the mixture as a whole should primarily be used to determine classification where applicable. If this cannot be done, further approaches to mixture classification may be applied.

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

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

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

REACH: Article 31(3)

The supplier shall provide the recipient at his request with a safety data sheet compiled in accordance with Annex II, where a preparation does not meet the criteria for classification as dangerous in...
Guidance to Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of substances and mixtures

accordance with Articles 5, 6 and 7 of Directive 1999/45/EC, but contains:

(a) in an individual concentration of ≥ 1 % by weight for non-gaseous preparations and ≥ 0,2 % by volume for gaseous preparations at least one substance posing human health or environ
(b) in an individual concentration of ≥ 0,1 % by weight for non-gaseous preparations at least one substance that is persistent, bio-accumulative and toxic or very persistent and very bio-accumulative in accordance with the criteria set out in Annex XIII or has been included for reasons other than those referred to in point (a) in the list established in accordance with Article 59(1); or
(c) a substance for which there are Community workplace exposure limits.

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

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

The classification of mixtures follows the sequence displayed in Figure 1.6.1, for each hazard class independently.
Figure 1.6.1 How to classify a mixture

1. There is a mixture to classify

2. All available information should be gathered

3. Are available test data for the mixture sufficient for classification? (CLP Article 9 (2)-(3))
   (For physical hazards: consider whether new testing needs to be performed. Consult the criteria.)
   YES: Classify the mixture accordingly
   NO:

4. Is there data available on similar tested mixtures and individual hazardous ingredients?
   YES: Is it possible to apply any of the bridging principles?
   YES: Classify the mixture accordingly
   NO:
   NO:

5. Are hazard data available for all or some ingredients?
   YES: Use the known or derived hazard data on the individual ingredients to classify the mixture using the other methods in each section of CLP Annex I, Part 3 and Part 4
   NO: Unable to classify the mixture – go back to ingredient suppliers to obtain additional information

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

The majority of the physical hazards of mixtures should be determined through testing based on the methods or standards referred to in CLP Annex I, Part 2. In few cases, such as hazard class “Flammable liquids”, the classification of mixtures can also be derived through a calculation, see CLP Annex I, 2.6.4.2 and 2.6.4.3.

The test methods can be found for example in the UN Manual of Tests and Criteria, see the website [http://www.unece.org/trans/publications/dg_tests.html](http://www.unece.org/trans/publications/dg_tests.html), which is normally used to classify substances and mixtures for transport. In cases where test results are available, based on other methods or standards, then these data may still be used, provided they are adequate for the purpose of hazard determination. To conclude on the adequacy the results should be checked by the expert involved to ensure that there is sufficient documentation to assess the suitability of the test used, and whether the test was carried out using an acceptable level of quality assurance.

Please note that in practice the physical hazards of a substance may differ from those shown by tests, such as some ammonium nitrate based compounds with explosivity or oxidising properties and some halogenated hydrocarbons with flammability properties. Such experience must be taken into account for the purpose of classification (CLP Article 12(a)).

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

1.6.3 Health and environmental hazards

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

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

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

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

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

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

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

1.6.3.1 Classification derived using data on the mixture itself

Deleted: http://www.unece.org/trans/publications/dg_tests.html,
Classification derived using data on the mixture itself, by applying the substance criteria of Annex I to CLP, is applicable in many cases. Exceptions are: CMR hazards (see CLP Article 6(3)), bioaccumulation and biodegradation properties and the evaluation within the ‘hazardous to the aquatic environment’ hazard class referred to in sections 4.1.2.8 and 4.1.2.9 of Annex I to CLP (see CLP Article 6(4)).

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

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

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

Where the criteria cannot be directly applied to the available data, expert judgement should be used for the evaluation of the available information in a weight of evidence determination (CLP Article 9(3) and CLP Annex I, 1.1.1).

### 1.6.3.2 Bridging principles

In the case of a classification for health or environmental hazards, information on the mixture itself may not always be available. However, where there are sufficient data on similar tested mixtures and individual hazardous ingredient substances, CLP allows bridging principles to be used to classify the mixture (CLP Annex I, 1.1.3). To apply these bridging principles certain conditions should be considered for their application which are summarised below.

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

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

#### 1.6.3.2.1 Dilution

Where the tested mixture is diluted with a substance (diluent) that has an equivalent or lower hazard category than the least hazardous original ingredient substance, then it can be assumed that the respective hazard of the new mixture is equivalent to that of the original tested mixture. The application of dilution for determining the classification of a mixture is illustrated by Figure 1.6.3.2.1.

**Figure 1.6.3.2.1 Application of the bridging principle: dilution for determining the acute toxicity classification of a mixture**
Example: Mixture A, which has been classified as acute toxic category 2 based on test data, is subsequently diluted with diluent B to form mixture C. If diluent B has an equivalent or lower acute toxicity classification than the least acutely toxic ingredient in mixture A and is not expected to affect the hazard classification of other ingredients, then mixture C may be also classified as acutely toxic category 2. However, this approach may over-classify mixture C, thus the supplier may choose to apply the additivity formula described in CLP Annex I, 3.1.3.6 (see section 1.6.3.4.1 of this document).

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

Consider using this particular bridging principle also when, for example, - diluting an irritant mixture with water, - diluting an irritant mixture with a non-classified ingredient, or - diluting a corrosive mixture with a non-classified or irritant ingredient.

In case a mixture is diluted with another mixture, see section 1.6.4 of this document.

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

1.6.3.2.2 Batching

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

1.6.3.2.3 Concentration of highly hazardous mixtures

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

1.6.3.2.4 Interpolation within one toxicity category

Assume there are three mixtures (A, B and C) which contain identical hazardous components. If mixtures A and B have been tested and are in the same hazard category, and mixture C is...
not tested and has concentrations of those hazardous components intermediate to the concentrations in mixtures A and B, then mixture C is assumed to be in the same hazard category as A and B. The application of interpolation for determining the classification of a mixture is illustrated by Figure 1.6.3.2.4. (CLP Annex I, 1.1.3.4).

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

1.6.3.2.5 Substantially similar mixtures

Two mixtures contain an identical ingredient at the same concentration. Each of the two mixtures contains an additional ingredient which is not identical with each other; however they are present in equivalent concentrations and the hazard category of these two ingredients is the same and neither of them is expected to affect the hazard classification of the other. If one of the mixtures is classified based on test data it may be assumed that the hazard category of the other mixture is the same. The application of substantially similar mixtures for determining the classification of a mixture is illustrated by Figure 1.6.3.2.5. (CLP Annex I, 1.1.3.5).

Figure 1.6.3.2.5 Application of the bridging principle: substantially similar mixtures for determining the skin irritation classification of a mixture
Example: If ingredient C has the same hazard category and the same potency as ingredient A, then mixture Q can be classified as Skin Irrit. 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**

<table>
<thead>
<tr>
<th>Initial concentration range of the constituent</th>
<th>Permitted variation in initial concentration of the constituent</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2.5 %</td>
<td>± 30 %</td>
</tr>
<tr>
<td>2.5 &lt; C ≤ 10 %</td>
<td>± 20 %</td>
</tr>
<tr>
<td>10 &lt; C ≤ 25 %</td>
<td>± 10 %</td>
</tr>
<tr>
<td>25 &lt; C ≤ 100 %</td>
<td>± 5 %</td>
</tr>
</tbody>
</table>

NOTE: The guidance below explaining Table 1.2 in the green box relates to a change in the composition of mixtures already classified as hazardous. A change in the composition of non-hazardous mixtures may result in concentration thresholds being reached and a need to classify the changed mixture as hazardous. Where the manufacturer, importer or downstream user introduces a change to a mixture not classified for a specific hazard, that manufacturer, importer or downstream user must therefore always carry out a new evaluation for that hazard in accordance with Chapter 2 of Title II to CLP (see Article 15(1) of CLP).

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

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

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

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

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

1.6.3.3 Aerosols (some health hazards only)

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

1.6.3.4 Classification based on calculation or concentration thresholds

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

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

1.6.3.4.1 Classification based on calculation

The calculation methods set out under the different chapters of Annex I to CLP mostly differ from those applied under DPD. More detailed guidance on the selection of the most appropriate method is provided in the specific section for each hazard class.

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

Annex I: 3.1.3.6.1.

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

$$\frac{100}{\text{ATE}_{\text{mix}}} = \sum \frac{C_i}{\text{ATE}_i}$$

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 $\leq 10$ % 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:

$$\sum \frac{C_{unknown}}{ATE_{max}} = \sum \frac{C_i}{ATE_i}$$

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

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

(a) Based on acute toxicity:

\[
\sum \frac{C_i}{L(E)C_{50m}} = \frac{\sum C_i}{\eta L(E)C_{50i}},
\]

where:

- \( C_i \) = concentration of component i (weight percentage)
- \( L(E)C_{50i} \) = (mg/l) LC\(_{50}\) or EC\(_{50}\) for component i
- \( \eta \) = number of components
- \( L(E)C_{50m} \) = \( L(E)C_{50} \) of the part of the mixture with test data

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

(b) Based on chronic aquatic toxicity:

\[
\sum C_i + \sum C_j = \sum_{n} \frac{C_i}{NOEC_i} + \sum_{n} 0.1 \times NOEC_j
\]

Where:

- \( C_i \) = concentration of component i (weight percentage) covering the rapidly degradable components
- \( C_j \) = concentration of component i (weight percentage) covering the non-rapidly degradable components
- \( NOEC_i \) = NOEC (or other recognised measures for chronic toxicity) for component i covering the rapidly degradable components, in mg/l;
- \( NOEC_j \) = NOEC (or other recognised measures for chronic toxicity) for component i covering the non-rapidly degradable components, in mg/l;
- \( n \) = number of components, and i and j are running from 1 to n;
- \( EqNOEC_{m} \) = Equivalent NOEC of the part of the mixture with test data;

NOTE: To make full use of this approach requires access to the whole aquatic toxicity data set and the necessary knowledge to select the best and most appropriate data. CLP has limited the use of the additivity formula to those circumstances where the substance hazard category is not known, although the acute and/or chronic toxicity data are available.

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

1.6.3.4.2 Classification based on concentration thresholds

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

- Generic cut-off values: these values are the minimum concentrations for a substance to be taken into account for classification purposes. These substances are also referred to as relevant ingredients in some hazard classes (see sections 3.1, 3.2 and 3.3). When a classified substance is present in a concentration above the generic cut-off value it contributes to the mixture classification even if it does not trigger classification of the mixture directly. The generic cut-off values are defined for some hazard classes and categories only and are listed in Table 1.1 of Annex I to CLP;

- Generic concentration limits: these values are the minimum concentrations for a substance which trigger the classification of a mixture if exceeded by the individual concentration or the sum of concentrations of relevant substances (where the individual substance concentrations can be ‘added’ to each other in a straight forward way); they are set out in parts 2-5 of Annex I for those hazard classes where they apply.

Generic concentration thresholds are generic for a hazard class, differentiation or category. The difference between a generic cut-off value and a generic concentration limit (GCL) is demonstrated through the example of the skin irritation hazard: while Table 1.1 of Annex I to CLP defines the generic cut-off value to be 1% a skin irritant substance which is present in a mixture would trigger classification of the mixture as skin irritant if it were present above or equal to the concentration limit of 10% in the mixture, see Table 3.2.3 of Annex I to CLP. However, at ≥ 1% and below 10%, it may still contribute to the classification of the mixture as skin irritant, since the concentration would be taken into account if other skin corrosive/irritant substances are present in the mixture below the relevant generic concentration limits. In some cases, classification as provided by the summation in CLP Annex I, Table 3.2.3 may be applicable, i.e.:

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

Specific concentration thresholds

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

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

2. Cut-off values that may be different from the generic values and that are to be used in specific cases are given in 1.1.2.2.2(a) and (b) of Annex I to CLP. For example concerning aquatic hazard, for a substance with an established M-factor, the cut-off value is always the generic cut-off value divided by the M-factor; hence, (0.1/M)% (see 1.1.2.2.2(b) and 4.1.3.1 of Annex I to CLP).

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

### 1.6.3.4.3 Additivity of hazards

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

**Non-additivity is applied for the following hazard classes:**

- skin and respiratory sensitisers;
- germ cell mutagenicity;
- carcinogenicity;
- reproductive toxicity;
- specific target organ toxicity, single and repeated exposure, categories 1 and 2;
- aspiration hazard (plus consideration of viscosity of the final mixture);
- skin corrosion/irritation in some special cases (see CLP Annex I, 3.2.3.3.4); and
- serious eye damage/eye irritation in some special cases (see CLP Annex I, 3.3.3.3.4).

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

**Additivity is used for the following hazard classes or differentiations:**

- skin corrosion/irritation (besides the cases mentioned in CLP Annex I, 3.2.3.3.4);
- serious eye damage/eye irritation (besides the cases mentioned in CLP Annex I, 3.3.3.3.4);
- specific target organ toxicity, single exposure Category 3 (respiratory tract irritation);
- specific target organ toxicity, single exposure Category 3 (narcotic effects); and
- acute and long-term aquatic hazards.

In these cases, if the sum of the concentrations of one or several classified substances in the mixture equals or exceeds the GCL set out for this hazard class/category, the mixture must be classified for that hazard. For substances that have an SCL or M-factor, these should be taken into account when applying the summation methods.

An example is provided for the hazard class serious eye damage/eye irritation: In case there are only substances classified as eye irritation Category 1 present in a mixture, then their sum must be equal to or exceed the generic concentration limit of 10% in order for the mixture to be classified in Category 2 as well. Note that only relevant substances should be summed up and contribute to mixture classification. Further guidance on the application of SCLs when using the summation method to derive skin corrosion/irritation or serious eye damage/eye irritation hazards can be found in sections 3.2 and 3.3 of this document.
1.6.4 Classification of mixtures in mixtures

For physical hazards, an adequate hazard classification is generally derived by testing. To determine the classification of a mixture for health or environmental hazards using the additivity or summation methods, information on all the constituent substances, including their individual hazard classification and concentration, is generally required. In the case where one or more mixtures are added to another mixture, the same requirement applies: it is generally necessary to know all ingredient substances, their hazard classifications and their concentrations to be able to derive a correct hazard classification of the final mixture. It is generally not possible to derive the correct hazard classification for the final mixture by using only the hazard classification(s) of the mixtures that were combined to make it with one exception. The exception is that in case the acute toxicity estimate (ATE) of a mixture is known (either actual or derived), this value can be used to derive a correct classification for acute toxicity if this mixture is added to another mixture.

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

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

1.6.4.1 Example: Classification of Mixture A

Note that the example only addresses health hazards. For compositional details see Table 1.6.4.1(a) and Table 1.6.4.1(b) below.

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

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

Acute toxicity

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

Following option (i) it is first necessary to calculate $\text{ATE}_{\text{mix}}$ of the 'fragrance mixture' (see 1.6.4.1(b)) taking into account 'FM component 1' and 'FM component 2' (other components can be excluded as their LD$_{50}$ values are > 2000 mg/kg):
\[
\frac{100}{\text{ATE}_{\text{mix}}} = \sum_{n} \frac{C_i}{\text{ATE}_i} \rightarrow
\]

1 \[\text{ATE}_{\text{mix}} = \frac{100}{\sum_{n} \frac{C_i}{\text{ATE}_i}} \rightarrow\]

\[
\text{ATE}_{\text{mix}} = \frac{100}{\frac{35.2 + 17.0}{1230} + \frac{17.0}{500}} = 1597 \text{mg/kg}
\]

2 The \(\text{ATE}_{\text{mix}}\) for the 'fragrance mixture' can then be included in the calculation of the \(\text{ATE}_{\text{mix}}\) for Mixture A:

\[
\text{ATE}_{\text{mix}} = \frac{100}{\frac{8.0 + 5.0}{1800} + \frac{5.0}{1597}} = 13300 \text{mg/kg}
\]

5 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 \(\text{ATE}_{\text{mix}}\) for Mixture A according to option (ii):

\[
\text{ATE}_{\text{mix}} = \frac{100}{\frac{8.0 + 1.76}{1800} + \frac{1.76}{1230}} = 17200 \text{mg/kg}
\]

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

N.B. If an acute oral toxicity test (i.e. an actual \(\text{LD}_{50}\) value) was available for the fragrance mixture, then this should be used in the calculation for the ATE of Mixture A.

Skin corrosion/irritation

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

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

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

Serious eye damage/eye irritation

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

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

**Skin sensitisation**

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

### Table 1.6.4.1(a) Ingredients in Mixture A

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>% w/w</th>
<th>Oral LD&lt;sub&gt;50&lt;/sub&gt; (rat)</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anionic surfactant</td>
<td>8.00</td>
<td>1800 mg/kg</td>
<td>Acute Tox. 4 (oral) Eye Dam. 1 Skin Irrit. 2</td>
</tr>
<tr>
<td>Thickening agent</td>
<td>0.80</td>
<td>&gt; 5000 mg/kg</td>
<td>Not classified</td>
</tr>
<tr>
<td>Dye</td>
<td>0.05</td>
<td>&gt; 5000 mg/kg</td>
<td>Not classified</td>
</tr>
<tr>
<td>Fragrance mixture (see list of ingredients below)</td>
<td>5.00</td>
<td>not tested</td>
<td>Acute Tox. 4 (inhalation, oral) Skin Sens. 1 Eye Dam. 1 Skin Irrit. 2 Aquatic Chronic 2</td>
</tr>
<tr>
<td>Water</td>
<td>86.15</td>
<td></td>
<td>Not classified</td>
</tr>
<tr>
<td><strong>Total:</strong></td>
<td>100.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 1.6.4.1(b) Ingredient 'Fragrance mixture'

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>% w/w</th>
<th>% in Mixture A</th>
<th>Oral LD&lt;sub&gt;50&lt;/sub&gt; (rat)</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>FM component 1</td>
<td>35.20</td>
<td>1.76</td>
<td>1230 mg/kg</td>
<td>Acute Tox. 4 (inhalation, oral)</td>
</tr>
<tr>
<td>FM component 2</td>
<td>17.00</td>
<td>0.85</td>
<td>not available (use cATpE 500)</td>
<td>Acute Tox. 4 (oral) Skin Sens. 1</td>
</tr>
<tr>
<td>FM component 3</td>
<td>16.00</td>
<td>0.8</td>
<td>3600 mg/kg</td>
<td>Skin Sens. 1 Skin Irrit. 2</td>
</tr>
<tr>
<td>FM component 4</td>
<td>13.40</td>
<td>0.67</td>
<td>3100 mg/kg</td>
<td>Skin Sens. 1</td>
</tr>
<tr>
<td>FM component 5</td>
<td>7.00</td>
<td>0.35</td>
<td>&gt; 2000 mg/kg</td>
<td>Eye Dam. 1 Aquatic Chronic 2</td>
</tr>
<tr>
<td>FM component 6</td>
<td>6.00</td>
<td>0.3</td>
<td>4400 mg/kg</td>
<td>Flam. Liq. 3 Skin Sens. 1 Skin Irrit. 2 Aquatic Chronic 1</td>
</tr>
<tr>
<td>FM component 7</td>
<td>2.80</td>
<td>0.14</td>
<td>&gt; 5000 mg/kg</td>
<td>Not classified</td>
</tr>
</tbody>
</table>
1.6.4.2 Example: Classification of Mixture B

Note that the example only addresses health hazards. For compositional details see Table 1.6.4.2(a) and Table 1.6.4.2(b) below.

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

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

Acute toxicity

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

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

\[
\frac{100}{ATE_{mix}} = \sum_{i} \frac{C_i}{ATE_i} \rightarrow
\]

\[
ATE_{mix} = \frac{100}{\sum_{i} \frac{C_i}{ATE_i}}
\]

\[
ATE_{mix} = \frac{100}{\frac{18.0}{500}} = 2778 \text{ mg/kg}
\]

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

\[
ATE_{mix} = \frac{100}{\frac{20.0}{2778} + \frac{18.0}{770} + \frac{8.0}{1800}} = 2860 \text{ mg/kg}
\]
Both options indicate that the calculated \( \text{ATE}_{\text{mix}} \) of Mixture B is > 2000 mg/kg. Therefore Mixture B is not classified as hazardous for acute toxicity by the oral route.

\( \text{ATE}_{\text{mix}} = \frac{100}{\frac{3.6}{500} + \frac{18.0}{770} + \frac{8.0}{1800}} = 2860 \text{mg/kg} \)

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

Skin corrosion/irritation

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

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

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

Serious eye damage/eye irritation

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

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

Respiratory sensitisation

Mixture B contains 0.7% of the ingredient 'enzymes' classified for respiratory sensitisation. However this is below the concentration triggering classification (CLP Annex I, Table 3.4.3) thus Mixture B is not classified as a respiratory sensitisier. However ingredient 'enzymes' trigger additional labelling information (CLP Annex II, 2.8).

STOT

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

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>% w/w</th>
<th>Oral ( \text{LD}_{50} ) (rat)</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base powder</td>
<td>20.00</td>
<td>not tested</td>
<td>Eye Dam.1</td>
</tr>
<tr>
<td>(see list of ingredients below)</td>
<td></td>
<td></td>
<td>Skin Irrit. 2</td>
</tr>
<tr>
<td>Oxygen bleach</td>
<td>18.00</td>
<td>770 mg/kg</td>
<td>Ox. Sol. 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Acute Tox. 4 (oral)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Eye Dam. 1</td>
</tr>
<tr>
<td>Silicates</td>
<td>11.00</td>
<td>3400 mg/kg</td>
<td>Eye Dam. 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Skin Irrit. 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>STOT SE 3 (respiratory</td>
</tr>
</tbody>
</table>
### Table 1.6.4.2(b) Ingredient ‘base powder’

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>% w/w</th>
<th>% in Mixture B</th>
<th>Oral LD₅₀ (rat)</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-ionic surfactant</td>
<td>18.00</td>
<td>3.6</td>
<td>500 mg/kg</td>
<td>Acute Tox. 4 (oral)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Eye Dam. 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Aquatic Acute 1</td>
</tr>
<tr>
<td>Anionic surfactant</td>
<td>20.00</td>
<td>4.0</td>
<td>&gt; 2000 mg/kg</td>
<td>Skin Irrit. 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Eye Irrit. 2</td>
</tr>
<tr>
<td>Builder</td>
<td>50.00</td>
<td>10.0</td>
<td>&gt; 5000 mg/kg</td>
<td>Not classified</td>
</tr>
<tr>
<td>Carbonate</td>
<td>8.00</td>
<td>1.6</td>
<td>4090 mg/kg</td>
<td>Eye Irrit. 2</td>
</tr>
<tr>
<td>Inorganic processing</td>
<td>4.00</td>
<td>0.8</td>
<td>&gt; 5000 mg/kg</td>
<td>Not classified</td>
</tr>
<tr>
<td>aid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total:</strong></td>
<td><strong>100.00</strong></td>
<td><strong>20.00</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 3.1.7 THE APPLICATION OF ANNEX VII

#### 3.1.7.1 Introduction

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

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

Note: Article 61 uses the term “conversion table” and Annex VII uses the term “translation table”. These terms have the same meaning i.e. the tables in Annex VII that relate classifications according to DSD or DPD to a classification according to CLP.
Although conceptually similar, the coverage of CLP and the DSD or DPD is different. In some places, there is a good relationship between the category of danger and corresponding R-phrases and hazard categories and corresponding hazard statements but in others, the relationship is less well defined. Additionally CLP introduces new hazard classes reflecting hazards that were not covered or only partly covered by DSD and DPD.

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

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

### 1.7.2 Use of Annex VII translation tables

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

This Annex includes a table to assist translation of a classification made for a substance or a mixture under Directive 67/548/EEC or Directive 1999/45/EC, respectively, into the corresponding classification under this Regulation. Whenever data for the substance or mixture are available, an evaluation and classification shall be done in accordance with Articles 9 to 13 of this Regulation.

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

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

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

#### 1.7.2.1 Applicability of the Annex VII translation tables

As mentioned in section 1.7.1 of this document, the Annex VII translation tables do not always give a direct translation. For certain hazard classes, including acute toxicity and STOT repeated exposure, there is a recommended minimum classification in CLP Annex VII Table 1.1. This minimum classification should only be used if no additional hazard information is available (see also CLP Annex VI, 1.2.1).

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

In addition to the differences indicated in Table 1.7.2.1(a), attention is drawn to the fact that for some hazards the DPD generic concentration limits, to be applied for mixtures, were lowered under CLP. Lower generic concentration limits were set for skin corrosion (R34 and
R35), severe eye damage and eye irritation (R41 and R36), skin irritancy (R38) and reproductive toxicity (R60, R61, R62 and R63). Where mixtures containing substances with risk phrases R34 or R41 have been classified on basis of the hazards of individual ingredients, the use of the translation table will lead to an under-classification of the mixture. Therefore, for mixtures with these R--phrases, the use of the translation table may not be appropriate and re-classification may be done by using the existing data.

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

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

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

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

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

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

<table>
<thead>
<tr>
<th>Classifications under DSD or DPD</th>
<th>Potential translation outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>E, R2 E, R3</td>
<td>1) Explosive. 2) Organic peroxide 3) Flammable solid 4) Oxidising solid 5) Self-reactive 6) No classification</td>
<td>Change of classification criteria and method; individual treatment See Table 1.7.2.1(b) for additional information using transport classifications</td>
</tr>
<tr>
<td>O, R8 (liquid)</td>
<td>Oxidising liquid</td>
<td>All liquid substances or mixtures classified O,R8 are classified as oxidising liquids under CLP. See Table 1.7.2.1(b) for additional information using transport classifications</td>
</tr>
<tr>
<td>O, R8 (solid)</td>
<td>Oxidising solid</td>
<td>The test methods for oxidising solids in 67/548/EEC and CLP are different. Most solids classified O, R8 are also classified as oxidising solids under CLP. See Table 1.7.2.1(b) for additional information using transport classifications</td>
</tr>
<tr>
<td>F, R11 (solid)</td>
<td>1) Flammable solid 1a) Possibly self-heating in addition 2) Self-reactive</td>
<td>Solid substances or mixtures classified F, R11 may be classified as flammable solids or self reactives under CLP. If classified as flammable solids, they may additionally be classified as self-heating. See Table 1.7.2.1(b) for additional information using transport classifications</td>
</tr>
<tr>
<td>F, R15</td>
<td>Substance or mixture which, in contact with water, emit(s) flammable gas(es)</td>
<td>See Table 1.7.2.1(b) for additional information using transport classifications</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Transport classification</th>
<th>Physical state</th>
<th>CLP-classification</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transport class and (sub)division (if applicable)</td>
<td>Packing group, division, type, group or code</td>
<td>Hazard class</td>
<td>Hazard category, division, type or group</td>
</tr>
<tr>
<td>Physical state</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

70
### Class 1

<table>
<thead>
<tr>
<th>Division 1.1</th>
<th>Division 1.2</th>
<th>Division 1.3</th>
<th>Division 1.4</th>
<th>Division 1.5</th>
<th>Division 1.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liquid or solid</td>
<td>Explosives</td>
<td>Division 1.1</td>
<td>Division 1.2</td>
<td>Division 1.3</td>
<td>Division 1.4</td>
</tr>
</tbody>
</table>

**Matching criteria.**

However, if explosives are unpacked or repacked, they have to be assigned to division 1.1 unless the hazard is shown to correspond to one of the other divisions.

### Class 2 - Gases

<table>
<thead>
<tr>
<th>1 Compressed gas</th>
<th>Gaseous</th>
<th>Gases under pressure</th>
<th>Compressed gas</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Liquefied gas.</td>
<td>Gaseous</td>
<td>Liquefied gas.</td>
<td></td>
</tr>
<tr>
<td>3 Refrigerated liquefied gas</td>
<td>Gaseous</td>
<td>Refrigerated liquefied gas</td>
<td></td>
</tr>
<tr>
<td>4 Dissolved gas</td>
<td>Gaseous</td>
<td>Dissolved gas</td>
<td></td>
</tr>
</tbody>
</table>

### Class 4.1

<table>
<thead>
<tr>
<th>Types B-F</th>
<th>Solid or liquid</th>
<th>Self-reactive substances</th>
</tr>
</thead>
</table>

### Class 4.1 (only readily combustible solids)

<table>
<thead>
<tr>
<th>Packing group II</th>
<th>Solid</th>
<th>Flammable solids</th>
</tr>
</thead>
</table>

### Class 4.1 (only readily combustible solids)

<table>
<thead>
<tr>
<th>Packing group III</th>
<th>Solid</th>
<th>Flammable solids</th>
</tr>
</thead>
</table>

---

**Guidance to Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of substances and mixtures**

---

71
### Guidance to Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of substances and mixtures

<table>
<thead>
<tr>
<th>Class 4.2</th>
<th>Packing group I</th>
<th>Liquid</th>
<th>Pyrophoric liquids</th>
<th>Category 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Solid</td>
<td>Pyrophoric solids</td>
<td>Category 1</td>
</tr>
<tr>
<td>Class 4.2</td>
<td>Packing group II</td>
<td>Solid</td>
<td>Self-heating substances and mixtures</td>
<td>Category 1</td>
</tr>
<tr>
<td>Class 4.2</td>
<td>Packing group III</td>
<td>Solid</td>
<td>Self-heating substances and mixtures</td>
<td>Category 2</td>
</tr>
<tr>
<td>Class 4.3</td>
<td>Packing group I</td>
<td>Liquid or solid</td>
<td>Substances which in contact with water emit flammable gases</td>
<td>Category 1</td>
</tr>
<tr>
<td></td>
<td>Packing group II</td>
<td></td>
<td></td>
<td>Category 1</td>
</tr>
<tr>
<td></td>
<td>Packing group III</td>
<td></td>
<td></td>
<td>Category 2</td>
</tr>
<tr>
<td>Class 5.1</td>
<td>Packing group I</td>
<td>Solid</td>
<td>Oxidising solid</td>
<td>Category 1</td>
</tr>
<tr>
<td></td>
<td>Packing group II</td>
<td></td>
<td></td>
<td>Category 2</td>
</tr>
<tr>
<td></td>
<td>Packing group III</td>
<td></td>
<td></td>
<td>Category 3</td>
</tr>
<tr>
<td>Class 5.1</td>
<td>Packing group I</td>
<td>Liquid</td>
<td>Oxidising liquid</td>
<td>Category 1</td>
</tr>
<tr>
<td></td>
<td>Packing group II</td>
<td></td>
<td></td>
<td>Category 2</td>
</tr>
<tr>
<td></td>
<td>Packing group III</td>
<td></td>
<td></td>
<td>Category 3</td>
</tr>
<tr>
<td>Class 5.2</td>
<td>Types B-F</td>
<td>Solid or liquid</td>
<td>Organic peroxides</td>
<td>Types B-F</td>
</tr>
<tr>
<td>Class 8</td>
<td>Packing group III</td>
<td>Liquid or solid</td>
<td>Corrosive to metals</td>
<td>Category 1</td>
</tr>
</tbody>
</table>

| Applies only when the substance or mixture is not classified C; R35 or C;R34 |

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

- Due to changes in the classification criteria, and lowering of several GCLs for mixtures, CLP may trigger classification for certain hazards which were not required by DPD or DSD.
- Table 1.7.3(c) below identifies when a substance or mixture, that does not require classification and labelling according to DSD or DPD, may require classification and labelling according to CLP.

Table 1.7.3(c) Examples when classification may not be required under DSD and DPD, but may be required under CLP.
### Non-classifications under DSD or DPD

<table>
<thead>
<tr>
<th>Non-classifications under DSD or DPD</th>
<th>Additional hazards under CLP</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-classified explosives</td>
<td>Explosive</td>
<td>Certain explosives, not classified as E, R2 or E, R3, which are manufactured with the view to producing a practical explosive or pyrotechnical effect will be classified as explosive under CLP. See Table 1.7.2.1(b) for additional information using transport classifications</td>
</tr>
<tr>
<td>Self-reactive substances or mixtures</td>
<td>Self-reactive substance</td>
<td>Self-reactive substances or mixtures may not be identified under the DSD. See Table 1.7.2.1(b) for additional information using transport classifications</td>
</tr>
<tr>
<td>Flammable aerosols</td>
<td>Flammable aerosol</td>
<td>Flammable aerosols are not explicitly identified under DSD or DPD. See Table 1.7.2.1(b) for additional information using transport classifications</td>
</tr>
<tr>
<td>Gases under pressure</td>
<td>Gas under pressure</td>
<td>Gases under pressure will not be identified as no R phrase for gases under pressure currently exists. The assignment of the correct group of a gas under pressure (compressed, liquefied or dissolved) depends on the physical state in which the gas is packaged or handled. It therefore has to be assigned individually. Note that the transport classification may be different</td>
</tr>
<tr>
<td>Self-heating substances or mixtures</td>
<td>Self-heating substance or mixture</td>
<td>Self-heating substances or mixtures will not be identified as no R phrase for self-heating substances or mixtures currently exists. See Table 1.7.2.1(b) for additional information using transport classifications</td>
</tr>
<tr>
<td>Substances or mixtures that are corrosive to metals, but not corrosive to skin</td>
<td>Corrosive to metal</td>
<td>Substances or mixtures that are corrosive to metals, but not corrosive to skin, will not be identified as no R phrase for corrosive to metals currently exists. See Table 1.7.2.1(b) for additional information using transport classifications</td>
</tr>
</tbody>
</table>
| Mixtures containing substances with non-additive effects for skin corrosion/irritation and eye damage/irritation | 1) Skin corrosive/serious eye damage (Category 1)  
2) Skin/eye irritant (Category 2) | The concept of non-additive effects for skin corrosion/irritation and eye damage/irritation is not explicitly considered in the current Directives (see CLP Annex I, Tables 3.2.4 and 3.3.4). |
| Mixtures containing 1-5% of R34 substances (and thus not classified) | Skin Irritant Category 2 | The generic concentration limit is 1% in the CLP but the corresponding limit is 5% in the DPD. |
| Mixtures containing 10 – 20% of R38 substances (and thus not classified) | 1) Skin irritant Category 2 | The generic concentration limit is 10% in the CLP but the corresponding limit is 20% in the DPD. |
| Mixtures containing 1-3% of R41 or R34 substances (and thus not classified) | 1) Eye irritant Category 2 | The lower generic concentration limit is 1% in the CLP but the corresponding limit is 5% in the DPD. |
| Mixtures containing 3-5% of R41 or R34 substances (and thus not classified) | 1) Serious eye damage Category 1 | The generic concentration limit is 3% in the CLP but the corresponding limit is 10% in the DPD. |
| Mixtures containing 10 – 20% of R36 substances (and thus not classified) | 1) Eye irritant Category 2 | The generic concentration limit is 10% in the CLP but the corresponding limit is 20% in the DPD. |
| Mixtures containing 3 - 5% of R62 or R63 substances (and thus not classified) | 1) Reproductive toxicant, Category 2 | The generic concentration limit is 3% in the CLP but the corresponding limit is 5% in the DPD. |
| Mixtures containing 0.3-0.5% of R60 or R61 substances (and thus not classified) | 1) Reproductive toxicant Category 1A/1B | The generic concentration limit is 0.3% in the CLP but the corresponding limit is 0.5% in the DPD. |
PART 2: PHYSICAL HAZARDS

2.1 INTRODUCTION

2.1.1 General remarks about the prerequisites of classification and testing

2.1.2 Safety

2.1.3 General conditions for testing

2.1.4 Physical state

2.1.5 Quality

2.2 EXPLOSIVES

2.2.1 Introduction

2.2.2 Definitions and general considerations for the classification of explosives

2.2.3 Classification of substances, mixtures or articles as explosives

2.2.3.1 Identification of hazard information

2.2.3.2 Screening procedures and waiving of testing

2.2.3.3 Classification criteria

2.2.3.4 Testing and evaluation of hazard information

2.2.3.5 Classification procedure and decision logics

2.2.3.5.1 Acceptance procedure

2.2.3.5.2 Assignment procedure to a division
2.4 Hazard communication for explosives

2.4.1 Pictograms, signal words, hazard statements and precautionary statements

2.4.2 Additional labelling provisions

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

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

2.5.2 Relation to transport classification

2.6 Examples of classification for explosives

2.6.1 Examples of substances and mixtures fulfilling the classification criteria

2.6.2 Examples of substances and mixtures not fulfilling the classification criteria

2.3 FLAMMABLE GASES

2.3.1 Introduction

2.3.2 Definitions and general considerations for the classification of flammable gases

2.3.3 Relation to other physical hazards

2.3.4 Classification of substances and mixtures as flammable gases

2.3.4.1 Identification of hazard information

2.3.4.2 Screening procedures and waiving of testing for gas mixtures

2.3.4.3 Classification criteria

2.3.4.4 Testing and evaluation of hazard information

2.3.4.5 Pictograms, signal words, hazard statements and precautionary statements

2.3.4.6 Additional labelling provisions

2.3.5 Re-classification of substances and mixtures classified as flammable gases according to DSD or already classified for transport
2.3.5.1 Re-classification of substances and mixtures classified in accordance with DSD

2.3.5.2 Relation to transport classification

2.3.6 Example of classification for flammable gases

2.4 FLAMMABLE AEROSOLS

2.4.1 Introduction

2.4.2 Definitions and general considerations for the classification of flammable aerosols

2.4.3 Classification of flammable aerosols

2.4.3.1 Classification criteria

2.4.3.2 Testing and evaluation of hazard information

2.4.3.3 Decision logic

2.4.4 Hazard communication for flammable aerosols

2.4.4.1 Pictograms, signal words, hazard statements and precautionary statements

2.4.4.2 Additional labelling provisions

2.4.5 Re-classification of flammable aerosols according to DSD

2.4.6 Examples of classification for flammable aerosols

2.4.6.1 Examples of aerosols fulfilling the classification criteria

2.4.6.2 Examples of aerosols not fulfilling the classification criteria

2.5 OXIDISING GASES

2.5.1 Introduction

2.5.2 Definitions and general considerations for the classification of oxidising gases

2.5.3 Classification of substances and mixtures as oxidising gases

2.5.3.1 Identification of hazard information
2.5.3.2 Screening procedures and waiving of testing
2.5.3.3 Classification criteria
2.5.3.4 Testing and evaluation of hazard information
2.5.4 Hazard communication for oxidising gases
2.5.4.1 Pictograms, signal words, hazard statements and precautionary statements
2.5.5 Re-classification of substances and mixtures classified as oxidising gases according to DSD or already classified for transport
2.5.5.1 Re-classification of substances and mixtures classified in accordance with DSD
2.5.5.2 Relation to transport classification

2.6 GASES UNDER PRESSURE
2.6.1 Introduction
2.6.1.1 Definition of “gas”
2.6.1.2 Definition of “gases under pressure”
2.6.2 Relation to other physical hazards
2.6.3 Classification of substances and mixtures as gases under pressure
2.6.3.1 Identification of hazard information
2.6.3.2 Classification criteria
2.6.3.3 Testing and evaluation of hazard information
2.6.4 Hazard communication for gases under pressure
2.6.4.1 Pictograms, signal words, hazard statements and precautionary statements
2.6.5 Re-classification of substances and mixtures classified as gases under pressure according to DSD or already classified for transport
2.6.5.1 Re-classification of substances and mixtures classified in accordance with DSD
2.6.5.2 Relation to transport classification
2.6.6 Examples of classification for gases under pressure

2.7 FLAMMABLE LIQUIDS

2.7.1 Introduction

2.7.2 Definitions and general considerations for the classification of flammable liquids

2.7.3 Relation to other physical hazards

2.7.4 Classification of substances and mixtures as flammable liquids

2.7.4.1 Identification of hazard information

2.7.4.2 Screening procedures and waiving of testing

2.7.4.2.1 Boiling point

2.7.4.2.2 Flash point

2.7.4.3 Classification criteria

2.7.4.4 Testing and evaluation of hazard information

2.7.4.4.1 Testing

2.7.4.4.2 Evaluation of hazard information

2.7.4.5 Decision logic

2.7.5 Hazard communication for flammable liquids

2.7.5.1 Pictograms, signal words, hazard statements and precautionary statements

2.7.5.2 Additional labelling provisions for flammable liquids

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

2.7.6.1 Re-classification according to DSD

2.7.7 Examples of classification for flammable liquids

2.7.7.1 Examples of substances and mixtures fulfilling the classification criteria

2.7.7.2 Examples of substances and mixtures not fulfilling the classification criteria

2.7.8 References
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.8</td>
<td>FLAMMABLE SOLIDS</td>
</tr>
<tr>
<td>2.8.1</td>
<td>Introduction</td>
</tr>
<tr>
<td>2.8.2</td>
<td>Definitions and general considerations for the classification of flammable solids</td>
</tr>
<tr>
<td>2.8.3</td>
<td>Relation to other physical hazards</td>
</tr>
<tr>
<td>2.8.4</td>
<td>Classification of substances and mixtures as flammable solids</td>
</tr>
<tr>
<td>2.8.4.1</td>
<td>Identification of hazard information</td>
</tr>
<tr>
<td>2.8.4.2</td>
<td>Screening procedures and waiving of testing</td>
</tr>
<tr>
<td>2.8.4.3</td>
<td>Classification criteria</td>
</tr>
<tr>
<td>2.8.4.4</td>
<td>Testing and evaluation of hazard information</td>
</tr>
<tr>
<td>2.8.4.5</td>
<td>Decision logic</td>
</tr>
<tr>
<td>2.8.5</td>
<td>Hazard communication for flammable solids</td>
</tr>
<tr>
<td>2.8.5.1</td>
<td>Pictograms, signal words, hazard statements and precautionary statements</td>
</tr>
<tr>
<td>2.8.6</td>
<td>Re-classification of substances and mixtures classified as flammable solids according to DSD or already classified for transport</td>
</tr>
<tr>
<td>2.8.6.1</td>
<td>Re-classification of substances and mixtures classified in accordance with DSD</td>
</tr>
<tr>
<td>2.8.6.2</td>
<td>Relation to transport classification</td>
</tr>
<tr>
<td>2.8.7</td>
<td>Examples of classification for flammable solids</td>
</tr>
<tr>
<td>2.8.7.1</td>
<td>Example of substances and mixtures fulfilling the classification criteria</td>
</tr>
<tr>
<td>2.8.7.2</td>
<td>Examples of substances and mixtures not fulfilling the classification criteria</td>
</tr>
<tr>
<td>2.9</td>
<td>SELF-REACTIVE SUBSTANCES</td>
</tr>
<tr>
<td>2.9.1</td>
<td>Introduction</td>
</tr>
<tr>
<td>2.9.2</td>
<td>Definitions and general considerations for the classification of self-reactives</td>
</tr>
<tr>
<td>2.9.3</td>
<td>Classification of substances and mixtures as self-reactive</td>
</tr>
</tbody>
</table>
2.9.3.1 Identification of hazard information
2.9.3.2 Classification criteria
2.9.3.3 Testing and evaluation of hazard information
  2.9.3.3.1 Thermal stability tests and temperature control
  2.9.3.3.2 Additional testing
  2.9.3.3.3 Additional classification considerations
2.9.3.4 Decision logic
2.9.4 Hazard communication for self-reactives
  2.9.4.1 Pictograms, signal words, hazard statements and precautionary statements
2.9.5 Re-classification of substances and mixtures classified as self-reactives according to DSD or already classified for transport
  2.9.5.1 Re-classification of substances and mixtures classified in accordance with DSD
  2.9.5.2 Relation to transport classification
2.9.6 Examples of classification for self-reactives
  2.9.6.1 Examples of substances and mixtures fulfilling the classification criteria
2.10 PYROPHORIC LIQUIDS AND SOLIDS
  2.10.1 Introduction
  2.10.2 Definitions and general considerations for the classification pyrophoric liquids and solids
  2.10.3 Relation to other physical hazards
  2.10.4 Classification of substances and mixtures as pyrophoric liquids and solids
    2.10.4.1 Identification of hazard information
    2.10.4.2 Screening procedures and waiving of testing
    2.10.4.3 Classification criteria
    2.10.4.4 Testing and evaluation of hazard information
    2.10.4.5 Decision logic
2.10.5 Hazard communication for pyrophoric liquids and solids

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

2.10.6.2 Relation to transport classification

2.10.7 Examples of classification for pyrophoric liquids and solids

2.10.7.1 Examples of substances and mixtures fulfilling the classification criteria

2.10.7.2 Examples of substances and mixtures not fulfilling the classification criteria

2.11 SELF-HEATING SUBSTANCES AND MIXTURES

2.11.1 Introduction

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

2.11.3 Relation to other physical hazards

2.11.4 Classification of self-heating substances and mixtures

2.11.4.1 Identification of hazard information

2.11.4.2 Screening procedures and waiving of testing

2.11.4.3 Classification criteria

2.11.4.4 Testing and evaluation of hazard information

2.11.4.4.1 General remarks

2.11.4.4.2 Sample preparation

2.11.4.4.3 Criteria and evaluation

2.11.4.5 Decision logic

2.11.4.6 Exemption

2.11.5 Hazard communication for self-heating substances and mixtures
2.11.5.1 Pictograms, signal words, hazard statements and precautionary statements

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

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

2.11.6.2 Relation to transport 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

2.11.7.2 Examples of substances and mixtures not fulfilling the classification criteria

2.11.8 References

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

2.12.1 Introduction

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

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

2.12.3.1 Identification of hazard information

2.12.3.2 Screening procedures and waiving of testing

2.12.3.3 Classification criteria

2.12.3.4 Testing and evaluation of hazard information

2.12.3.4.1 Testing procedure

2.12.3.4.2 Evaluation of hazard information

2.12.3.5 Decision logic

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

2.12.4.1 Pictograms, signal words, hazard statements and precautionary statements for substances and mixtures
2.12.4.2 Additional labelling provisions

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

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

2.12.5.1.1 Differences in classification and labelling

2.12.5.1.2 Differences in the test procedures

2.12.5.2 Relation to transport classification

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

2.12.6.1 Example of a substance fulfilling the classification criteria

2.12.6.2 Example of a substance not fulfilling the classification criteria

2.12.7 References

2.13 OXIDISING LIQUIDS AND OXIDISING SOLIDS

2.13.1 Introduction

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

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

2.13.3.1 Identification of hazard information

2.13.3.1.1 Non-testing data

2.13.3.2 Classification criteria

2.13.3.2.1 General

2.13.3.2.2 Oxidising liquids

2.13.3.2.3 Oxidising solids

2.13.3.3 Testing and evaluation of hazard information

2.13.3.4 Decision logic

2.13.3.4.1 Decision logic 2.13 for oxidising liquids
2.13.3.5 Pictograms, signal words, hazard statements and precautionary statements

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

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

2.13.4.1.1 Liquids

2.13.4.1.2 Solids

2.13.4.2 Relation to transport classification

2.13.5 Examples of classification for oxidising liquids and oxidising solids

2.13.5.1 Examples of substances and mixtures fulfilling the classification criteria

2.13.5.1.1 Liquids

2.13.5.1.2 Solids

2.13.5.2 Examples of substances and mixtures not fulfilling the classification criteria

2.13.5.2.1 Liquids

2.13.5.2.2 Solids

2.13.6 Reference

2.14 ORGANIC PEROXIDES

2.14.1 Introduction

2.14.2 Definitions and general considerations for the classification of organic peroxides

2.14.3 Relation to other physical hazards

2.14.4 Classification of substances and mixtures as organic peroxides

2.14.4.1 Identification of hazard information

2.14.4.2 Classification criteria

2.14.4.3 Testing and evaluation of hazard information

2.14.4.3.1 Thermal stability tests and temperature control

2.14.4.3.2 Additional testing

2.14.4.3.3 Additional classification considerations
2.14.4 Decision logic

2.14.5 Hazard communication for organic peroxides

2.14.5.1 Pictograms, signal words, hazard statements and precautionary statements

2.14.5.2 Additional labelling provisions for organic peroxides

2.14.6 Re-classification of substances and mixtures classified as organic peroxides according to DSD or already classified according to transport

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

2.14.6.2 Relation to transport classification

2.14.7 Examples of classification for organic peroxides

2.14.7.1 Examples of substances and mixtures fulfilling the classification criteria

2.14.8 Additional remarks

2.15 CORROSIVE TO METALS

2.15.1 Introduction

2.15.2 Definitions and general considerations for the classification of substances and mixtures corrosive to metals

2.15.3 Classification of substances and mixtures as corrosive to metals

2.15.3.1 Identification of hazard information

2.15.3.2 Screening procedures and waiving of testing

2.15.3.3 Classification criteria

2.15.3.4 Testing and evaluation of hazard information

2.15.3.4.1 General considerations

2.15.3.4.2 Additional notes on best practice for testing

2.15.4 Hazard communication for substances and mixtures corrosive to metals

2.15.4.1 Pictograms, signal words, hazard statements and precautionary statements
Re-classification of substances and mixtures classified as corrosive to metals according to DSD

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

Relation to transport classification

Examples of classification for substances and mixtures corrosive to metals

Example of metal specimen plates after exposure to a corrosive mixture

References
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. The definition in CLP reflects the fact that the evidence for acute toxicity is usually obtained from animal testing. In particular, acute toxicity is usually characterised in terms of lethality and exposure times are based around those used in experimental protocols. However, classification for acute toxicity can also be based on human evidence which shows lethality following human exposure.

There are two hazard classes for acute toxicity – “Acute toxicity” and “STOT-SE”. These are independent of each other and both may be assigned to a substance or a mixture if the respective criteria are met. However, care should be taken not to assign each class for the same effect, essentially giving a “double classification”, even where the criteria for both classes are fulfilled. In such a case the most appropriate class should be assigned.

Acute toxicity classification is generally assigned on the basis of evident lethality (e.g. an LD<sub>50</sub>/LC<sub>50</sub> value), or, where the potential to cause lethality can be concluded from evident toxicity (e.g. from the fixed dose procedure). STOT-SE should be considered where there is clear evidence of toxicity to a specific organ, especially when it is observed in the absence of lethality (see section 3.8).

For more details see IR/CSA, section R.7.4.1.1.

Annex I: 3.1.1.2. The hazard class Acute Toxicity is differentiated into:
- Acute oral toxicity;
- Acute dermal toxicity;
- Acute inhalation toxicity.

The classification shall be considered for each route of exposure, using the appropriate approach as described in section 3.1.2.2. If different hazard categories are assigned, the more severe hazard category will be used for the classification for acute toxicity, with the appropriate pictogram and signal word. For each relevant route of exposure, the hazard statement will correspond to the classification of this specific route.

3.1.2 Classification of substances for acute toxicity

3.1.2.1 Identification of hazard information

3.1.2.1.1 Identification of human data

Relevant information with respect to acute toxicity may be available from case reports, epidemiological studies, medical surveillance and reporting schemes and national poison centres. Human data to be considered for acute toxicity should report severe effects after...
single exposure or exposure of less than 24h, but data on severe effects after a few exposures over a few days can also be considered on a case by case basis.

For more details see IR/CSA, Section R.7.4.3.2.

3.1.2.1.2 Identification of non-human data

Non-testing data:

Physicochemical data

Physico-chemical properties, such as pH, physical state, form, solubility, vapour pressure and particle size, can be important parameters in evaluating toxicity studies and in determining the most appropriate classification. This is especially valid with respect to inhalation where physical form and particle size can have a significant impact on toxicity (see section 3.1.2.3.2).

(Q)SAR models, expert systems and grouping methods

“Non-testing data can be provided by the following approaches: a) structure-activity relationships (SARs) and quantitative structure-activity relationships (QSARs), collectively called (Q)SARs; b) expert systems incorporating (Q)SARs and/or expert rules; and c) grouping methods (read-across and categories. These approaches can be used to assess acute toxicity if they provide relevant and reliable (adequate) data for the chemical of interest. … Compared with some endpoints, there are relatively few (Q)SAR models and expert systems capable of predicting acute toxicity.” (IR/CSA, section R.7.4.3.1).

Testing data:

In vitro data

There are currently no in vitro tests that have been officially adopted by the EU or OECD for assessment of acute toxicity (IR/CSA, Section R.7.4.3.1). Any available studies should be assessed by using expert judgement.

Animal data

A number of different types of studies have been used to investigate acute toxicity. Older standard studies were designed to determine lethality and estimate the LD$_{50}$/LC$_{50}$. In contrast, contemporary study protocols, such as the fixed dose procedure, use signs of overt (“evident”) toxicity rather than lethality as indications of acute toxicity. These studies are generally conducted using preferred species, i.e. the rat for acute oral and inhalation toxicity studies, and in addition rabbit for dermal toxicity studies.

The animal studies are listed in IR/CSA, section R.7.4.3.1.

3.1.2.2 Classification criteria

Annex I: 3.1.2.1. Substances can be allocated to one of four toxicity categories based on acute toxicity by the oral, dermal or inhalation route according to the numeric criteria shown in Table 3.1.1. Acute toxicity values are expressed as (approximate) 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>
<thead>
<tr>
<th>Exposure Route</th>
<th>Category 1</th>
<th>Category 2</th>
<th>Category 3</th>
<th>Category 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table 3.1.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Guidance to Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of substances and mixtures**

<table>
<thead>
<tr>
<th>Oral (mg/kg bodyweight) See Note (a)</th>
<th>ATE ≤ 5</th>
<th>5 &lt; ATE ≤ 50</th>
<th>50 &lt; ATE ≤ 300</th>
<th>300 &lt; ATE ≤ 2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermal (mg/kg bodyweight) See Note (a)</td>
<td>ATE ≤ 50</td>
<td>50 &lt; ATE ≤ 200</td>
<td>200 &lt; ATE ≤ 1000</td>
<td>1000 &lt; ATE ≤ 2000</td>
</tr>
<tr>
<td>Gases (ppmV) see: Note (a) Note (b)</td>
<td>ATE ≤ 100</td>
<td>100 &lt; ATE ≤ 500</td>
<td>500 &lt; ATE ≤ 2500</td>
<td>2500 &lt; ATE ≤ 20000</td>
</tr>
<tr>
<td>Vapours (mg/l) see: Note (a) Note (b) Note (c)</td>
<td>ATE ≤ 0.5</td>
<td>0.5 &lt; ATE ≤ 2.0</td>
<td>2.0 &lt; ATE ≤ 10.0</td>
<td>10.0 &lt; ATE ≤ 20.0</td>
</tr>
<tr>
<td>Dusts and Mists (mg/l) see: Note (a) Note (b)</td>
<td>ATE ≤ 0.05</td>
<td>0.05 &lt; ATE ≤ 0.5</td>
<td>0.5 &lt; ATE ≤ 1.0</td>
<td>1.0 &lt; ATE ≤ 5.0</td>
</tr>
</tbody>
</table>

*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<sub>50</sub>/LC<sub>50</sub> where available.

(b) The acute toxicity estimate (ATE) for the classification of a substance in a mixture is derived using:
- the LD<sub>50</sub>/LC<sub>50</sub> 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) Generic concentration limits for inhalation toxicity in the table are based on 4 hour testing exposures. Conversion of existing inhalation toxicity data which have been generated using a 1 hour exposure can be carried out by dividing by a factor of 2 for gases and vapours and 4 for dusts and mists.

(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.

---

Comment to Table 3.1.1, Note (b): The classification criteria for acute inhalation toxicity relate to a 4-hour experimental exposure period. Where LC<sub>50</sub> values have been obtained in studies using exposure durations shorter or longer than 4 hours these may be adjusted to a 4-hour equivalent using...
Haber’s law \((C^n \cdot t = k)\) for direct comparison with the criteria. The value of \(n\), which is specific to individual substances, should be chosen using expert judgement. If an appropriate value of \(n\) is not available in the literature then it may sometimes be derived from the available mortality data using probits (i.e. the inverse cumulative distribution functions associated with the standard normal distribution). Alternatively, some default values are recommended (IR/CSA, section R.7.4.4.1).

Particular care should be taken when using Haber’s law to assess inhalation data on substances which are corrosive or locally active. In all cases, Haber’s law should only be used in conjunction with expert judgement.

It is noted that the statements in IR/CSA, section R.7.4.4.1, with respect to Haber’s law are not consistent with those of CLP. However the CLP approach must be used for classification and labelling.

Comment to Table 3.1.1, Note (c):
The term “aerosol” is commonly used for “dust and mists”.

### 3.1.2.3 Evaluation of hazard information

#### 3.1.2.3.1 Evaluation of human data

The evaluation of human data often becomes difficult due to various limitations frequently found with the types of studies and data highlighted in section 3.1.2.1.1. These include uncertainties relating to exposure assessment (i.e. unreliable information on the amount of substance the subjects were exposed to) and uncertain exposure to other substances. As such, human data needs careful expert evaluation to properly judge the reliability of the findings. It should be acknowledged that human data often do not provide sufficiently robust evidence on their own to support classification. They may however contribute to a weight of evidence assessment with other available information such as data from animal studies.

The classification for acute toxicity is based primarily on the dose/concentration that causes mortality (the Acute Toxicity Estimate, ATE). This is then related to the numerical values in the classification criteria according to CLP Annex I, Table 3.1.1 (see section 3.1.2.2) for substances or for use in the additivity formula in CLP Annex I, 3.1.3.6.1 and 3.1.3.6.2.3 for mixtures (see section 3.1.3.3). The ATE is usually obtained from animal studies but in principle suitable human data can also be used if available. Where human data are available they should be used to estimate the ATE which can be used directly for classification as described above.

The minimum dose/concentration or range shown or expected to cause mortality after a single human exposure can be used to derive the human ATE directly, without any adjustments or uncertainty factors. See Example 1 (methanol).

If there are no exact/quantitative lethal dose data the procedure described in CLP Annex I, 3.1.3.6.2.1(b) (see section 3.1.3.3.4) would have to be followed using Table 3.1.2, (see section 3.1.3.3.3) with an assessment of the available information on a semi-quantitative or qualitative basis.

Expert judgement is needed in a total weight of evidence approach taking relevance, reliability, and adequacy of the information into account. See Example 2 (N,N-dimethylaniline).

If the available human data alone are too limited to support a classification they may still provide supporting evidence in the overall weight of evidence assessment.
3.1.2.3.2 Evaluation of non-human data

**Annex I: 3.1.2.2. Specific considerations for classification of substances as acutely toxic**

3.1.2.2.1. The preferred test species for evaluation of acute toxicity by the oral and inhalation routes is the rat, while the rat or rabbit are preferred for evaluation of acute dermal toxicity. When experimental data for acute toxicity are available in several animal species, scientific judgement shall be used in selecting the most appropriate LD$_{50}$ value from among valid, well-performed tests.

Evaluation of non-testing and *in vitro* data:

Results of (Q)SAR, grouping and read-across may be used instead of testing, and substances will be classified and labelled on this basis if the method fulfils the criteria described in Annex XI of REACH. See also IR/CSA, section R.7.4.4.1.

**ATE – establishing:**

- Basis LD$_{50}$/LC$_{50}$: An available LD$_{50}$/LC$_{50}$ is an ATE at first stage.
- Results from a range test: According to CLP Annex I, Table 3.1.2 results from range tests (i.e. doses/exposure concentrations that cause acute toxicity in the range of numeric criteria values) can be assigned to the four different categories of acute toxicity for each possible route of exposure (centre column). Further, Table 3.1.2 allows allocating a single value, the converted acute toxicity point estimate (cATpE), to each experimentally obtained acute toxicity range estimate or classification category (right column), see Note (a) to Table 3.1.1. This cATpE can be used in the additivity formulae (Annex I, 3.1.3.6.1 and 3.1.3.6.2.3) to calculate the acute toxicity of mixtures.

- In case of multiple LD$_{50}$/LC$_{50}$s or from several species:
  Where several experimentally determined ATE values (i.e. LD$_{50}$, LC$_{50}$ values or ATE derived from studies using signs of non-lethal toxicity) are available, expert judgement needs to be used to choose the most appropriate value for classification purposes. Each study needs to be assessed for its suitability in terms of study quality and reliability, and also for its relevance to the substance in question in terms of technical specification and physical form. Studies not considered suitable on reliability or other grounds should not be used for classification.

In general, classification is based on the lowest ATE value available i.e. the lowest ATE in the most sensitive appropriate species tested. However, expert judgement may allow another ATE value to be used in preference, provided this can be supported by a robust justification. If there is information available to inform on species relevance, then the studies conducted in the species most relevant for humans should normally be given precedence over the studies in other species. If there is a wide range of ATE values from the same species, it may be informative to consider the studies collectively, to understand possible reasons for the different results obtained. This would include consideration of factors such as the animal strains used, the experimental protocols, the purity of the substance and form/phase in which it was tested (e.g. the particle size distribution of any aerosols or dusts tested), as well as exposure mode and numerous technical factors in inhalation studies. This assessment may aid selection of the most appropriate study on which to base the classification.

If there are different LD$_{50}$ values from tests using different vehicles e.g. water vs. corn oil or neat substance vs. corn oil), generally the lowest valid value would be the basis for classification. It is not considered appropriate to combine or average the available ATE values. The studies may not be equivalent (in terms of experimental design such as protocol,
purity of material tested, species of animal used etc) making such a collation or combination unsound.

If there is a study available with a post-observation period of only ca 7 days (instead of the 14 days according to the OECD guidelines) and there are effects still observed at the end of the study, the resulting LD$_{50}$ might be misleading. A long persistency of effects may be indicative of cumulative toxicity, sometimes coinciding with flat dose-response relationships, sometimes with species differences. Such information should be included in the weight of evidence consideration.

**Annex I:** 3.1.2.3. Specific considerations for classification of substances as acutely toxic by the inhalation route

3.1.2.3.1 Units for inhalation toxicity are a function of the form of the inhaled material. Values for dusts and mists are expressed in mg/l. Values for gases are expressed in ppmV. Acknowledging the difficulties in testing vapours, some of which consist of mixtures of liquid and vapour phases, the table provides values in units of mg/l. However, for those vapours which are near the gaseous phase, classification shall be based on ppmV.

9 Conversions:

Differentiation between vapour and mist will be made on the basis of the saturated vapour concentration (SVC) for a volatile substance, which can be calculated by the following equation:

\[
\text{SVC [mg/l] = 0.0412 x MW x vapour pressure in hPa at 20°C.}
\]

The conversion from mg/l to ppm assuming an ambient pressure of 1 atm = 101.3 kPa and 25°C is: ppm=0.0245 mg/l x 1/MW.

An LC$_{50}$ well below the SVC will be considered for classification according to the criteria for vapours; whereas an LC$_{50}$ close to or above the SVC will be considered for classification according to the criteria for mists (see also Draft OECD TG 39).

Considerations with respect to physical forms or states / bioavailability:

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

For further details see sections 1.2 and 1.3.

Special considerations concerning aerosols:

The test guidelines for acute inhalation toxicity with aerosols require rodents to be exposed to an aerosol containing primarily respirable particles (with a Mass Median Aerodynamic Diameter (MMAD) of 1 – 4 µm), so that particles can reach all regions of the respiratory tract. The use of such fine aerosols helps to avoid partial overloading of extra-thoracic airways in obligate nasal breathing species like rats. Results from studies in which substances with particle size with a MMAD > 4 µm have been tested can generally not be used for classification, but expert judgement is needed in cases where there are indications of high toxicity.

The use of highly respirable aerosols is ideal to fully investigate the potential inhalation hazard of the substance. However, it is acknowledged that these exposures may not necessarily reflect realistic conditions. For instance, solid materials are often micronised to a
highly respirable form for testing, but in practice exposures will be to a dust of much lower respirability. Similarly, pastes or highly viscous materials with low vapour pressure need strong measures to be taken to generate airborne particulates of sufficiently high respirability, whereas for other materials this may occur spontaneously. In such situations, specific problems may arise with respect to classification and labelling, as these substances are tested in a form (i.e. specific particle size distribution) that is different from all the forms in which these substances are placed on the market and in which they can reasonably be expected to be used.

A scientific concept has been developed as a basis for relating the conditions of acute inhalation tests to those occurring in real-life, in order to derive an adequate hazard classification. This concept is applicable only to substances or mixtures which are proven to cause acute toxicity through local effects and do not cause systemic toxicity (Pauluhn, 2008).

**Corrosive substances**

It is presumed that corrosive substances (and mixtures) will cause toxicity by inhalation exposure. In cases where no acute inhalation test has been performed special consideration should be given to the need to communicate this potential hazard.

Corrosive substances (and mixtures) may be acutely toxic after inhalation to a varying degree and by different modes of action. Therefore, it is not possible to estimate the acute inhalation toxicity from the corrosivity data alone.

There are special provisions for hazard communication of acutely toxic substances by a corrosive effect, see section 3.1.4.2.

### 3.1.2.3 Weight of evidence

In cases where there is sufficient human evidence that meets the criteria given in section 3.1.2.2 then this will normally lead to classification for acute toxicity, irrespective of other information available.

If there are human data indicating no classification but there are also non-human data indicating classification then the classification is based on the non-human data unless it is shown that the human data cover the exposure range of the non-human data or that the non-human data are not relevant for humans. If the human and non-human data both indicate no classification then classification is not required.

If there are no human data then the classification is based on the non-human data.

For the role and application of expert judgement and weight of evidence determination, see CLP Annex I, 1.1.1.

### 3.1.2.4 Decision on classification

The classification has to be performed with respect to all routes of exposure (oral, dermal, inhalation) on the basis of all adequate and reliable available information.

### 3.1.2.5 Setting of specific concentration limits

Specific concentration limits are not applicable for acute toxicity classification. Rather, the relative potency of substances is implicitly taken into account in the additivity formula (see section 3.1.3.3.3). For this reason specific concentration limits for acute toxicity will not appear in CLP Annex VI, Table 3.1 or in the classification and labelling inventory (CLP Article 42).
3.1.2.6 Decision logic

The decision logic below is provided as additional guidance. It is strongly recommended that the person responsible for classification is fully familiar with the criteria for acute toxicity classification before using the decision logic.

For a complete classification of a substance, the decision logic must be worked out for each route of exposure for which data and/or information is available. For example, if a certain substance is classified in Category 1 based on an oral $LD_{50} \leq 5 \text{ mg/kg bodyweight}$ (the answer was 'Yes' in box 2 for item (a)), it is still necessary to go back to box 2 in the decision logic and complete the classification for the dermal (b) and inhalation (c)-(e) route of exposure, when data is available for one or both of these routes of exposure. In case there are data for all three routes of exposure, the classification for acute toxicity of the substance will include the three differentiations of the hazard class, which might end up in three different categories. The route of exposure will then be specified in the corresponding hazard statement.
Are there data and/or information to evaluate acute toxicity?

NO  Classification not possible

YES

According to the criteria in CLP Annex I, 3.1.2 to 3.1.3.4, does it have an:
(a) Oral 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?

NO

YES  Category 1  Danger

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?

NO

YES  Category 2  Danger

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?

NO

YES  Category 3  Danger

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?

NO

YES  Category 4  Warning

No classification
3.1.3 Classification of mixtures for acute toxicity

3.1.3.1 General considerations for classification

The procedure for classifying mixtures is a tiered i.e. a stepwise approach based on a hierarchy principle and depending on the type and amount of available data/information. If valid test data are available for the whole mixture they have precedence. If no such data exist, the so called bridging principles have to be applied if possible. If the bridging principles are not applicable an assessment on the basis of ingredient information will be applied (see sections 3.1.3.3.3, 3.1.3.3.4 and 3.1.3.5).

3.1.3.2 Identification of hazard information

Where toxicological information from human evidence and animal studies is available on a mixture, this should be used to derive the appropriate classification. Such information may be available from the mixture manufacturer. Where such information on the mixture itself is not available, information on similar mixtures and/or the component substances in the mixture must be used, as described in section 3.1.3.3.

Alternatively, the hazard information on all individual components in the mixture could be identified as described in section 3.1.2.2.

3.1.3.3 Classification criteria

The classification shall be considered for each route of exposure, using the appropriate approach as described in section 3.1.2.3. If different hazard categories are assigned, the more severe hazard category will be used for the classification for acute toxicity, with the appropriate pictogram and signal word. For each relevant route of exposure, the hazard statement will correspond to the classification of this specific route.

3.1.3.3.1 When data are available for the complete mixture

In general, where a mixture has been tested those data should be used to support classification according to the same criteria as used for substances. However, there should be some consideration of whether the test is appropriate. For instance, if the mixture contains a substance for which the test species is not considered appropriate (for instance a mixture

Deleted: §
Deleted: §
Deleted: §
Deleted: §
Deleted: §
Deleted: §
containing methanol tested in rats which are not sensitive to methanol toxicity), then the
appropriateness of these data for classification should be considered using expert judgement.

With respect to the classification of mixtures in the form of dust for acute inhalation toxicity,
the particle size can affect the toxicity and the resulting classification should take this into
account (see section 3.1.2.3.2).

3.1.3.3.2 When data are not available for the complete mixture: bridging principles

Annex I: 3.1.3.5.1. Where the mixture itself has not been tested to determine its acute toxicity, but
there are sufficient data on the individual ingredients and similar tested mixtures to adequately
characterise the hazards of the mixture, these data shall be used in accordance with the bridging
rules set out in section 1.1.3.

3.1.3.3.3 When data are available for all components or only for some components

Annex I: 3.1.3.6. Classification of mixtures based on ingredients of the mixture (Additivity
formula)

3.1.3.6.1. Data available for all ingredients

In order to ensure that classification of the mixture is accurate, and that the calculation need only be
performed once for all systems, sectors, and categories, the acute toxicity estimate (ATE) of
ingredients shall be considered as follows:

(a) Include ingredients with a known acute toxicity, which fall into any of the acute toxicity
categories shown in Table 3.1.1;

(b) Ignore ingredients that are presumed not acutely toxic (e.g. water, sugar);

(c) Ignore components if the data available are from a limit dose test (at the upper threshold for
Category 4 or 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:

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

where:

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

$i$ = the individual ingredient from 1 to $n$

$n$ = the number of ingredients

$ATE_i$ = Acute Toxicity Estimate of ingredient $i$.

The additivity formula cannot be used directly for mixtures containing substances tested for
inhalation toxicity as vapours and others as dust, because it is unclear when the numeric
values for vapours or dusts must be used. Therefore for acute inhalation toxicity the additivity
formula should be used separately for each relevant physical form (i.e. gas, vapour and/or

---

Note that the legal text uses both “ingredients” and “components” interchangeably, and so does this guidance.
Guidance to Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of substances and mixtures

dust/mist), using the appropriate categories in Table 3.1.1. In case of different outcomes, the most severe classification applies.

---

### Annex I: Table 3.1.2

Conversion from experimentally obtained acute toxicity range values (or acute toxicity hazard categories) to acute toxicity point estimates for classification for the respective routes of exposure

<table>
<thead>
<tr>
<th>Exposure routes</th>
<th>Classification category or experimentally obtained acute toxicity range estimate</th>
<th>Converted acute toxicity point estimate (see Note 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral (mg/kg bodyweight)</td>
<td>0 &lt; Category 1 ≤ 5</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>5 &lt; Category 2 ≤ 50</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>50 &lt; Category 3 ≤ 300</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>300 &lt; Category 4 ≤ 2000</td>
<td>500</td>
</tr>
<tr>
<td>Dermal (mg/kg bodyweight)</td>
<td>0 &lt; Category 1 ≤ 50</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>50 &lt; Category 2 ≤ 200</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>200 &lt; Category 3 ≤ 1000</td>
<td>300</td>
</tr>
<tr>
<td></td>
<td>1000 &lt; Category 4 ≤ 2000</td>
<td>1100</td>
</tr>
<tr>
<td>Gases (ppmV)</td>
<td>0 &lt; Category 1 ≤ 100</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>100 &lt; Category 2 ≤ 500</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>500 &lt; Category 3 ≤ 2500</td>
<td>700</td>
</tr>
<tr>
<td></td>
<td>2500 &lt; Category 4 ≤ 2000</td>
<td>4500</td>
</tr>
<tr>
<td>Vapours (mg/l)</td>
<td>0 &lt; Category 1 ≤ 0.5</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>0.5 &lt; Category 2 ≤ 2</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>2.0 &lt; Category 3 ≤ 10.0</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>10.0 &lt; Category 4 ≤ 20.0</td>
<td>11</td>
</tr>
<tr>
<td>Dust/mist (mg/l)</td>
<td>0 &lt; Category 1 ≤ 0.05</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>0.05 &lt; Category 2 ≤ 0.5</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>0.5 &lt; Category 3 ≤ 1.0</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>1.0 &lt; Category 4 ≤ 5.0</td>
<td>1.5</td>
</tr>
</tbody>
</table>

**Note 1:**

These values are designed to be used in the calculation of the ATE for classification of a mixture based on its components and do not represent test results.

Some converted Acute Toxicity point Estimates (cATpEs) are equal to the upper limit of the next lower category, for example the cATpE of oral Category 2 (5 mg/kg) is equal to the upper limit of oral Category 1 (also 5 mg/kg).

This can lead to a problem when using the cATpE values for calculating the acute toxicity of mixtures. For instance, using the cATpEs for a mixture containing only substances classified in Category 2 actually results in a Category 1 classification for the mixture. Similarly, a
mixture containing substances classified as Category 3 for dust/mist results in a Category 2 classification. Clearly these outcomes are incorrect and are an unintended side-effect of the approach. To address this problem the following proposal has been endorsed at UN SCE-GHS: “If the acute toxicity range values (or acute toxicity hazard classification categories) for all ingredients of a mixture are within the same range or category, then the mixture should be classified in that category.” Applying this to the cases highlighted above, these mixtures would be classified in Category 2 and 3, respectively.

Annex I: 3.1.3.3.(b) where a classified mixture is used as an ingredient of another mixture, the actual or derived acute toxicity estimate (ATE) for that mixture may be used, when calculating the classification of the new mixture using the formulas in section 3.1.3.6.1 and paragraph 3.1.3.6.2.3.

It is important that the downstream user has sufficient information in order to enable him to perform a correct classification of mixtures.

3.1.3.3.4 When data are not available for all components

Annex I: 3.1.3.6.2.1. Where an ATE is not available for an individual ingredient of the mixture, but available information such as that listed below can provide a derived conversion value such as those laid out in Table 3.1.2, the formula in paragraph 3.1.3.6.1 shall be applied.

This includes evaluation of:

(a) extrapolation between oral, dermal and inhalation acute toxicity estimates (1). Such an evaluation could require appropriate pharmacodynamic and pharmacokinetic data;

(b) evidence from human exposure that indicates toxic effects but does not provide lethal dose data;

(c) evidence from any other toxicity tests/assays available on the substance that indicates toxic acute effects but does not necessarily provide lethal dose data; or

(d) data from closely analogous substances using structure/activity relationships.

____________________

(1) 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, MS CAs may require testing for a specific route. In those cases, classification shall be performed for that route based upon the MS CAs requirement.

Derivation of ATEs from available information:

When ingredients have a known acute toxicity (LC\textsubscript{50} or LD\textsubscript{50} values), this value has to be used in the additivity formula. However, for many substances, acute toxicity data will not be available for all exposure routes.

CLP allows for two ways of deriving acute toxicity conversion values. One option is to use the converted acute toxicity point estimates supplied in Annex I, Table 3.1.2. The other option, expert judgement would recommend in substantiated cases the use of the directly derived ATE values.

a) Route-to-route extrapolation (CLP Annex I, 3.1.3.6.2.1.(a)):

Route-to-route extrapolation is defined as the prediction of the total amount of a substance administered by one route that would produce the same systemic toxic response as that obtained by a given amount of a substance administered by another route. Thus, route-to-route extrapolation is only applicable for the evaluation of systemic effects. It is not appropriate to assess direct local effects.
This extrapolation is possible if certain conditions are met, which substantiate the assumption that an internal dose causing a systemic effect at the target is related to an external dose/concentration; preferably the absorption can be quantified. Therefore information on the physico-chemical and biokinetic properties should be available and assessed in order to allow such a conclusion and performing an extrapolation across routes. In the absence of any information on absorption, 100% absorption has to be presumed as a worst case for the dermal and inhalation route. Extrapolating from the oral route to other routes, the assumption of absorption of 100% for the oral route is, however, not a worst case. Absorption of less than 100% by the oral route will lead to lower ATEs. Another important factor is the local and systemic metabolic pathways; in particular it must be assured that no route-specific metabolism/degradation of substance occurs.

If extrapolating from oral data, the influence of first-pass metabolism in the stomach/intestines and the liver should be considered, especially if the substance is detoxified. Such first pass metabolism is unlikely to occur to any significant extent by the dermal or inhalation routes, and so this would lead to an underestimate of toxicity by these routes. Thus if based on kinetic or (Q)SAR data a specific first-pass effect is excluded, oral data may be used for extrapolation purposes.

For an extrapolation to the dermal route, information on the potential skin penetration may be derived from the chemical structure (polar vs. non-polar structure elements, Log P, molecular weight) if kinetic data are not available which would allow a quantitative comparison. When no such information is available 100% dermal absorption should be presumed.

Similarly for an extrapolation to the inhalation route if there is no quantitative information on absorption then 100% absorption should be presumed. Inhalation volatility is an important factor which on one hand may increase the exposure, but on the other hand may reduce absorption due to higher exhalation rates. The solubility (in water and non-polar solvents) has to be considered, as well as particle size, which plays a particularly important role in inhalation toxicity.

Route-to-route extrapolation is not always appropriate. For example where there is a substantial difference in absorption between oral and inhalation uptake (e.g. poorly soluble particles, substances that decompose within the gastrointestinal-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).

\( \text{i: Extrapolation oral } \rightarrow \text{ inhalation:} \)

If the mentioned conditions are met an extrapolation from oral data would be performed as follows:

\[
\text{Incorporated dose} = \text{concentration} \times \text{respiratory volume} \times \text{exposure time}
\]

1 mg/kg bw = 0.0052 mg/l/4h

using a respiratory volume for a 250 g rat of 0.20 l/min and 100% absorption and postulating 100% deposition and absorption (IR/CSA, Chapter R7C, Table R.7.12-10).

Valid information that the deposition and/or absorption rate for the extrapolated route is lower would allow a higher equivalent derived ATE (see section 3.1.6.1.9, Example 9).

\( \text{ii: Extrapolation oral } \rightarrow \text{ dermal} \)
If based on kinetic or SAR data a high penetration rate can be assumed and a specific first pass-effect is excluded, oral and dermal toxicity might be regarded as equivalent. This is rarely the case.

Solids themselves may have a very low absorption rate, but if diluted in an appropriate solvent there may be appreciable absorption. Thus depending on the kinetic and physico-chemical properties and kind of mixture varying ATEs will result. An example for these differences is butyn-1,4-diol which dermally applied as solid shows no mortality in rats at 5000 mg/kg, whereas the aqueous solution giving \( \text{LD}_{50} \) of 659 and 1,240 mg/kg, the oral \( \text{LD}_{50} \) are in the range of 200 mg/kg.

For more details on inter-route extrapolation see IR/CSA, Section R.7C.12.1.5. Example 9 and 10 illustrate this approach.

b) Evidence from human exposure:

Human evidence can be used to derive an appropriate ATE to use in the additivity approach for mixtures (CLP Annex I, 3.1.3.6.1 and 3.1.3.6.2.3). Therefore it is necessary to extrapolate from adequate and reliable data and taking the potency (i.e. the magnitude of the lethal dose reported) of the effects in humans into account. Thus an equivalent ATE may be derived on the basis of valid human toxicity data (minimum dose/concentration) and used directly in the additivity formulae (see Section 3.1.6.1.1 Example 1). The alternative to the derivation of an equivalent ATE is the allocation to a category. The category should be justified by semi-quantitative or qualitative data and a subsequent derivation of a converted ATE (cATpE) according to CLP Annex I, Table 3.1.2 and subsequently use in the formulae (see section 3.1.6.1.2, Example 2). See also section 3.1.2.3.1 for more details.

c) Evidence from other toxicity tests:

Information from other types of studies can sometimes be useful in deriving an acute toxicity classification. (see section 3.1.2.2). These studies will not usually provide an LD\(_{50}\)/ATE value that can be used directly for classification, but they may provide enough information to allow an estimate of acute toxicity to be made, which would be sufficient to support a decision on classification.

Example:

Available information: In a range finding study with respect to repeated dose toxicity daily oral doses of 1000 mg/kg over 5 days prove to be neither lethal nor cause serious symptoms in rats at the end of the observation period of 14 days.

Conclusion: the LD\(_{50}\)=ATE is >2000 mg/kg since 2 doses following (within roughly) 24 h are not lethal (see section 3.1.2.2). Thus this ingredient can be ignored in the additivity procedure.

d) Use of (Q)SAR:

LD\(_{50}\)/LC\(_{50}\) values predicted by a highly reliable model (see Section 2.1.2) may be used according to Note (a) to Annex I, Table 3.1.1 directly as LD\(_{50}\)/LC\(_{50}\)=ATE in the additivity formula CLP Annex I, 3.1.3.6.1. If the assessment using (Q)SARs gives a more general result a cATpE acc. to Table 3.1.2 may be derived. It has to be emphasised that these approaches generally require substantial technical information, and expert judgement, to reliably estimate acute toxicity.

Annex I: 3.1.3.6.2.2. In the event that a component without any useable information for classification is used in a mixture at a concentration of 1% or greater, it is concluded that the mixture cannot be attributed a definitive acute toxicity estimate. In this situation the mixture shall...
be classified based on the known components only, with the additional statement in the label and the SDS that ‘x percent of the mixture consists of component(s) of unknown toxicity’.

Further guidance on how to apply this provision is given in section 3.1.3.3.5.

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

$$\frac{100 - \sum C_{\text{unknown}} \text{if } > 10\%}{\text{ATE}_{\text{mix}}} = \sum \frac{C_i}{\text{ATE}_i}$$

3.1.3.3.5 Components that should be taken into account for the purpose of classification

Annex I: 3.1.3.3.(a) the ‘relevant ingredients’ of a mixture are those which are present in concentrations of 1 % (w/w for solids, liquids, dusts, mists and vapours and v/v for gases) or greater, unless there is a reason to suspect that an ingredient present at a concentration of less than 1 % is still relevant for classifying the mixture for acute toxicity (see Table 1.1).

When a mixture contains a “relevant” ingredient (i.e. constituting ≥ 1%; Annex I, 3.1.3.3 (a)) for which there is inadequate acute toxicity data then the mixture must be classified on the basis of the ingredients with known toxicity, with an additional statement to indicate that the mixture contains ingredients of unknown toxicity (CLP Annex I, 3.1.3.6.2.2). The determination of the classification depends on what proportion of the mixture such ingredients of unknown toxicity constitute. If these ingredients constitute ≤10% of the total mixture, the additivity formula in 3.6.1.1 may be used. However, in cases where these ingredients constitute over 10%, a modified additivity formula, which adjusts for the presence of a significant proportion of ingredients of unknown toxicity, is used. This reflects the greater uncertainty as to the true toxicity of the mixture (CLP Annex I, 3.3.3.2.4).

### Annex I: Table 1.1

<table>
<thead>
<tr>
<th>Hazard class</th>
<th>Generic cut-off values to be taken into account</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Toxicity:</td>
<td></td>
</tr>
<tr>
<td>Category 1-3</td>
<td>0.1 %</td>
</tr>
<tr>
<td>Category 4</td>
<td>1 %</td>
</tr>
</tbody>
</table>

**Note:** Generic cut-off values are in weight percentages except for gaseous mixtures where they are in volume percentage.

As indicated in CLP Annex I, Table 1.1, when components are present in low concentrations they do not need to be taken into account when determining the classification of the mixture, according to the approaches detailed in CLP Annex I, 3.1.3.6.1 and 3.1.6.2.3 (see section 3.1.6.3.1, Example 11). Accordingly, all components classified in Categories 1-3 at a concentration <0.1 % and Category 4 <1% are not taken into account. Similarly unknown ingredients present at <1% are not taken into account.

3.1.3.4 Generic concentration limits for substances triggering classification of mixtures

103
Generic concentration limits as such are not applicable for acute toxicity classification; therefore specific concentration limits are also not applicable (see section 3.1.2.5).

Nevertheless, according to CLP Annex VI, 1.2.1 the classification for entries with the reference * in the column specific concentration limits is of special concern; the * means that those entries have an SCL in CLP Annex VI, Table 3.2 originating from Annex I to DSD. Therefore when assessing a mixture according to the procedure set out in CLP Annex I, a thorough search for the data (animal, human experience or other information) which had been the basis for the respective SCL in Annex I of DSD is indicated as being necessary. The assessment shall take all available information into account using a weight of evidence approach and expert judgement with special emphasis on possibly available human experience or information. These validated data will then be used in the additivity formula in Annex I, 3.1.3.6.1 as ATEs or cATpEs (Annex I, Table 3.1.2).

### 3.1.3.5 Decision on classification

The assessment on classification has to be performed with respect to the relevant routes of exposure (oral, dermal, inhalation) on the basis of all adequate reliable data. If a classification is warranted in different categories for different routes, then the mixture has to be classified in the more severe category, the other routes fulfilling the criteria for a classification are taken care by allocating the corresponding hazard statement(s) and appropriate precautionary statement(s). If for example, a mixture fulfils the criteria for oral toxicity Category 3 and for inhalation Category 2, then the mixture will be classified in Category 2, the corresponding hazard statements for both inhalation Category 2 and oral Category 3 will be assigned.
3.1.3.6 Decision logic

The decision logic is provided as additional guidance. It is strongly recommended that the person responsible for classification, study the criteria for classification before and during use of the decision logic.

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

\[
\frac{100}{\text{ATE}_{\text{mix}}} = \sum \frac{C_i}{\text{ATE}_i}
\]

where:

- \( C_i \) = concentration of ingredient \( i \)
- \( i \) = the individual ingredient from 1 to \( n \)
- \( n \) = the number of ingredients

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 \( \leq 10\% \)?

YES

Apply the acute toxicity estimate calculation (i.e. when the total concentration of ingredients with unknown acute toxicity is > 10%):

\[
100 - \sum \frac{C_{\text{unknown}} \text{if } > 10\%}{\text{ATE}_{\text{mix}}} = \sum \frac{C_i}{n \text{ ATE}_i}
\]

NO

ATE\text{ mix} to Decision logic in 3.1.2.6

Deleted: 3.1.2.6

Formatted: Font: 10 pt, Highlight

Deleted: 3.1.2.6

Formatted: Font: 11 pt, Highlight
3.1.4 Hazard communication in form of labelling for acute toxicity

3.1.4.1 Pictograms, signal words, hazard statements and precautionary statements

<table>
<thead>
<tr>
<th>Annex I: Table 3.1.3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute toxicity label elements</strong></td>
<td></td>
</tr>
<tr>
<td>Classification</td>
<td>Category 1</td>
</tr>
<tr>
<td>GHS Pictograms</td>
<td><img src="image" alt="Picture" /></td>
</tr>
<tr>
<td>Signal Word</td>
<td>Danger</td>
</tr>
<tr>
<td>Hazard Statement:</td>
<td></td>
</tr>
<tr>
<td>– Oral</td>
<td>H300: Fatal if swallowed</td>
</tr>
<tr>
<td>– Dermal</td>
<td>H310: Fatal in contact with skin</td>
</tr>
<tr>
<td>– Inhalation (see Note 1)</td>
<td>H330: Fatal if inhaled</td>
</tr>
<tr>
<td>Precautionary Statement Prevention (oral)</td>
<td>P264</td>
</tr>
<tr>
<td>Precautionary Statement Response (oral)</td>
<td>P262 + P310</td>
</tr>
<tr>
<td>Precautionary Statement Storage (oral)</td>
<td>P405</td>
</tr>
<tr>
<td>Precautionary Statement Prevention (dermal)</td>
<td>P262</td>
</tr>
<tr>
<td>Precautionary Statement</td>
<td>P302 + P350</td>
</tr>
</tbody>
</table>
Note 1
In addition to classification for inhalation toxicity, if data are available that indicates that the mechanism of toxicity is corrosivity, the substance or mixture shall also be labelled as EUH071: ‘corrosive to the respiratory tract’ — see advice at 3.1.2.3.3. In addition to an appropriate acute toxicity pictogram, a corrosivity pictogram (used for skin and eye corrosivity) may be added together with the statement ‘corrosive to the respiratory tract’.

Note 2
In the event that an ingredient without any useable information at all is used in a mixture at a concentration of 1 % or greater, the mixture shall be labelled with the additional statement that ‘x percent of the mixture consists of ingredient(s) of unknown toxicity’ — see advice at 3.1.3.6.2.2.

EUH071 can also be applied to inhaled corrosive substances not tested for acute inhalation toxicity according to CLP Annex II, Section 1.2.6.

If a mixture fulfils the classification criteria with respect to different routes the classification will be based on the more severe one. This and other routes have then to be addressed with the respective hazard statements to CLP Annex I, Table 3.1.3.

### Additional labelling provisions

**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 of 1% or greater, it is concluded that the mixture cannot be attributed a definitive acute toxicity estimate. In this situation the mixture shall be classified based on the known ingredients only, with the additional statement that x percent of the mixture consists of ingredient(s) of unknown toxicity.
be classified based on the known components only, with the additional statement in the label and the SDS that ‘x percent of the mixture consists of component(s) of unknown toxicity’.

Although there is no standardised statement with respect to the requirement of CLP Annex I, 3.1.3.6.2.2, the following statement would be appropriate, specifying that the information gap refers only to acute toxicity: “This mixture contains x % of component(s) of unknown acute (…….*) toxicity (* to be specified on a case by case basis if appropriate: oral, dermal, inhalation)”, to be included in the section for supplemental information on the label.

Corrosivity:

**Annex I: 3.1.2.3.3.** In addition to classification for inhalation toxicity, if data are available that indicates that the mechanism of toxicity was corrosivity, the substance or mixture shall also be labelled as ‘corrosive to the respiratory tract’ (see note 1 in 3.1.4.1). Corrosion of the respiratory tract is defined by destruction of the respiratory tract tissue after a single, limited period of exposure analogous to skin corrosion; this includes destruction of the mucosa. The corrosivity evaluation can be based on expert judgment using such evidence as: human and animal experience, existing (*in vitro*) data, pH values, information from similar substances or any other pertinent data.

In addition to the application of the classification for acute inhalation toxicity, the mixture shall also be labelled as EUH071 where data are available which indicate that the mode of toxic action was corrosivity (see Note 1 to Table 3.1.3). Such information can be derived from data which warrant classification as corrosive according to the hazard skin corrosion/irritation (see section 3.2). In this case the substance or mixture has to be classified and labelled for skin corrosion with the pictogram for corrosivity, GHS05, hazard statement H314 and also labelling with EUH071 (for criteria, see CLP Annex II) is required.

Corrosive mixtures may be acutely toxic after inhalation to a varying degree, although this is only occasionally proved by testing. In case no acute inhalation study is available for a corrosive mixture, it is strongly recommended to apply the precautionary statement P260: Do not breathe dust/fume/gas/mist/vapours/spray.

Toxic by eye contact:

In cases where a substance or mixture has shown clear signs of severe systemic toxicity or mortality in an eye irritation study a supplemental labelling phrase EUH070 “Toxic by eye contact” is required. This additional labelling, based on relevant data, is independent of any classification in an acute toxicity category.

### 3.1.5 Re-classification of substances and mixtures classified for acute toxicity according to DSD and DPD

#### 3.1.5.1 Is direct “translation” of classification and labelling possible?

The CLP allows a minimum classification of substances and mixtures classified according to DSD and DPD, by use of a translation table in Annex VII (Table 1.1) into the corresponding classification under CLP. For more details see section 1.7 on the application of Annex VII.

#### 3.1.5.2 Re-evaluation of data

If there is new information which might be relevant with respect to classification a re-evaluation has to be performed. Classified gases should be re-evaluated because the guidance values changed from general guidance values in mg/l for aerosols, vapours and gases to a specific guidance value for gases in ppm. Often the values for classification are higher...
according to CLP compared to DSD which may require a re-evaluation on a case by case basis.

3.1.6 Examples of classification for acute toxicity

*Remark:* The classification proposals for the examples refer only to Acute Toxicity.

3.1.6.1 Examples of substances fulfilling the criteria for classification

3.1.6.1.1 Example 1: Methanol

<table>
<thead>
<tr>
<th>Application</th>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Data</td>
<td>Classification</td>
</tr>
<tr>
<td>Available information</td>
<td>Animal data: Oral LD&lt;sub&gt;50&lt;/sub&gt; rat ≥ 5000 mg/kg</td>
</tr>
<tr>
<td>Human experience: Methanol is known to cause lethal intoxications in humans (mostly via ingestion) in relatively low doses: “…minimal lethal dose in the absence of medical treatment is between 300 and 1000 mg/kg” (IPCS, Environmental Health Criteria 196, Methanol, WHO, 1997)</td>
<td>Category 3</td>
</tr>
<tr>
<td>Remarks</td>
<td>Test data in rats from mixtures containing methanol should not be used directly in additivity formula.</td>
</tr>
</tbody>
</table>

3.1.6.1.2 Example 2: N,N-Dimethylaniline

<table>
<thead>
<tr>
<th>Application</th>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Data</td>
<td>Classification</td>
</tr>
<tr>
<td>Available information</td>
<td>Animal data: Acute dermal toxicity: LD&lt;sub&gt;50&lt;/sub&gt; values &gt; 1690 mg/kg bw rabbit.</td>
</tr>
<tr>
<td>Human experience: Broad human experience, reported in many case reports, demonstrating death from MetHB following relatively</td>
<td>Category 3 (oral, dermal, inhalation)</td>
</tr>
</tbody>
</table>

[94x731]Guidance to Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of substances and mixtures
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.

suggests lower sensitivity to MetHB formation than humans which is consistent with what is known from other rabbit tests with substances known to induce MetHB in humans. The rabbit data are therefore not considered to be adequate for acute toxicity classification. Therefore the human data on this and structurally related substances are used to give a converted Acute Toxicity point Estimate (cATpE) according to Table 3.1.2 for Category 3; e.g. cATpE dermal = 300 mg/kgbw, which is then falling in a higher category than the rabbit data.

<table>
<thead>
<tr>
<th>Remarks</th>
</tr>
</thead>
</table>

1. **3.1.6.1.3 Example 3**

<table>
<thead>
<tr>
<th>Application</th>
<th>No exact LD&lt;sub&gt;50&lt;/sub&gt; value available. Expert judgement needed.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Data</td>
<td>Classification Rationale</td>
</tr>
<tr>
<td>Available information</td>
<td>Corrosive volatile liquid.</td>
</tr>
<tr>
<td>Animal data:</td>
<td></td>
</tr>
<tr>
<td>In a GLP-compliant acute oral toxicity study in rats, the following results were observed:</td>
<td></td>
</tr>
<tr>
<td>At a test dose of 200 mg/kg bw: no mortality, only transient symptoms and no necropsy findings.</td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>Category 4</td>
<td>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&lt;sub&gt;50&lt;/sub&gt; is &gt; 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.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Remarks</th>
<th>Labelling: C (pictogram optional)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Additional Hazard statement: EUH071 Corrosive to the respiratory tract</td>
</tr>
</tbody>
</table>
### Application
Use of non-standard-guideline test data.

<table>
<thead>
<tr>
<th>Test Data</th>
<th>Classification</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Available information</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Animal data:**
A study to evaluate the acute dermal (percutaneous) toxicity was performed in rabbits. The following test data results were reported:
- At the dose level of 50 mg/kg bw: no mortality was observed
- At 200 mg/kg bw: 100% mortality

Therefore, LD$_{50}$ was estimated to be between 50mg/kg bw and 200mg/kg bw

**Category 2**

**Rationale for classification:**
Since the dermal LD$_{50}$ is above 50 mg/kg bw and less than 200 mg/kg bw, Category 2 classification is warranted (see Table 3.1.2)

### Remarks

#### 3.1.6.1.5 Example 5
Use of Table 3.1.1 and experimentally obtained LC$_{50}$ value

<table>
<thead>
<tr>
<th>Test Data</th>
<th>Classification</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Available information</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Animal data:**
A GLP-compliant test for acute inhalation toxicity (gaseous form) was performed in accordance with test guideline 403 in rats. The following LC$_{50}$ was calculated: LC$_{50}$: 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 (Table 3.1.1), this value corresponds to Category 4. Therefore Category 4 Acute Inhalation Toxicity classification is warranted.

### Remarks

#### 3.1.6.1.6 Example 6
Time extrapolation; Note (b) in Table 3.1.1; Haber’s law

<table>
<thead>
<tr>
<th>Test Data</th>
<th>Classification</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Available information</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Animal data:**
The acute inhalation toxicity was studied in rats in a GLP-compliant study performed in

**Category 3**

**The classification criteria for acute inhalation toxicity in Table 3.1.1 refer to a 4h exposure time; therefore to classify a substance, existing inhalation toxicity data**
principle according to test guideline 403, but with respect for transport only with 1-h exposure. The \( L_{C_50} \) (1-h) of 3 mg/l was calculated. generated from 1-hour exposure should be converted accordingly: \( L_{C_50} \) values with 1h have to be converted by dividing by 4 (Haber’s rule/law, dusts and mists) \( L_{C_50} \) (4-h) = \( L_{C_50} \) (1-h) : 4 = (3mg/l : 4) = 0.75 mg/l, thus Category 3 classification is warranted according to Table 3.1.1.

<table>
<thead>
<tr>
<th>Remarks</th>
</tr>
</thead>
</table>

**3.1.6.1.7 Example 7: 2,3-Dichloropropene**

**Application**  
Discrimination from STOT-SE

<table>
<thead>
<tr>
<th>Available information</th>
<th>Test Data</th>
<th>Classification</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal data:</td>
<td></td>
<td>Category 3 oral and Category 3 inhalation</td>
<td></td>
</tr>
<tr>
<td>- Oral ( L_{D_{50}} ), rat 250-320 mg/kg (assumption: results from different tests; lowest ( L_{D_{50}} ) is valid)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Inhalation ( L_{C_{50}} ), rat 2.3 mg/l/4h (vapour)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observations: extensive liver and kidney damage following oral and inhalation exposure to lethal doses (insufficient information)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Remarks</th>
</tr>
</thead>
</table>

The substance is classified for acute toxicity and not for STOT-SE, since the observed organ toxicity is clearly the cause of the lethality.

**3.1.6.1.8 Example 8**

**Application**  
Route-to-route extrapolation: oral to inhalation (Section 3.1.3.3.4). Expert judgement.

<table>
<thead>
<tr>
<th>Available information</th>
<th>Test Data</th>
<th>Extrapolated inhalation ATE/CATpE</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal data:</td>
<td></td>
<td></td>
<td>a) Using the extrapolation formula 1mg/kgbw = 0.0052 mg/l/4h: 250 x 0.0052 mg/l/4h = 1.3 mg/l/4h ( \rightarrow ) Category 2</td>
</tr>
<tr>
<td>( L_{D_{50}} ), oral rat: 250 mg/kg bw (Category 3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) No specific kinetic information</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b) Robust kinetic information allows the conclusion that only 50% is absorbed due to</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5 mg/l/4h (cATpE)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.6 mg/l/4h (ATE)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
an exhalation rate of 50 \%.

b) Based on the 50\% inhalation absorption rate the equivalent ATE would be 2.6 (2 \times 1.3) \rightarrow Category 3 according to Table 3.1.2

Remarks: Robust kinetic and other information would allow the use of directly derived ATEs in the additivity formulae by expert judgement.

### 3.1.6.1.9 Example 9

<table>
<thead>
<tr>
<th>Application</th>
<th>Route-to-route extrapolation: oral to dermal (Section 3.1.3.3.4). Expert judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Data</td>
<td>Extrapolated dermal ATE/cATpE</td>
</tr>
<tr>
<td>Available information</td>
<td>Animal data:</td>
</tr>
<tr>
<td></td>
<td>LD_{50} rat oral: 270 mg/kg bw; 100 % oral absorption assumed</td>
</tr>
<tr>
<td></td>
<td>a) Assumed dermal absorption rate: 100%</td>
</tr>
<tr>
<td></td>
<td>b) Dermal absorption rate based on robust kinetic/SAR information: 25%</td>
</tr>
<tr>
<td>Remarks</td>
<td>Robust kinetic and other information would allow the use of directly derived ATEs in the additivity formulae by expert judgement</td>
</tr>
</tbody>
</table>

### 3.1.6.2 Examples of substances not fulfilling the criteria for classification

#### 3.1.6.2.1 Example 10

<table>
<thead>
<tr>
<th>Application</th>
<th>Available data are of different quality. Expert judgement. WoE:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Data</td>
<td>Classification</td>
</tr>
<tr>
<td>Available information</td>
<td>A liquid</td>
</tr>
</tbody>
</table>
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 LC₅₀ 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)

The LC₅₀ = ATE > 20 mg/l/4h. The criteria for Category 4 are not fulfilled.

### Remarks

1. Classification via application of substance criteria is not possible since acute toxicity test data was not provide for the complete mixture (Annex I, 3.1.3.4).
2. Classification via the application of bridging principles is not possible since data on a similar mixture was not provided (Annex I, 3.1.3.5.1).
3. Classification based on ingredient data for the mixture can be considered (Annex I, 3.1.3.6).
4. Applying the “relevant ingredients” concept from Annex I, 3.1.3.3 a) means that Ingredient 4 is excluded from the \( \text{ATE}_{\text{max}} \) calculation since its concentration is < 1%. The same reasoning cannot apply to Ingredient 5, though its concentration is below the “relevant ingredients” threshold of 1% but it is higher than the cut-off value of 0.1% for a Category 2 ingredient in Annex I, Table 1.1.

5. The total concentration of ingredients with unknown acute toxicity (i.e., Ingredient 2) is 92%; therefore, the \( \text{ATE}_{\text{max}} \) equation in Annex I, 3.1.3.6.2.3 must be used. This calculation corrects for relevant ingredients with unknown acute toxicity above 10% of the mixture.

6. Ingredients 1, 3 and 5 are included in the \( \text{ATE}_{\text{max}} \) calculation because they have data that fall within a CLP acute toxicity category, Annex I, 3.1.3.6.1 (a).

7. Applying the guidance in Note (a) to Table 3.1.1 results in using the actual \( \text{LD}_{50} \) data for Ingredients 1, 3 & 5 in the \( \text{ATE}_{\text{max}} \) calculation since data is available.

**Additional Labelling:** “The mixture contains 92% of ingredients of unknown acute oral toxicity”

### Example 12 a

<table>
<thead>
<tr>
<th>Application</th>
<th>Different phases in inhalation exposure. Extrapolation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test Data</strong></td>
<td><strong>Classification</strong></td>
</tr>
<tr>
<td><strong>Available information</strong></td>
<td>Use /exposure as aerosol (mist)</td>
</tr>
<tr>
<td>Animal data (rat): ( \text{LC}_{50} ) (mg/l/4h)</td>
<td></td>
</tr>
<tr>
<td>Ingredient 1 solid (6%)</td>
<td></td>
</tr>
<tr>
<td>Ingredient 2 solid (11%)</td>
<td>0.6</td>
</tr>
<tr>
<td>Ingredient 3 solid (10%)</td>
<td>6 (dust)</td>
</tr>
<tr>
<td>Ingredient 4 liquid (40%)</td>
<td>11 (vapour)</td>
</tr>
<tr>
<td>Ingredient 5 (33%)</td>
<td>-</td>
</tr>
</tbody>
</table>

**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/\( \text{ATE}_{\text{max}} \) = 6/1.5+11/0.6+40/1.5+0 = 49
\( \Rightarrow \text{ATE}_{\text{max}} = 2.04 \text{ mg/l/4h} \) \( \Rightarrow \) Category 4

Conclusion: The mixture Example 12a) has to be classified formally in Category 4 with respect to inhalation toxicity. It is notable that this classification is only derived from the calculation for the aerosol phase, not for the vapour phase.

3.1.6.4 Examples of mixtures not fulfilling the criteria for classification

3.1.6.4.1 Example 12b

<table>
<thead>
<tr>
<th>Application</th>
<th>Different phases in inhalation exposure. Extrapolation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Data</td>
<td>Classification</td>
</tr>
<tr>
<td>Available information</td>
<td>Use / exposure as vapour</td>
</tr>
<tr>
<td>Animal data (rat): ( \text{LC}_{50} ) (mg/l/4h)</td>
<td></td>
</tr>
<tr>
<td>Ingredient 1 solid (6%)</td>
<td></td>
</tr>
<tr>
<td>Ingredient 2 solid (11%)</td>
<td>0.6 (dust)</td>
</tr>
<tr>
<td>Ingredient 3 solid (10%)</td>
<td>6 (dust)</td>
</tr>
<tr>
<td>Ingredient 4 liquid (40%)</td>
<td>11 (vapour)</td>
</tr>
<tr>
<td>Ingredient 5 (33%)</td>
<td>-</td>
</tr>
</tbody>
</table>

Remarks

**Classification:** NC

Inhalation is appropriate route since one hazardous ingredient with appreciable vapour pressure.

No test data on the whole mixture.

Bridging principles not applicable since no test data on similar mixtures available.

Classification is therefore based on ingredients.

Use additivity formula in Annex I, 3.1.3.6.1 as information is available for all ingredients.

There is no contributions from ingredients 1 and 2 in the formula since the diluted solid ingredients do not sublime, and thus are not present in the vapour phase; ingredient 3 is in addition not classified in any acute toxicity category. Ingredient 5 does not show acute toxicity.

\[ 100/\text{ATE}_{\text{mix}} = 0 + 0 + 0 + 40/11 + 0 = 3.64 \Rightarrow \text{ATE}_{\text{mix}} = 27.5 \]

27.5 mg/l/4h is above the upper generic concentration limit for vapour \( \Rightarrow \) NC

3.1.7 References
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

CLP Article 7(3) specifies that testing on humans is not allowed for the purposes of CLP; however it does acknowledge that existing data obtained from other sources can be used for classification purposes.

Human data may be retrieved from a number of sources, e.g. epidemiological studies, clinical studies, well-documented case reports, poison information units and accident databases or occupational experience.

In this context the quality and relevance of existing human data for hazard assessment should be critically reviewed. There may be a significant level of uncertainty in human data due to poor reporting and lack of specific information on exposure. Diagnosis confirmed by expert physicians may be missing. Confounding factors may not have been accounted for. Small group sizes may flaw the statistical strength of evidence. Many other factors may compromise the validity of human data. In clinical studies the selection of individuals for the test and the control groups must be carefully considered. A critical review of the value of human studies is provided in IR/CSA, section R.4.3.3 and more specific considerations for skin corrosion/irritation are given in IR/CSA, section R.7.2.4.2.

Data indicates that human skin is, in most cases, less sensitive than rabbits (ECETOC, 2002).

3.2.2.2 Identification of non human data

Non human data include physico-chemical properties, results from (Q)SARs and expert systems, and results from in vitro and in vivo tests. Available skin corrosion/irritation
information on substances may include existing data generated by the test methods in the Test
Methods Regulation or by methods based on internationally recognised scientific principles.
Several of the following non-testing methods and in vitro methods have been validated
against the DSD criteria but not against CLP criteria for classification. As the criteria differ
slightly between DSD and CLP, it should be checked whether the method is sufficiently
validated for classification according to CLP.

3.2.2.1.2.1 Consideration of physico-chemical properties
Substances with oxidising properties can give rise to highly exothermic reactions in contact
with other substances and human tissue. High temperatures thus generated may
damage/destroy biological materials. This applies, for example, to organic peroxides, which
can be assumed to be skin irritants, unless evidence suggests otherwise (IR/CSA Section
R.7.2.3.1).
For a hydro peroxide classification as Skin Corrosive Category 1B should be considered,
whereas Skin Irritation Category 2 should be considered for peroxides. Appropriate evidence
must be provided in order to consider non-classification of substances with oxidising
properties.

3.2.2.1.2.2 Non-testing methods: (Q)SARs and expert systems
Non-testing methods such as (Q)SARs and expert systems may be considered on a case-by-case basis. (Q)SAR systems that also account for skin effects are for example TOPKAT,
TerraQSAR, and the BfR-DSS. These systems go beyond the structural similarity
considerations encompassing also other parameters such as topology, geometry and surface
properties. For full guidance consult IR/CSA sections R.6 and R.7.2.3.1.
The BfR-DSS has been recommended in IR/CSA section R.7.2.4 since there is no other
model that sufficiently describes the absence of effects. The BfR rules to predict skin
irritation and corrosion have been integrated in the internet tool “toxtree”,
Conclusion on no classification can be made if the (Q)SAR or expert system has been shown
to adequately predict the absence of the classified effect (IR/CSA Figure R.7.2-2, footnote f).
Since a formal adoption procedure for those non-testing methods is not foreseen and no
formal validation process is in place, appropriate documentation is very important. In order to
achieve acceptance under REACH the documentation must conform the so-called QSAR
Model Reporting Format (QMRF). For more details consult the IR/CSA section R.6.1.

3.2.2.1.2.3 Testing-methods: pH and acid/alkaline reserve

Annex I: 3.2.2.2. Likewise, pH extremes like ≤ 2 and ≥ 11,5 may indicate the potential to cause
skin effects, especially when buffering capacity is known, although the correlation is not perfect.
Generally, such substances are expected to produce significant effects on the skin. If consideration
of alkali/acid reserve suggests the substance may not be corrosive despite the low or high pH value,
then further testing shall be carried out to confirm this, preferably by use of an appropriate
validated in vitro test.
The acid/alkaline reserve is a measure of the buffering capacity of chemicals. For details of
the methodology, see Young et al, 1988, and Young and How, 1994.
3.2.2.1.2.4 Testing methods: in vitro methods

Table R.7.2-2 in IR/CSA lists the status of validation and regulatory acceptance for in vitro test methods for skin corrosion and skin irritation.

In vitro methods for skin corrosion

In recent years, the OECD has accepted new guidelines for in vitro skin corrosion tests as alternatives for the standard in vivo rabbit skin test (OECD TG 404). Accepted in vitro tests for skin corrosivity are found in the Test Methods Regulation (TM) and in OECD Test Guidelines (TG):

- The transcutaneous electrical resistance (TER; using rat skin) test (TM B.40; OECD TG 430)
- Human skin model (HSM) tests (TM B.40 bis; OECD TG 431)
- The in vitro membrane barrier test method (OECD TG 435)

Positive in vitro results do not generally require further testing and can be used for classification. Negative in vitro corrosivity responses must be subject to further evaluation.

Whereas the TER test and the human skin models at present only allow a classification into Skin Corrosion Category 1A, the membrane barrier test allows for the differentiation into the three Categories 1A, 1B and 1C. The applicability domain of the three tests outlined here (TER-, HSM- and membrane barrier test) with regard to the alkalinity and acidity of the tested substance should be carefully considered to decide which data are most appropriate for the actual substance.

The TER and the HSM assays have been validated for the classification of skin corrosion. The results of this validation are well founded, because the CLP criteria for skin corrosion are identical with the ones referred to in the past validation study.

The membrane barrier method has been endorsed as a scientifically validated test for a limited range of substances - mainly acids, bases and their derivatives (ECVAM, 2000).

In vitro methods for skin irritation

Three in vitro skin irritation test methods based on reconstructed human epidermis (RHE) technology have been accepted in July 2010 by the OECD (TG 439) and have been included in the EU Test Method Regulation (TM B.46, included in 2009) as test methods able to reliably distinguish non-irritants from irritant substances (CLP Skin Irrit. 2). The three assays are the EpiSkin™, the modified EpiDerm™ and the SkinEthic RHE™ test method. The EpiSkin and EpiDerm assays have undergone formal ECVAM validation from 2003 – 2007 (Spielmann et al, 2007). In 2007 the EpiSkin was considered valid by ESAC as a full replacement test (ECVAM/ESAC, 2007). Originally validated for use in a testing strategy for the identification of positives only (ECVAM/ESAC, 2007), the EpiDerm test methods protocol was subsequently modified. In November 2008, also the modified EpiDerm and the SkinEthic assay were found reliable and relevant test methods capable of distinguishing non-irritants from irritants and may therefore fully replace the traditional skin irritation test (ECVAM/ESAC, 2008). It should be noted that conclusions on the applicability domain of the three methods rest mainly on the optimisation and validation data set. All three methods are valid for the classification of substances for skin irritancy according to CLP criteria (ECVAM/ESAC, 2009).

The Skin integrity function test (SIFT) is also listed in IR/CSA, Table R.7.2-2. This test has only undergone prevalidation so far and the applicability domain is limited to surfactants.
Positive data from SIFT may be used in a weight of evidence approach to consider classification for irritation, while negative data are not conclusive for a non-classification.

**Other suitable in vitro methods**

Positive data from other suitable *in vitro* methods may be used in a weight of evidence approach to determine classification as irritant, while negative data are not conclusive for a non-classification. In this context 'suitable' means sufficiently well developed according to internationally agreed development criteria (see REACH Annex XI, section 1.4).

### 3.2.2.1.2.5 Testing methods: *In vivo* data

The *in vivo* test in rabbits according to TM B.4 (OECD TG 404) is the standard test for the hazard assessment and classification required under the REACH Annex VIII provisions (10 tons per year and more). However it should be noted that according to REACH (Annexes VII to X) *in vivo* testing of corrosive substances at concentration/dose levels causing corrosivity shall be avoided.

Until 1987 the OECD standard protocol used occlusive patching for the application of the test substance, which resulted in more rigorous test conditions compared to the semi-occlusive patching used today. Especially in borderline cases of classification the method of application should be accounted for in the evaluation of effects.

Studies performed according to the USA Federal Hazardous Substances Act (US-FHSA) may be used for classification purposes although they deviate in their study protocol from the OECD TG 404. They do not include a 48-hour observation time and involve a 24-hour test material exposure followed by observations at 24 hour and 72 hours. Moreover, the test material is patched both on abraded and on intact skin of six rabbits. Studies usually are terminated after 72 hours. In case of no or minimal responses persisting until the 72 hours time points it is feasible to use such data for classification by calculating the mean values for erythema and oedema on the basis of only the 24 and 72 hours time points. Calculation of mean scores should normally be restricted to the results obtained from intact skin. In case of pronounced responses at the 72 hours time point an expert judgement is needed as to whether the data is appropriate for classification.

Data on skin effects on animals may be available from tests that were conducted for other primary purposes than the investigation of skin corrosion / irritation. Such information may be gained from acute or repeated dose dermal toxicity studies on rabbits or rats (TM B.3, OECD TG 402; TM B.9, OECD TG 410), guinea pig skin sensitisation studies (TM B.6, OECD guideline 406) and from irritation studies in hairless mice.

### 3.2.2.2 Classification criteria

**Annex I: 3.2.2.6. Corrosion**

3.2.2.6.1. On the basis of the results of animal testing a substance is classified as corrosive, as shown in Table 3.2.1. A corrosive substance is a substance that produces destruction of skin tissue, namely, visible necrosis through the epidermis and into the dermis, in at least 1 tested animal after exposure up to a 4 hour duration. Corrosive reactions are typified by ulcers, bleeding, bloody scabs and, by the end of observation at 14 days, by discoloration due to blanching of the skin, complete areas of alopecia and scars. Histopathology shall be considered to discern questionable lesions.

3.2.2.6.2. Three subcategories are provided within the corrosive category: subcategory 1A – where responses are noted following up to 3 minutes exposure and up to 1 hour observation; subcategory 1B – where responses are described following exposure between 3 minutes and 1 hour and observations up to 14 days; and subcategory 1C – where responses occur after exposures between 1
Guidance to Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of substances and mixtures

hour and 4 hours and observations up to 14 days.

3.2.2.6.3. The use of human data is discussed in paragraphs 3.2.2.1 and 3.2.2.4 and also in paragraphs 1.1.1.3, 1.1.1.4 and 1.1.1.5.

Table 3.2.1
Skin Corrosive category and subcategories

<table>
<thead>
<tr>
<th>Corrosive subcategory</th>
<th>Exposure</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1: Corrosive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1A</td>
<td>≤ 3 minutes</td>
<td>≤ 1 hour</td>
</tr>
<tr>
<td>1B</td>
<td>&gt; 3 minutes - ≤ 1 hour</td>
<td>≤ 14 days</td>
</tr>
<tr>
<td>1C</td>
<td>&gt; 1 hour - ≤ 4 hours</td>
<td>≤ 14 days</td>
</tr>
</tbody>
</table>

3.2.2.7. Irritation

3.2.2.7.1. Using the results of animal testing a single irritant category (Category 2) is presented in Table 3.2.2. The use of human data is discussed in paragraphs 3.2.2.1 and 3.2.2.4 and also in paragraphs 1.1.1.3, 1.1.1.4 and 1.1.1.5. The major criterion for the irritant category is that at least 2 of 3 tested animals have a mean score of ≥2,3 - ≤4,0.

Table 3.2.2
Skin irritation category

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 2: Irritant</td>
<td></td>
</tr>
<tr>
<td>(1) Mean value of ≥2,3 - ≤4,0 for erythema/eschar or for oedema in at least 2 of 3 tested animals from gradings at 24, 48 and 72 hours after patch removal or, if reactions are delayed, from grades on 3 consecutive days after the onset of skin reactions; or</td>
<td></td>
</tr>
<tr>
<td>(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</td>
<td></td>
</tr>
<tr>
<td>(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.</td>
<td></td>
</tr>
</tbody>
</table>

3.2.2.8. Comments on responses obtained in skin irritation tests in animals

3.2.2.8.1. Animal irritant responses within a test can be quite variable, as they are with corrosion. The major criterion for classification of a substance as irritant to skin, as shown in paragraph 3.2.2.7.1, is the mean value of the scores for either erythema/eschar or oedema calculated in at least 2 of 3 tested animals. A separate irritant criterion accommodates cases when there is a significant irritant response but less than the mean score criterion for a positive test. For example, a test material might be designated as an irritant if at least 1 of 3 tested animals shows a very elevated mean score throughout the study, including lesions persisting at the end of an observation period of normally 14 days. Other responses could also fulfil this criterion. However, it should be ascertained that the responses are the result of chemical exposure.

3.2.2.8.2. Reversibility of skin lesions is another consideration in evaluating irritant responses. When inflammation persists to the end of the observation period in 2 or more test animals, taking into consideration alopecia (limited area), hyperkeratosis, hyperplasia and scaling, then a material shall be considered to be an irritant.

* Note: In Table 3.2.1 it should read "Corrosive in ≥1 of 3 animals". There is a misprint in the BG, CS, ET, EL, EN, LV, PT, and RO versions of CLP published in the Official Journal 31.12.2008.
3.2.2.3 Evaluation of hazard information

Annex I: 3.2.2.4.

Although information might be gained from the evaluation of single parameters within a tier (see paragraph 3.2.2.5), e.g. caustic alkalis with extreme pH shall be considered as skin corrosives, there is merit in considering the totality of existing information and making an overall weight of evidence determination. This is especially true when there is information available on some but not all parameters. Generally, primary emphasis shall be placed upon existing human experience and data, followed by animal experience and testing data, followed by other sources of information, but case-by-case determinations are necessary.

3.2.2.5. A tiered approach to the evaluation of initial information shall be considered, where applicable, recognising that all elements may not be relevant in certain cases.

3.2.2.3.1 Evaluation of human data

The usefulness of human data for classification purposes will depend on the extent to which the effect, and its magnitude, can be reliably attributed to the substance of interest. Further guidance on evaluation of human data for skin corrosion/irritation can be found in IR/CSA Section R.7.2.4.2.

The criteria in Annex I, Table 3.2.2 are not applicable to human data.

3.2.2.3.2 Evaluation of non human data

3.2.2.3.2.1 In vitro data

In evaluation of data from in vitro tests the applicability domain has to be taken into account. The in vitro membrane barrier test method e.g. is mainly applicable for acids and bases and is not applicable for solutions with pH values between 4.5 and 8.

3.2.2.3.2.2 In vivo data

Tests in albino rabbits (OECD TG 404)

Evaluation criteria for local effects on the skin are severity of the damage and reversibility.

For the severity of damage the responses are evaluated according to the Draize score ranking from “0” (no response”) up to “4” (severe response”). Evaluation takes place separately for erythema and oedema.

Reversibility of skin lesions is the other decisive factor in evaluating responses in the animal test. The criteria are fulfilled if, for

- corrosion
  - the full thickness of the skin is destroyed resulting in ulcers, bleeding, bloody scabs discoloration, complete areas of alopecia and scars. In questionable cases a pathologist should be consulted. One animal showing this response at the end of the observation period is sufficient for the classification as corrosive.

- irritation
  - a limited degree of alopecia, hyperkeratosis, hyperplasia and scaling occurs. Two animals showing this response are sufficient for the classification as irritant.
very elevated mean scores throughout the study are revealed, including lesions
persisting at the end of an observation period of normally 14 days. **One** animal showing
this response throughout and at the end of the observation period is sufficient for the
classification as irritant (In cases of suspected corrosives, existing test data may only be
available for one animal due to testing restrictions, see Example 2.).

With regard to severity the main criterion for classification of a substance as irritant to skin,
is the mean score per animal for either erythema/eschar or oedema. During the observation
period following the removal of the patch each animal is scored on erythema and oedema.
For each of the three test animals the average scores for three consecutive days (usually 24,
48 and 72 hours) are calculated separately for oedema and erythema. If 2/3 animals exceed
the cut-off-values defined in CLP, the classification has to be done accordingly.

With regard to reversibility the test report must prove that these effects are transient i.e. the
affected sites are repaired within the observation period of the test (see Example 1).

Non-classification as corrosive can be only justified, if the test was performed with at least
three animals and the test results were negative for all three animals.

**Tests that have been conducted with more than three animals**

Current guidelines foresee a sequential testing of rabbits until a response is confirmed.
Typically, up to 3 rabbits may be used. The basis for a positive response is the individual
rabbit value averaged over days 1, 2, and 3. The mean score for each individual animal is
used as a criterion for classification. The Skin Irritant Category 2 is used if at least 2 of 3
animals show a mean score of 2.3 or above. Other test methods, however, have been using up
to 6 rabbits. This is also the case for the studies performed according to the US-FSHA.

For existing test data with more than three animals, specific provisions need to be applied.
For the sake of flexibility basically two approaches can be accepted for evaluation:

− the overall average over all animals will be used (see Example 3a). This has been
  common practice under the DSD.

− According to the second approach the average score is determined per animal (see
  Example 3b). In this case Skin Irritant Category 2 is assigned if 4 of 6 rabbits show a
  mean score of 2.3 or above. Likewise, if the test was performed with 4 or 5 animals, for at
  least 3 individuals the mean score must exceed the value of 2.3 to classify as Skin Irritant
  Category 2.

The more stringent result has to be used if the evaluation according to the method shown
under Example 3a is different to that under Example 3b.

**Other dermal tests in animals**

Relevant data may also be available from animal studies that were conducted for other
primary purposes than the investigation of skin corrosion/irritation. However, due to the
different protocols and the interspecies differences in sensitivity, the use of such data in
general needs to be evaluated on a case-by-case basis. These are considered significant if the
effects seen are comparable to those described above. For further guidance how to evaluate
data from studies on dermal toxicity or skin sensitisation, see IR/CSA Figure R.7.2-2
footnotes d) and e), respectively.

**3.2.2.3 Weight of evidence**
Where the criteria cannot be applied directly to available identified information, a weight of the evidence determination using expert judgement shall be applied in accordance with CLP Article 9(3).

A weight of the evidence determination means that all available and scientifically justified information bearing on the determination of hazard is considered together, such as physico-chemical parameters (e.g., pH, reserve alkalinity/acidity), information from the application of the category approach (grouping, read-across), (Q)SAR results, the results of suitable in vitro tests, relevant animal data, skin irritation information/data on other similar mixtures, human experience such as occupational data and data from accident databases, epidemiological and clinical studies and well-documented case reports and observations. The quality and consistency of the data shall be given appropriate weight. Both positive and negative results shall be assembled together in a single weight of evidence determination.

Evaluation must be performed on a case-by-case basis and with expert judgement. However, normally positive results that are adequate for classification should not be overruled by negative findings.

Annex I: 1.1.1.4. For the purpose of classification for health hazards (Part 3) established hazardous effects seen in appropriate animal studies or from human experience that are consistent with the criteria for classification shall normally justify classification. Where evidence is available from both humans and animals and there is a conflict between the findings, the quality and reliability of the evidence from both sources shall be evaluated in order to resolve the question of classification. Generally, adequate, reliable and representative data on humans (including epidemiological studies, scientifically valid case studies as specified in this Annex or statistically backed experience) shall have precedence over other data. However, even well-designed and conducted epidemiological studies may lack a sufficient number of subjects to detect relatively rare but still significant effects, to assess potentially confounding factors. Therefore, positive results from well-conducted animal studies are not necessarily negated by the lack of positive human experience but require an assessment of the robustness, quality and statistical power of both the human and animal data.

For further guidance, if both human and animal data are available, see IR/CSA Section R.7.2.3.2.

3.2.2.4 Decision on classification

Where the substance is classified as a skin corrosive but the data used for classification does not allow differentiation between the skin corrosion subcategories 1A/1B/1C, then the substance should be assigned Skin Corrosive Category 1.

3.2.2.5 Setting of specific concentration limits

Whenever adequate and reliable scientific information shows that the hazard of a substance is present in a mixture when the substance is present below the generic concentration limit (GCL), this information shall be used to establish a specific concentration limit (SCL) for the substance (second subparagraph of CLP Article 10(1)).

It is more difficult to prove the absence of a hazardous property. Therefore, only in exceptional circumstances, where adequate, reliable and conclusive scientific information is available showing that an irritation hazard for humans of that particular substance in a mixture above the GCL is not evident, may a specific concentration limit which is higher than the generic one be set (third subparagraph of Article 10(1) of CLP).
An SCL overrules any GCL set out in Tables 3.2.3 and 3.2.4 of Annex I to CLP (CLP Article 10(6)). Furthermore, an SCL is substance-specific and should be applicable to all mixtures containing the substance.

What type of information may be the basis for setting a specific concentration limit?

The aim of the standard test method for skin corrosion/irritation TM B.4/OECD TG 404 is to identify a corrosive or an irritant. The method uses a sequential testing strategy starting with one animal and using a maximum of three animals. The test substance is generally administered undiluted. Thus, no dose-response relationship can be obtained from this test. The test is therefore not designed and is not sufficiently sensitive to directly identify a threshold below which a substance in a mixture may not be corrosive or irritant to humans. Consequently, the method is not appropriate for testing dilutions in order to demonstrate non-irritating thresholds, as required to set a higher SCL than the GCL. In other words, this test method cannot generate data which are sufficiently adequate, reliable and conclusive to form a scientifically valid basis upon which a generic scheme for deriving higher SCLs reflecting a threshold for irritation in humans can be built.

However, existing human data may in certain cases (especially if dose-response information is available) indicate that the threshold for the irritation hazard in humans would be higher or lower than the GCL for a substance in a mixture. 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 the degree of statistical certainty of both the human and animal data.

Also, if adequate, relevant and conclusive data exists from already performed animal studies (other than TM B.4/TG 404) with a sufficient number of animals tested to ensure a high degree of statistical 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.

However, it should be noted that any additional animal testing (of dilutions) of already classified corrosive or irritant substances, is not encouraged and may only take place on a case-by-case basis if there are no alternatives providing adequate reliability and quality of data (see CLP Articles 7(1) and 8(1)).

Annex VI to CLP includes example substances for which a higher or lower SCL was set under Directive 67/548/EEC (old DSD system). An example of the justification for a lower SCL can be found in the EU Technical Committee for Classification and Labelling (TC C&L) documents ECBI/46/95 Add. 41.

As demonstrated in the TC C&L document ECBI/46/95 Add. 41 mentioned above, a lower SCL should be considered if corrosive or irritant effects are caused by dilutions. Thus, testing dilutions based on TM B.4/TG 404 could be justified on a case-by-case basis but only with the view to setting lower SCLs and if there are no alternatives etc (see above and Articles 7(1) and 8(1) of CLP).

### 3.2.2.6 Decision logic for classification of substances

The decision logic, which is based on IR/CSA, Figure R.7.2-2 has been revised to meet CLP requirements. It is strongly recommended that the person responsible for classification, study...
the criteria for classification, as well as the guidance above, before and during use of the decision logic.

<table>
<thead>
<tr>
<th>Step</th>
<th>Instruction</th>
<th>Decision</th>
</tr>
</thead>
</table>
| 1a   | Is the substance an organic hydro peroxide or an organic peroxide? | YES ➔  
|      | NO          | ➔         |
|      | Consider classifying as corrosive (Skin Corr. 1B) if the substance is a hydro peroxide, or irritating (Skin Irrit. 2) if the substance is a peroxide.  
|      | OR          |  
|      | Provide evidence for the contrary and proceed to step 1b |
| 1b   | Is the pH of the substance ≤ 2 or ≥ 11.5? | YES ➔  
|      | NO          | ➔         |
|      | Consider classifying as corrosive.  
|      | – Where classification is based upon consideration of pH alone (i.e. buffering capacity is not known), Skin Corr. 1A should be applied.  
|      | – Where consideration of alkali/acid reserve suggests that the substance is not corrosive, this has to be confirmed (preferably by use of an appropriate in vitro test). Proceed to step 1c |
| 1c   | Are there other physical or chemical properties that indicate that the substance is irritating / corrosive? | YES ➔  
|      | NO          | ➔         |
|      | Use this information for weight of evidence (WoE) determination (step 7).  
|      | Proceed to step 2 |
| 2    | Are there adequate existing human data which provide evidence that the substance is corrosive or irritant? | YES ➔  
|      | NO          | ➔         |
|      | Classify accordingly. |
| 3    | Are there data from existing studies on irritation and corrosion in laboratory animals, which provide sound conclusive evidence that the substance is a corrosive, irritant or non-irritant? | YES ➔  
|      | NO          | ➔         |
|      | Classify accordingly (either Skin Corr. 1A/1B/1C or Skin Irrit. 2 or no classification). |
| 4a   | Has the substance proven to be a corrosive, irritant or non-irritant in a suitable acute dermal toxicity test? | YES ➔  
|      | NO          | ➔         |
|      | If test conditions are consistent with OECD TG 404, classify accordingly (Skin Corr. 1A/1B/1C or Skin Irrit. 2 or no classification). |
If test conditions are not consistent with OECD TG 404, use this information in the WoE determination (step 7) and proceed to step 4b

<table>
<thead>
<tr>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>4b</td>
</tr>
<tr>
<td>NO</td>
</tr>
</tbody>
</table>

Classification cannot be considered directly. Use this information for WoE determination (step 7). Proceed to step 5a

<table>
<thead>
<tr>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
</tr>
<tr>
<td>NO</td>
</tr>
</tbody>
</table>

Consider to classify as Skin Corr. 1. Proceed to step 5b

<table>
<thead>
<tr>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>5b</td>
</tr>
<tr>
<td>NO</td>
</tr>
</tbody>
</table>

Consider to classify as Skin Irrit. 2. Proceed to step 6a

<table>
<thead>
<tr>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
</tr>
<tr>
<td>NO</td>
</tr>
</tbody>
</table>

Classify as corrosive. If discrimination between Skin Corr. 1A/1B/1C is not possible, Skin Corr. 1 must be chosen.

<table>
<thead>
<tr>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>6b</td>
</tr>
<tr>
<td>NO</td>
</tr>
</tbody>
</table>

Consider to classify accordingly (Skin Irrit. 2 or no classification). Proceed to step 6c

<table>
<thead>
<tr>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>6c</td>
</tr>
<tr>
<td>NO</td>
</tr>
</tbody>
</table>

Consider to classify as Skin Irrit. 2 Proceed to step 7

<table>
<thead>
<tr>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
</tr>
</tbody>
</table>

Classify accordingly (Skin Corr. 1A or Skin Corr. 1B or Skin Corr. 1C or Skin
**3.2.3 Classification of mixtures for skin corrosion/irritation**

**3.2.3.1 Identification of hazard information**

The procedure for classifying mixtures is a tiered, i.e. a stepwise, approach based on a hierarchy principle and depending on the type and amount of available data/information starting from evaluating existing human data on the mixture, followed by a thorough examination of the existing in vivo data, physico-chemical properties, and finally in vitro data available on the mixture. For mixtures that have been on the market for a long time, human data and experience may exist that may provide useful information on the skin irritation potential of the respective mixtures. See section 3.2.2.1.1 for further information on the identification of human data.

If valid test data are available for the whole mixture they have precedence. If no such data exist, the so called bridging principles have to be applied if possible. If the bridging principles are not applicable an assessment on the basis of data for the components of the mixture will be applied.

Where it is decided to base the classification of a mixture upon consideration of pH alone, Skin corrosion Category 1A should be applied. In this case no further retrieval of information on the mixture itself is needed.

**3.2.3.2 Classification criteria**

**3.2.3.2.1 When data are available for the complete mixture**

Annex I: 3.2.3.1.1. The mixture will be classified using the criteria for substances, and taking into account the testing and evaluation strategies to develop data for these hazard classes.

3.2.3.1.2. Unlike other hazard classes, there are alternative tests available for skin corrosivity of certain types of substances and mixtures that can give an accurate result for classification purposes, as well as being simple and relatively inexpensive to perform. When considering testing of the mixture, classifiers are encouraged to use a tiered weight of evidence strategy as included in the criteria for classification of substances for skin corrosion and irritation (paragraph 3.2.2.5), to help ensure an accurate classification as well as avoid unnecessary animal testing. A mixture is considered corrosive to skin (Skin Category 1) if it has a pH of 2 or less or a pH of 11.5 or greater. If consideration of alkali/acid reserve suggests the substance or mixture may not be corrosive despite the low or high pH value, then further testing shall be carried out to confirm this, preferably by use of an appropriate validated in vitro test.

There are a range of available in vitro test systems that have been validated for their suitability in assessing skin corrosion/irritation potential of substances. Some but not all test...
systems have been validated for mixtures and not all available *in vitro* test systems work equally well for all types of mixtures. Prior to testing a mixture in a specific *in vitro* assay for classification purposes, it has to be assured that the respective test has been previously shown to be suitable for the prediction of skin corrosion/irritation properties for the type of mixture to be evaluated.

### 3.2.3.2.1 Mixtures with extreme pH

As a general rule, mixtures with a pH of $\leq 2$ or $\geq 11.5$ should be considered as corrosive. However, assessment of the buffering capacity of the mixture indicated by its acid or alkali reserve should be considered. If the additional consideration of the acid/alkali reserve according to Young *et al.* (1987, 1994) suggests that classification for corrosion or even irritation may not be warranted, then further *in vitro* testing to confirm final (or no) classification shall be carried out. The consideration of acid/alkali reserve should not be used alone to exonerate mixtures from classification.

Where the mixture has an extreme pH value but the only corrosive/irritant ingredient present in the mixture is an acid or base with an assigned SCL (either in CLP Annex VI or set by supplier), then the mixture should be classified according to the SCL. In this instance, pH of the mixture should not be considered a second time since it would have already been taken into account when deriving the SCL for the substance.

If this is not the case, then the steps to be taken into consideration when classifying a mixture with pH $\leq 2$ or $\geq 11.5$ are described in the following decision logic:

<table>
<thead>
<tr>
<th>Mixture without <em>in vivo</em> data on skin corrosion or relevant data from similar tested mixtures, pH is $\leq 2$ or $\geq 11.5$</th>
</tr>
</thead>
</table>
| **Does the acid alkaline reserve indicate that the mixture may not be corrosive?** **NO** ➔ Classify as corrosive, Skin Corr. Cat. 1A. **YES** ➔ **Is the mixture tested in an OECD adopted *in vitro* test for skin corrosion?** **NO** ➔ Classify as corrosive, Skin Corr. Cat. 1A. **YES** ➔ **Does the mixture demonstrate corrosive properties in an OECD adopted *in vitro* test?** **NO** ➔ **Apply methods in Annex I, sections 3.2.3.3.2 (Table 3.2.3) / 3.2.3.3.4 (Table 3.2.4)** (When validated *in vitro* skin irritation test methods are available, these may be used to generate data to classify the mixture instead of using the summation method.) **YES** ➔ Classify accordingly. **The mixture must be classified as Skin corrosion Category 1 should the supplier decide not to carry out the required confirmatory testing.** **It is also important to note that the pH-acid/alkali reserve to change classification from corrosive to irritant or from irritant to not classified assumes that the potential corrosivity or irritancy is due to the effect of the ionic entities. When this is not the case, especially when**
the mixture contains non-ionic (non-ionisable) substances themselves classified as corrosive or irritant, then the pH-reserve method cannot be a basis for modifying the classification but should be considered in a weight of evidence analysis.

3.2.3.2.2 When data are not available for the complete mixture: bridging principles

**Annex I: 3.2.3.2.1.** Where the mixture itself has not been tested to determine its skin irritation/corrosion hazards, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterise the hazards of the mixture, these data shall be used in accordance with the bridging rules set out in section 1.1.3.

In order to apply bridging principles, there needs to be sufficient data on similar tested mixtures as well as the components of the mixture.

When the available identified information is inappropriate for the application of the bridging principles then the mixture should be classified using the methods described in section 1.6.3.

3.2.3.2.3 When data are available for all components or only for some components

3.2.3.2.3.1 Components that should be taken into account for the purpose of classification

**Annex I: 3.2.3.3.1.** …Assumption: the 'relevant ingredients' of a mixture are those which are present in concentrations of 1% (w/w for solids, liquids, dusts, mists and vapours and v/v for gases) or greater, unless there is a presumption (e.g., in the case of corrosive ingredients) that an ingredient present at a concentration of less than 1% can still be relevant for classifying the mixture for skin irritation/corrosion.

3.2.3.2.3.2 The additivity approach is applicable

**Annex I: 3.2.3.3.2.** In general, the approach to classification of mixtures as irritant or corrosive to skin when data are available on the components, but not on the mixture as a whole, is based on the theory of additivity, such that each corrosive or irritant component contributes to the overall irritant or corrosive properties of the mixture in proportion to its potency and concentration. A weighting factor of 10 is used for corrosive components when they are present at a concentration below the generic concentration limit for classification with Category 1, but are at a concentration that will contribute to the classification of the mixture as an irritant. The mixture is classified as corrosive or irritant when the sum of the concentrations of such components exceeds a concentration limit.

3.2.3.3.3. Table 3.2.3 provides the generic concentration limits to be used to determine if the mixture is considered to be an irritant or a corrosive to the skin.

When the supplier is unable to derive the classification using either data on the mixture itself or bridging principles, he must determine the skin corrosion/irritation properties of the mixture using data on the individual ingredients. The supplier must ascertain whether the additivity approach is applicable, the first step in the process being to identify all the ingredients in the mixture (i.e. their name, chemical type, concentration level, hazard classification and any SCLs) and the pH of the mixture. In addition to for example surfactant interaction, neutralisation of acids/bases could also occur in a mixture, which also makes it important to consider effects of the entire mixture (i.e. pH and the acid/alkaline reserve) rather than considering contributions of individual ingredients. Additivity may not apply where the mixture contains substances mentioned in Annex I, 3.2.3.3.4, see section 3.2.3.2.3.
Application of SCLs when applying the additivity approach

The generic concentration limits (GCLs) are specified in Annex I, Table 3.2.3. However, according to CLP Article 10(5) SCLs take precedence over GCLs. Thus, if a given substance has a SCL, then this limit has to be taken into account when applying the summation (additivity) method for skin corrosion/irritation (see Examples 5 and 6).

In cases where additivity applies for skin corrosion/irritation to a mixture with two or more substances some of which may have SCLs assigned, then the following formula should be used:

The mixture is classified for skin corrosion/irritation if the

\[ \text{Sum of (ConcA / clA) + (ConcB / clB) + \ldots + (ConcZ / clZ) is } \geq 1 \]

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.

This approach is similar to that used in the DPD where a substance SCL replaces the default limits in the conventional method equations.

3.2.3.3.3 The additivity approach is not applicable

Annex I: 3.2.3.3.4.1. Particular care must be taken when classifying certain types of mixtures containing substances such as acids and bases, inorganic salts, aldehydes, phenols, and surfactants. The approach explained in paragraphs 3.2.3.3.1 and 3.2.3.3.2 may not be applicable given that many of such substances are corrosive or irritant at concentrations < 1%.

3.2.3.3.4.2. For mixtures containing strong acids or bases the pH shall be used as a classification criterion (see paragraph 3.2.3.1.2) since pH is a better indicator of corrosion than the concentration limits of Table 3.2.3.

3.2.3.3.4.3. A mixture containing ingredients that are corrosive or irritant to the skin and that cannot be classified on the basis of the additivity approach (Table 3.2.3), due to chemical characteristics that make this approach unworkable, shall be classified as Skin Corrosive Category 1A, 1B or 1C if it contains ≥ 1% of an ingredient classified in Category 1A, 1B or 1C respectively or as Category 2 when it contains ≥ 3% of an irritant ingredient. Classification of mixtures with ingredients for which the approach in Table 3.2.3 does not apply is summarised in Table 3.2.4.

3.2.3.3.5. On occasion, reliable data may show that the skin corrosion/irritation hazard of an ingredient will not be evident when present at a level above the generic concentration limits mentioned in Tables 3.2.3 and 3.2.4. In these cases the mixture shall be classified according to that data (see also Articles 10 and 11). On other occasions, when it is expected that the skin corrosion/irritation hazard of an ingredient is not evident when present at a level above the generic concentration limits mentioned in Tables 3.2.3 and 3.2.4, testing of the mixture shall be considered. In those cases the tiered weight of evidence strategy shall be applied, as described in paragraph 3.2.2.5.

3.2.3.3.6. If there are data showing that (an) ingredient(s) is/are corrosive or irritant at a concentration of < 1 % (corrosive) or < 3 % (irritant), the mixture shall be classified accordingly.

3.2.3.3 Generic concentration limits for substances triggering classification of mixtures
3.2.3.3.1 When the additivity approach is applicable

<table>
<thead>
<tr>
<th>Sum of ingredients classified as:</th>
<th>Concentration triggering classification of a mixture as:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Skin Corrosive</td>
</tr>
<tr>
<td></td>
<td>Skin Irritant</td>
</tr>
<tr>
<td>Skin corrosive Categories 1A, 1B, 1C</td>
<td>≥ 5%</td>
</tr>
<tr>
<td>Skin irritant Category 2</td>
<td>≥ 10%</td>
</tr>
<tr>
<td>(10 x Skin corrosive Category 1A, 1B, 1C) + Skin irritant Category 2</td>
<td>≥ 10%</td>
</tr>
</tbody>
</table>

**Note**

The sum of all ingredients of a mixture classified as Skin Corrosive Category 1A, 1B or 1C respectively, shall each be ≥ 5% respectively in order to classify the mixture as either Skin Corrosive Category 1A, 1B or 1C. If the sum of the Skin Corrosive Category 1A ingredients is < 5% but the sum of Category 1A+1B ingredients is ≥ 5%, the mixture shall be classified as Skin corrosive Category 1B. Similarly, if the sum of Skin corrosive Category 1A+1B ingredients is < 5% but the sum of Category 1A+1B+1C ingredients is ≥ 5% the mixture shall be classified as Skin Corrosive Category 1C.

3.2.3.3.2 When the additivity approach is not applicable

<table>
<thead>
<tr>
<th>Ingredient:</th>
<th>Concentration:</th>
<th>Mixture classified as: Skin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid with pH ≤ 2</td>
<td>≥ 1%</td>
<td>Category 1</td>
</tr>
<tr>
<td>Base with pH ≥ 11.5</td>
<td>≥ 1%</td>
<td>Category 1</td>
</tr>
<tr>
<td>Other corrosive (Categories 1A, 1B, 1C) ingredients for which additivity does not apply</td>
<td>≥ 1%</td>
<td>Category 1</td>
</tr>
<tr>
<td>Other irritant (Category 2) ingredients for which additivity does not apply, including acids and bases</td>
<td>≥ 3%</td>
<td>Category 2</td>
</tr>
</tbody>
</table>

3.2.3.4 Decision logic for classification of mixtures

The decision logic, which is based on IR/CSA, Figure R.7.2-2, is revised to meet CLP requirements. It is strongly recommended that the person responsible for classification, study the criteria for classification, as well as the guidance above, before and during use of the decision logic.
### 1. When data are available for the complete mixture

<table>
<thead>
<tr>
<th>Step</th>
<th>Question</th>
<th>YES</th>
<th>NO</th>
<th>Notes</th>
</tr>
</thead>
</table>
| 1a   | Is the pH of the mixture ≤ 2 or ≥ 11.5? | YES | NO | Consider to classify as corrosive.  
- Where classification is based upon consideration of pH alone (i.e. buffering capacity is not known), Skin Corr. 1A should be applied.  
- Where consideration of alkali/acid reserve suggests that the substance is not corrosive, this has to be confirmed (preferably by use of an appropriate *in vitro* test). Proceed to step 1b. |
| 1b   | Are there other physical or chemical properties that indicate that the mixture is corrosive/irritating? | YES | NO | Use this information for WoE analysis (step 6).  
Proceed to step 2 |
| 2    | Is there adequate existing human experience which provides evidence that the mixture is corrosive or irritant? | YES | NO | Classify accordingly (Skin Corr. 1 or Skin Irrit. 2). |
| 3    | Are there data from existing studies on *irritation and corrosion* in laboratory animals, which provide sound conclusive evidence that the mixture is corrosive, irritant or non-irritant? | YES | NO | Classify accordingly (Skin Corr. 1A or Skin Corr. 1B or Skin Corr. 1C or Skin Irrit. 2 or no classification). |
| 4a   | Has the mixture proven to be a corrosive, irritant or non-irritant in a suitable acute dermal toxicity test? | YES | NO |  
- If test conditions are consistent with OECD TG 404, classify accordingly (Skin Corr. 1A/1B/1C or Skin Irrit. 2 or no classification).  
- If test conditions are not consistent with OECD TG 404, use this information in the WoE determination (step 6) and proceed to step 4b |
| 4b   | Has the mixture proven to be a corrosive or an irritant in sensitisation studies or after repeated exposure? | YES | NO | Classification cannot be considered directly. Use this information for WoE determination (step 6).  
Proceed to step 5a |
<p>| 5a   | Has the mixture demonstrated corrosive properties in an OECD adopted <em>in vitro</em> test? | YES | NO | Classify as corrosive. If discrimination between Skin Corr. 1A/1B/1C is not possible, Skin Corr. 1 must be chosen. |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NO</strong></td>
<td></td>
</tr>
<tr>
<td><strong>↓</strong></td>
<td></td>
</tr>
</tbody>
</table>

| 5b | Are there acceptable data from a validated *in vitro* test (adopted by OECD or not), which provide evidence that the mixture is an irritant or non-irritant? **YES** | Consider to classify accordingly (Skin Irrit. 2 or no classification). **NO** |
|    | Proceed to step 5c |   |

| 5c | Are there data from a suitable *in vitro* test, which provide sound conclusive evidence that the mixture is an irritant? **YES** | Consider to classify as Skin Irrit. 2. **NO** |
|    | Proceed to step 6 |   |

| 6 | Taking all existing and relevant data (steps 1-5) into account including potential synergistic/antagonistic effects and bioavailability, is there sufficient information to make a decision on classification? **YES** | Classify accordingly (Skin Corr. 1A or Skin Corr. 1B or Skin Corr. 1C or Skin Irrit. 2 or no classification) **NO** |

### 2. When data are not available for the complete mixture: bridging principles

| 7a | Are existing sufficient skin corrosion/irritation data available on similar tested mixtures and on the individual ingredients? **YES** | Proceed to step 8 **NO** |
|    |   |   |
| 7b | Can bridging principles be applied? **YES** | Classify in appropriate category (Skin Corr. 1A or Skin Corr. 1B or Skin Corr. 1C or Skin Irrit. 2 or no classification) **NO** |
|    |   |   |

### 3. When data are available for all components or only for some components of the mixture

| 8a | Is pH of the mixture ≤ 2 or ≥ 11.5? **YES** | Follow decision logic in Section 3.2.3.2.1.1 and classify accordingly. **NO** |
|    |   |   |
| 8b | Is there any indication that the additivity principle does not apply? **YES** | Annex I, section 3.2.3.3.4 and Table 3.2.4 may apply. Take into account relevant ingredients (Annex I, 3.2.3.3.1. and SCLs as appropriate. Classify in appropriate category (Skin Corr. 1A/1B/1C or Skin Irrit. 2 or no classification) **NO** |

|   |   |
Annex I, section 3.2.3.3.2 and Table 3.2.3 applies. Take into account relevant ingredients (Annex I, 3.2.3.3.1. and SCLs as appropriate. Classify in appropriate category (Skin Corr. 1A/1B/1C or Skin Irrit. 2 or no classification). Where the mixture is classified as corrosive but the data used for classification does not allow differentiation between the skin corrosion subcategories 1A/1B/1C, then the mixture should be assigned Skin corrosion Category 1.

3.2.4 Hazard communication in form of labelling for skin corrosion/irritation

3.2.4.1 Pictograms, signal words, hazard statements and precautionary statements

**Annex I: 3.2.4.1.** Label elements shall be used for substances or mixtures meeting the criteria for classification in this hazard class in accordance with Table 3.2.5.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Category 1A / 1B / 1C</th>
<th>Category 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GHS Pictograms</strong></td>
<td><img src="image" alt="Pictogram" /></td>
<td><img src="image" alt="Pictogram" /></td>
</tr>
<tr>
<td><strong>Signal Word</strong></td>
<td>Danger</td>
<td>Warning</td>
</tr>
<tr>
<td><strong>Hazard Statement</strong></td>
<td>H314: Causes severe skin burns and eye damage</td>
<td>H315: Causes skin irritation</td>
</tr>
<tr>
<td><strong>Precautionary Statement Prevention</strong></td>
<td>P260, P264, P280</td>
<td>P260, P264, P280</td>
</tr>
<tr>
<td><strong>Precautionary Statement Storage</strong></td>
<td>P405</td>
<td></td>
</tr>
<tr>
<td><strong>Precautionary Statement Disposal</strong></td>
<td>P501</td>
<td></td>
</tr>
</tbody>
</table>

3.2.4.2 Additional labelling provisions

**Annex II: 1.2.6. EUH071 — Corrosive to the respiratory tract**

For substances and mixtures in addition to classification for inhalation toxicity, if data are available that indicate that the mechanism of toxicity is corrosivity, in accordance with section 3.1.2.3.3 and Note 1 of Table 3.1.3 in Annex I.

For substances and mixtures in addition to classification for skin corrosivity, if no acute inhalation test data are available and which may be inhaled.
Corrosive substances (and mixtures) may be acutely toxic after inhalation to a varying degree, which is only occasionally proved by testing. In case no acute inhalation study is available for a corrosive substance (or mixture) and such substance (or mixture) may be inhaled, a hazard of respiratory tract corrosion may exist. As a consequence, substances and mixtures have to be supplementary labelled with EUH071. Moreover, in such a case it is strongly recommended to apply the precautionary statement P260: “Do not breathe dust/fume/gas/mist/vapours/spray.”

Annex II: 1.2.4. EUH066 — Repeated exposure may cause skin dryness or cracking
For substances and mixtures which may cause concern as a result of skin dryness, flaking or cracking but which do not meet the criteria for skin irritancy in section 3.2 of Annex I, based on either:
— practical observations; or
— relevant evidence concerning their predicted effects on the skin.

3.2.5 Re-classification of substances and mixtures classified for skin corrosion/irritation according to DSD and DPD

3.2.5.1 Is direct “translation” of classification and labelling possible?
A direct translation as indicated in the translation table in Annex VII to CLP is generally possible. Translation from classification according to DSD or DPD to the classification according to CLP is as follows:
- C; R35 is translated into Skin Corr. 1A; H314. The criteria in CLP and in DSD are identical.
- C; R34 is translated into Skin Corr. 1B; H314 with the following note:

Annex VII: Table 1.1
Note 2
It is recommended to classify in Category 1B even if it also could be possible that 1C could be applicable for certain cases. Going back to original data, may not result in a possibility to distinguish between Category 1B or 1C, since the exposure period has normally been up to 4 hours according to Regulation (EC) No 440/2008. However, for the future, when data are derived from tests following a sequential approach as foreseen in the Regulation (EC) No 440/2008, Category 1C should be considered.

- Xi; R38 is translated into Skin Irrit. 2; H315. The criteria in CLP and DSD are almost identical.

It should be noted that where mixtures containing substances with risk phrase R34 have been classified on basis of the hazards of individual ingredients, the use of the translation table may lead to an under-classification of the mixture. This is because the general concentration limits, to be applied for mixtures, are lowered under CLP compared to DPD. For mixtures containing substances with this classification the use of the translation table may therefore not be appropriate and re-classification done by using the existing data would be more correct. For more details see section 1.7.

3.2.5.2 Re-evaluation of data
If there is new information which might be relevant with respect to classification a re-evaluation has to be performed.

3.2.6 Examples of classification for skin corrosion/irritation
3.2.6.1 Examples of substances fulfilling the criteria for classification

3.2.6.1.1 Example 1: Standard test according to OECD TG 404 with three animals

In a guideline test according to OECD TG 404 the test substance was applied for three minutes and 1 hour. No scars or other irreversible effects were found. The scoring results obtained after 4 hours application time are listed in the following table:

<table>
<thead>
<tr>
<th>Animal Nr.</th>
<th>Degree of erythema after …[observation time]</th>
<th>Degree of oedema after …[observation time]</th>
<th>Ø 24/48/72 h &gt;2.3 ?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1h 24h 48h 72h 7d 14d</td>
<td>1h 24h 48h 72h 7d 14d</td>
<td>Erythema Oedema</td>
</tr>
<tr>
<td>1</td>
<td>3 3 3 2 0</td>
<td>1 2 2 2 0</td>
<td>Yes No</td>
</tr>
<tr>
<td></td>
<td>Ø 24/48/72 h = 2.7</td>
<td>Ø 24/48/72 h = 2.0</td>
<td>=&gt;&quot;positive Responder&quot;</td>
</tr>
<tr>
<td>2</td>
<td>3 3 3 3 0</td>
<td>1 2 2 1 0</td>
<td>Yes No</td>
</tr>
<tr>
<td></td>
<td>Ø 24/48/72 h = 3</td>
<td>Ø 24/48/72 h = 1.7</td>
<td>=&gt;&quot;positive Responder&quot;</td>
</tr>
<tr>
<td>3</td>
<td>1 1 1 0 0</td>
<td>1 1 1 1 0</td>
<td>No No</td>
</tr>
<tr>
<td></td>
<td>Ø 24/48/72 h = 0.66</td>
<td>Ø 24/48/72 h = 1</td>
<td></td>
</tr>
</tbody>
</table>

Classification: Skin Irritant Category 2

The classification is made on basis of 2/3 "positive responder" exceeding 2.3 mean score for erythema.

3.2.6.1.2 Example 2: Test carried out with one animal with a test substance which is suspected as corrosive

Due to the unprecedented structure the biological effects of the substance cannot be anticipated. Therefore, the test according to OECD TG 404 was started with one animal only in line with testing restrictions. Exposure times were 3 min and 1h. The following scores/effects were observed:

<table>
<thead>
<tr>
<th>Exposure time</th>
<th>Degree of erythema after …[observation time]</th>
<th>Degree of oedema after …[observation time]</th>
<th>Visible necrosis, irreversible skin damage After 14d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1h 24h 48h 72h ...</td>
<td>1h 24h 48h 72h ...</td>
<td></td>
</tr>
<tr>
<td>3 min</td>
<td>0 0 0 0 0</td>
<td>0 0 0 0 0</td>
<td>No</td>
</tr>
<tr>
<td>1h</td>
<td>0 1 2 3</td>
<td>0 2 2 3</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Classification: Skin Corrosion Category 1B

Rationale for the classification is destruction of the tissue within 1 hour exposure.
3.2.6.1.3 Example 3a: Test carried out with more than three animals

A substance was tested on acute skin irritation / corrosion according to OECD TG 404. Contact time was 4 hours. No effects were seen after a contact time of 3 min and one hour. The following scores were obtained:

<table>
<thead>
<tr>
<th>Animal Nr</th>
<th>Degree of erythema after ...[observation time]</th>
<th>Degree of oedema after ...[observation time]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1h</td>
<td>24h</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Evaluation was made based on the arithmetic mean of all animals.

The arithmetic mean after 24/48/72 hours for erythema $M_E = 21:12 = 1.8$; and for oedema $M_O = 25:12 = 2.1$. Both values are below 2.3, i.e. no classification warranted for skin irritation.

3.2.6.1.4 Example 3b: Test carried out with more than three animals

A substance was tested on acute skin irritation / corrosion according to OECD TG 404. Contact time was 4 hours. No effects were seen after a contact time of 3 min and one hour. The following scores were obtained after a contact time of 4 hours:

<table>
<thead>
<tr>
<th>Observation time</th>
<th>Erythema</th>
<th>Oedema</th>
<th>Erythema</th>
<th>Oedema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal Nr</td>
<td>1h</td>
<td>24h</td>
<td>48h</td>
<td>72h</td>
</tr>
<tr>
<td></td>
<td>Erythema</td>
<td>Oedema</td>
<td>Erythema</td>
<td>Oedema</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Evaluation was made based on the average score per animal.

Only 1/4 of the animals reached the cut-off value of 2.3, i.e. only animal No 1 is a positive responder. No classification is warranted with regard to skin irritation.

3.2.6.2 Examples of mixtures fulfilling the criteria for classification

Where the mixture is made up of ingredients with no assigned SCLs, then the appropriate summation(s) and generic concentration limits from CLP Annex I, Table 3.2.3 should be used.

3.2.6.2.1 Example 4

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Skin corrosion / irritation classification</th>
<th>Concentration (% w/w)</th>
<th>SCL</th>
</tr>
</thead>
</table>

138
pH of the mixture is 9.0 – 10.0, thus extreme pH provisions do not apply. The mixture contains a surfactant and an acid but neither are corrosive/irritant below 1% (as identified by the absence of SCLs in either CLP Annex VI or the Classification and Labelling Inventory). Additivity is considered to apply.

Substance B, substance D and water can be disregarded as they are not classified for skin corrosion/irritation.

The mixture contains 2% acid, the only ingredient classified as Skin Corr. Cat 1. As this is below the 5% GCL, the mixture is not classified Skin Corr. Cat. 1 but is classified Skin Irrit. Cat. 2 (≥ 1% < 5%).

### Example 5

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Skin corrosion / irritation classification</th>
<th>Concentration (% w/w)</th>
<th>SCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surfactant A</td>
<td>Skin Cat 2</td>
<td>3.8</td>
<td>Not assigned</td>
</tr>
<tr>
<td>Substance B</td>
<td>Not classified</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Base E</td>
<td>Skin Cat 1B</td>
<td>5.4</td>
<td>C ≥ 10%: Skin Cat 1B 5% ≤ C &lt; 10%: Skin Cat 2</td>
</tr>
<tr>
<td>Substance D</td>
<td>Not classified</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Substance F</td>
<td>Skin Cat 1B</td>
<td>2</td>
<td>Not assigned</td>
</tr>
<tr>
<td>Water</td>
<td>Not classified</td>
<td>84.3</td>
<td></td>
</tr>
</tbody>
</table>

pH of the mixture is 10.5 – 11.0, thus extreme pH provisions do not apply. The mixture contains a surfactant and a base but none are corrosive/irritant below 1% (as identified by absence of specific concentration limits in either CLP Annex VI or the Classification and Labelling Inventory). Additivity is considered to apply.

Substance B, substances D and water can be disregarded as they are not classified for skin corrosion/irritation.

SCLs are neither assigned to substance F nor surfactant A, thus GCLs apply for these ingredients. SCLs are assigned to Base E (see section 3.2.3.2.3.2 under Application of SCLs when applying the additivity approach).

**Skin Cat 1:**

\[
\frac{\text{% substance F/GCL}}{\text{GCL}} + \frac{\text{base E/SCL}}{\text{SCL}} = \frac{2}{5} + \frac{5.4}{10} = 0.94 < 1, \text{ thus mixture is not classified as Skin Corr. Cat 1}
\]

**Skin Cat 2:**

\[
\frac{\text{% substance F/GCL}}{\text{GCL}} + \frac{\text{base E/SCL}}{\text{SCL}} + \frac{\text{surfactant A/GCL}}{\text{GCL}} = \frac{2}{1} + \frac{5.4}{5} + \frac{3.8}{10} = 3.46 \text{ which is } > 1, \text{ thus the mixture is classified Skin Irrit. Cat. 2}
\]
3.2.6.3 Examples of mixtures not fulfilling the criteria for classification

3.2.6.3.1 Example 6

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Skin corrosion / irritation classification</th>
<th>Concentration (% w/w)</th>
<th>SCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surfactant C</td>
<td>Skin Cat 2</td>
<td>0.4</td>
<td>Not assigned</td>
</tr>
<tr>
<td>Surfactant G</td>
<td>Skin Cat 2</td>
<td>3.0</td>
<td>Not assigned</td>
</tr>
<tr>
<td>Surfactant A</td>
<td>Skin Cat 2</td>
<td>0.7</td>
<td>Not assigned</td>
</tr>
<tr>
<td>Substance H</td>
<td>Skin Cat 1A</td>
<td>3.0</td>
<td>C ≥ 70 %: Skin Cat 1A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50 % ≤ C &lt; 70 %: Skin Cat 1B</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>35 % ≤ C &lt; 50 %: Skin Cat 2</td>
</tr>
<tr>
<td>Substance D</td>
<td>Not classified</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Water</td>
<td>Not classified</td>
<td>90.9</td>
<td></td>
</tr>
</tbody>
</table>

pH of the mixture is: 2.5 – 3.0, thus extreme pH provisions do not apply. The mixture contains three surfactants but none are corrosive/irritant below 1% (as identified by the absence of specific concentration limits in either CLP Annex VI or the Classification and Labelling Inventory). Additivity is considered to apply.

Substance D and water can be disregarded as they are not classified for skin corrosion/irritation. Also surfactant C and surfactant A can be disregarded as both are present below 1%.

A SCL is not assigned to surfactant G, thus GCL apply for this ingredient.

Skin Cat 1:

The mixture contains 3% substance H, the only ingredient classified as Skin Corr. Cat. 1. As this is below the 50% SCL for substance H, the mixture is not classified as Skin Corr. Cat. 1.

Skin Cat 2:

\[(\% \text{ substance H} / \text{SCL}) + (\% \text{ surfactant G} / \text{GCL}) = (3/35) + (3/10) = 0.39\] which is < 1, thus the mixture is not classified Skin Irrit. Cat. 2.

3.2.7 References

ECETOC (2002), Use of human data in hazard classification for irritation and sensitisation, Monograph No 32, Brussels ISSN 0773-6374-32


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/

Irritation: Report on the Validity of the EPISKIN and EpiDerm Assays and on the Skin Integrity Function Test. ATLA 35, 559-601.


3.3 SERIOUS EYE DAMAGE/EYE IRRITATION

It should be noted that if a substance or mixture is classified as skin corrosive category 1 then serious damage to eyes is implicit and there is no need to proceed with classification for eye effects.

3.3.1 Definitions for classification for serious eye damage/eye irritation

Annex I: 3.3.1.1. Serious eye damage means the production of tissue damage in the eye, or serious physical decay of vision, following application of a test substance to the anterior surface of the eye, which is not fully reversible within 21 days of application.

Eye irritation means the production of changes in the eye following the application of test substance to the anterior surface of the eye, which are fully reversible within 21 days of application.

3.3.2 Classification of substances for serious eye damage/eye irritation

3.3.2.1 Identification of hazard information

3.3.2.1.1 Identification of human data

Existing data on eye effects in humans may include well-documented epidemiological studies, clinical studies, case reports, and data from poison information units and accident databases or occupational experience. Their quality and relevance for hazard assessment should be thoroughly reviewed. A critical review of the value of human studies is provided in IR/CSA, section R.4.3.3 and more specific considerations for eye damage/irritation are given in IR/CSA, section R.7.2.4.2.

3.3.2.1.2 Identification of non human data

Available serious eye damage/eye irritation information on substances may include existing data generated by the test methods in the Test Methods Regulation or by methods based on internationally recognised scientific principles.

Several of the following non-testing and in vitro methods have been validated against the DSD criteria but not against the CLP criteria for classification. Therefore it should be checked whether the method is sufficiently validated for classification according to CLP.

3.3.2.1.2.1 Consideration of physico-chemical properties

Substances with oxidising properties can give rise to highly exothermic reactions in contact with other substances and human tissue. High temperatures thus generated may
damage/destroy biological materials. This applies, for example, to organic peroxides, which can be assumed to be eye irritants, unless evidence suggests otherwise (IR/CSA Section R.7.2.3.1).

For a hydro peroxide classification as eye damage category 1 should be considered, whereas eye irritation Category 2 should be considered for peroxides. Appropriate evidence must be provided in order to consider non-classification of substances with oxidising properties.

3.3.2.1.2.2 Non-testing methods: (Q)SARs and expert systems

Non-testing methods such as (Q)SARs and expert systems may be considered on a case-by-case basis. (Q)SARs are in general not very specific for eye irritancy. In many cases rules are used in a similar manner to those used for skin irritation and corrosion. (Q)SAR systems that also account for eye effects are for example TOPKAT, Derek for Windows, and SICRET. For full guidance, consult the IR/CSA Section R.6 ("QSAR and grouping of chemicals"), in which also the many shortcomings of the existing systems are discussed.

Since a formal adoption procedure for those non-testing methods is not foreseen and no formal validation process is in place, appropriate documentation is crucial. In order to achieve acceptance under REACH, the documentation must conform to the so-called QSAR Model Reporting Format (QMRF). For more details consult the IR/CSA Section R.6.1.

3.3.2.1.2.3 Testing-methods: pH and the acid/alkaline reserve

Substances can be predicted to be corrosive, if the pH is ≤ 2 or ≥ 11.5. Where extreme pH is the only basis for classification as serious eye damage, it is important to take into consideration the acid/alkaline reserve, a measure of the buffering capacity (Young et al, 1988, and Young and How, 1994). However, lack of buffering capacity should not be used alone to exonerate from classification as corrosive.

If pH is < 3.2 or > 8.6, then consider the substance for severe eye damage/eye irritation (IR/CSA Section R.7.2.4.1). Further information and/or reasoning is needed to conclude whether the substance is causing severe eye damage or eye irritation. This model is not recommended for the stand-alone discrimination between eye irritants and non-irritants. However, it could be used in the context of a tiered testing strategy to identify eye irritants (due to its very low false positive rate) but not for non-irritants (due to its relatively high false negative rate).

3.3.2.1.2.4 Testing methods: in vitro methods

Two in vitro test methods, the Bovine Corneal Opacity and Permeability (BCOP) test and the Isolated Chicken Eye (ICE) test, have been accepted by the OECD in September 2009 (TG 437 and 438) and included in the EU Test Method Regulation in December 2010 (B.47 and B.48) as test methods able to distinguish seriously eye damaging substances (Serious eye damage Category 1). Furthermore, there is regulatory acceptance in the EU that a substance can be considered as seriously damaging the eye (Serious eye damage Category 1) based on positive results in the Isolated Rabbit Eye (IRE) test or the Hen’s Egg Test on Chorio-allantoic Membrane (HET-CAM) test. Negative in vitro corrosivity responses in these tests must be followed by further testing (IR/CSA Section R.7.2.4.1)
There are no in vitro tests with regulatory acceptance for eye irritation at present, but the two human corneal epithelium models, EpiOcular™ and SkinEthic™, have been submitted to ECVAM for validation.

3.3.2.1.2.5 Testing methods: In vivo data

Testing for eye irritation would not be carried out on substances known or predicted to be corrosive to skin. Such substances are automatically considered to be severely damaging to the eye. A parallel classification with serious eye damage in addition to skin corrosion is not required.

The in vivo test in rabbits according to OECD TG 405 (B.5 in the Test Methods Regulation) is the standard test for the hazard assessment under the REACH.

The Low Volume Eye Test (LVET; Griffith et al 1980) is a modification of the standard OECD TG 405 test method, the differences being:

- the test material is placed directly on the cornea instead of introducing it in the conjunctival sac inside the lower lid;
- a reduction in the volume of test material applied (0.01 ml (or corresponding weight for solids) compared with the standard 0.1 ml).

Data from the LVET should be considered but must be carefully evaluated. The applicability domain up to now is limited to detergent and cleaning products. It is stated that positive data are a trigger for appropriate classification, but that negative data are not conclusive for a non-classification (IR/CSA R.7.2.4.1). However, they should be considered in a weight of evidence determination.

3.3.2.2 Classification criteria

Annex I: 3.3.2.6. Irreversible effects on the eye/serious damage to eyes (Category 1)

3.3.2.6.1. Substances that have the potential to seriously damage the eyes are classified in Category 1 (irreversible effects on the eye). Substances are classified in this hazard category on the basis of the results of animal testing, in accordance with the criteria listed in Table 3.3.1. These observations include animals with grade 4 cornea lesions and other severe reactions (e.g., destruction of cornea) observed at any time during the test, as well as persistent corneal opacity, discoloration of the cornea by a dye substance, adhesion, pannus, and interference with the function of the iris or other effects that impair sight. In this context, persistent lesions are considered those which are not fully reversible within an observation period of normally 21 days. Substances are also classified in Category 1 if they fulfil the criteria of corneal opacity \( \geq 3 \) or iritis > 1.5 detected in a Draize eye test with rabbits, recognising that such severe lesions usually do not reverse within a 21 days observation period.

<table>
<thead>
<tr>
<th>Table 3.3.1 Category for irreversible eye effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Category</strong></td>
</tr>
<tr>
<td>Irreversible effects on the eye (Category 1)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
Annex I: 3.3.2.7. Reversible effects on the eye (Category 2)

3.3.2.7.1. Substances that have the potential to induce reversible eye irritation are classified in Category 2 (irritating to eyes).

Table 3.3 2
Category for reversible eye effects

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irritating to eyes (Category 2)</td>
<td>if, when applied to the eye of an animal, a substance produces:</td>
</tr>
<tr>
<td></td>
<td>– at least in 2 of 3 tested animals, a positive response of:</td>
</tr>
<tr>
<td></td>
<td>– corneal opacity ≥ 1 and/or</td>
</tr>
<tr>
<td></td>
<td>– iritis ≥ 1, and/or</td>
</tr>
<tr>
<td></td>
<td>– conjunctival redness ≥ 2 and/or</td>
</tr>
<tr>
<td></td>
<td>– conjunctival oedema (chemosis) ≥ 2</td>
</tr>
<tr>
<td></td>
<td>– 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</td>
</tr>
</tbody>
</table>

3.3.2.7.2. For those substances where there is pronounced variability among animal responses, this information shall be taken into account in determining the classification.

The classification criteria apply to the results of the OECD TG 405 and to the results of the LVET. Negative data from the LVET are not conclusive for non-classification, but should be considered in a weight of evidence determination.

3.3.2.3. Evaluation of hazard information

3.3.2.3.1. Evaluation of human data

Quality data on substance-induced eye irritation in humans are likely to be rare. Where human data are available, the usefulness of such data for classification purposes will depend on the extent to which the effect, and its magnitude, can be reliably attributed to the substance of interest. The quality and relevance of such data for hazard assessment should be critically reviewed.

If a substance is diagnostically confirmed by a physician to be the cause for decay in vision with the effects not being transient but persistent this should lead to the most serious eye classification, i.e. Eye Damage Category 1.

Further information on the evaluation of human data for eye irritation can be found in IR/CSA Section R7.2.4.2.
3.3.2.3.2 Evaluation of non-human data

The results of the non-testing methods fulfilling the criteria of REACH Annex XI paragraphs 1.3 and 1.5 should be used instead of testing or as part of the weight of evidence approach.

3.3.2.3.2.1 In-vitro data

Only positive results in the BCOP, ICE, IRE and HET-CAM in vitro assays can be used for classification as severe eye irritants. Negative results are not conclusive for a non-classification.

There are currently no validated in vitro eye irritation test methods available. However, two reconstituted human tissue models (the EpiOcular™ and SkinEthic™ HCE models) are undergoing formal validation.

3.3.2.3.2.2 In-vivo data

Tests in albino rabbits (OECD TG 405)

Evaluation criteria for local effects on the eye are severity of the damage and reversibility.

For the severity of damage the degree of inflammation is assessed. Responses are graded according to the grading of ocular lesions in OECD TG 405.

Evaluation takes place separately for cornea, iris and conjunctiva (erythema and swelling). If the scoring meets the criteria in Annex I, Tables 3.3.1 / 3.3.2, the substances are classified as Category 1 for serious eye damage or Category 2 for eye irritation, respectively.

Reversibility of eye lesions is the other decisive factor in evaluating responses in the animal test. If the effects are not transient within the observation time of 21 days but cause persistent damage, they are considered irreversible and the test substance needs to be classified into Category 1. In the case of studies with a shorter observation period with irreversible effects, classification based on expert judgement should be considered.

With regard to reversibility the test report must prove that these effects are transient, i.e. the affected sites are repaired within the observation period of the test (see Example 1). Evaluation of reversibility or irreversibility of the observed effects does not need to exceed 21 days after instillation for the purpose of classification.

According to OECD TG 405, in cases of suspected serious eye damage, the test is started with one animal only. If effects in this animal are irreversible until the end of the observation period, sufficient information is available to classify the substance for serious eye damage. For a decision on no classification for serious eye damage and/or irritation or for a decision on classification as irritant, two additional animals have to be tested.

For each of the three test animals the average scores for three consecutive days (usually 24, 48 and 72 hours) are calculated separately for the cornea, iris and conjunctiva (erythema and swelling). If the mean scores for 2 out of 3 animals exceed the values in Tables 3.3.1 / 3.3.2, classification has to be assigned accordingly.

Tests that have been conducted with more than three animals

Older test methods, however, have been using up to six rabbits. The CLP does not provide criteria for the evaluation of such studies. The current US EPA/UN Recommendation may be considered (see Example 2):

In case of 6 rabbits the following applies:
Classification as serious eye damage – Category 1 if at least in one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days; and/or at least 4 out of 6 rabbits show a mean score of ≥ 3 for the cornea and/or ≥ 1.5 for the iris.

Classification as eye irritation – Category 2 if at least 4 out of 6 rabbits show a mean score of ≥ 1 for the cornea and/or ≥ 1 for the iris and/or ≥ 2 conjunctival erythema and/or ≥ 2 conjunctival swelling.

In case of 5 rabbits the following applies:

Classification as serious eye damage – Category 1 if at least in one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days; and/or at least 3 out of 5 rabbits show a mean score of ≥ 3 for the cornea and/or ≥ 1.5 for the iris.

Classification as eye irritation – Category 2 if at least 3 out of 5 rabbits show a mean score of ≥ 1 for the cornea and/or ≥ 1 for the iris and/or ≥ 2 conjunctival erythema and/or ≥ 2 conjunctival swelling.

In case of 4 rabbits the following applies:

Classification as serious eye damage – Category 1 if at least in one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days; and/or at least 3 out of 4 rabbits show a mean score of ≥ 3 for the cornea and/or ≥ 1.5 for the iris.

Classification as eye irritation – Category 2 if at least 3 out of 4 rabbits show a mean score of ≥ 1 for the cornea and/or ≥ 1 for the iris and/or ≥ 2 conjunctival erythema and/or ≥ 2 conjunctival swelling.

In this case the irritant categories 1 and 2 are used if 4 of 6 rabbits show a mean score as outlined in the criteria. Likewise, if the test was performed with 4 or 5 animals, for at least 3
individuals the mean score must exceed the values laid down in the classification criteria. A single animal showing irreversible or otherwise serious effects consistent with corrosion will necessitate classification as serious eye damage Category 1 irrespective of the number of animals used in the test.

Other animal tests
The LVET uses the same scoring system as for results from the OECD TG 405, but data from the test is not conclusive for a non-classification. However, they can be included in a weight of evidence determination.

Note that in case there are test data that originate from non-OECD tests and scoring has not been performed according to the Draize system, the values in Annex I, Tables 3.3.1 / 3.3.2 are no longer applicable for classification purposes. However these data from non-OECD tests should be considered in a weight of evidence determination.

3.3.2.3 Weight of evidence
Where the criteria cannot be applied directly to available identified information, a weight of the evidence determination using expert judgement shall be applied in accordance with CLP Article 9(3).

A weight of the evidence determination means that all available and scientifically justified information bearing on the determination of hazard is considered together, such as human experience (including occupational data and data from accident databases, epidemiological and clinical studies, and well-documented case reports and observations), relevant animal data, skin irritation information/data, physico-chemical parameters (e.g., pH, reserve alkalinity/acidity), the results of suitable in vitro tests, information from the application of the category approach (grouping, read-across), QSAR results. The quality and consistency of the data shall be given appropriate weight. Both positive and negative results shall be assembled together in a single weight of evidence determination. Evaluation must be performed on a case-by-case basis and with expert judgement. However, normally positive results that are adequate for classification should not be overruled by negative findings.

For further guidance, if both human and animal data are available, see IR/CSA Section R.7.2.3.2.

3.3.2.4 Decision on classification
A skin corrosive substance is considered to also cause serious eye damage which is indicated in the hazard statement for skin corrosion (H 314: Causes severe skin burns and eye damage).
Thus, in case a substance has to be classified for skin corrosion an additional classification with H318 “Causes serious eye damage” is not indicated.

3.3.2.5 Setting of specific concentration limits

Whenever adequate and reliable scientific information shows that the hazard of a substance is present in a mixture when the substance is present below the generic concentration limit (GCL), this information shall be used to establish a specific concentration limit (SCL) for the substance (second subparagraph of CLP Article 10(1)).

It is more difficult to prove the absence of a hazardous property. Therefore, only in exceptional circumstances, where adequate, reliable and conclusive scientific information is available showing that an irritation hazard for humans of that particular substance in a mixture above the GCL is not evident, may a specific concentration limit which is higher than the generic one be set (third subparagraph of Article 10(1) of CLP).

An SCL overrules any GCL set out in Tables 3.2.3 and 3.2.4 of Annex I to CLP (CLP Article 10(6)). Furthermore, an SCL is substance-specific and should be applicable to all mixtures containing the substance.

What type of information may be the basis for setting a specific concentration limit?

The aim of the standard test method for acute eye irritation/corrosion TM B.5/OECD TG 405 is to identify a corrosive or an irritant. The method uses a sequential testing strategy starting with one animal and using a maximum of three animals. The test substance is generally administered undiluted. Thus, no dose-response relationship can be obtained from this test. The test is therefore not designed and is not sufficiently sensitive to directly identify a threshold below which a substance in a mixture may not cause serious eye damage/eye irritation to humans. Consequently, the method is not appropriate for testing dilutions in order to demonstrate non-irritating thresholds, as required to set a higher SCL than the GCL. In other words, this test method cannot generate data which are sufficiently adequate, reliable and conclusive to form a scientifically valid basis upon which a generic scheme for deriving higher SCLs reflecting a threshold for irritation in humans can be built.

However, existing human data may in certain cases (especially if dose-response information is available) indicate that the threshold for the irritation hazard in humans would be higher or lower than the GCL for a substance in a mixture. 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, 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 degree of statistical certainty of both the human and animal data.

Also, if adequate, relevant and conclusive data exist from already performed animal studies (other than TM B.5/TG 405) with a sufficient number of animals tested to ensure a high degree of statistical 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.

However, it should be noted that any additional animal testing (of dilutions) of already classified as a serious eye irritant/eye irritant substance, is not encouraged and may only take place on a case-by-case basis if there are no alternatives providing adequate reliability and quality of data (see CLP Articles 7(1) and 8(1)).
Annex VI to CLP includes example substances for which a higher or lower SCL was set under Directive 67/548/EEC (old DSD system). An example of the justification for a lower SCL can be found in the EU Technical Committee for Classification and Labelling (TC C&L) documents ECBI/46/95 Add. 41.

As demonstrated in the TC C&L document ECBI/46/95 Add. 41 mentioned above, a lower SCL should be considered if serious eye damage/eye irritation are caused by dilutions. Thus, testing dilutions based on TM B.5/TG 405 could be justified on a case-by-case basis but only with a view to setting lower SCLs and if there are no alternatives etc (see above and Articles 7(1) and 8(1) of CLP).

### 3.3.2.6 Decision logic

The decision logic which is based on IR/CSA, Figure R.7.2-3 is revised to meet CLP requirements. It is strongly recommended that the person responsible for classification, study the criteria for classification before and during use of the decision logic.

<table>
<thead>
<tr>
<th>Step</th>
<th>Question</th>
<th>Pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Is the substance classified as a skin corrosive?</td>
<td>When classified as Skin Corr. 1, the risk of severe damage to eyes is considered implicit. No need to proceed.</td>
</tr>
<tr>
<td></td>
<td>YES ➔</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NO ➔</td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td>Is the substance an organic hydro peroxide or an organic peroxide?</td>
<td>Consider to classify as serious eye damage (Eye Dam. 1) if the substance is a hydro peroxide, or eye irritating (Eye Irrit. 2) if the substance is a peroxide. OR Provide evidence for the contrary and proceed to step 1b</td>
</tr>
<tr>
<td></td>
<td>YES ➔</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NO ➔</td>
<td></td>
</tr>
<tr>
<td>1b</td>
<td>Is the pH of the substance ≤ 2 or ≥ 11.5?</td>
<td>Where classification is based upon consideration of pH alone (i.e. buffering capacity not known), Eye Dam. 1 should be applied. When assigned Skin Corr. 1, the risk of severe damage to eyes is considered implicit. Where consideration of the alkali/alkaline reserve suggests that the substance is not corrosive, this has to be confirmed (preferably by use of an appropriate in vitro test). Proceed to step 1c</td>
</tr>
<tr>
<td></td>
<td>YES ➔</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NO ➔</td>
<td></td>
</tr>
<tr>
<td>1c</td>
<td>Are there other physical or chemical properties that indicate that the substance has the potential to cause serious eye damage or is irritating to the eye?</td>
<td>Use this information for weight of evidence (WoE) determination (step 6). Proceed to step 2</td>
</tr>
<tr>
<td></td>
<td>YES ➔</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NO ➔</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Is there adequate existing human experience</td>
<td>Classify accordingly (Eye Dam. 1 or Eye</td>
</tr>
</tbody>
</table>

Deleted: Whenever adequate and reliable scientific information shows that the hazard of a substance is present in a mixture below the generic concentration limit, this information should be used to establish a specific concentration limit for the substance. This limit overrules the generic concentration limit detailed in CLP tables 3.2.3 and 3.2.4 ¶. It is more difficult to prove the lack of a hazardous property. Therefore, only in exceptional circumstances, where adequate, reliable and conclusive scientific information is available, a specific concentration limit which is higher than the generic one could be set. ¶ Note that an SCL is substance specific and should be applicable on all mixtures containing the substance. ¶ Confirmation is also needed that the dilutions of the test substance were made using a suitable vehicle to ensure the test substance was actually dissolved and was not a sole dispersion. ¶
which provides evidence that the substance has the potential to cause serious eye damage or is irritating to the eye? **YES ➔**

**NO ➔**

| 3 | Are there data from existing studies *on eye irritation* in laboratory animals, which provide sound conclusive evidence that the substance has the potential to cause serious eye damage, is an eye irritant or non-irritant? **YES ➔**

| 4 | Are there structurally related substances (suitable “read-across” or grouping), which are classified as serious eye damage or eye irritant, or do valid QSAR methods indicate the presence/absence of serious eye damage/eye irritation potential of the substance? **YES ➔**

| 5a | Are there data from a validated *in vitro* test (adopted by OECD or not), which provide evidence that the substance is an eye irritant or non-irritant? **YES ➔**

| 5b | Are there acceptable data from a suitable *in vitro* test, which provide evidence that the substance is a severe eye irritant? **YES ➔**

| 6 | Taking all existing and relevant data into account, is there sufficient information to make a decision on classification? **YES ➔**

| Unable to classify substance for serious eye damage/eye irritation | Decision to undertake generation of new test data should be made in compliance with REACH and Article 8 of the CLP. It is recommended that ECHA guidance R.7.2.6 should also be considered. |
3.3.3 Classification of mixtures for serious eye damage/eye irritation

3.3.3.1 Identification of hazard information

The procedure for classifying mixtures is a tiered i.e. a stepwise approach based on a hierarchy principle and depending on the type and amount of available data/information starting from evaluating existing human data on the mixture, followed by a thorough examination of the existing \textit{in vivo} data, physico-chemical properties, and finally \textit{in vitro} data available on the mixture. If valid test data are available for the whole mixture they have precedence. If no such data exist, the so called bridging principles have to be applied if possible. If the bridging principles are not applicable an assessment on the basis of data for the components of the mixture will be applied.

Where it is decided to base the classification of a mixture upon consideration of pH alone, Eye Damage Category 1 should be applied. In this case no further retrieval of information on the mixture itself is needed.

3.3.3.1.1 Identification of existing human data

For mixtures that have been on the market for a long time, some human data and experience may exist that could provide useful information on the eye irritation potential of the respective mixtures. However, lack of data on effects in humans may be due to, for example, poor reporting or adequate preventive measures. Therefore, lack of data cannot be taken as evidence of the mixture being non-hazardous. See section 3.3.2.1.1 for further information on the identification of human data.

3.3.3.2 Classification criteria

3.3.3.2.1 When data are available for the complete mixture

\textbf{Annex I: 3.3.3.1.1.} The mixture will be classified using the criteria for substances, and taking into account the testing and evaluation strategies used to develop data for these hazard classes.

Unlike other hazard classes, there are alternative tests available for skin corrosivity of certain types of mixtures that give an accurate result for classification purposes, as well as being simple and relatively inexpensive to perform. When considering testing of the mixture classifiers are encouraged to use a tiered weight of evidence strategy as included in the criteria for classification of substances for skin corrosion and serious eye damage and eye irritation to help ensure an accurate classification, as well as avoid unnecessary animal testing. A mixture is considered to cause serious eye damage (Category 1) if it has a pH ≤ 2.0 or ≥ 11.5. If consideration of alkali/acid reserve suggests the mixture may not have the potential to cause serious eye damage despite the low or high pH value, then further testing needs to be carried out to confirm this, preferably by use of an appropriate validated \textit{in vitro} test.

Where the criteria cannot be applied directly to available identified information, a weight of evidence determination using expert judgement shall be applied in accordance with CLP Article 9(3). A weight of the evidence determination means that all available and scientifically justified information bearing on the determination of hazard is considered together, such as physico-chemical parameters, the results of suitable \textit{in vitro} tests, relevant animal data, and human experience. The quality and consistency of the data shall be given appropriate weight. Both positive and negative results shall be assembled together in a single weight of evidence determination.

The integration of all information to come to a final hazard assessment based on weight of evidence in general requires in-depth toxicological expertise.
There are a number of available \textit{in vitro} test systems that currently being validated for their suitability in assessing serious eye damage/eye irritation potential of substances and mixtures. When validated \textit{in vitro} eye irritation test methods are available in the future the results from such tests can be used for classification. Then these results can also be used to classify the mixture. However, not all available in vitro test systems work equally well for all types of mixtures. Prior to testing a mixture in a specific in vitro assay for classification purposes, it has to be assured that the respective test has been previously shown to be suitable for the prediction of serious eye damage/eye irritation properties for the type of mixture to be evaluated.

3.3.3.2.1 Mixtures with extreme pH

Where the mixture has an extreme pH value but the only corrosive/irritant ingredient present in the mixture is an acid or base with an assigned SCL (either CLP Annex VI or set by supplier), then the mixture should be classified accordingly. In this instance, pH of the mixture should not be considered a second time since it would have already been taken into account when deriving the SCL for the substance.

If this is not the case, then the steps to be taken into consideration when classifying a mixture with pH $\leq 2$ or $\geq 11.5$ are described in the following decision logic:

\begin{tabular}{|l|l|}
\hline
Mixture not classified as Skin Corr. 1 and without \textit{in vivo} data on serious eye damage/eye irritation or relevant data from similar tested mixtures. & \\
\textbf{pH} is $\leq 2$ or $\geq 11.5$ & \\
\hline
Does the acid/alkaline reserve indicate that the mixture may not be corrosive? & Classify as serious eye damaging, Eye Dam. 1. \\
\textbf{YES} & \\
\textbf{NO} & \\
\hline
Is the mixture tested for serious eye damaging properties in an accepted \textit{in vitro} test? & Classify as serious eye damaging, Eye Dam. 1. \\
\textbf{YES} & \\
\textbf{NO} & \\
\hline
Does the mixture demonstrate serious eye damaging properties in an accepted \textit{in vitro} test? & Classify as serious eye damaging, Eye Dam. 1. \\
\textbf{NO} & \\
\textbf{YES} & \\
\hline
Apply methods in Annex I, 3.3.3.3.2 (Table 3.3.3) / 3.3.3.3.4 (Table 3.3.4) (When validated \textit{in vitro} eye irritation test methods are available, these may be used to generate data to classify the mixture instead of using the summation method.) & Classify accordingly. \\
\end{tabular}

If consideration of extreme pH and acid/alkaline reserve indicates the mixture may not have the potential to cause serious eye damage, then the supplier should carry out further testing to confirm this (Annex I, section 3.3.3.2.1). The mixture must be classified as Serious eye damage Category 1 if the supplier decide not to carry out the required confirmatory testing.
If further testing confirms that the mixture should not be classified for serious eye damage effects, then the supplier should assess the mixture for eye irritation either using *in vitro* eye irritation test methods when available or the summation method.

It must be 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-reserve method cannot be a basis for modifying the classification.

Where the mixture has an extreme pH value and contains some other corrosive/irritant ingredients (some of which may have SCLs assigned) in addition to an acid or base with or without an assigned SCL, then the mixture shall follow the procedure described in the decision logic.

### 3.3.3.2.2 When data are not available for the complete mixture: bridging principles

Annex I: 3.3.3.2.1. Where the mixture itself has not been tested to determine its skin corrosivity or potential to cause serious eye damage or irritation, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterise the hazards of the mixture, these data shall be used in accordance with the bridging rules set out in section 1.1.3.

In order to apply bridging principles, there needs to be sufficient data on similar tested mixtures as well as the components of the mixture.

When the available identified information is inappropriate for the application of the bridging principles then the mixture should be classified using the methods described in Section 1.1.3.2.3.

### 3.3.3.2.3 When data are available for all components or only for some components of the mixture

#### 3.3.3.2.3.1 Components that should be taken into account for the purpose of classification

Annex I: 3.3.3.3.1. ….. Assumption: The 'relevant ingredients' of a mixture are those which are present in concentrations of 1% (w/w for solids, liquids, dusts, mists and vapours and v/v for gases) or greater, unless there is a presumption (e.g. in the case of corrosive ingredients) that an ingredient present at a concentration of less than 1% is still relevant for classifying the mixture for eye irritation/serious eye damage.

#### 3.3.3.2.3.2 The additivity approach is applicable

Annex I: 3.3.3.3.2. In general, the approach to classification of mixtures as eye irritant or seriously damaging to the eye when data are available on the components, but not on the mixture as a whole, is based on the theory of additivity, such that each corrosive or irritant component contributes to the overall irritant or corrosive properties of the mixture in proportion to its potency and concentration. A weighting factor of 10 is used for corrosive components when they are present at a concentration below the generic concentration limit for classification in Category 1, but are at a concentration that will contribute to the classification of the mixture as an irritant. The mixture is classified as seriously damaging to the eye or eye irritant when the sum of the concentrations of such components exceeds a concentration limit.

3.3.3.3.3. Table 3.3.3 provides the generic concentration limits to be used to determine if the mixture shall be classified as irritant or as seriously damaging to the eye.
When the supplier is unable to derive the classification using either data on the mixture itself or bridging principles, he must determine the serious eye damage/eye irritation properties of his mixture using data on the individual ingredients. The supplier must ascertain whether the additivity approach is applicable, the first step in the process being to identify all the ingredients in the mixture (i.e. their name, chemical type, concentration level, hazard classification and any SCLs) and the pH of the mixture. In addition, for example surfactant interaction or neutralisation of acids/bases could occur in a mixture, which makes it important to consider not only the contribution of individual ingredients but also the effects of the entire mixture.

Additivity may not apply where the mixture contains substances mentioned in Annex I, 3.3.3.3.4.1 which may be corrosive/irritant at concentrations below 1%, see section 3.3.3.3.3.3.

**Application of SCLs when applying the additivity approach**

The generic concentration limits are specified in Table 3.3.3. However, Article 10.5 indicates that specific concentration limits (SCLs) take precedence over generic concentration limits. Thus, if a given substance has a SCL, then this specific concentration limit has to be taken into account when applying the summation (additivity) method for serious eye damage/eye irritation (see Examples 4 and 5).

In cases where additivity applies for serious eye damage/eye irritation to a mixture with two or more substances some of which may have SCLs assigned, then the following formula should be used:

The mixture is classified for serious eye damage/eye irritation if the sum of the concentrations of all substances divided by their concentration limits is greater than or equal to 1.

Where:

- ConcA = the concentration of substance A in the mixture;
- clA = the concentration limit (either specific or generic) of substance A;
- ConcB = the concentration of substance B in the mixture;
- clB = the concentration limit (either specific or generic) of substance B; etc.

This approach is similar to that used in the DPD where a substance SCL can replace the default limits in the conventional method equations.

### 3.3.3.3.3.3 The additivity approach is not applicable

#### 3.3.3.3.3.4.1

Particular care must be taken when classifying certain types of mixtures containing substances such as acids and bases, inorganic salts, aldehydes, phenols, and surfactants. The approach explained in paragraphs 3.3.3.3.1 and 3.3.3.3.2 might not work given that many of such substances are corrosive or irritant at concentrations < 1 %.

#### 3.3.3.3.3.4.2

For mixtures containing strong acids or bases the pH shall be used as classification criteria (see paragraph 3.3.2.3) since pH will be a better indicator of serious eye damage than the generic concentration limits of Table 3.3.3.

#### 3.3.3.3.3.4.3

A mixture containing corrosive or irritant ingredients that cannot be classified based on the additivity approach (Table 3.3.3), due to chemical characteristics that make this approach unworkable, shall be classified as Category 1 for effects on the eye if it contains ≥ 1 % of a corrosive ingredient and as Category 2 when it contains ≥ 3 % of an irritant ingredient. Classification of mixtures with ingredients for which the approach in Table 3.3.3 does not apply is summarised in Table 3.3.4.

#### 3.3.3.3.5

On occasion, reliable data may show that the reversible/irreversible eye effects of an...
1.  

**3.3.3 Generic concentration limits for substances triggering classification of mixtures**

2.  

**3.3.3.1 When the additivity approach is applicable**

<table>
<thead>
<tr>
<th>Sum of ingredients classified as:</th>
<th>Concentration triggering classification of a mixture as:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Irreversible Eye Effects</td>
</tr>
<tr>
<td>Eye effects Category 1 or Skin corrosive Category 1A, 1B, 1C</td>
<td>≥ 3 %</td>
</tr>
<tr>
<td>Eye Effects Category 2</td>
<td></td>
</tr>
<tr>
<td>(10 x Eye Effects Category 1) + Eye effects Category 2</td>
<td></td>
</tr>
<tr>
<td>Skin Corrosive Category 1A, 1B, 1C + Eye Effects Category 1</td>
<td>≥ 3 %</td>
</tr>
<tr>
<td>10 x (Skin corrosive Category 1A, 1B, 1C + Eye Effects Category 1) + Eye Effects Category 2</td>
<td></td>
</tr>
</tbody>
</table>

4.  

**3.3.3.2 When the additivity approach is not applicable**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Concentration</th>
<th>Mixture classified as: Eye</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid with pH ≤ 2</td>
<td>≥ 1%</td>
<td>Category 1</td>
</tr>
<tr>
<td>Base with pH ≥ 11.5</td>
<td>≥ 1%</td>
<td>Category 1</td>
</tr>
<tr>
<td>Other corrosive (Categories 1) ingredients for which additivity does not apply</td>
<td>≥ 1%</td>
<td>Category 1</td>
</tr>
<tr>
<td>Other irritant (Category 2) ingredients for which additivity does not apply</td>
<td>≥ 3%</td>
<td>Category 2</td>
</tr>
</tbody>
</table>
There are ongoing discussions at UN level whether 'Other irritant (Category 2) ingredients' in Table 3.3.4 (last row) include skin and eye irritants or only eye irritants.

### 3.3.3.4 Decision logic

The decision logic which is based on IR/CSA, Figure R.7.2-3 is revised to meet CLP requirements. It is strongly recommended that the person responsible for classification, study the criteria for classification before and during use of the decision logic.

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
<th>Decision 1</th>
<th>Decision 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Is the mixture classified as a skin corrosive?</td>
<td>YES ➔ No need to proceed.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td>Is the pH of the mixture ≤ 2 or ≥ 11.5?</td>
<td>YES ➔ Where classification is based upon consideration of pH alone (i.e. buffering capacity not known), Eye Dam. 1 should be applied. When assigned Skin Corr. 1, the risk of severe damage to eyes is considered implicit. Where consideration of the acid/alkaline reserve suggests that the substance is not corrosive, this has to be confirmed (preferably by use of an appropriate in vitro test). Proceed to step 1b.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1b</td>
<td>Are there other physical or chemical properties that indicate that the mixture has the potential to cause serious eye damage or is irritating to the eye?</td>
<td>YES ➔ Use this information for weight of evidence (WoE) determination (step 6). Proceed to step 2.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Are there adequate existing human experience data which provide evidence that the mixture has the potential to cause serious eye damage or is irritating to the eye?</td>
<td>YES ➔ Classify accordingly (Eye Dam. 1 or Skin Irrit. 2).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Are there data from existing studies on eye irritation in laboratory animals, which provide sound conclusive evidence that the mixture has the potential to cause serious eye damage, is an eye irritant or non-irritant?</td>
<td>YES ➔ Classify accordingly (Eye Dam. 1 or Eye Irrit. 2 or no classification).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4a</td>
<td>Are there data from a validated in vitro or ex</td>
<td>Consider to classify accordingly (Eye Dam.</td>
<td></td>
</tr>
</tbody>
</table>

156
<table>
<thead>
<tr>
<th><strong>Guidance to Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of substances and mixtures</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>vivo</strong> test (adopted by OECD or not), which provide evidence that the mixture is an eye irritant or non-irritant? <strong>YES</strong></td>
</tr>
<tr>
<td><strong>NO</strong></td>
</tr>
<tr>
<td><strong>4b</strong></td>
</tr>
<tr>
<td><strong>NO</strong></td>
</tr>
<tr>
<td><strong>5</strong></td>
</tr>
<tr>
<td><strong>NO</strong></td>
</tr>
<tr>
<td><strong>2. When data are not available for the complete mixture: bridging principles</strong></td>
</tr>
<tr>
<td><strong>6a</strong></td>
</tr>
<tr>
<td><strong>YES</strong></td>
</tr>
<tr>
<td><strong>6b</strong></td>
</tr>
<tr>
<td><strong>NO</strong></td>
</tr>
<tr>
<td><strong>3. When data are available for all components or only for some components of the mixture</strong></td>
</tr>
<tr>
<td><strong>7a</strong></td>
</tr>
<tr>
<td><strong>NO</strong></td>
</tr>
<tr>
<td><strong>7b</strong></td>
</tr>
<tr>
<td><strong>NO</strong></td>
</tr>
</tbody>
</table>
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>
<thead>
<tr>
<th>Classification</th>
<th>Category 1</th>
<th>Category 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>GHS Pictograms</td>
<td><img src="image" alt="Pictogram" /></td>
<td><img src="image" alt="Pictogram" /></td>
</tr>
<tr>
<td>Signal Word</td>
<td>Danger</td>
<td>Warning</td>
</tr>
<tr>
<td>Hazard Statement</td>
<td>H318: Causes serious eye damage</td>
<td>H319: Causes serious eye irritation</td>
</tr>
<tr>
<td>Precautionary Statement Prevention</td>
<td>P280</td>
<td>P264</td>
</tr>
<tr>
<td>Precautionary Statement Response</td>
<td>P305 + P351 + P338 P310</td>
<td>P305 + P351 + P338 P337 + P313</td>
</tr>
<tr>
<td>Precautionary Statement Storage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precautionary Statement Disposal</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A skin corrosive mixture is considered to also cause serious eye damage which is indicated in the hazard statement for skin corrosion, H 314: Causes severe skin burns and eye damage. Thus, in case a mixture has to be classified for skin corrosion an additional classification with H318: Causes serious eye damage is not indicated.

3.3.5 Re-classification of substances and mixtures classified for serious eye damage/eye irritation according to DSD and DPD

3.3.5.1 Is direct “translation” of classification and labelling possible?

A direct translation as indicated in the translation table in Annex VII to CLP is generally possible. However, an evaluation and classification must be carried out in accordance with CLP Articles 9 – 13 when data for the mixture are available. Translation from classification according to DSD to the classification according to CLP is as follows:

- Xi; R41 is translated into Eye Dam. 1; H318. The criteria in DSD are completely covered by the criteria in CLP.
- Xi; R36 is translated into Eye Irrit. 2; H 319. The criteria in DSD are completely covered by the criteria in CLP.
It should be noted that CLP eye irritation Category 2 will include more substances which are currently not classified under the DSD, but with values of cornea opacity >1 and <2 or values of conjunctival redness >2 and < 2.5, will be classified as eye irritants under CLP.

It should be noted that where mixtures containing substances with risk phrase R41 have been classified on basis of the hazards of individual ingredients, the use of the translation table may lead to an under-classification of the mixture. This is because the general concentration limits, to be applied for mixtures, are lowered under CLP compared to DPD. For mixtures containing substances with this classification the use of the translation table may therefore not be appropriate and re-classification done by using the existing data would be more correct. For more details see Chapter 1.7.

3.3.5.2 Re-evaluation of data

If there is new information which might be relevant with respect to classification a re-evaluation has to be performed.

3.3.6 Examples of classification for serious eye damage/eye irritation

3.3.6.1 Examples of substances fulfilling the criteria for classification

3.3.6.1.1 Example 1: Standard test according to OECD TG 405 with three animals

In a study according to OECD 405 the test substance was applied on the eyes of three rabbits. The scoring results obtained are listed in the following table:

<table>
<thead>
<tr>
<th>Animal Nr</th>
<th>Evaluation after …</th>
<th>Positive responder?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 hr</td>
<td>24 hrs</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Effects are reversible

<table>
<thead>
<tr>
<th>Animal Nr</th>
<th>Evaluation after …</th>
<th>Positive responder?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 hr</td>
<td>24 hrs</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
### Guidance to Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of substances and mixtures

<table>
<thead>
<tr>
<th>Animal #</th>
<th>1 hr</th>
<th>24 hrs</th>
<th>48 hrs</th>
<th>72 hrs</th>
<th>21 days</th>
<th>Positive responder?</th>
<th>Score …</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>Yes</td>
<td>≥ 2</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

Effects are reversible

**Conjunctiva – Erythema:**

<table>
<thead>
<tr>
<th>Animal #</th>
<th>1 hr</th>
<th>24 hrs</th>
<th>48 hrs</th>
<th>72 hrs</th>
<th>21 days</th>
<th>Positive responder?</th>
<th>Score …</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>Yes</td>
<td>≥ 2</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

Effects are reversible

**Conjunctiva – Swelling:**

<table>
<thead>
<tr>
<th>Animal #</th>
<th>1 hr</th>
<th>24 hrs</th>
<th>48 hrs</th>
<th>72 hrs</th>
<th>21 days</th>
<th>Positive responder?</th>
<th>Score …</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>Yes</td>
<td>≥ 2</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

Effects are reversible

Classification according to CLP: Eye irritant Category 2

Rationale: Cornea and Conjunctiva "positive responder" ≥ 2: 2/3 animals

Iris "positive responder" ≥ 1: 3/3 animals

3.3.6.1.2 Example 2: Test carried out with more than 3 rabbits

Cornea:
### Guidance to Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of substances and mixtures

#### Evaluation after …

<table>
<thead>
<tr>
<th>Anima l No.</th>
<th>1h</th>
<th>24h</th>
<th>48h</th>
<th>72h</th>
<th>7d</th>
<th>14d</th>
<th>21d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>∅24/48/72h = 2.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>∅24/48/72h = 2.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>∅24/48/72h = 2.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>∅24/48/72h = 3.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>∅24/48/72h = 2.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>∅24/48/72h = 2.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>∅24/48/72h = 2.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Effects are reversible**

#### Iris:

<table>
<thead>
<tr>
<th>Anima l No.</th>
<th>1h</th>
<th>24h</th>
<th>48h</th>
<th>72h</th>
<th>7d</th>
<th>14d</th>
<th>21d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>∅24/48/72h = 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>∅24/48/72h = 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>∅24/48/72h = 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>∅24/48/72h = 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Effects are reversible**

#### Conjunctiva – Erythema:

<table>
<thead>
<tr>
<th>Anima l No.</th>
<th>1h</th>
<th>24h</th>
<th>48h</th>
<th>72h</th>
<th>7d</th>
<th>14d</th>
<th>21d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>∅24/48/72h = 1.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

161
Effects are NON-reversible

Conjunctiva – Swelling:

<table>
<thead>
<tr>
<th>Animal No.</th>
<th>Evaluation after …</th>
<th>Positive responder?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1h 24h 48h 72h 7d 14d 21d</td>
<td>Ø Score …</td>
</tr>
<tr>
<td>1</td>
<td>2 2 2 1 1 1 0</td>
<td>Ø 24/48/72h = 1.7</td>
</tr>
<tr>
<td>2</td>
<td>2 2 1 1 0 0 0</td>
<td>Ø 24/48/72h = 1.3</td>
</tr>
<tr>
<td>3</td>
<td>2 2 2 1 1 1 1</td>
<td>Ø 24/48/72h = 1.7</td>
</tr>
<tr>
<td>4</td>
<td>2 2 2 1 1 1 1</td>
<td>Ø 24/48/72h = 1.7</td>
</tr>
</tbody>
</table>

Effects are NON-reversible

Classification according to CLP: Serious eye damage Category 1

Rationale: Conjunctiva with irreversible effects

3.3.6.2 Examples of mixtures fulfilling the criteria for classification

3.3.6.2.1 Example 3: Application of the additivity approach for mixtures containing ingredients without SCLs

Where the mixture is made up of ingredients with no assigned SCLs, then the appropriate summation(s) from Table 3.3.3 should be used.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Skin / eye classification</th>
<th>Concentration (% w/w)</th>
<th>SCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surfactant A</td>
<td>Eye Cat 1</td>
<td>1.8</td>
<td>Not assigned</td>
</tr>
<tr>
<td>Substance B</td>
<td>Eye Cat 2</td>
<td>0.5</td>
<td>Not assigned</td>
</tr>
<tr>
<td>Substance C</td>
<td>Eye Cat 1</td>
<td>5.4</td>
<td>Not assigned</td>
</tr>
<tr>
<td>Substance D</td>
<td>Not classified</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>Acid E</td>
<td>Skin Cat 1A</td>
<td>2.0</td>
<td>Not assigned</td>
</tr>
</tbody>
</table>
pH of the mixture is 9.0 – 10.0, thus extreme pH provisions do not apply. The mixture contains a surfactant and an acid but neither are corrosive/irritant below 1% (as identified by the absence of specific concentration limits in either CLP Annex VI or the Classification and Labelling Inventory). Additivity is considered to apply. Substance D and water can be disregarded as they are not classified for serious eye damage/eye irritation. Substance B can also be disregarded as present below 1%.

Mixture contains 7.2% Eye Cat 1 ingredients as well as 2% acid E so the summation {Skin corrosion Cat 1A, 1B, 1C + Eye Cat 1} applies and is > 3%, thus mixture is classified Eye Cat 1.

### 3.3.6.2.2 Example 4: Application of the additivity approach for mixtures containing ingredients which may have SCLs

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Skin / eye classification</th>
<th>Concentration (% w/w)</th>
<th>SCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surfactant A</td>
<td>Eye Cat 1</td>
<td>2.0</td>
<td>Not assigned</td>
</tr>
<tr>
<td>Substance B</td>
<td>Eye Cat 2</td>
<td>0.5</td>
<td>Not assigned</td>
</tr>
<tr>
<td>Substance C</td>
<td>Skin Cat 1B</td>
<td>5.4</td>
<td>C ≥ 10 %: Skin Cat 1B 5 % ≤ C &lt; 10 %: Eye Cat 2</td>
</tr>
<tr>
<td>Substance D</td>
<td>Not classified</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>Substance E</td>
<td>Skin Cat 1B</td>
<td>2.0</td>
<td>Not assigned</td>
</tr>
<tr>
<td>Water</td>
<td>Not classified</td>
<td>86.1</td>
<td></td>
</tr>
</tbody>
</table>

pH of the mixture is 10.5 – 11.0, thus extreme pH provisions do not apply. The mixture contains a surfactant, an acid and a base but none are corrosive/irritant below 1% (as identified by the absence of specific concentration limits in either CLP Annex VI or the Classification and Labelling Inventory). Additivity is considered to apply. Substance D and water can be disregarded as they are not classified for serious eye damage/eye irritation. Substance B can also be disregarded as present below 1%.

SCLs are not assigned to substance E or surfactant A, thus generic concentration limits (GCL) apply for these ingredients

### 3.3.6.2.3 Example 5: Application of the additivity approach for mixtures containing ingredients which may have SCLs

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Serious eye damage/eye irritation classification</th>
<th>Concentration (% w/w)</th>
<th>SCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surfactant B</td>
<td>Eye Cat 1</td>
<td>0.7</td>
<td>Not assigned</td>
</tr>
<tr>
<td>Substance C</td>
<td>Eye Cat 2</td>
<td>74.9</td>
<td>Not assigned</td>
</tr>
<tr>
<td>Substance D</td>
<td>Eye Cat 1</td>
<td>8.5</td>
<td>C ≥ 25 %: Eye Cat 1 10 % ≤ C &lt; 25 %: Eye Cat 2</td>
</tr>
</tbody>
</table>
Guidance to Regulation (EC) No 1272/2008 on Classification, Labelling and packaging of Substances and Mixtures

| Substance E | Not classified | 15.9 |

pH of the mixture is 10.0 – 10.5 (10% solution), thus extreme pH provisions do not apply.

The mixture contains a surfactant which is not corrosive/irritant below 1% (as identified by the absence of specific concentration limits in either CLP Annex VI or the Classification and Labelling Inventory). Additivity is considered to apply.

Substance E can be disregarded as it is not classified for serious eye damage/eye irritation.

Surfactant B can also be disregarded as present below 1%.

SCLs are not assigned to substance C, thus GCL apply for this ingredient.

Substance E Not classified 15.9

Mixture contains 8.5% substance D, the only ‘relevant’ ingredient classified as Eye Cat. 1. As this is below the 25% SCL for substance D, the mixture is not classified Eye Cat. 1

Eye Cat. 1

Mixture contains 8.5% substance D, the only ‘relevant’ ingredient classified as Eye Cat. 1. As this is below the 25% SCL for substance D, the mixture is not classified Eye Cat. 1.

Eye Cat. 2

(%substance D / SCL) + (%substance C / GCL) = (8.5/10) + (74.9/10) which is > 1 thus mixture is classified Eye Cat. 2

3.3.7 References


3.4 RESPIRATORY OR SKIN SENSITISATION

3.4.1 Definitions and general considerations for respiratory or skin sensitisation

Annex I: 3.4.1.1. Respiratory sensitiser means a substance that will lead to hypersensitivity of the airways following inhalation of the substance.

3.4.1.2. Skin sensitiser means a substance that will lead to an allergic response following skin contact.

3.4.1.3. For the purpose of section 3.4, sensitisation includes two phases: the first phase is induction of specialised immunological memory in an individual by exposure to an allergen. The second phase is elicitation, i.e. production of a cell-mediated or antibody-mediated allergic response by exposure of a sensitised individual to an allergen.

3.4.1.4. For respiratory sensitisation, the pattern of induction followed by elicitation phases is shared in common with skin sensitisation. For skin sensitisation, an induction phase is required in

164
which the immune system learns to react; clinical symptoms can then arise when subsequent exposure is sufficient to elicit a visible skin reaction (elicitation phase). As a consequence, predictive tests usually follow this pattern in which there is an induction phase, the response to which is measured by a standardised elicitation phase, typically involving a patch test. The local lymph node assay is the exception, directly measuring the induction response. Evidence of skin sensitisation in humans normally is assessed by a diagnostic patch test.

3.4.1.5. Usually, for both skin and respiratory sensitisation, lower levels are necessary for elicitation than are required for induction. Provisions for alerting sensitised individuals to the presence of a particular sensitiser in a mixture can be found at section 3.4.4.

3.4.1.6. The hazard class Respiratory or Skin Sensitisation is differentiated into:

- Respiratory Sensitisation;
- Skin Sensitisation.

3.4.2 Classification of substances for respiratory or skin sensitisation

3.4.2.1 Identification of hazard information

There are no formally recognised and validated animal tests for respiratory sensitisation. However there may be data from human observation indicating respiratory sensitisation in exposed populations.

With respect to identification of relevant information for skin sensitisation see IR/CSA, section R.7.3.3.

3.4.2.1.1 Identification of human data

Relevant information with respect to respiratory or skin sensitisation may be available from case reports, epidemiological studies, medical surveillance and reporting schemes. For more details see IR/CSA, Section R.7.3.3.2.

3.4.2.1.2 Identification of non human data

At present no validated non-testing systems exist to predict skin sensitising potential. The chemical structure of a molecule, when similar to that of known sensitisers, may form part of the weight of evidence for classification (see also IR/CSA, section R.7.3.3).

The subject of in vitro testing for skin sensitisation has also been dealt with in IR/CSA, section R.7.3.3. At present no validated in vitro methods exist to identify the sensitising potential of a chemical.

There are three animal test methods used to evaluate skin sensitisation for substances: the mouse local lymph node assay (LLNA), the guinea pig maximisation test (GPMT) and the Buehler occluded patch test. They are further described in IR/CSA, Section R.7.3.3, and in the context of classification in section 3.4.2.3.4.

3.4.2.2 Classification criteria for substances

Annex I: 3.4.2.1. Respiratory sensitisers

Substances shall be classified as respiratory sensitisers (Category 1) in accordance with the criteria in Table 3.4.1:

<table>
<thead>
<tr>
<th>Hazard category for respiratory sensitisers</th>
</tr>
</thead>
</table>

Table 3.4.1

Deleted: S

Formatted: Highlight

Deleted: §

Deleted: $
Guidance to Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of substances and mixtures

### Table 3.4.2: Hazard category for skin sensitisers

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
</tr>
</thead>
</table>
| Category 1 | Substances shall be classified as skin sensitisers (Category 1) in accordance with the following criteria:  
(i) if there is evidence in humans that the substance can lead to sensitisation by skin contact in a substantial number of persons, or  
(ii) if there are positive results from an appropriate animal test (see specific criteria in paragraph 3.4.2.2.4.1). |

### 3.4.2.3 Evaluation of hazard information

#### 3.4.2.3.1 Human data on respiratory sensitisation

Substances shall be classified as respiratory sensitisers if there is evidence in humans that the substance can lead to specific respiratory hypersensitivity.

#### 3.4.2.3.2 Human data on skin sensitisation

Annex I: 3.4.2.2.2.1. For classification of a substance as a skin sensitiser, evidence shall include any or all of the following:

- (a) positive data from patch testing, normally obtained in more than one dermatology clinic;
- (b) epidemiological studies showing allergic contact dermatitis caused by the substance;  
  Situations in which a high proportion of those exposed exhibit characteristic symptoms are to be looked at with special concern, even if the number of cases is small;
- (d) positive data from experimental studies on humans (see Article 7(3));
- (e) well documented episodes of allergic contact dermatitis, normally obtained in more than one dermatology clinic.

#### 3.4.2.3.3 Non human data on respiratory sensitisation

No formally recognised and validated animal tests currently exist for respiratory sensitisation.

#### 3.4.2.3.4 Non human data on skin sensitisation

Currently CLP allows classification of skin sensitisers in only one hazard category. Since it is possible to refine the evaluation of skin sensitisers on the basis of the potency of the sensitising effect, this guidance advises how to evaluate the potency on the basis of the recommended test methods. The potency considerations may be used as a basis for setting
specific concentration limits (see section 3.4.2.5) and it is also concluded in the GHS that this potency consideration will be included as further classification criteria in the future.

There are currently three recognised and officially accepted animal test methods for skin sensitisation defined by OECD Test Guidelines. These are the Mouse Local lymph Node Assay (LLNA), Guinea Pig Maximisation Test by Magnusson & Kligman (GPMT) and the Buehler occluded patch test in the guinea pig. The mouse and guinea pig methods differ fundamentally with respect to the endpoints used; whereas the mouse LLNA measures the responses provoked during the induction of sensitisation, the two guinea pig tests measure challenge induced elicitation reactions in previously sensitised animals. For new testing of substances the LLNA is now the method of first choice. In the exceptional circumstance that the LLNA is not appropriate, one of the alternative tests may be used (Buehler or GPMT), but justification shall be provided (see IR/CSA, section R.7.3.2.1).

Test results from the LLNA, GPMT and the Buehler test could be used directly for classification. They may also be used for potency evaluation.

A sensitising potential of a substance is identified if a significant effect has been obtained in an acceptable in vivo test. A significant skin sensitising effect in each of the three recognised animal tests is defined as follows:

**Table 3.4.2.3.4: Definition of significant skin sensitising effect**

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse local lymph node assay (LLNA)</td>
<td>Stimulation Index $\geq$ 3</td>
</tr>
<tr>
<td>Guinea pig maximisation test (GPMT)</td>
<td>Redness in $\geq$ 30% of the test animals</td>
</tr>
<tr>
<td>Buehler occluded patch test</td>
<td>Redness in $\geq$ 15% of the test animals</td>
</tr>
</tbody>
</table>

A substance may be classified a skin sensitiser on the basis of a positive test result in one of the above described animal tests. A positive result obtained by another not officially recognised test method may also justify classification as a skin sensitiser, but can normally not overrule a negative result obtained in one of the three recognised, above described animal tests. A new animal study should not be conducted in an attempt to negate a clearly positive response in a not officially recognised test method particularly where there is other supporting evidence that the substance is a skin sensitiser.

**3.4.2.3.4.1 Mouse Local Lymph Node Assay (LLNA, OECD TG 429)**

The LLNA is used both for determination of skin sensitising potential (hazard identification) and for determination of relative skin sensitisation potency (hazard characterisation). In both instances the metric is cellular proliferation induced in draining lymph nodes following topical exposure to a chemical, lymph node cell proliferation being causally and quantitatively correlated with the acquisition of skin sensitisation (Basketter et al. 2002a, 2002b). A correlation has been demonstrated between the concentration of chemical required for the acquisition of skin sensitisation in humans according to historical predictive data and skin sensitisation potency as measured in the mouse LLNA (Schneider and Akkan 2004, Basketter et al. 2005b). Potency is measured as a function of derived EC3-values. The EC3-value is the amount of test chemical (% concentration, molar value or dose per unit area) required to elicit a stimulation index of 3 in the standard LLNA (Kimber et al. 2003). An inverse relationship exists between EC3-value and potency meaning that extremely potent sensitisers have extremely low EC3-values. The relevance of potency derives from an appreciation that skin sensitisers vary by up to four or five orders of magnitude with respect to the minimum concentration required inducing skin sensitisation. Potency is graded on the
basis of these minimum concentrations each grade reflecting a concentration range of approximately one order of magnitude.

The following scheme could be used for determination of potency categories for sensitisers. However, classification into potency categories is currently not a requirement in the classification of sensitisers.

### Table 3.4.2.3.4.1: Skin Sensitisation Potency in the Mouse Local Lymph Node Assay

<table>
<thead>
<tr>
<th>EC3-value (% w/v)</th>
<th>Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \leq 0.2 )</td>
<td>Extreme</td>
</tr>
<tr>
<td>( &gt; 0.2 - \leq 2 )</td>
<td>Strong</td>
</tr>
<tr>
<td>( &gt; 2 )</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

Potency may be considered when setting a specific concentration limit for a substance in mixtures (see section 3.4.2.5).

### 3.4.2.3.4.2 Guinea Pig Maximisation Test (GPMT, OECD TG 406)

This test has been used for almost 40 years to detect the sensitising potential of chemicals through a test system maximizing the sensitivity by both intradermal and epidermal induction and use of an adjuvant (Freund’s Complete Adjuvant). The intradermal induction is made by injection. Consequently the test is not suited for products which cannot be made up into a liquid formulation.

The GPMT was originally designed to maximise the ability to identify a sensitisation hazard, rather than to determine skin sensitisation potency. Yet, when only a GPMT test result is available, potency categorisation is possible on the basis of the concentration of test material used for intradermal induction and the percentage of guinea pigs sensitised. However, it should be recognised that there is often a degree of uncertainty associated with the derivation of allergenic potencies from the GPMT. If the test has been conducted in full compliance with OECD Test Guideline 406 and with the technical details ensuring proper data interpretation as specified by Schlede and Eppler (1995), the following scheme may be used.

The following scheme could be used for determination of potency categories for sensitisers. However, classification into potency categories is currently not a requirement in the classification of sensitisers.

### Table 3.4.2.3.4.2: Potency on basis of the Guinea Pig Maximisation Test

<table>
<thead>
<tr>
<th>Concentration for intradermal induction (% w/v)</th>
<th>Incidence sensitised guinea pigs (%)</th>
<th>Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \leq 0.1 )</td>
<td>( \geq 60 )</td>
<td>Extreme</td>
</tr>
<tr>
<td>( \leq 0.1 )</td>
<td>( \geq 30 ) - ( &lt; 60 )</td>
<td>Strong</td>
</tr>
<tr>
<td>( &gt; 0.1 - \leq 1.0 )</td>
<td>( \geq 60 )</td>
<td>Strong</td>
</tr>
<tr>
<td>( &gt; 0.1 - \leq 1.0 )</td>
<td>( \geq 30 ) - ( &lt; 60 )</td>
<td>Moderate</td>
</tr>
<tr>
<td>( &gt; 1.0 )</td>
<td>( \geq 30 )</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

Potency may be considered when setting a specific concentration limit for a substance in mixtures (see section 3.4.2.5).
3.4.2.3.4.3 Buehler occluded patch test (OECD TG 406)

This test has been in use for the last 40 years as a more realistic, although still a sensitive, test to detect skin sensitisers using epidermal occluded exposure. The skin barrier of the test species (guinea pig) is kept intact in this assay, thus providing for a more relevant exposure scenario for the human situation. Potency can be categorised using the results of the Buehler test on the basis of the number of animals sensitised and the concentration of the test material used for the epidermal induction. However, it should be recognised that there is often a degree of uncertainty associated with the derivation of allergenic potencies from the Buehler test. The following scheme could be used for determination of potency categories, if the test has been conducted in full compliance with OECD TG 406 and with the technical details ensuring proper data interpretation as specified by Robinson et al (1990).

Classification into potency categories is currently not a requirement in the classification of sensitisers.

Table 3.4.2.3.4.3: Potency on basis of the Buehler Occluded Patch Test

<table>
<thead>
<tr>
<th>Concentration for intradermal induction (% w/v)</th>
<th>Incidence sensitised guinea pigs (%)</th>
<th>Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 0.2</td>
<td>≥ 60</td>
<td>Extreme</td>
</tr>
<tr>
<td>≤ 0.2</td>
<td>&gt; 15 - &lt; 60</td>
<td>Strong</td>
</tr>
<tr>
<td>&gt; 0.2 - ≤ 20</td>
<td>≥ 60</td>
<td>Strong</td>
</tr>
<tr>
<td>&gt; 0.2 - &lt; 20</td>
<td>≥ 15 - &lt; 60</td>
<td>Moderate</td>
</tr>
<tr>
<td>&gt; 20</td>
<td>≥ 15</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

Potency may be considered when setting a specific concentration limit for a substance in mixtures (see section 3.4.2.4).

3.4.2.3.4.4 Non-compliant skin sensitisation tests

In vivo test methods which do not comply with recognised guidelines are strongly discouraged for the identification of skin sensitisers or assessment of skin sensitising potency. The results of such tests have to be evaluated carefully, but may provide supportive evidence. If doubts exist about the validity and the interpretation of the results, the evaluation needs to be taken by using a weight-of-evidence approach.

3.4.2.3.4.5 Animal test methods conducted for purposes other than sensitisation

 Occasionally signs of skin sensitisation occur in repeated dose tests. These tests are often dermal toxicity tests on rats. Clearly, if signs of erythema/oedema occur in animals after repeated application, the possibility of skin sensitisation should be considered, and ideally assessed in an appropriate study.

3.4.2.3.5 Weight of evidence

 Positive effects seen in either humans or animals for skin sensitisation will normally justify classification. Evidence from animal studies on skin sensitisation is usually more reliable than evidence from human exposure, although reliable human data is, of course, most relevant to man. In cases where evidence is available from both sources, and there is conflict between the results, the quality and reliability of the evidence from both sources must be assessed in order to decide on the classification on a case-by-case basis. Negative human data should not normally negate positive findings in animal studies.
Since the data used in hazard or risk assessment should be relevant, reliable and sufficient for the regulatory purpose, it is necessary to base the assessment on the totality of available information, i.e. to apply Weight of Evidence (WoE) considerations.

The WoE assessment can be based on the total of experimental data, as well as post-market surveys and/or occupational experience data. In the case of mixtures, extrapolation from similar mixtures or from data available on the components may often provide reliable means of assessment. Estimated data might be used to supplement and increase confidence in the available experimental data, whereas in some others, such data might be used instead of experimental data.

WoE assessment can be divided into two stages:

a) Assessment of each single test result and, if needed, of other data. It may be helpful to apply criteria for reliability as defined by Klimisch et al (1997). These criteria include details on the recognition of the test method, reporting detail, method relevance, test parameters, etc.

b) Comparison of the weighed single test results. Good quality data on the substance itself have more weight than such data extrapolated from similar substances.

3.4.2.4 Decision on classification

According to CLP Annex I, section 3.4.2.1 substances fulfilling the criteria for respiratory sensitisation will be classified as such in Category I, and according to CLP Annex I, section 3.4.2.2 substances fulfilling the criteria for skin sensitisation will be classified as such in Category 1. In addition substances classified in Category 1 for skin sensitisation can be allocated specific concentration limits as described in section 3.4.2.5.

3.4.2.5 Setting of specific concentration limits

Respiratory sensitisers cannot be identified reliably on the basis of animal tests as yet, since no recognised validated test exists to determine sensitising potential and potency by inhalation. Therefore specific concentration limits (SCLs) cannot be set on the basis of animal data. Moreover, there is no concept available to set SCLs on the basis of human data for respiratory sensitisers.

SCLs for skin sensitisation can be set based on the assumption that a substance can be categorised according to their skin sensitisation potency based on the results from animal testing as reported in sections 3.4.2.3.4.1, 3.4.2.3.4.2 and 3.4.2.3.4.3 above, 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 3.4.3.1.1 of Annex I).

The generic concentration limit (GCL) for the classification of sensitisers in mixtures is 1% (CLP Annex I, Table 3.4.3). However, for certain sensitisers 1% is not sufficiently protective. Therefore a specific concentration limit (SCL) shall be set (CLP, Article 10) which will better reflect the hazard of mixtures containing that skin sensitiser.

SCLs shall be set when there is adequate and reliable scientific information available showing that the specific hazard is evident below the GCL, 1%, for classification. As such the SCL should normally be as suggested in Table 3.4.2.5. However, supported by reliable data the SCL could have some other value below 1%. Reliable data could be human data from e.g. workplace studies where the exposure is defined.
It is more difficult to prove the absence of sensitising properties at certain concentration levels. Therefore an SCL above the GCL, 1%, may only be set in exceptional circumstances, if scientific information is adequate, reliable and conclusive for that particular skin sensitiser. However there is currently no guidance on how to set SCL above the GCL.

The concentration limits for skin sensitisers categorised according to their sensitisation potency in the Table 3.4.2.5 are recommendations from an EU expert group on skin sensitisation (Basketter et al., 2005a).

**Table 3.4.2.5**: Skin sensitising potency for substances and recommendations on specific concentration limits

<table>
<thead>
<tr>
<th>Potency</th>
<th>Concentration Limit (% w/v)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extreme</td>
<td>0.001 (SCL)</td>
</tr>
<tr>
<td>Strong</td>
<td>0.1 (SCL)</td>
</tr>
<tr>
<td>Moderate</td>
<td>1 (GCL)</td>
</tr>
</tbody>
</table>
3.4.2.6 Decision logic for classification of substances

It is strongly recommended that the person responsible for classification study the criteria for classification before and during use of the decision logic.

Decision logic for respiratory sensitisation

1. Does the substance have respiratory sensitisation data?
   - NO: Classification not possible
   - YES:
     a) Is there evidence in humans that the substance can lead to specific respiratory hypersensitivity, and/or
     b) are there positive results from an appropriate animal test?
       - NO: Not classified
       - YES: Category 1 Danger
Decision logic for skin sensitisation

1 Does the substance have skin sensitisation data?

2 NO Classification not possible

3 YES

4 (a) Is there evidence in humans that the substance can lead to sensitisation by skin contact in a substantial number of persons, or
(b) are there positive results from an appropriate animal test?

5 NO Not classified

6 YES Category 1

7 Warning
3.4.3 Classification of mixtures for respiratory or skin sensitisation

3.4.3.1 General considerations for classification

The same principles apply as for substances (see section 3.4.2).

3.4.3.2 Identification of hazard information for skin sensitisation

For identification of the sensitisation potential of a mixture the following information may be available:

(a) test results on one or more, preferably all of its potentially sensitising components; or
(b) test results on the mixture itself; or
(c) test results of a similar mixture.

Test methods are outlined in section 3.4.2.3.4. However, these animal tests have been developed to identify sensitising substances and not mixtures. Therefore the results obtained on mixtures need to be evaluated with care. For a mixture the cut-off in the mouse LLNA should be seen as a threshold for identification of a sensitiser rather than as a threshold for sensitisation. A conclusion on the absence of sensitising potential of a mixture based on the negative outcome in a test must be taken with great caution.

On the other hand test data on a mixture take into account effects of possible interactions of its components. For instance, it is known that presence of a vehicle may significantly influence the skin sensitising potency, by influencing the penetration of the sensitising component(s) through the skin, (Basketter et al. 2001, Dearman et al. 1996, Heylings et al. 1996) or through other mechanisms involved in the acquisition of sensitisation (Cumberbatch et al. 1993; Dearman et al. 1996).

Repeated exposure to mixtures, that are non-sensitising under standard LLNA exposure conditions, might induce skin sensitisation, if the sensitising component in this mixture has sufficient accumulation potential in the skin to reach the minimum concentration for a positive effect (De Jong et al. 2007). Uncertainty also exists about the effect of such mixture after exposure on a larger skin area. Therefore additional information is important, if the outcome of sensitisation tests on mixtures contrasts with the classification based on the content of sensitising component(s). For example, the validity of a well conducted LLNA on a mixture with a negative outcome can scientifically be confirmed by spiking the test mixture with another sensitiser (positive control) at different concentrations, or by showing a dose response relationship. Such LLNA tests could have been designed to provide such information without use of extra animals. Additional animal testing for the purpose of classification and labelling shall be undertaken only where no other alternatives, which provide adequate reliability and quality of data, are possible (CLP Article 7(1)).

3.4.3.3 Classification criteria

3.4.3.3.1 When data are available for all components or only for some components

Annex I: 3.4.3.3.1. The mixture shall be classified as a respiratory or skin sensitiser when at least one ingredient has been classified as a respiratory or skin sensitiser and is present at or above the appropriate generic concentration limit as shown in Table 3.4.3 below for solid/liquid and gas respectively.
3.4.3.3.2. Some substances that are classified as sensitisers may elicit a response, when present in a mixture in quantities below the concentrations established in Table 3.4.1, in individuals who are already sensitised to the substance or mixture (see Note 1 to Table 3.4.3).

### Table 3.4.3

<table>
<thead>
<tr>
<th>Ingredient classified as:</th>
<th>Concentration triggering classification of a mixture as:</th>
<th>Skin Sensitiser</th>
<th>Respiratory Sensitiser</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>All physical states</td>
<td>Solid/Liquid</td>
</tr>
<tr>
<td>Skin Sensitiser</td>
<td></td>
<td>≥ 0,1 % (Note 1)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 1,0 % (Note 2)</td>
<td>-</td>
</tr>
<tr>
<td>Respiratory Sensitiser</td>
<td></td>
<td>≤ 0,1 % (Note 1)</td>
<td>≥ 0,1 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 1,0 % (Note 3)</td>
<td>≥ 0,2 %</td>
</tr>
</tbody>
</table>

**Note 1**  
This concentration limit is generally used for the application of the special labelling requirements of Annex II section 2.8 to protect already sensitised individuals. A SDS is required for the mixture containing an ingredient above this concentration.

**Note 2**  
This concentration limit is used to trigger classification of a mixture as a skin sensitisers.

**Note 3**  
This concentration limit is used to trigger classification of a mixture as a respiratory sensitisers.

---

All sensitising components of a mixture at or above their generic or specific concentration limit should be taken into consideration for the purpose of classification. Specific concentration limits (see Section 3.4.2.5) will always take precedence over the generic concentration limits.

The additivity concept is not applicable for respiratory or skin sensitisation, i.e. if one single classified substance is present in the mixture above the generic concentration limit, the mixture must be classified for that hazard. If the mixture contains two substances each below the generic concentration limits, the mixture will not be classified, as far as no SCL has been set.

### 3.4.3.3.2 When data are available for the complete mixture

**Annex I: 3.4.3.1.1.** When reliable and good quality evidence from human experience or appropriate studies in experimental animals, as described in the criteria for substances, is available for the mixture, then the mixture can be classified by weight-of-evidence evaluation of these data. Care
shall be exercised in evaluating data on mixtures, that the dose used does not render the results inconclusive.

In case classification of a mixture is based on test results for the mixture as a whole, this data must be shown to be conclusive. Especially it should be taken into account that in case of skin sensitisation current test methods are based on application of maximised dose, which only can be obtained using a substance by itself and not diluted in a mixture.

It is recognised that mixtures not showing sensitisation in a test, may still contain a low concentration of sensitising component.

For specific guidance on the test methods and evaluation of the results see section 3.4.2.3.4, section 3.4.3.1 and CLP Annex I, 3.4.3.1.1.

3.4.3.3 When data are not available for the complete mixture: Bridging Principles

Annex I: 3.4.3.2.1. Where the mixture itself has not been tested to determine its sensitising properties, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterise the hazards of the mixture, these data shall be used in accordance with the bridging rules out in section 1.1.3.

In absence of a test on the mixture, data from tests on a similar mixture, i.e. containing the same sensitising component in a similar concentration, may be used for skin sensitising potential estimation.
3.4.3.4 Decision logic for classification of mixtures

It is strongly recommended that the person responsible for classification study the criteria for classification before and during use of the decision logic.

Decision logic for respiratory sensitisation

1. Does the mixture as a whole or its ingredients have respiratory sensitisation data?

   NO Classification not possible

   YES

   Does the mixture as a whole have respiratory sensitisation data?

     NO

     YES

     a) Is there evidence in humans that the mixture can lead to specific respiratory hypersensitivity, and/or
        (b) are there positive results from an appropriate animal test?

     NO

     YES

     Can bridging principles be applied?

     NO

     YES

     Care shall be exercised in evaluating data on mixtures, that the dose used does not render the results inconclusive. Is this the case?

     NO

     YES

     Does the mixture contain one or more ingredients classified as a respiratory sensitiserr at $\geq 1.0\%$ w/w (solid/liquid) or $\geq 0.2\%$ v/v (gas) or above a SCL set for the ingredient(s)?

     NO

     YES

     Category 1 Danger

     NO

     Not classified

     YES

     Category 1 Danger

     Not classified
Decision logic for skin sensitisation

Does the mixture as a whole or its ingredients have skin sensitisation data?

- NO Classification not possible

YES

Does the mixture as a whole have skin sensitisation data?

- NO Category 1 Warning

YES

(a) Is there evidence in humans that the mixture can lead to sensitisation by skin contact in a substantial number of persons, or

(b) are there positive results from an appropriate animal?

- NO Classify in appropriate category

YES

Can bridging principles be applied?

- NO Not classified

YES

Care shall be exercised in evaluating data on mixtures, that the dose used does not render the results inconclusive. Is this the case?

- NO Not classified

YES

Does the mixture contain one or more ingredients classified as a skin sensitisier at ≥ 1.0 % or above a SCL set for the ingredient(s)?

- NO Category 1 Warning

YES
3.4.4 Hazard communication for respiratory or skin sensitisation

3.4.4.1 Pictograms, signal words, hazard statements and precautionary statements

### Annex I: 3.4.4.1. Label elements shall be used for substances or mixtures meeting the criteria for classification in this hazard class in accordance with Table 3.4.2

#### Table 3.4.4

<table>
<thead>
<tr>
<th>Classification</th>
<th>Respiratory sensitisation</th>
<th>Skin sensitisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>GHS Pictograms</td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image1" alt="Respiratory Sensitisation" /></td>
<td><img src="image2" alt="Skin Sensitisation" /></td>
<td></td>
</tr>
<tr>
<td>Signal Word</td>
<td>Danger</td>
<td>Warning</td>
</tr>
<tr>
<td>Hazard Statement</td>
<td>H334: May cause allergy or asthma symptoms or breathing difficulties if inhaled</td>
<td>H317: May cause an allergic skin reaction</td>
</tr>
<tr>
<td>Precautionary Statement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevention</td>
<td>P261</td>
<td>P261</td>
</tr>
<tr>
<td></td>
<td>P285</td>
<td>P272</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P280</td>
</tr>
<tr>
<td>Response</td>
<td>P304 + P341</td>
<td>P302 + P352</td>
</tr>
<tr>
<td></td>
<td>P342 + P311</td>
<td>P333 + P313</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P321</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P363</td>
</tr>
<tr>
<td>Storage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disposal</td>
<td>P501</td>
<td>P501</td>
</tr>
</tbody>
</table>

If the hazard pictogram “GHS08” applies for respiratory sensitisation, the hazard pictogram “GHS07” shall not appear for skin sensitisation or for skin and eye irritation (CLP, Article 26).

In the SDS for a substance, information on the generic or specific concentration limit should be provided.

3.4.4.2 Additional labelling provisions

### Annex II: 2.8. Mixtures not classified as sensitising but containing at least one sensitising substance

The label on the packaging of mixtures containing at least one substance classified as sensitising and present in a concentration equal to or greater than 0.1% or in a concentration equal to or greater than that specified under a specific note for the substance in part 3 of Annex VI shall bear the statement:
3.4.5 Re-classification of substances and mixtures classified for respiratory or skin sensitisation according to DSD and DPD

3.4.5.1 Is direct “translation” of classification and labelling possible?

Direct translation from DSD to CLP is possible for sensitising substances. Any existing SCLs may be transferred across to CLP and used for classification of mixtures. Where there is no existing SCL for an already classified substance, the substance shall be classified in the default Category 1, and a generic concentration limit of 1% applied.

3.4.5.2 Re-evaluation of the skin sensitisation data

Re-evaluation of non-tested mixtures has to be done on the basis of any relevant new data that might have become available after the time of the latest classification or if an SCL has been set.

3.4.6 Examples of classification for skin sensitisation

3.4.6.1 Examples of substances and mixtures fulfilling the criteria for classification for skin sensitisation

3.4.6.1.1 Example 1

Substance X gave a positive result in the LLNA with an EC3-value of 10.4%. As this EC3-value is above the cut-off of 2%, the substance is considered to be a moderate skin sensitiser, and should be classified as Skin Sens. Cat.1. The GCL for classification of mixtures containing substance X is 1%.

3.4.6.1.2 Example 2

Substance Y tested positive in the LLNA with an EC3-value of 0.5%. In the GPMT a dermal induction concentration of 0.375% produced a positive response in 70% of the animals. On the basis of both these positive results, the substance is considered to be a strong sensitiser requiring classification as Skin Sens. Cat.1. A specific concentration limit of 0.1% is suggested.

3.4.6.1.3 Example 3

Herby is a herbicide formulation containing 28 g/l substance X, a moderate skin sensitiser (see example 1). There is no sensitisation data for the formulation itself. As Herby contains more than the GCL (1%) of this sensitising a.i., and in the absence of any additional information, it should be classified as Skin Sens. Cat.1.

3.4.6.1.4 Example 4

Methyl/Chloromethyl-isothiazolinone is an example of an extreme sensitiser. This substance is listed in CLP Annex VI (Index-No. 613-167-00-5) with harmonised classification. Being an extreme sensitiser it has a specific concentration limit with regard to skin sensitisation, and due to this property any mixture containing the substance in a concentration ≥ 0.0015% must be classified with Skin Sens. 1.

3.4.6.2 Example of substances or mixtures not fulfilling the criteria for classification for skin sensitisation

Deleted: a Category 1 skin sensitizer.

Deleted: The label must also bear the statement EUH208.
3.4.6.2.1 Example 5

Substance A was tested in the LLNA and gave a maximum stimulation index of 2.4. On the basis of a stimulation index below 3, substance A is not considered to be a skin sensitiser, and does not require classification.

3.4.6.2.2 Example 6

Insecto super is an insecticide formulation containing 9 g/l substance X (see Example 1). Substance X is a moderate skin sensitiser (generic concentration limit in mixtures 1%). Based on the classification of substance X, the insecticide formulation shall not be classified as sensitising as the concentration of the a.i. is below the GCL of 1%. The label must bear the statement EUH208.

3.4.7 References


3.5 GERM CELL MUTAGENICITY

3.5.1 Definitions and general considerations for classification for germ cell mutagenicity

Annex I: 3.5.1.1. A mutation means a permanent change in the amount or structure of the genetic material in a cell. The term “mutation” applies both to heritable genetic changes that may be manifested at the phenotypic level and to the underlying DNA modifications when known (including specific base pair changes and chromosomal translocations). The term “mutagenic” and “mutagen” will be used for agents giving rise to an increased occurrence of mutations in populations of cells and/or organisms.

3.5.1.2. The more general terms “genotoxic” and “genotoxicity” apply to agents or processes which alter the structure, information content, or segregation of DNA, including those which cause DNA damage by interfering with normal replication processes, or which in a non-physiological manner (temporarily) alter its replication. Genotoxicity test results are usually taken as indicators for mutagenic effects.

Germ cell mutations are those that occur in the egg or sperm cells (germ cells) and therefore can be passed on to the organism's offspring. Somatic mutations are those that happen in cells other than the germ cells, and they cannot be transmitted to the next generation. This is an important distinction to keep in mind in terms of both the causes and the effects of mutation.

Annex I: 3.5.2.1 This hazard class is primarily concerned with substances that may cause mutations in the germ cells of humans that can be transmitted to the progeny. However, the results from mutagenicity or genotoxicity tests in vitro and in mammalian somatic and germ cells in vivo are also considered in classifying substances and mixtures within this hazard class.

Annex I: 3.6.2.2 Specific considerations for classification of substances as carcinogens

3.6.2.2.6. Mutagenicity: It is recognised that genetic events are central in the overall process of cancer development. Therefore evidence of mutagenic activity in vivo may indicate that a substance has a potential for carcinogenic effects.

Hazard classification for germ cell mutagenicity primarily aims to identify substances causing heritable mutations or being suspected of causing heritable mutations. A secondary aim is that the hazard class germ cell mutagenicity offers supporting information with respect to the classification of carcinogenic substances. This is expressed by the broad meaning of the hazard statements “H340: May cause genetic defects” and “H341: Suspected of causing genetic defects” which comprises heritable genetic damage as well as somatic cell mutagenicity. Thus, classification as a germ cell mutagen (Category 1A, 1B, and 2) classifies...
for the hazard heritable genetic damage as well as providing an indication that the substance
could be carcinogenic.

It is also warranted that where there is evidence of only somatic cell genotoxicity, substances
are classified as suspected germ cell mutagens. Classification as a suspected germ cell
mutagen may also have implications for potential carcinogenicity classification. This holds
true especially for those genotoxicants which are incapable of causing heritable mutations
because they cannot reach the germ cells (e.g. genotoxicants only acting locally, "site of
contact" genotoxicants). This means that if positive results in vitro are supported by at least
one positive local in vivo, somatic cell test, such an effect should be considered as enough
evidence to lead to classification in Category 2. If there is also negative or equivocal data, a
weight of evidence approach using expert judgement has to be applied.

3.5.2 Classification of substances for germ cell mutagenicity

3.5.2.1 Identification of hazard information

3.5.2.1.1 Identification of human data

Occasionally, studies of genotoxic effects in humans exposed by, for example, accident,
occupation or participation in clinical studies (e.g. from case reports or epidemiological
studies) may be available. Generally, cells circulating in blood are investigated for the
occurrence of various types of genetic alterations; see also IR/CSA, Section R.7.7.3.2.

3.5.2.1.2 Identification of non human data

Animal data

Some test methods have an officially adopted EU/OECD guideline for the testing procedure,
although for many test methods this is not the case. Furthermore, modifications to OECD
protocols have been developed for various classes of substances and may serve to enhance
the accuracy of test results. Use of such modified protocols is a matter of expert judgement
and will vary as a function of the chemical and physical properties of the substance to be
evaluated. Commonly used non-guideline in vivo tests employ methods by which any tissue
of an animal can be examined for effects on the genetic material, giving the possibility to
examine site-of-contact tissues (i.e., skin, epithelium of the respiratory or gastro-intestinal
tract) in genotoxicity testing. In addition, test methods developed over the past decades in
Drosophila and in various species of plants and fungi are available; see also IR/CSA, Section
R.7.7.3.

Other in vivo tests in somatic cells which provide supporting evidence on
genotoxicity/mutagenicity may include, for example, a Comet single cell gel electrophoresis
assay for DNA strand breaks, or a test for gene mutations in transgenic rodent models using
reporter genes.

With the exception of in vivo studies proving “site of contact” effects, genotoxicity data from
such non-standard in vivo studies are not sufficient but may offer supporting information for
classification.

In vitro data

Typically, in vitro tests are performed with cultured bacterial cells, human or other
mammalian cells. The sensitivity and specificity of tests will vary with different classes of
substances; see also IR/CSA, Section R.7.7.3.
Use of other data

Existing test methods

3.5.2.2 Classification criteria for substances

Annex I: 3.5.2.2. For the purpose of classification for germ cell mutagenicity, substances are allocated to one of two categories as shown in Table 3.5.1.

Table 3.5.1
Hazard categories for germ cell mutagens

<table>
<thead>
<tr>
<th>Categories</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>CATEGORY 1:</td>
<td>Substances known to induce heritable mutations or to be regarded as if they induce heritable mutations in the germ cells of humans.</td>
</tr>
<tr>
<td>Category 1A:</td>
<td>The classification in Category 1A is based on positive evidence from human epidemiological studies.</td>
</tr>
<tr>
<td>Category 1B:</td>
<td>The classification in Category 1B is based on:</td>
</tr>
<tr>
<td></td>
<td>- positive result(s) from in vivo heritable germ cell mutagenicity tests in mammals; or</td>
</tr>
<tr>
<td></td>
<td>- positive result(s) from in vivo somatic cell mutagenicity tests in mammals, in combination with some evidence that the substance</td>
</tr>
<tr>
<td></td>
<td>has potential to cause mutations to germ cells. It is possible to derive this supporting evidence from mutagenicity/genotoxicity tests in</td>
</tr>
<tr>
<td></td>
<td>germ cells in vivo, or by demonstrating the ability of the substance or its metabolite(s) to interact with the genetic material of germ cells;</td>
</tr>
<tr>
<td></td>
<td>- positive results from tests showing mutagenic effects in the germ cells of humans, without demonstration of transmission to progeny; for</td>
</tr>
<tr>
<td></td>
<td>example, an increase in the frequency of aneuploidy in sperm cells of exposed people.</td>
</tr>
<tr>
<td>CATEGORY 2:</td>
<td>Substances which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans.</td>
</tr>
<tr>
<td></td>
<td>The classification in Category 2 is based on:</td>
</tr>
<tr>
<td></td>
<td>- Positive evidence obtained from experiments in mammals and/or in some cases from in vitro experiments, obtained from:</td>
</tr>
<tr>
<td></td>
<td>- Somatic cell mutagenicity tests in vivo, in mammals; or</td>
</tr>
<tr>
<td></td>
<td>- Other in vivo somatic cell genotoxicity tests which are supported by positive results from in vitro mutagenicity assays.</td>
</tr>
<tr>
<td></td>
<td>Note: Substances which are positive in in vitro mammalian mutagenicity assays, and which also show chemical structure activity relationship</td>
</tr>
<tr>
<td></td>
<td>to known germ cell mutagens, shall be considered for classification as Category 2 mutagens.</td>
</tr>
</tbody>
</table>

3.5.2.3 Evaluation of hazard information

Annex I: 3.5.2.3.3 Classification for heritable effects in human germ cells is made on the basis of
well conducted, sufficiently validated tests, preferably as described in Regulation (EC) No 440/2008 adopted in accordance with Article 13(3) of Regulation (EC) No 1907/2006 (‘Test Method Regulation’) such as those listed in the following paragraphs. Evaluation of the test results shall be done using expert judgement and all the available evidence shall be weighed in arriving at a classification.

3.5.2.3.1 Evaluation of human data

Human data have to be assessed carefully on a case-by-case basis. The interpretation of such data requires considerable expertise. Attention should be paid especially to the adequacy of the exposure information, confounding factors, co-exposures and to sources of bias in the study design or incident. The statistical power of the test may also be considered (See IR/CSA, section R.7.4.4.2).

3.5.2.3.2 Evaluation of non human data

Evaluation of genotoxicity test data should be made with care. Regarding positive findings, responses generated only at highly toxic/cytotoxic concentrations should be interpreted with caution, and the presence or absence of a dose-response relationship should be considered. In case of negative findings in vivo toxicokinetic and other available information should be considered e.g. to verify whether the substance has reached the target organ (for detailed guidance see IR/CSA, section R.7.7.4.1).

3.5.2.4 Decision on classification

Annex I: 3.5.2.3.9. The classification of individual substances shall be based on the total weight of evidence available, using expert judgement (See 1.1.1). In those instances where a single well-conducted test is used for classification, it shall provide clear and unambiguously positive results. If new, well validated, tests arise these may also be used in the total weight of evidence to be considered. The relevance of the route of exposure used in the study of the substance compared to the most likely route of human exposure shall also be taken into account.

Classification as a Category 1A mutagen

Epidemiological studies have to date unable to provide evidence to classify a substance as a Category 1A mutagen. Hereditary diseases in humans for the most part have an unknown origin and show a varying distribution in different populations. Due to the random distribution of mutations in the genome it is not expected that one particular substance would induce one specific genetic disorder. Therefore, it is unlikely that such evidence may be obtained by epidemiological studies to enable you to classify a substance as a Category 1A mutagen.

Classification as a Category 1B mutagen

Classification in Category 1B may be based on positive results of at least one valid in vivo mammalian germ cell mutagenicity test. In case there are also negative or equivocal data, a weight of evidence approach using expert judgement has to be applied.

If there are only positive results of at least one valid in vivo mammalian somatic mutagenicity test but no respective data on mammalian germ cells are available, additional evidence is
required to be able to classify as mutagen in Category 1B. Such additional data must prove
that the substance or its metabolite(s) interacts \textit{in vivo} with the genetic material of germ cells.
It is also possible to obtain supporting evidence in an \textit{in vivo} genotoxicity test with
mammalian germ cells. In addition, genetic damage to germ cells in exposed humans proven
to be caused by substance exposure may offer respective information. In case of other
supporting evidence or where there are also negative or equivocal data, a weight of evidence
approach using expert judgement has to be applied.

It could be argued that in a case where \textit{in vivo} mutagenicity/genotoxicity is proven and the
substance under consideration is systemically available, then that substance should also be
considered as a Category 1B mutagen. Germ cell mutagens as the spermatogonia are
generally not protected from substance exposure by the blood-testes barrier formed by the Sertoli cells. In such circumstances the relevant criteria are as follows:

\begin{Verbatim}
Annex I: 3.5.2.2. (extract from Table 3.5.1)
Category 1B
\begin{itemize}
\item positive result(s) from in vivo somatic cell mutagenicity tests in mammals, in combination with
some evidence that the substance has potential to cause mutations to germ cells. It is possible to
derive this supporting evidence from mutagenicity/genotoxicity tests in germ cells \textit{in vivo}, or by
demonstrating the ability of the substance or its metabolite(s) to interact with the genetic
material of germ cells;
\end{itemize}
\end{Verbatim}

This wording expresses that supporting evidence in addition to an \textit{in vivo} somatic cell
mutagenicity test in mammals is needed to be able to classify a substance in a Category 1B
mutagen. The second sentence in the green box above gives examples for such evidence,
from these examples it is clear that such supporting evidence is experimental evidence. There
has to be either data indicating that germ cell mutagenicity/genotoxicity is caused by the
substance or data showing that the substance or its metabolite(s) interact with the genetic
material of germ cells. Thus, in such circumstances, in addition to an \textit{in vivo} somatic cell
mutagenicity test, further experimental evidence is needed to be able to classify a substance
as a Category 1B mutagen.

\textbf{Classification as a Category 2 mutagen}

Classification in Category 2 may be based on positive results of a least one \textit{in vivo} valid
mammalian somatic cell mutagenicity test, indicating mutagenic effects in somatic cells. A
Category 2 mutagen classification may also be based on positive results of a least one \textit{in vivo}
valid mammalian genotoxicity test, supported by positive \textit{in vitro} mutagenicity results.
Genetic damage to somatic cells in exposed humans shown to be caused by substance
exposure supported by positive \textit{in vitro} mutagenicity results may also offer respective
information warranting classification as a Category 2 mutagen. \textit{In vitro} results can only lead
to a Category 2 mutagen classification in a case where there is support by chemical structure
activity relationship to known germ cell mutagens. In the case where there are also negative
or equivocal data, a weight of evidence approach using expert judgement has to be applied.

In general, mutations can be differentiated into gene mutations (\textit{e.g.} point or frame shift
mutation), chromosome mutations (structural chromosome changes) and genome mutations
(loss or gain of whole chromosomes). Different mutagenicity tests may detect different types
of mutations and genotoxic effects which have to be taken into account in the weight of
evidence determination. For instance, a substance which only causes chromosome mutations
may be negative in a test for detecting point mutations. A complex data situation with
positive and negative results might still lead to classification. This is because all tests
detecting a certain type of mutation (e.g. point mutations) have been positive and all tests
detecting chromosome mutations have been negative. Such circumstances clearly warrant
classification although several tests have been negative which is plausible in this case.

A positive result for somatic or germinal mutagenicity in a test using intraperitoneal
administration only shows that the tested substance has an intrinsic mutagenic property, and
the fact that negative results are exhibited by other routes of dosage may be related to factors
influencing the distribution/metabolism of the substance which may be characteristic to the
tested animal species. It cannot be ruled out that a positive test result in intraperitoneal studies
in rodents only may be relevant to humans.

If there are positive results in at least one valid *in vivo* mutagenicity test using intraperitoneal
application, or from at least one valid *in vivo* genotoxicity test using intraperitoneal
application plus supportive *in vitro* data, classification is warranted. In cases where there are
additional data from further *in vivo* tests with oral, dermal or inhalative substance application,
a weight of evidence approach using expert judgement has to be applied in order to come
to a decision. For instance, it may be difficult to reach a decision on whether or not to classify
in the case where there are positive *in vivo* data from at least one *in vivo* test using
intraperitoneal application but (only) negative test data from (an) *in vivo* test(s) using oral,
dermal, or inhalative application. In such a case, it could be argued that
mutagenicity/genotoxicity can only be shown at internal body substance concentrations
which can not be achieved using application routes other than intraperitoneal. However, it
also has to be taken into account that there is generally no threshold for mutagenicity unless
there is specific proof for the existence of such a threshold as may be the case for aneugens.

Thus, if mutagenicity/genotoxicity can only be demonstrated for the intraperitoneal route
exclusively, then this may mean that the effect in the *in vivo* tests using application routes
other than intraperitoneal may have been present, but it may not have been detected because
it was below the detection limit of the oral, dermal, or inhalative test assays.

In summary, classification as a Category 2 mutagen would generally apply if only
intraperitoneal *in vivo* tests show mutagenicity/genotoxicity and the negative test results from
the *in vivo* tests using other routes of application are plausible. Factors influencing
plausibility are e.g. the doses tested and putative kinetic data on the test substance. However,
on a case-by-case analysis using a weight of evidence approach and expert judgement, non-
classification may also result.

### Setting of specific concentration limits

There is no detailed and accepted guidance developed for the setting of specific concentration
limits (SCLs) for mutagenicity, as is the case for carcinogenic substances. Guidance such as
the T<sub>25</sub> concept for carcinogens covering all relevant aspects would need to be developed in
order to derive SCLs for mutagens in a standardized manner. There are several reasons why it
is considered impossible to set SCLs for mutagens without a comprehensive guidance, one of
them being that mutagenicity tests have not been specifically developed for the derivation of
a quantitative response. Moreover, different mutagenicity tests have different sensitivities in
detecting mutagens. Thus, it is very difficult to describe the minimum data requirements
which would allow a standardized SCL derivation. Another drawback in practice is that the
results obtained for the most part do not offer sufficient information on dose-response,
especially in the case for *in vivo* tests. In conclusion, the possibility to set SCL for germ cell
mutagenicity is therefore not considered possible in the process of self-classification as there
is no standardized methodical approach available which adequately takes into account all relevant information.
3.5.2.6 Decision logic for substances

The decision logic which follows is provided as additional guidance. It is strongly recommended that the person responsible for classification study the criteria before and during use of the decision logic.

Does the substance have data on mutagenicity?

- **NO** Classification not possible
- **YES**

According to the criteria, is the substance:

- **(a)** Known to induce heritable mutations in germ cells of humans, or
- **(b)** Should it be regarded as if it induces heritable mutations in the germ cells of humans?

Application of the criteria needs expert judgement in a weight of evidence approach.

- **YES** Category 1
- **NO**

According to the criteria, does the substance cause concern for humans owing to the possibility that it may induce heritable mutations in the germ cells of humans?

Application of the criteria needs expert judgement in a weight of evidence approach.

- **YES** Category 2
- **NO** Not classified
3.5.3 Classification of mixtures for germ cell mutagenicity

3.5.3.1 Classification criteria for mixtures

Classification of mixtures will be based on the available test data for the individual ingredients of the mixture, using concentration limits for those ingredients. Under rare circumstances, the classification may be modified on a case-by-case basis based on the available test data for the mixture as a whole or based on bridging principles (see Article 6(3)).

3.5.3.1.1 When data are available for the complete mixture

Annex I: 3.5.3.2.1. When data are available for the complete mixture, the mixture shall be classified as a mutagen when at least one ingredient has been classified as a Category 1A, Category 1B or Category 2 mutagen and is present at or above the appropriate generic concentration limit as shown in Table 3.5.2.

<table>
<thead>
<tr>
<th>Ingredient classified as:</th>
<th>Concentration limits triggering classification of a mixture as:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Category 1A mutagen</td>
</tr>
<tr>
<td>Category 1A mutagen</td>
<td>≥ 0,1 %</td>
</tr>
<tr>
<td>Category 1B mutagen</td>
<td>—</td>
</tr>
<tr>
<td>Category 2 mutagen</td>
<td>—</td>
</tr>
</tbody>
</table>

Note

The concentration limits in the table above apply to solids and liquids (w/w units) as well as gases (v/v units).

3.5.3.1.2 When data are not available for the complete mixture: bridging principles

Annex I: 3.5.3.3.1. Where the mixture itself has not been tested to determine its germ cell mutagenicity hazard, but there are sufficient data on the individual ingredients and similar tested mixtures (subject to paragraph 3.5.3.2.1), to adequately characterise the hazards of the mixture, these data shall be used in accordance with the applicable bridging rules set out in section 1.1.3.

3.5.3.2 Generic concentration limits for substances triggering classification of mixtures

Annex I: 3.5.3.1.1. The mixture shall be classified as a mutagen when at least one ingredient has been classified as a Category 1A, Category 1B or Category 2 mutagen and is present at or above the appropriate generic concentration limit as shown in Table 3.5.2 for Category 1A, Category 1B and Category 2 respectively.

Table 3.5.2

Generic concentration limits of ingredients of a mixture classified as germ cell mutagens that trigger classification of the mixture.
The option to set SCL for germ cell mutagenicity is not considered possible in the process of self-classification as there is no standardized methodical approach available which adequately takes into account all relevant information (See section 3.5.2.5).

3.5.3.3 Decision logic for mixtures

The decision logic which follows is provided as additional guidance. It is strongly recommended that the person responsible for classification study the criteria before and during use of the decision logic. This decision logic deviates (slightly) from the original GHS guidance, to meet CLP requirements.
Classification based on individual ingredients of the mixture

Does the mixture contain one or more ingredients classified as a Category 1 mutagen at ≥ 0.1%?

YES

Category

Danger

NO

Does the mixture contain one or more ingredients classified as a Category 2 mutagen at ≥ 1.0%?

YES

Category 2

Warning

NO

Not classified

Modified classification on a case-by-case basis

Test data on mixtures may be used for classification when demonstrating effects that have not been established from the evaluation based on the individual ingredients (CLP, section 3.5.3.2.1, see also CLP Article 6(3)).

Are test data available for the mixture itself demonstrating a mutagenic effect not identified from the data on individual substances?

YES

Are the test results on the mixture conclusive taking into account dose and other factors such as duration, observations and analysis (e.g. statistical analysis, test sensitivity) of germ cell mutagenicity test systems?

YES

Classify in appropriate category

Danger or Warning

or

No classification

NO

NO

No classification

Can bridging principles be applied?

YES

See above: Classification based on individual ingredients of the mixture.
3.5.4 Hazard communication in form of labelling for germ cell mutagenicity

3.5.4.1 Pictograms, signal words, hazard statements and precautionary statements

Annex I: 3.5.4.1. Label elements shall be used in accordance with Table 3.5.3, for substances or mixtures meeting the criteria for classification in this hazard class.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Category 1A or Category 1B</th>
<th>Category 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>GHS Pictograms</td>
<td><img src="image1" alt="Pictogram" /></td>
<td><img src="image2" alt="Pictogram" /></td>
</tr>
<tr>
<td>Signal Word</td>
<td>Danger</td>
<td>Warning</td>
</tr>
<tr>
<td>Hazard Statement</td>
<td>H340: May cause genetic defects (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)</td>
<td>H341: Suspected of causing genetic defects (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)</td>
</tr>
<tr>
<td>Precautionary Statement Prevention</td>
<td>P201</td>
<td>P202</td>
</tr>
<tr>
<td>Precautionary Statement Response</td>
<td>P308 + P313</td>
<td>P308 + P313</td>
</tr>
<tr>
<td>Precautionary Statement Storage</td>
<td>P405</td>
<td>P405</td>
</tr>
<tr>
<td>Precautionary Statement Disposal</td>
<td>P501</td>
<td>P501</td>
</tr>
</tbody>
</table>

The hazard statement to be applied for the classification germ cell mutagenicity has to be amended to state the route of exposure if it is conclusively proven that no other routes of exposure will lead to the respective effect. A conclusive proof means that valid in vivo test data need to be available for all three exposure routes clearly indicating that only one exposure route leads to positive results. Moreover, such findings should be plausible with respect to the mode of action. It is estimated that such circumstances rarely, if ever, exist. Therefore, amending the hazard statement with the route of exposure generally does not have to be considered.

3.5.4.2 Additional labelling provisions

There are no additional labelling provisions for substances and mixtures classified for germ cell mutagenicity in CLP, however there are provisions laid out in Annex XVII to REACH. The packaging of substances classified for germ cell mutagenicity Category 1A or Category 1B, and mixtures containing such substances, "must be marked visibly, legibly and indelibly as follows: ‘Restricted to professional users’." (REACH, Annex XVII, point 29).
3.5.5 Re-classification of substances classified for germ cell mutagenicity according to DSD and DPD

Direct translation of classification and labelling is generally possible for substances and mixtures classified as germ cell mutagens.

In CLP, there is clear discrimination of in vivo mutagenicity tests and in vivo genotoxicity tests with respect to their relevance for classification. Moreover, in some circumstances which are assumed to occur very rarely if at all, a different classification may be the consequence if expert judgement is not applied.

For instance, positive results from studies showing mutagenic effects in germ cells of exposed humans can lead to classification as a Category 1B mutagen under CLP. However, using the criteria in DSD it is not clear how to classify in such a case. Moreover, in vivo somatic cell genotoxicity tests need to be supported by in vitro data in order to classify as a Category 2 mutagen under CLP. In such circumstances under DSD, in vivo data do not necessarily need to be supported by in vitro data. However, it has to be taken into account that such circumstances will rarely occur as the testing strategy uses in vitro tests as a starting point.

3.6 CARCINOGENICITY

3.6.1 Definitions and general considerations for classification for carcinogenicity

Annex I: 3.6.1.1. Carcinogen means a substance or a mixture of substances which induce cancer or increase its incidence. Substances which have induced benign and malignant tumours in well performed experimental studies on animals are considered also to be presumed or suspected human carcinogens unless there is strong evidence that the mechanism of tumour formation is not relevant for humans.

More explicitly, chemicals are defined as carcinogenic if they induce tumours, increase tumour incidence and/or malignancy or shorten the time to tumour occurrence. Benign tumours that are considered to have the potential to progress to malignant tumours are generally considered along with malignant tumours. Chemicals can potentially induce cancer by any route of exposure (e.g., when inhaled, ingested, applied to the skin or injected), but carcinogenic potential and potency may depend on the conditions of exposure (e.g., route, level, pattern and duration of exposure).

Carcinogenic chemicals have conventionally been divided according to the presumed mode of action; genotoxic or non-genotoxic, see section 3.6.2.3.2 (k).

Classification of a substance as a carcinogen is based on consideration of the strength of the evidence of available data for classification with considerations of all other relevant information (weight of evidence) being taken into account as appropriate. Strength of evidence involves the enumeration of tumours in human and animal studies and determination of their level of statistical significance. A number of other factors need to be considered that influence the overall likelihood that a substance poses a carcinogenic hazard in humans (weight of evidence determination). The list of factors for additional consideration is long and requires the most up-to-date scientific knowledge. It is recognised that, in most cases, expert judgement is necessary to be able to determine the most appropriate category for classification for carcinogenicity.
3.6.2.1 Identification of hazard information

Carcinogens may be identified from epidemiological studies, from animal experiments and/or other appropriate means that may include (Quantitative) Structure-Activity Relationships ((Q)SAR) analyses and/or extrapolation from structurally similar substances (read-across). In addition some information on the carcinogenic potential can be inferred from \textit{in vivo} and \textit{in vitro} germ cell and somatic cell mutagenicity studies, \textit{in vitro} cell transformation assays, and gap junction intercellular communication (GJIC) tests.

Extensive guidance on data requirements, information sources and strategies for the identification of potential carcinogens are given in IR/CSA, section R.7.7.9 (Information requirements on carcinogenicity) and IR/CSA, section R.7.7.10 (Information and its sources on carcinogenicity) and for potential mutagens IR/CSA, section R.7.7.3 (Information and its sources on mutagenicity).

For more about non testing data see section 3.6.2.3.4.

3.6.2.2 Classification criteria for substances

Substances are classified according to their potential to cause cancer in humans. In some cases there will be direct evidence on the carcinogenicity to humans from epidemiological studies. However, in most cases the available information on carcinogenicity will be primarily from animal studies. In this case the relevance of the findings in animals to humans must be considered.

**Annex I: 3.6.2.1.** For the purpose of classification for carcinogenicity, substances are allocated to one of two categories based on strength of evidence and additional considerations (weight of evidence). In certain instances, route-specific classification may be warranted, if it can be conclusively proved that no other route of exposure exhibits the hazard.

<table>
<thead>
<tr>
<th>Hazard categories for carcinogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Categories</td>
</tr>
</tbody>
</table>
196

**Guidance to Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of substances and mixtures**

**CATEGORY 1:** Known or presumed human carcinogens

A substance is classified in Category 1 for carcinogenicity on the basis of epidemiological and/or animal data. A substance may be further distinguished as:

- **Category 1A:** Category 1A, known to have carcinogenic potential for humans, classification is largely based on human evidence, or
- **Category 1B:** Category 1B, presumed to have carcinogenic potential for humans, classification is largely based on animal evidence.

The classification in Category 1A and 1B is based on strength of evidence together with additional considerations (see section 3.6.2.2). Such evidence may be derived from:
- human studies that establish a causal relationship between human exposure to a substance and the development of cancer (known human carcinogen); or
- animal experiments for which there is sufficient (1) evidence to demonstrate animal carcinogenicity (presumed human carcinogen).

In addition, on a case-by-case basis, scientific judgement may warrant a decision of presumed human carcinogenicity derived from studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals.

**CATEGORY 2:** Suspected human carcinogens

The placing of a substance in Category 2 is done on the basis of evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the substance in Category 1A or 1B, based on strength of evidence together with additional considerations (see section 3.6.2.2). Such evidence may be derived either from limited (1) evidence of carcinogenicity in human studies or from limited evidence of carcinogenicity in animal studies.

(1) Note: See 3.6.2.2.4.

### 3.6.2.3 Evaluation of hazard information

**Annex I: 3.6.2.2.1.** Classification as a carcinogen is made on the basis of evidence from reliable and acceptable studies and is intended to be used for substances which have an intrinsic property to cause cancer. The evaluations shall be based on all existing data, peer-reviewed published studies and additional acceptable data.

**3.6.2.2.2.** Classification of a substance as a carcinogen is a process that involves two interrelated determinations: evaluations of strength of evidence and consideration of all other relevant information to place substances with human cancer potential into hazard categories.

Classification of a substance as a carcinogen requires expert judgement and consideration of many different factors (weight and strength of evidence) included in the hazard information on carcinogenicity. The guidance provides an approach to data analysis rather than hard and fast rules. A stepwise approach to the classification can be taken where all the factors, both weight and strength of evidence, that may influence the outcome are considered systematically. Such approach, including consideration of these factors is outlined, in McGregor et al, 2009 and Boobis et al, 2006. Also the IPCS “Conceptual Framework for Evaluating a Mode of Action for Chemical carcinogenesis” (2001), ILSI “Framework for
Human Relevance Analysis of Information on Carcinogenic Modes of Action” (Meek et al., 2003; Cohen et al., 2003, 2004) and the International Agency for Research on Cancer (IARC, 2006 - Preamble Section B) provide a basis for systematic assessments which may be performed in a consistent fashion internationally; however they are not intended to provide lists of criteria to be checked off.

Specific considerations that are necessary are outlined in CLP, Annex I, section 3.6.2.3 (see section 3.6.2.3.1 of this document) and other important factors to consider in CLP, Annex I, section 3.6.6.2.6 (see section 3.6.2.3.2 of this document). Further guidance on these important factors is given in this document.

### 3.6.2.3.1 Specific considerations for classification

There is a strong link between CLP and the IARC classification criteria. The definitions for sufficient and limited evidence as defined by IARC are part of the criteria (Annex I, section 3.6.2.2.3). IARC, however, understands the criteria of “sufficient” and “limited” as follows:

‘It is recognized that the criteria for these evaluations, described below, cannot encompass all of the factors that may be relevant to an evaluation of carcinogenicity. In considering all of the relevant scientific data, the Working Group may assign the agent to a higher or lower category than a strict interpretation of these criteria would indicate.’ (IARC 2006, Preamble to section 6, Evaluation and rationale). This sentence emphasises that in certain circumstances expert judgement may overrule the strict interpretation of the IARC criteria for "sufficient" and "limited". These same limitations apply with the current criteria in that expert judgement is necessary and can override the strict interpretation of the definitions.

### Annex I: 3.6.2.2.3

Strength of evidence involves the enumeration of tumours in human and animal studies and determination of their level of statistical significance. Sufficient human evidence demonstrates causality between human exposure and the development of cancer, whereas sufficient evidence in animals shows a causal relationship between the substance and an increased incidence of tumours. Limited evidence in humans is demonstrated by a positive association between exposure and cancer, but a causal relationship cannot be stated. Limited evidence in animals is provided when data suggest a carcinogenic effect, but are less than sufficient. The terms 'sufficient' and 'limited' have been used here as they have been defined by the International Agency for Research on Cancer (IARC) and read as follows:

(a) Carcinogenicity in humans

The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories:

- sufficient evidence of carcinogenicity: a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence;

- limited evidence of carcinogenicity: a positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

(b) Carcinogenicity in experimental animals

Carcinogenicity in experimental animals can be evaluated using conventional bioassays, bioassays that employ genetically modified animals, and other in-vivo bioassays that focus on one or more of the critical stages of carcinogenesis. In the absence of data from conventional long-term bioassays or from assays with neoplasia as the end-point, consistently positive
results in several models that address several stages in the multistage process of carcinogenesis should be considered in evaluating the degree of evidence of carcinogenicity in experimental animals. The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories:

- **sufficient evidence of carcinogenicity**: a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide sufficient evidence. A single study in one species and sex might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites;

- **limited evidence of carcinogenicity**: the data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs.

For human studies, the quality and power of the epidemiology studies require expert consideration and would normally lead to a Category 1A classification if data of adequate quality shows causality of exposure and cancer development. IR/CSA, section R.7.7.10.2, further discusses the types of human epidemiology data available and the limitations of the data. Where there is sufficient doubt in the human data then classification in Category 1B may be more appropriate. On the other hand epidemiological studies may fail, because of uncertainties in the exposure assessment and/or limited sensitivity and statistical power, to confirm the carcinogenic properties of a substance as identified in animal studies (WHO Working group, 2000).

### 3.6.2.3.2 Additional considerations for classification

**Annex I: 3.6.2.2.4.** Additional considerations (as part of the weight of evidence approach (see 1.1.1)). Beyond the determination of the strength of evidence for carcinogenicity, a number of other factors need to be considered that influence the overall likelihood that a substance poses a carcinogenic hazard in humans. The full list of factors that influence this determination would be very lengthy, but some of the more important ones are considered here.

**3.6.2.2.5.** The factors can be viewed as either increasing or decreasing the level of concern for human carcinogenicity. The relative emphasis accorded to each factor depends upon the amount and coherence of evidence bearing on each. Generally there is a requirement for more complete information to decrease than to increase the level of concern. Additional considerations should be used in evaluating the tumour findings and the other factors in a case-by-case manner.

**3.6.2.2.6.** Some important factors which may be taken into consideration, when assessing the overall level of concern are:

1. tumour type and background incidence;
2. multi-site responses;
3. progression of lesions to malignancy;
(d) reduced tumour latency;
(e) whether responses are in single or both sexes;
(f) whether responses are in a single species or several species;
(g) structural similarity to a substance(s) for which there is good evidence of carcinogenicity;
(h) routes of exposure;
(i) comparison of absorption, distribution, metabolism and excretion between test animals and humans;
(j) the possibility of a confounding effect of excessive toxicity at test doses;
(k) mode of action and its relevance for humans, such as cytotoxicity with growth stimulation, mitogenesis, immunosuppression, mutagenicity.

As indicated above, the evaluation of animal carcinogenicity data requires consideration of a number of important additional factors which may increase or decrease the level of concern and the classification category. The list in Annex I, section 3.6.2.6 is not exhaustive. Each of these factors is discussed individually below.

(a) Tumour type and background incidence

Knowledge about the tumour type including its tumour biology is indispensable to decide on the relevance of observed tumours for humans.

By default, carcinogenic effects in experimental animals are considered relevant to humans and are considered for classification as carcinogens. Only when there is sufficient evidence showing that a certain type of tumour is not relevant to humans should this tumour type be excluded for classification.

Certain tumour types observed in animal carcinogenicity studies are of questionable or no relevance to humans. In case of multiple tumours anticipated to have no relevance for humans justification should be given for each tumour type. The justification for dismissing any particular tumour should be presented as a scientifically robust and transparent argument.

There are several reasons why a tumour observed in animals may be judged to be not relevant for humans or may be judged to be of lower concern. In most of these cases the tumour arises via a mode of action which does not occur in humans (see this Section part k). In some cases the tumour may arise in a tissue known to be overly susceptible in the species tested to development of certain tumours and consequently may be judged to be less relevant for humans. In a few cases a tumour may occur in a tissue with no equivalent in humans.

*Tumours occurring in tissues with no human equivalent*

Some of the commonly used animal species have some tissues with no equivalent in humans.

Tumours occurring in these tissues include the following

– Forestomach tumours in rodents following administration by gavage of irritating or corrosive, non mutagenic substances. In rodents, the stomach is divided into two parts by the muco-epidermoid junction separating squamous from glandular epithelium. The proximal part, or forestomach, is non-glandular, forms a continuum with the oesophagus, and is lined by keratinized, stratified squamous epithelium. While humans do not have a forestomach, they do have comparable squamous epithelial tissues in the oral cavity and the upper two-thirds of the oesophagus. See also this Section (k), IARC (2003), and RIVM (2003).
– Tumours in the Zymbal’s glands. Zymbal’s glands are located beneath squamous epithelium at the anterior and posterior aspect of the ear canal. The external portion of the gland in rats is 3 to 5 millimetres in diameter.

– Tumours in the Harderian glands. Harderian glands are found in all vertebrates that possess a nictitating membrane, or third eyelid. They are located behind the eyeball in the orbit nictitating membrane, encircling the optic nerve. Humans have a rudimentary one.

Tumours occurring in such tissues indicate that the substance has the potential to induce carcinogenic effects in the species tested. It cannot automatically be ruled out that the substance could cause similar tumours of comparable cell/tissue origin (e.g. squamous cell tumours at other epithelial tissues) in humans. Careful consideration and expert judgement of these tumours in the context of the complete tumour response (i.e. if there are also tumours at other sites) and the assumed mode of action is required to decide if these findings would support a classification. However, tumours observed only in these tissues, with no other observed tumours are unlikely to lead to classification. However, such determinations must be evaluated carefully in justifying the carcinogenic potential for humans; any occurrence of other tumours at distant sites must also be considered.

*Considering the background incidence and use of historical control data*

Any statistically significant increase in tumour incidence, especially where there is a dose-response relationship, is generally taken as positive evidence of carcinogenic activity. However, in some cases the results involve an increase incidence of tumours in treated animals which lies at the borderline of biological and/or statistical significance or there is an increase in a spontaneous tumour type, then comparison of the tumour incidence with historical control tumour data is strongly encouraged.

Historical control data provide useful information on the normal pattern and range of tumour types and incidences for a particular strain/species, which may not be reflected by the tumour findings in the concurrent controls in any individual study. This can be particularly relevant for animal strains which have a propensity to develop a particular type of tumour spontaneously with variable and potentially high incidence. In such a case the tumour incidence in the treated group may be significantly above the concurrent control but could still be within the historical incidence range for that tumour type in that species and therefore may not be providing reliable evidence of treatment related carcinogenicity.

Some examples of animal tissues with a high spontaneous tumour incidence are:

– Adrenal pheochromocytoma in male F344 rats (NTP, 2007a), Sprague-Dawley rats (NTP, 2005; RIVM, 2001; Ozaki et al., 2002);

– Pituitary adenomas in F344 rats (NTP, 2007a), Sprague-Dawley rats (NTP 2005; RIVM 2005);

– Mammary gland tumours (adenomas and carcinomas) in female Sprague-Dawley rats (NTP, 2005);

– Mononuclear cell leukaemia in F344 rats (NTP, 2007a; RIVM, 2005);

– Liver tumours in B6C3F1 mice (NTP, 2007b; Haseman et al. 1998; Battershill, J.M. and Fielder, R.J., 1998);

– Leydig cell adenomas in male F344 rats (Cook et al., 1999; Mati et al., 2002; RIVM, 2004; EU Specialised Experts Report, 2004).

Historical control data can also be useful to judge the biological significance of marginal increases in uncommon tumours. If there is a small increase in a particular tumour type which
Guidance to Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of substances and mixtures

historical data shows to be very uncommon and unlikely to have occurred by chance then this may support a conclusion of carcinogenicity without the requirement for a statistically significant increase.

Use of historical control data should be on a case by case basis with due consideration of the appropriateness and relevance of the historical control data for the study under evaluation. In a general sense, the historical control data set should be matched as closely as possible to the study being evaluated. The historical data must be from the same animal strain/species, and ideally, be from the same laboratory to minimise any potential confounding due to variations in laboratory conditions, study conditions, animal suppliers, husbandry etc. It is also known that tumour incidences in control animals can change over time, due to factors such as genetic drift, changes in diagnostic criteria for pathological changes/tumour types, and husbandry factors (including the standard diet used), so the historical data should be contemporary to the study being evaluated (e.g. within a period of up to around 5 years of the study). Historical data older than this should be used with caution and acknowledgement of its lower relevance and reliability. (RIVM, 2005; Fung et al, 1996; Greim et al, 2003).

Even when a particular tumour type may be discounted, expert judgment must be used in assessing the total tumour profile in any animal. However, appearance of only spontaneous tumours, especially if they appear only at high dose levels, may be sufficient to downgrade a classification from Category 1B to Category 2, or even no classification. Where the only available tumour data are liver tumours in certain sensitive strains of mice, without any other supplementary evidence, the substance may not be classified in any of the categories, (Battershill and Fielder, 1998). Expert judgment is required to evaluate the relevance of the results.

(b) Multi-site responses

In general, chemicals are evaluated for carcinogenic potential in two-year bioassays conducted in mice and rats. The chemicals produce a spectrum of responses ranging from no effects in either species to induction of malignant neoplasms in multiple tissues in both species. Between these two extremes, there are variable responses in tissues, sexes and species, which demonstrate that there are important differences among the carcinogens, as well as between the species in which they are tested. The tumour profile observed with a substance should be taken into account when considering the most appropriate classification.

Evidence shows that substances which cause tumours in either multiple sites and/or multiple species tend to be more potent carcinogens than those causing tumours at only one site in one species (Dybing et al., 1997). This is often true for substances which are mutagenic. Also, where human carcinogens have been tested in two or more species, the majority have caused cancer in several species (Tennant, 1993). Thus, if a substance causes tumours at multiple sites and/or in more than one species then this usually provides strong evidence of carcinogenicity. Typically such a tumour profile would lead to a classification in category 1B.

(c) Progression of lesions to malignancy

In general, if a substance involves a treatment related increase in tumours then it will meet the criteria for classification as a carcinogen.

If the substance has been shown to cause malignant tumours this will usually constitute sufficient evidence of carcinogenicity supporting Category 1B (Annex I, section 3.6.2.2.3)

The induction of only benign tumours usually provides a lower strength of evidence for carcinogenicity than the induction of malignant tumours and will usually support Category 2
(Annex I, Section 3.6.2.2.3). However, benign tumours may also be of significant concern and the strength of evidence for carcinogenicity that they provide should be considered using expert judgement. For instance, some benign tumours may have the potential to progress to malignant tumours and therefore any indication that the observed tumours have the potential to progress to malignancy may increase the level of concern. Also, some benign tumours, for example brain tumours, may be of concern in themselves.

(d) Reduced tumour latency

The latency of tumour development i.e. how quickly a substance induces tumours, often reflects the potency of a carcinogen. This is particularly true for mutagenic substances which often induce tumours with relatively short latency and usually more rapidly than non-genotoxic agents. Tumour latency is not generally investigated in detail in standard carcinogenicity studies, although some information may be provided if the study used serial sacrifices.

The latency of tumour formation does not materially affect the classification and hazard category. Any substance causing cancer will attract classification regardless of the latency for tumour development. This also includes tumour responses at late treatment/life periods if substance-related. However unusual tumour types or tumours occurring with reduced latency may add to the weight of evidence for the carcinogenic potential of a substance, even if the tumours are not statistically significant.

(e) Whether responses are in single or both sexes

In general, in standard carcinogenicity studies both male and female animals are tested. There may be cases where tumours are only observed in one sex.

Tumours in one sex only may arise for two broad reasons. The tumours may occur in a gender-specific tissue, for instance the uterus or testes (sex-specific tissue), or in a non-sex-specific tissue, in one sex only. Tumours may also be induced by a mechanism that is gender (or sex)-specific, for instance a hormonally-mediated mechanism or one involving gender (or sex) -specific differences in toxicokinetics. As with all cases the strength of evidence of carcinogenicity should be assessed based on the totality of the information available using a weight of evidence type approach. A default position is that such tumours are still evidence of carcinogenicity and should be evaluated in light of the total tumorigenic response to the substance observed at other sites (multi-site responses or incidence above background) in determining the carcinogenic potential and the classification category.

If tumours are seen only in one sex of an animal species, the mode of action should be carefully evaluated to see if the response is consistent with the postulated mode of action. Effects seen only in one sex in a test species may be less convincing than effects seen in both sexes, unless there is a clear patho-physiological difference consistent with the mode of action to explain the single sex response. However, there is no requirement for a mechanistic understanding of tumour induction in order to use these findings to support classification. If there is clear evidence for induction of either a gender (or a sex)-specific tumour then classification in Cat 1B may be appropriate. However, it has to be taken into account that according to the criteria additional data are required to provide sufficient evidence for animal carcinogenicity (1B).

(f) Whether responses are in a single species or several species

The criteria indicate that carcinogenicity in a single animal study (both sexes, ideally in a GLP study) could be sufficient evidence and could therefore lead to a Category 1B classification in the absence of any other data. This represents a change compared to the
previous EU-system where such a study would rarely lead to the equivalent of a Category 1B classification. For classification as a Category 2 carcinogen under DSD either positive results in two animal species should be available or clear positive evidence in one species, together with supporting evidence such as genotoxicity data, metabolic or biochemical studies, induction of benign tumours, structural relationship with other known carcinogens, or data from epidemiological studies suggesting an association.

However, as defined under 'sufficient' evidence (Annex I, section 3.6.2.2.3 (b)), a single study in one species and sex might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites. Moreover a single study in one species and sex in combination with positive in-vivo mutagenicity data would be considered to provide sufficient evidence of carcinogenicity.

Positive responses in several species add to the weight of evidence, that a chemical is a carcinogen.

(g) Structural similarity or not to a chemical(s) for which there is good evidence of carcinogenicity

See section 3.6.2.3.4.

(h) Routes of exposure;

Annex I: 3.6.2.2.8. The classification shall take into consideration whether or not the substance is absorbed by a given route(s); or whether there are only local tumours at the site of administration for the tested route(s), and adequate testing by other major route(s) show lack of carcinogenicity.

The classification for carcinogenicity generally does not specify specific routes of exposure. If a chemical has been shown to cause tumours by any route of administration then it may require classification, unless there is a robust justification for dismissing the findings from a particular route. However, under the previous EU system (Annex VI to DSD), classification specifically via inhalation was accepted by application of the risk phrase R49; May cause cancer by inhalation and a specific hazard statement has been established in CLP, H350i; May cause cancer by inhalation (CLP, Annex VII, Table 1.1).

Most standard carcinogenicity studies use physiological routes of exposure for humans, namely inhalation, oral or dermal exposure. The findings from such routes are usually considered directly relevant for humans. Studies using these routes will generally take precedence over similar studies using other routes of exposure.

Sometimes other non-physiological routes are used, such as intra-muscular, sub-cutaneous, intra-peritoneal and intra-tracheal injections or instillations. Findings from studies using these routes may provide useful information but should be considered with caution. Usually dosing via these routes provides a high bolus dose which gives different toxicokinetics to normal routes and can lead to atypical indication of carcinogenicity. For instance, the high local concentration can lead to local tumours at the site of injection. These would not normally be considered reliable indications of carcinogenicity as they most likely arose from the abnormally high local concentration of the test substance and would lead to a lower category classification or no classification.

Where findings are available from studies using standard routes and non-physiological routes, the former will generally take precedence. Usually studies using non-standard routes provide supporting evidence only.
The hazard statement allows for identifying the route of exposure “if it is conclusively proven that no other routes of exposure cause the hazard” (Annex I, section 3.6.4.1). In this case the hazard statement may be modified accordingly. Genotoxic carcinogens are generally suspected to be carcinogenic by any route.

(i) Comparison of absorption, distribution, metabolism and excretion between test animals and humans:

**Annex I: 3.6.2.2.9.** It is important that whatever is known of the physico-chemical, toxicokinetic and toxicodynamic properties of the substances, as well as any available relevant information on chemical analogues, i.e. structure activity relationship, is taken into consideration when undertaking classification.

Consideration of absorption, distribution, metabolism and excretion (toxicokinetics) of the substance in the test animal species and in humans is one important consideration, including where a substance is metabolised to an active carcinogenic metabolite. Toxicokinetic behaviour is normally assumed to be similar in animals and humans, at least from a qualitative perspective. On the other hand, certain tumour types in animals may be associated with toxicokinetics or toxicodynamics that are unique to the animal species tested and may not be predictive of carcinogenicity in humans. Where significant qualitative and quantitative differences in toxicokinetics exist between animals and humans this can impact on the relevance of the animal findings for humans and in certain instances may influence the category of classification. Where a carcinogenic metabolite identified in animals is demonstrated not to be produced in humans, no classification may be warranted where it can be shown that this is the only mechanism of action for carcinogenicity.

The use of physiologically-based pharmacokinetic (PB/PK) modelling requires more validation and while it may not lead directly to a modification of classification, however expert judgement in conjunction with PB/PK modelling may help to modify the concern for humans.

(j) The possibility of a confounding effect of excessive toxicity at test doses

In lifetime bioassays compounds are routinely tested using at least three dose levels to enable hazard identification and hazard characterisation as part of risk assessment. Of these doses, the highest dose needs to induce minimal toxicity, such as characterised by an approximately 10% reduction in body weight gain (maximal tolerated dose, MTD dose). The MTD is the highest dose of the test agent during the bioassay that can be predicted not to alter the animal’s normal longevity from effects other than carcinogenicity. Data obtained from a sub-chronic or other repeated dose toxicity study are used as the basis for determining the MTD.

Excessive toxicity, for instance toxicity at doses exceeding the MTD, can affect the carcinogenic responses in bioassays. Such toxicity can cause effects such as cell death (necrosis) with associated regenerative hyperplasia, which can lead to tumour development as a secondary consequence unrelated to the intrinsic potential of the substance itself to cause tumours at lower less toxic doses.

Tumours occurring only at excessive doses associated with severe toxicity generally have a more doubtful potential for carcinogenicity in humans. In addition, tumours occurring only at sites of contact and/or only at excessive doses need to be carefully evaluated for human relevance for carcinogenic hazard. For example, as indicated in this Section (a) 'Tumour type and background incidence', forestomach tumours, following administration by gavage of an irritating or corrosive, non-mutagenic chemical, may be of questionable relevance, both due to the lack of a corresponding tissue in humans, but importantly, due to the high dose direct
effect on the tissue. However, such determinations must be evaluated carefully in justifying the carcinogenic potential for humans; any occurrence of other tumors at distant sites must also be considered.

The proceedings of a WHO/IPCS workshop on the Harmonization of Risk Assessment for Carcinogenicity and Mutagenicity (Germ cells) - A Scoping Meeting (IPCS, 1995; Ashby et al, 1996), points to a number of scientific questions arising for classification of chemicals, e.g. mouse liver tumors, peroxisome proliferation, receptor-mediated reactions, chemicals which are carcinogenic only at toxic doses and which do not demonstrate mutagenicity.

If a test compound is only found to be carcinogenic at the highest dose(s) used in a lifetime bioassay, and the characteristics associated with doses exceeding the MTD as outlined above are present, this could be an indication of a confounding effect of excessive toxicity. This may support a classification of the test compound in Category 2 or no classification.

(k) Mode of action and its relevance for humans, such as mutagenicity, cytotoxicity with growth stimulation, mitogenesis, immunosuppression

Carcinogenic chemicals have conventionally been divided into two categories according to the presumed mode of action; genotoxic or non-genotoxic. Genotoxic modes of action involve genetic alterations caused by the chemical interacting directly with DNA to possibly result in a change in the primary sequence of DNA after cell division. A chemical can also cause genetic alterations indirectly following interaction with other cellular processes (e.g., secondary to the induction of oxidative stress). Non-genotoxic modes of action include epigenetic changes, i.e., effects that do not involve alterations in DNA but that may influence gene expression, altered cell-cell communication, or other factors involved in the carcinogenic process. For example, chronic cytotoxicity with subsequent regenerative cell proliferation is considered a mode of action by which tumor development can be enhanced: the induction of urinary bladder tumors in rats may, in certain cases, be due to persistent irritation/inflammation, tissue erosion and regenerative hyperplasia of the urothelium following the formation of bladder stones. Other modes of non-genotoxic action can involve specific receptors (e.g., peroxisome proliferator-activated receptor-alpha (PPARα) which is associated with liver tumors in rodents; or tumors induced by various hormonal mechanisms). More detail is given in IR/CIS Section R7.7.8.

Some modes of action of tumor formation are considered to be not relevant to humans. Where such a mechanism is identified then classification may not be appropriate Only if a mode of action of tumour development is conclusively determined not to be operative in humans may the carcinogenic evidence for that tumour be discounted. However, a weight of evidence evaluation for a substance calls for any other tumorigenic activity to be evaluated as well. In addition, the existence of a secondary mechanism of action with the implication of a practical threshold above a certain dose level (e.g., hormonal effects on target organs or on mechanisms of physiological regulation, chronic stimulation of cell proliferation) may lead to a downgrading of a Category 1 to Category 2 classification.

The various international documents on carcinogen assessment all note that mode of action in and of itself, or consideration of comparative metabolism, should be evaluated on a case-by-case basis and are part of an analytic evaluative approach. One must look closely at any mode of action in animal experiments taking into consideration comparative toxicokinetics/toxicodynamics between the animal test species and humans to determine the relevance of the results to humans. This may lead to the possibility of discounting very specific effects of certain types of chemicals. Life stage-dependent effects on cellular differentiation may also lead to qualitative differences between animals and humans.
To establish a mode of action will usually require specific investigative studies over and above the standard carcinogenicity study. All available data must be considered carefully to judge if it can be concluded with confidence that the tumours are being induced through that specific mechanism. The IPCS Framework for Analyzing the Relevance of a Cancer Mode of Action for Humans (2007) can be a useful way to construct and present a robust and transparent assessment of such data.

Some mechanisms of tumour formation considered not relevant for humans:

- Kidney tumours in male rats associated with substances causing α2µ-globulin nephropathy (IARC, 1999)
- Pheochromocytomas in male rats exposed to particulates through inhalation secondary to hypoxemia (Ozaki et al., 2002)
- Leydig cell adenomas induced by dopamine antagonists or gonadotropin-releasing hormone (GnRH) (EU Specialised Experts, 2004; RIVM, 2004)
- Urinary bladder tumours due to crystals in the bladder (IARC, 1999)
- Foregut tumours in rodents following administration by gavage of irritating or corrosive, non-genotoxic substances (RIVM, 2003; IARC 2003)
- Certain thyroid tumours in rodents mediated by UDP glucuronyltransferase (UGT) induction (IARC, 1999; EU Specialised Experts, 1999)
- Liver tumours in rodents conclusively linked to peroxisome proliferation (IARC, 1994)

### 3.6.2.3 Consideration of mutagenicity

#### Annex I: 3.6.2.2.6. Mutagenicity: It is recognised that genetic events are central in the overall process of cancer development. Therefore evidence of mutagenic activity in vivo may indicate that a substance has a potential for carcinogenic effects.

As indicated in section 3.6.2.1 and above, carcinogenic chemicals have conventionally been divided according to the presumed mode of action; genotoxic or non-genotoxic. Evidence of genotoxic activity is gained from studies on mutagenic activity. It should be noted that in general if a substance is mutagenic then it will be considered to be potentially carcinogenic in humans however mutagenicity data alone are insufficient information to justify a carcinogen classification. In some cases where only in vitro and in vivo mutagenicity are present without carcinogenicity data, a Category 2 classification can be considered when all factors have been considered such as type and quality of the mutagenicity data, structure activity relationships etc. A single positive carcinogenicity study in one species and sex in combination with positive in-vivo mutagenicity data would be considered to provide sufficient evidence of carcinogenicity.

Lack of genotoxicity is an indicator that other mechanisms are in operation as indicated in section 3.6.2.3.2 of the above. Thus careful analysis based on all available information is required to identify the mechanism and derive a classification category taking into account the factors leading to the tumours observed, in the animals.

### 3.6.2.4 Non testing data

#### Annex I: 3.6.2.2.7. A substance that has not been tested for carcinogenicity may in certain instances be classified in Category 1A, Category 1B or Category 2 based on tumour data from a structural analogue together with substantial support from consideration of other important factors.
such as formation of common significant metabolites, e.g. for benzidine congener dyes.

A chemical that has not been tested for carcinogenicity may in certain instances be classified as a carcinogen based on tumour data from a structurally similar chemical with which it is predicted to have similar carcinogenic activity. Such an approach must always be based on a robust and transparent argument to support this supposition. There may also be evidence demonstrating similarity in terms of other important factors such as toxicokinetics or mutagenic activity etc. (OECD 2004, 2005, 2007; IR/CSA, section R.6, QSARs and grouping of chemicals).

In the absence of carcinogenicity data, read-across can be used to support a classification for carcinogenicity when the chemical in question is similar to a known or suspected carcinogen (Category 1A, 1B or 2). The similarity between chemicals is considered in terms of structural features, physico-chemical properties and overall toxicological profile.

In general the chemicals will share a common structural element or functional group (i.e., a toxiphore) that has been shown to be integral to the underlying mechanism of carcinogenicity for chemicals with this toxiphore in well conducted studies. These toxiphores can be identified through expert judgement or through automated systems such as (Q)SARs. The read-across should also consider the physico-chemical properties of the chemical and data from other toxicity studies to judge the similarity between the chemicals in terms of bioavailability by relevant routes of exposure and toxicokinetics. The toxicity profile from other studies should also be compared (e.g., acute and repeated-dose toxicity and mutagenicity) and should share similarities in nature and severity. Data from shorter term toxicity studies may be useful, particularly for non-genotoxic carcinogens, to indicate that the chemicals cause the same underlying pathological changes (e.g., hyperplasia), and act via a common mode of action. Any predictions made on the basis of read-across should take into account the totality of data on the chemicals in question, including the physico-chemical properties, toxicological profile, toxicokinetics, structural analogy and the performance of any (Q)SAR models used, in a weight of evidence approach driven by expert judgement. The final decision must be clear, scientifically defensible and transparent.

The specific category depends on the category of the known carcinogen and the degree of confidence in the robustness of the read-across prediction. The category will not be higher than the chemical used to read-across from, but normally may be the same. However a lower category may be applied if the read-across highlights a possible carcinogenic hazard, and thus supports a classification, but there is uncertainty as to the robustness of the read-across prediction or there is evidence, for instance from mechanistic or other studies, that the chemical may be of lower concern for carcinogenicity.

If a chemical is similar to a substance known to be carcinogenic and shares the toxiphore that is considered to be causally related to carcinogenicity, then it is unlikely that there will be sufficient confidence in a prediction of no hazard (for instance based on arguments relating to differences in physico-chemical or steric properties), to justify no classification in the absence of supporting negative experimental data. However, the bioavailability of the toxiphore will need evaluation (IR/CSA R.6).

### Decision on classification

As mentioned throughout, classification as a carcinogen is based on consideration of the strength of evidence with additional considerations (weight of evidence) being taken into account as appropriate. It is recognised that, in most cases, expert judgment is necessary to determine the classification category.
3.6.2.5 Setting of specific concentration limits

Experimental studies have revealed large variations in the doses of various carcinogenic substances needed to induce tumours in animals. Thus, the amounts of chemical carcinogens required to induce tumours vary with a factor of up to $10^5$-$10^9$ for different compounds. It is reasonable to assume that there is similar variation in the potency of substances carcinogenic to humans (Sanner and Dybing, 2005).

The carcinogenic properties of mixtures are normally not tested. The classification and labelling of mixtures for carcinogenicity is therefore based on the classification of the ingredients and the percentage of each ingredient in the mixture. As indicated in section 3.6.3, the criteria contain default percentages for classification of mixtures with carcinogenic properties but CLP, Article 10(1) allows the use of specific concentration limits (SCL) based on the potency of the carcinogen(s). The EU has adopted the T25 concept for carcinogenicity (Dybing et al., 1997) with additional considerations as a measure for intrinsic potency and a guidance document (EC, 1999) to assist in establishing SCLs for carcinogens. By using this approach the SCL may occasionally be reduced or raised from the default generic concentration limits.
3.6.2.6  Decision logic for classification of substances

The decision logic which follows is taken from the GHS Guidance. It is strongly recommended that the person responsible for classification, study the criteria for classification before and during use of the decision logic.

Does the substance have carcinogenicity data?

NO

Classification not possible

YES

According to the criteria, is the substance:
(a) Known to have carcinogenic potential for humans, or
(b) Presumed to have carcinogenic potential for humans?
Application of the criteria needs expert judgement in a strength and weight of evidence approach.

NO

According to the criteria (see 3.6.2), is the substance a suspected human carcinogen?
Application of the criteria needs expert judgement in a strength and weight of evidence approach.

NO

Not classified

YES

Category 1
Danger

YES

Category 2
Warning
3.6.3 Classification of mixtures for carcinogenicity

3.6.3.1 Classification criteria for mixtures

Classification of mixtures will be based on the available test data for the individual ingredients of the mixture, using cut-off values/concentration limits for those ingredients and taking into account potency consideration. The classification may be a case-by-case basis, based on the available test data for the mixture as a whole (see section 3.6.3.1.2) or based on bridging principles (see section 3.6.3.1.3).

3.6.3.1.1 When data are available for all ingredients or only for some ingredients

Annex I: 3.6.3.1.1. The mixture will be classified as a carcinogen when at least one ingredient has been classified as a Category 1A, Category 1B or Category 2 carcinogen and is present at or above the appropriate generic concentration limit as shown in Table 3.6.2 below for Category 1A, Category 1B and Category 2 respectively.

Table 3.6.2

<table>
<thead>
<tr>
<th>Ingredient classified as:</th>
<th>Category 1A carcinogen</th>
<th>Category 1B carcinogen</th>
<th>Category 2 carcinogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1A carcinogen</td>
<td>≥ 0,1 %</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Category 1B carcinogen</td>
<td>—</td>
<td>≥ 0,1 %</td>
<td>—</td>
</tr>
<tr>
<td>Category 2 carcinogen</td>
<td>—</td>
<td>—</td>
<td>≥ 1,0 % [Note 1]</td>
</tr>
</tbody>
</table>

Note
The concentration limits in the table above apply to solids and liquids (w/w units) as well as gases (v/v units).

Note 1
If a Category 2 carcinogen is present in the mixture as an ingredient at a concentration ≥ 0,1% a SDS shall be available for the mixture upon request.

In case a SCL has been established for one or more ingredients these SCLs have precedence over the respective GCLs. See section 3.6.2.5 for the setting of SCLs for substances.

3.6.3.1.2 When data are available for the complete mixture

Annex I: 3.6.3.2.1. Classification of mixtures will be based on the available test data for the individual ingredients of the mixture using concentration limits for the ingredients classified as carcinogens. On a case-by-case basis, test data on mixtures may be used for classification when demonstrating effects that have not been established from the evaluation based on the individual ingredients. In such cases, the test results for the mixture as a whole must be shown to be conclusive taking into account dose and other factors such as duration, observations, sensitivity and statistical analysis of carcinogenicity test systems. Adequate documentation supporting the
3.6.3.1.3 When data are not available for the complete mixture: bridging principles

**Annex I: 3.6.3.1.** Where the mixture itself has not been tested to determine its carcinogenic hazard, but there are sufficient data on the individual ingredients and similar tested mixtures (subject to the provisions of paragraph 3.6.3.2.1) to adequately characterise the hazards of the mixture, these data shall be used in accordance with the applicable bridging rules set out in section 1.1.3.

Note that not all bridging principles in Annex I, section 1.1.3 are applicable when classifying for carcinogenicity.
3.6.3.2 Decision logic for classification of mixtures

The decision logic which is based on the GHS Guidance is revised to meet CLP requirements. It is strongly recommended that the person responsible for classification, study the criteria for classification before and during use of the decision logic.

Classification based on individual ingredients of the mixture

Does the mixture contain one or more ingredients classified as a Category 1 carcinogen at $\geq 0.1\%$, or above a SCL set for the ingredient(s)?

YES

Category 1
Danger

NO

Does the mixture contain one or more ingredients classified as a Category 2 carcinogen at $\geq 1.0\%$, or above a SCL set for the ingredient(s)?

YES

Category 2
Warning

NO

Not classified

Modified classification on a case-by-case basis

Test data on mixtures may be used for classification when demonstrating effects that have not been established from the evaluation based on the individual ingredients (CLP Section 3.6.3.1.1, see also CLP Article 6(3)).

Are test data available for the mixture demonstrating a carcinogenic effect not identified from the data on individual substances?

YES

Are the test results on the mixture conclusive taking into account dose and other factors such as duration, observations and analysis (e.g. statistical analysis, test sensitivity) of carcinogenicity test systems?

YES

Classify in appropriate category
Danger or Warning

or

No classification

NO

Can bridging principles be applied?

YES

See above: Classification based on individual ingredients of the mixture.

NO
3.6.4 Hazard communication in form of labelling for carcinogenicity

3.6.4.1 Pictograms, signal words, hazard statements and precautionary statements

Annex 1; 3.6.4.1 Label elements shall be used in accordance with Table 3.6.3, for substances or mixtures meeting the criteria for classification in this hazard class.

*Table 3.6.3*

<table>
<thead>
<tr>
<th>Classification</th>
<th>Category 1A or Category 1B</th>
<th>Category 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>GHS Pictograms</td>
<td><img src="image" alt="Pictogram" /></td>
<td><img src="image" alt="Pictogram" /></td>
</tr>
<tr>
<td>Signal Word</td>
<td>Danger</td>
<td>Warning</td>
</tr>
<tr>
<td>Hazard Statement</td>
<td>H350: May cause cancer (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)</td>
<td>H351: Suspected of causing cancer (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)</td>
</tr>
<tr>
<td>Precautionary Statement Prevention</td>
<td>P201</td>
<td>P201</td>
</tr>
<tr>
<td></td>
<td>P202</td>
<td>P202</td>
</tr>
<tr>
<td></td>
<td>P281</td>
<td>P281</td>
</tr>
<tr>
<td>Precautionary Statement Response</td>
<td>P308 + P313</td>
<td>P308 + P313</td>
</tr>
<tr>
<td>Precautionary Statement Storage</td>
<td>P405</td>
<td>P405</td>
</tr>
<tr>
<td>Precautionary Statement Disposal</td>
<td>P501</td>
<td>P501</td>
</tr>
</tbody>
</table>

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

Where there is conclusive proof that cancer is caused only by certain route(s), then this route may be stated in the hazard statement. In case of Category 1 carcinogens where there is conclusive proof that cancer is caused only by inhalation, the hazard phrase “H350i: May cause cancer by inhalation” applies (CLP Annex VII, Table 1.1).

3.6.4.2 Additional labelling provisions

There are no additional labelling provisions for carcinogenic substances and mixtures in CLP, however there are provisions laid out in Annex XVII to REACH. The packaging of substances with harmonised classification as carcinogenic Category 1A or Category 1B, or mixtures containing such substances, "must be marked visibly, legibly and indelibly as follows: ‘Restricted to professional users’. " (REACH, Annex XVII, point 28).
3.6.5 Re-classification of substances and mixtures classified for carcinogenicity according to DSD and DPD

3.6.5.1 Is direct “translation” of classification and labelling possible?

A direct translation as indicated in the translation table in Annex VII to CLP is generally possible. Translation from classification according to DSD and DPD to the classification according to CLP is as follows:

- Carc. Cat. 1 is translated into Carc. 1A;
- Carc. Cat. 2 is translated into Carc. 1B, and
- Carc. Cat. 3 is translated into Carc. 2, respectively.

3.6.5.2 Some additional considerations for re-classification

There are only few situations where the direct translation may lead to different results, however, these are likely to be very rare.

The first difference in applying the CLP criteria is that sufficient evidence (Carc. 1B) for carcinogenicity in animals can also be derived from two or more independent studies in one species carried out at different times or in different laboratories or under different protocols.

The second difference applying the CLP criteria is that sufficient evidence (Carc. 1B) for carcinogenicity in animals can be derived from an increased incidence of tumours in both sexes of a single species in a well-conducted study, ideally conducted under GLP. The criteria according to DSD allowed classification in Carc. Cat. 2 (analogous to CLP Carc. 1B) where there were positive results in two animal species or clear positive evidence in one species, together with supporting evidence such as genotoxicity data, metabolic or biochemical studies, induction of benign tumours, structural relationship with other known carcinogens, or data from epidemiological studies suggesting an association.

Another difference can be derived from the IARC classification as ‘possibly carcinogenic to humans (IARC 2B)’. This category is used for substances for which there is less than sufficient evidence of carcinogenicity in experimental animals. According to IARC, classification as ‘possibly carcinogenic to humans’ may be derived from solely strong evidence from mechanistic and other relevant data. This means that no in vivo carcinogenicity nor (Q)SAR data need to be available to arrive at classification for limited evidence of carcinogenicity.

3.6.6 Examples of classification for carcinogenicity

Classification for carcinogenicity involves the consideration of many different factors, as outlined above, and is a complex task which needs expert judgement. Therefore no examples of classification for carcinogenicity are included in this guidance document.

3.6.7 References


EU Commission Group of Specialised Experts in the fields of carcinogenicity, mutagenicity and reprotoxicity: Non genotoxic thyroid carcinogens in the rodent bioassay, ECBI/49/99 Add. 1 Rev. 2 excerpt of agenda point 3.1, 1999.

EU Commission Group of Specialised Experts in the fields of carcinogenicity, mutagenicity and reprotoxicity: Leydig tumours 2004, ECBI/08/04 Rev. 2, 2004


http://www.oecd.org/document/23/0,2340,en_2649_34379_33957015_1_1_1_1,00.html


http://www.oecd.org/document/70,2340,en_2649_34379_1947463_1_1_1_1,00.html


ENV/JM/MONO(2006)25


216
3.7 REPRODUCTIVE TOXICITY

3.7.1 Definitions and general considerations for reproductive toxicity

Annex I: 3.7.1.1. Reproductive toxicity includes adverse effects on sexual function and fertility in adult males and females, as well as developmental toxicity in the offspring. The definitions presented below are adapted from those agreed as working definitions in IPCS/EHC Document N°225, Principles for Evaluating Health Risks to Reproduction Associated with Exposure to Chemicals. For classification purposes, the known induction of genetically based heritable effects in the offspring is addressed in Germ Cell Mutagenicity (section 3.5), since in the present classification system it is considered more appropriate to address such effects under the separate hazard class of germ cell mutagenicity.

In this classification system, reproductive toxicity is subdivided under two main headings:

(a) Adverse effects on sexual function and fertility;

(b) Adverse effects on development of the offspring.

Some reproductive toxic effects cannot be clearly assigned to either impairment of sexual function and fertility or to developmental toxicity. Nonetheless, substances with these effects, or mixtures containing them, shall be classified as reproductive toxicants.
3.7.1.2. For the purpose of classification the hazard class Reproductive Toxicity is differentiated into:
- adverse effects
  - on sexual function and fertility, or
  - on development;
- effects on or via lactation

3.7.1.3. Adverse effects on sexual function and fertility

Any effect of substances that has the potential to interfere with sexual function and fertility. This includes, but is not limited to, alterations to the female and male reproductive system, adverse effects on onset of puberty, gamete production and transport, reproductive cycle normality, sexual behaviour, fertility, parturition, pregnancy outcomes, premature reproductive senescence, or modifications in other functions that are dependent on the integrity of the reproductive systems.

3.7.1.4. Adverse effects on development of the offspring

Developmental toxicity includes, in its widest sense, any effect which interferes with normal development of the conceptus, either before or after birth, and resulting from exposure of either parent prior to conception, or exposure of the developing offspring during prenatal development, or postnatally, to the time of sexual maturation. However, it is considered that classification under the heading of developmental toxicity is primarily intended to provide a hazard warning for pregnant women, and for men and women of reproductive capacity. Therefore, for pragmatic purposes of classification, developmental toxicity essentially means adverse effects induced during pregnancy, or as a result of parental exposure. These effects can be manifested at any point in the life span of the organism. The major manifestations of developmental toxicity include (1) death of the developing organism, (2) structural abnormality, (3) altered growth, and (4) functional deficiency.

3.7.1.1 Special considerations on effects on or via lactation

This classification is intended to indicate when a substance may cause harm due to its effects on or via lactation. This can be due to the substance being absorbed by women and adversely affecting milk production or quality, or due to the substance (or its metabolites) being present in breast milk in amounts sufficient to cause concern for the health of a breastfed child.

Annex I: 3.7.1.5. Adverse effects on or via lactation are included under reproductive toxicity, but for classification purposes such effects are treated separately. This is because it is desirable to be able to classify substances specifically for an adverse effect on lactation so that a specific hazard warning about this effect can be provided for lactating mothers.

Therefore, if the adverse effects that lead to impaired development in the offspring also occur after in utero exposure then the substance would also be classified for developmental toxicity. In other words, the classification for effects on or via lactation is independent of consideration of the reproductive toxicity of the substance, and a substance can be classified for effects on or via lactation whether or not the substance is also classified for reproductive toxicity.

Classification for effects on or via lactation alone is not sufficient for a substance to be subject to harmonised classification and labelling in accordance with CLP Article 36.

3.7.2 Classification of substances for reproductive toxicity

3.7.2.1 Identification of hazard information

3.7.2.1.1 Identification of human data
Guidance to Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of substances and mixtures

Epidemiological studies as well as clinical data and case reports may be available as stated in CLP, Annex I, 3.7.2.2.3 and further under IR/CSA, Section R.7.6.3.2.

3.7.2.1.2 Identification of non human data

In-vitro, animal data and non-testing information used for classification is outlined in CLP Annex I, section 3.7.2.5. and further specific references to different testing methods are listed in IR/CSA, section R.7.6.3.1.

3.7.2.2 Classification criteria

### Annex I: 3.7.2.1.1

For the purpose of classification for reproductive toxicity, substances are allocated to one of two categories. Within each category, effects on sexual function and fertility, and on development, are considered separately. In addition, effects on lactation are allocated to a separate hazard category.

### Table 3.7.1 (a)

**Hazard categories for reproductive toxicants**

<table>
<thead>
<tr>
<th>Categories</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CATEGORY 1</strong></td>
<td>Known or presumed human reproductive toxicant</td>
</tr>
<tr>
<td>Category 1A</td>
<td>Known human reproductive toxicant</td>
</tr>
<tr>
<td></td>
<td>The classification of a substance in this Category 1A is largely based on evidence from humans.</td>
</tr>
<tr>
<td>Category 1B</td>
<td>Presumed human reproductive toxicant</td>
</tr>
<tr>
<td></td>
<td>The classification of a substance in this Category 1B is largely based on data from animal studies. Such data shall provide clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate.</td>
</tr>
<tr>
<td><strong>CATEGORY 2</strong></td>
<td>Suspected human reproductive toxicant</td>
</tr>
<tr>
<td></td>
<td>Substances are classified in Category 2 for reproductive toxicity when there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development, and where the evidence is not sufficiently convincing to place the substance in Category 1. If deficiencies in the study make the quality of evidence less convincing, Category 2...</td>
</tr>
</tbody>
</table>
3.7.2.2.1 Classification in the presence of parental toxicity

3.7.2.2.1.1 Effects to be considered in the presence of marked systemic effects

In general all findings on reproductive toxicity should be considered for classification purposes irrespective of the level of parental toxicity. A comparison between the severity of the effects on fertility/development and the severity of other toxicological findings must be performed.

Fertility effects

Adverse effects on fertility and reproductive performance seen only at dose levels causing marked systemic toxicity (e.g. lethality, dramatic reduction in absolute body weight, coma) are not relevant for classification purposes.

There is no established relationship between fertility effects and less marked systemic toxicity. Therefore it should be assumed that effects on fertility seen at dose levels causing less marked systemic toxicity are not a secondary consequence of this toxicity. However, mating behaviour can be influenced by parental effects not directly related to reproduction (e.g. sedation, paralysis), and such effects on mating behaviour may not warrant classification.

Developmental effects:

Annex I: 3.7.2.4. Maternal toxicity

3.7.2.4.1 Development of the offspring throughout gestation and during the early postnatal stages can be influenced by toxic effects in the mother either through non-specific mechanisms related to stress and the disruption of maternal homeostasis, or by specific maternally-mediated mechanisms. In the interpretation of the developmental outcome to decide classification for developmental effects it is important to consider the possible influence of maternal toxicity. This is a complex issue because of uncertainties surrounding the relationship between maternal toxicity and developmental outcome. Expert judgement and a weight of evidence approach, using all available studies, shall be used to determine the degree of influence that shall be attributed to maternal toxicity when interpreting the criteria for classification for developmental effects. The adverse effects in the embryo/foetus shall be first considered, and then maternal toxicity, along with any other factors which are likely to have influenced these effects, as weight of evidence, to help reach a conclusion about classification.

3.7.2.4.2 Based on pragmatic observation, maternal toxicity may, depending on severity, influence development via non-specific secondary mechanisms, producing effects such as depressed foetal weight, retarded ossification, and possibly resorptions and certain malformations in some strains of certain species. However, the limited number of studies which have investigated the relationship between developmental effects and general maternal toxicity have failed to demonstrate a consistent, reproducible relationship across species. Developmental effects which occur even in the presence of maternal toxicity are considered to be evidence of developmental toxicity, unless it can be unequivocally demonstrated on a case-by-case basis that the developmental effects are secondary to maternal toxicity. Moreover, classification shall be considered where there is a significant toxic effect in the offspring, e.g. irreversible effects such as structural malformations, embryo/foetal lethality, significant post-natal functional deficiencies.
3.7.2.4.3. Classification shall not automatically be discounted for substances that produce developmental toxicity only in association with maternal toxicity, even if a specific maternally-mediated mechanism has been demonstrated. In such a case, classification in Category 2 may be considered more appropriate than Category 1. However, when a substance is so toxic that maternal death or severe inanition results, or the dams are prostrate and incapable of nursing the pups, it is reasonable to assume that developmental toxicity is produced solely as a secondary consequence of maternal toxicity and discount the developmental effects. Classification is not necessarily the outcome in the case of minor developmental changes, when there is only a small reduction in foetal/pup body weight or retardation of ossification when seen in association with maternal toxicity.

Adverse effects on postnatal survival and growth seen only at dose levels causing maternal toxicity may be due to lack of maternal care or other causes such as adverse effects on or via lactation or developmental toxicity. In case post-natal effects are caused by lack of maternal care classification for developmental effects may not be warranted.

3.7.2.2.1.2 Relevance of specific effects in the parent

All types of reproductive toxic effects may be considered as secondary to parental toxicity. With current knowledge it is not possible to identify specific effects indicating toxicity in parental animals which do not have any relevance to reproductive toxicity (e.g. peroxisome proliferation). However parental toxicity that is less than marked should not influence the classification for reproductive toxicity independent of the specific parental effects observed.

In general it is very difficult to prove a causal relationship between a parentally mediated mechanism and adverse effects in the offspring. Usually data are insufficient to conclude if an effect on the offspring is a direct effect or secondary to parental toxicity. In order to determine whether a reproductive toxic effect is independent or secondary to a parental effect, it would be most appropriate to correlate individual data for offspring and their parents. Nevertheless, associations between parental and offspring effects do not by default prove a causal relationship.

In cases where a causal relationship is established between reproductive and parental toxicity and the effects on the offspring can be proved to be secondary to maternal toxicity, they may still be relevant for developmental classification, dependent on the severity of the effects.

A comparison between the severity of the maternal toxicity and the severity of the findings in the offspring must be performed. There are several examples showing that the developing organism can be more susceptible and the long-term consequences can be more severe than in the adult. The mother might recover while the offspring could be permanently affected.

Annex I: 3.7.2.4.4. Some of the end points used to assess maternal effects are provided below. Data on these end points, if available, need to be evaluated in light of their statistical or biological significance and dose response relationship.

Maternal mortality:
an increased incidence of mortality among the treated dams over the controls shall be considered evidence of maternal toxicity if the increase occurs in a dose-related manner and can be attributed to the systemic toxicity of the test material. Maternal mortality greater than 10 % is considered excessive and the data for that dose level shall not normally be considered for further evaluation.

Mating index
(no. animals with seminal plugs or sperm/no. mated x 100)(1)

Fertility index
(no. animals with implants/no. of matings x 100)

Gestation length
(if allowed to deliver)

Body weight and body weight change:
Consideration of the maternal body weight change and/or adjusted (corrected) maternal body weight shall be included in the evaluation of maternal toxicity whenever such data are available. The calculation of an adjusted (corrected) mean maternal body weight change, which is the difference between the initial and terminal body weight minus the gravid uterine weight (or alternatively, the sum of the weights of the foetuses), may indicate whether the effect is maternal or intrauterine. In rabbits, the body weight gain may not be useful indicators of maternal toxicity because of normal fluctuations in body weight during pregnancy.

Food and water consumption (if relevant):
The observation of a significant decrease in the average food or water consumption in treated dams compared to the control group is useful in evaluating maternal toxicity, particularly when the test material is administered in the diet or drinking water. Changes in food or water consumption need to be evaluated in conjunction with maternal body weights when determining if the effects noted are reflective of maternal toxicity or more simply, unpalatability of the test material in feed or water.

Clinical evaluations (including clinical signs, markers, haematology and clinical chemistry studies):
The observation of increased incidence of significant clinical signs of toxicity in treated dams relative to the control group is useful in evaluating maternal toxicity. If this is to be used as the basis for the assessment of maternal toxicity, the types, incidence, degree and duration of clinical signs shall be reported in the study. Clinical signs of maternal intoxication include: coma, prostration, hyperactivity, loss of righting reflex, ataxia, or laboured breathing.

Post-mortem data:
Increased incidence and/or severity of post-mortem findings may be indicative of maternal toxicity. This can include gross or microscopic pathological findings or organ weight data, including absolute organ weight, organ-to-body weight ratio, or organ-to-brain weight ratio. When supported by findings of adverse histopathological effects in the affected organ(s), the observation of a significant change in the average weight of suspected target organ(s) of treated dams, compared to those in the control group, may be considered evidence of maternal toxicity.

(1) It is recognised that the Mating index and the Fertility index can also be affected by the male.

3.7.2.2 Substances causing effects on or via lactation

<table>
<thead>
<tr>
<th>EFFECTS ON OR VIA LACTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Annex I: Table 3.7.1 (b)</strong></td>
</tr>
<tr>
<td>Hazard category for lactation effects</td>
</tr>
</tbody>
</table>

Effects on or via lactation are allocated to a separate single category. It is recognised that for many substances there is no information on the potential to cause adverse effects on the offspring via lactation. However, substances which are absorbed by women and have been shown to interfere with lactation, or which may be present (including metabolites) in breast milk in amounts sufficient to cause concern for the health of a breastfed child, shall be classified and labelled to indicate this property hazardous to breastfed babies. This classification can be assigned on the:

(a) human evidence indicating a hazard to babies during the lactation period; and/or
(b) results of one or two generation studies in animals which provide clear evidence of adverse effect in the offspring due to transfer in the milk or adverse effect on the quality of the milk; and/or

(c) absorption, metabolism, distribution and excretion studies that indicate the likelihood that the substance is present in potentially toxic levels in breast milk.

There are the two general criteria for this classification.

(i) …are absorbed by women and have been shown to interfere with lactation.

This relates to effects in the mother that impact adversely on the breast milk, either in terms of the quantity produced or the quality of the milk produced (i.e. the composition). Any effect on the quantity or quality of the breast milk is likely to be due to systemic effects in the mother. However, overt maternal toxicity may not be seen (e.g. the substance may just affect the transfer of a nutrient into the milk with no consequence for the mother). The type and magnitude of the maternal effects and their potential influence on lactation/milk production need to be considered on a case-by-case basis to determine whether classification for effects on or via lactation is necessary.

This relates to effects in the mother that impact adversely on the breast milk, either in terms of the quantity produced or the quality of the milk produced (i.e. the composition). Any effect on the quantity or quality of the breast milk is likely to be due to systemic effects in the mother. However, overt maternal toxicity may not be seen (e.g. the substance may just affect the transfer of a nutrient into the milk with no consequence for the mother). The type and magnitude of the maternal effects and their potential influence on lactation/milk production need to be considered on a case-by-case basis to determine whether classification for effects on or via lactation is necessary.

If a substance causes marked overt systemic toxicity in the mother at the same dose level then it is possible that this may indirectly impair milk production or impair maternal care as a non-specific secondary effect. The type and magnitude of the maternal effects and their potential influence on lactation/milk production needs to be considered on a case-by-case basis using expert judgment. If there is robust evidence to indicate that the effects on lactation are not caused directly by the substance then it should not be classified as such.

A substance which does not cause overt toxicity in the mother but which interferes with milk production or quality will normally be classified for effects on or via lactation because in this case the effect on lactation is most likely a direct substance-related effect.

(ii) … may be present (including metabolites) in breast milk in amounts sufficient to cause concern for the health of a breastfed child.

This relates to the ability of the substance (including metabolites), to enter the breast milk in amounts sufficient to cause a concern. When the effect on the offspring is caused by the substance (or metabolite) after transport through the milk then the maternal toxicity has no relevance for classification. In general, positive data should usually be available to show that a substance leads to an adverse effect in offspring due to effects on lactation to support classification. However, in exceptional circumstances, if there are substantiated grounds for concern that the substance may have an adverse effect via lactation then it may be classified as such in the absence of direct evidence. This should be based on a quantitative comparison of the estimated transfer via the milk and the threshold for toxicity in the pups. This might apply in cases where the substance has the capacity to bioaccumulate which would lead to a potentially higher burden in the offspring, or where there is evidence that the offspring may be more sensitive to the substance’s toxicity than adult.

The mere presence of the substance in the milk alone, without a strong justification for a concern to offspring, would normally not support classification for effects on or via lactation.

### 3.7.2.3 Evaluation of hazard information

Appropriate classification will always depend on an integrated assessment of all available data and their interrelationship using a weight of evidence approach. Individual datasets should be analysed case by case using expert judgment.

### 3.7.2.3.1 Use of data from standard repeat dose tests
Fertility effects:
Toxicological effects, including marked effects, observed in a standard repeat dose study could be considered valid for the pre-mating phase for adult females and the pre- and post-mating phase for adult males. However in case of contradictions between the standard repeat dose studies and reproductive studies, the result from the latter should be considered more relevant.
For pregnant and lactating females and juveniles data from standard repeat dose studies cannot easily be extrapolated.

Developmental effects:
A detailed assessment of toxicity in pregnant animals cannot be extrapolated from studies with non-pregnant animals. However information from general toxicity studies might give an indication of the maternal toxicity that could be anticipated in a subsequent developmental toxicity study.

3.7.2.3 Study design
Assessment of the dose-response relationships of parental and reproductive toxicity endpoints and their possible interrelationship require study designs where the dose intervals are not too far apart. This will improve dose-response assessment and will also reduce the chance of masking malformations by severe toxicity (e.g. resorptions, lethality) at high dose levels. This may lead to experimental designs in which more than the standard three dose groups and a control are tested. Endpoints from repeat dose toxicity studies may be considered useful for inclusion in subsequent reproductive toxicity studies. These endpoints should be evaluated both in parental animals and in offspring.

3.7.2.3.3 Evaluation of evidence relating to effects on or via lactation
(a) Human evidence indicating a hazard to babies during the lactation period;
This criterion acknowledges that human data, e.g. from epidemiological studies or case reports, indicating a hazard to babies during the lactation period can also be used to support classification for effects on or via lactation. The use of human data is self-explanatory and any study should be assessed on its merits for which expert judgment may be required. Observations in humans that give evidence of adverse effects in breastfed babies of mothers exposed to the chemical in question should be taken to provide clear evidence supporting classification. Such studies which do not show an adverse effect need to be considered carefully. Human studies investigate the risk under the specific conditions of exposure, and a negative finding may just reflect inadequate methods to detect effects or insufficient exposures rather than prove the absence of a hazard.
In practice, useful human data are likely to be rare due to the nature of the endpoint. More likely are survey type studies which measure the levels of the chemical in breast milk. Such studies may provide useful information on the potential for maternal exposure to lead to the presence of the chemical in the breast milk and so they may be of use in assessing the need for classification for effects on or via lactation.
(b) Results of one or two generation studies in animals which provide clear evidence of adverse effect in the offspring due to transfer in the milk or adverse effect on the quality of the milk;
Ideally, studies will be available which inform directly on whether the substance causes adverse effects in the offspring due to an adverse effect on lactation. One generation or multi-
generation reproductive toxicity studies, which involve direct exposure or exposure via the milk of the offspring postnatally, usually provide information on this. The most common study performed today is the two-generation study, but one-generation studies with new study designs, like the screening study OECD TG421/422 or the developmental neurotoxicity study OECD TG426, also exist. The value of these studies is that they directly observe the pups during lactation and any adverse effects, such as deaths, decreased viability, clinical signs such as reduced bodyweight gain etc, can be directly observed and quantified. However, expert judgement is required to decide whether these effects in pups are due to a direct adverse effect on lactation, or are due to impaired nursing behaviour which is a non specific secondary consequence of maternal toxicity. If the impaired nursing behaviour is proven to be a substance related specific effect on behaviour, then classification for effects on or via lactation may be appropriate. It should also be noted that some developmental effects resulting from exposure in utero would only manifest post-natally and those should not be used for classification for effects on or via lactation. Cross-fostering studies, where available, may help establish whether effects are due to in utero or lactational exposure. If there is sufficient data that animal results are not relevant to humans, they should not be taken into account.

(c) Absorption, metabolism, distribution and excretion studies that indicate the likelihood that the substance is present in potentially toxic levels in breast milk;

The criterion indicates that toxicokinetic studies showing that the substance can be present at potentially toxic levels in breast milk can support classification. The implicit assumption behind this clause is that the pups may receive a body burden of the toxic entity through suckling that is sufficient to cause toxicity when the level of the toxic entity in the milk is above a certain threshold level (“a level to cause concern”). There is no robust way to estimate what this threshold is, although the likely body burden expected in the breastfed child may be compared to the toxicity data in adults (e.g. an appropriate NOAEL or BMD) to indicate whether toxicity is likely. The mere presence of a substance in the milk, without a robust argument that these levels may be potentially toxic to offspring would not normally support classification.

The toxicokinetics of a substance and the likelihood that it will enter the breast milk may be predicted on the basis of the physico-chemical properties of the chemical (e.g. using pKa, logP, water solubility, and molecular weight etc) and this information could be used as part of the argumentation outlined above. The potential of a substance to bioaccumulate following repeated exposure may also be an important factor to consider as this may contribute to the body burden reaching a potentially toxic level in the offspring. Studies where the offspring/neonates have extended exposure, such as multi-generation studies, implicitly allow for bioaccumulation and so findings from these studies can, in themselves, be taken to provide information on the potential effects of bioaccumulation. Where these types of studies are not available, potential bioaccumulation can be taken into consideration as part of the toxicokinetic assessment using expert judgement.

There may be toxicokinetic and toxicodynamic reasons why neonates may potentially be more or less vulnerable to a particular adverse effect than adults due to the fact that certain systems (e.g. the immune and metabolic systems) and tissues/organs are immature and are still developing. Whether the neonate is more or less vulnerable than adults will depend on the specific chemical and will be determined by factors such as the hazardous properties of the chemical, its’ physico-chemical properties and how it is metabolised. Therefore, the relative sensitivity of neonates and adults to a substance must be judged on a case by case basis using expert judgement. In the absence of any reliable and robust information to inform
on this, it should be assumed that neonates and adults are equivalent in terms of sensitivity to
the substance.

Overall, classification for effects on or via lactation can be assigned on the basis of
toxicokinetic data or a well substantiated estimate of the exposure through the milk alone
provided that it is supported by an argument clearly justifying that the level present in the
breast milk would be likely to harm developing offspring.

3.7.2.4 Decision on classification

According to CLP Annex I, section 3.7.2.1.1, reproductive toxic substances are allocated to
either Category 1A, 1B or 2. Effects on lactation are allocated to a separate hazard category
and should be ascribed to a substance irrespective if it classified in any other category for
reproductive toxicity or not.

3.7.2.5 Setting of specific concentration limits

3.7.2.5.1 Procedure

The available data from animal and human studies are evaluated to establish the reproductive
toxicity dose descriptor, ED_{10} (effective dose with a 10% effect level above the background),
as described below. A preliminary conclusion as to whether the substance shows high,
medium or low potency is taken based on the ED_{10} data. The preliminary potency evaluation
may be modified after due consideration of a number of modifying factors as described in
chapter 3.7.2.5.5. This results in the final potency group. Each final potency group is
connected with a GCL or a SCL. In this way SCLs are then set taking into account all
relevant considerations. See figure 3.7.2.5.1. A background document containing the
justification of the boundaries of the potency groups and the SCLs is available in Annex VI to
this document.

Figure 3.7.2.5.1 Procedure for setting SCL for reproductive toxicity

---

Determine ED_{10} using the available data

Determine preliminary potency group

Determine final potency group considering the modifying factors

Determine SCL
3.7.2.5.2 Cases where potency evaluation is difficult or unfeasible

The process for evaluating potency assumes the availability of certain types of data. However, these data may not always be available. Also, the classification of substances as reproductive toxicants may be based on information such as grouping, read-across and the use of QSARs. In such cases, no direct estimate of the reproductive toxicity potency based on an ED_{10} value is possible. While there are often good reasons for extrapolation of the hazardous properties from one or more substances to another, the expected potency of the individual substances within the group may vary. In these cases a potency evaluation may be difficult or impossible. However, determination of the classification and the potency using non-testing methods is possible in some cases. These cases could include interpolation of an ED_{10} within a group of substances with comparable structures and effects or correction for molecular weight in case of extrapolation between different salts with comparable availability. If the classification of a substance in Category 2 is done on the basis of "limited evidence", the quality of the available data will in such cases determine whether a potency assessment is possible. In cases where no further evaluation is possible, the generic concentration limits of CLP apply. In general, more conclusive evidence is required when moving a substance to a lower potency group than to a higher potency group.

3.7.2.5.3 Determination of the ED_{10} value

The ED_{10} value is defined as the lowest dose which induces reproductive toxic effects which fulfil the criteria for classification for reproductive toxicity with an incidence or magnitude of 10% after correction for the spontaneous incidence. Determining exactly which effect or combination of effects is the one that fulfils the classification criteria may seem difficult. However, for the majority of substances in the database, the developmental effect(s) evident at the lowest dose level for which developmental effects could be observed was/were an increase in malformations and/or lethality of the offspring. The ED_{10} for effects on sexual function and fertility is mainly based on effects on fertility and histopathological changes of the reproductive organs. These effects clearly fulfil the classification requirements. Also, allocation to the final SCLs is based on a limited number of potency groups and not on the exact ED_{10} value. Therefore, in practice, it is likely that the ED_{10} values for several different effects fall into the same potency grouping, resulting in the same SCL.

The ED_{10} may be obtained either directly or by linear interpolation from experimental data, or estimated using BMD software. The use of BMD software will result in a more precise estimate of the ED_{10} because all data from the dose-response curve are used. The use of BMD software is needed when an ED_{10} cannot be determined using linear interpolation due to the absence of a NOAEL when the LOAEL has an effect size above 10%. In general, however, the use of BMD software is not required because of the wide potency groups used for setting the SCLs. However, it could be important for substances which are close to the boundary of a potency group. When an ED_{10} cannot be calculated by linear interpolation or by the use of BMD software, the LOAEL should be used instead of the ED_{10}. In such cases, only SCLs below the GCL can be determined and not those above the GCL, if no other reliable information is available, because it may be difficult in these cases to prove the absence of effects at lower dose levels.
3.7.2.5.3.1 Determination in practice

In practice, often several effects on reproduction are observed in various studies, and the classification is based on the weight of evidence of all results. As a first step, it should be determined whether the classification is for effects on development, for effects on sexual function and fertility or both. The effects used for classification for developmental toxicity should be used to determine the potency for developmental toxicity only. The same applies to effects on sexual function and fertility. This means that for substances fulfilling the criteria for classification for both developmental effects and effects on sexual function and fertility, two ED_{10} values are derived which may differ. The lowest ED_{10} of the effect(s) that fulfil the criteria for classification in the different studies is then used as the ED_{10} that determines the potency of that substance. Where there are doubts as to whether a specific effect fulfils the classification criteria, ED_{10} values for different effects could be taken forward to the next step to determine the impact.

The calculation of the ED_{10} by linear interpolation requires a different approach depending on whether the effect is measured as an incidence (quantal data, non-parametric data), a magnitude (continuous data, parametric data) or both.

3.7.2.5.3.2 Quantal or non-parametric data

For effects that are measured as changes in incidence, such as an increase in the number of malformations or resorptions, the ED_{10} is defined as the dose level at which 10% of the test population above the incidence in the concurrent control shows the effect. There may be occasions where the historical control data have to be taken into account. In the example in Table 3.7.2.5.1, the ED_{10} is 90 mg/kg bw/day because at this dose level 12% - 2% (control) = 10% of the test population shows the effect.

Table 3.7.2.5.1 Example of the calculation of the ED_{10}

<table>
<thead>
<tr>
<th>Dose</th>
<th>0 mg/kg</th>
<th>10 mg/kg</th>
<th>30 mg/kg</th>
<th>90 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malformations</td>
<td>2%</td>
<td>3%</td>
<td>7%</td>
<td>12%</td>
</tr>
</tbody>
</table>

For some effects the results of the calculation of the ED_{10} based on the incidence in pups may be different from that based on the incidence in litters. Mechanism of action studies may indicate which parameter is more appropriate, but in the absence of such information it is not possible to estimate which ED_{10} is more appropriate for a specific effect. In such cases, both the incidence in offspring and the incidence in litters should be calculated, and the lowest ED_{10} value should be used.

3.7.2.5.3.3 Continuous or parametric data

For effects that are measured as changes in magnitude such as pup weight or testis weight, the ED_{10} is defined as the dose at which a change of 10% compared to the control group is observed. In the example in Table 3.7.2.5.2, the ED_{10} is 19.3 mg/kg bw/day because at this dose level the mean foetal bodyweight is calculated to be 90% of the control value. A 10% reduction of the control value of 6.2 g gives 5.58 g. Interpolation between 10 and 30 mg/kg bw/day to a dose level which would be expected to result in a foetal bodyweight of 5.58 g gives a value of 19.3 mg/kg bw/day.
Table 3.7.2.5.2 Example on the calculation of the ED\textsubscript{10}

<table>
<thead>
<tr>
<th>dose</th>
<th>0 mg/kg</th>
<th>10 mg/kg</th>
<th>30 mg/kg</th>
<th>90 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>foetal bodyweight (g)</td>
<td>6.2</td>
<td>6.0</td>
<td>5.1</td>
<td>4.5</td>
</tr>
<tr>
<td>NOAEL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOAEL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3.7.2.5.3.4 Data combining incidence and magnitude

Some effects such as histopathological changes in the testis are a combination of effects on incidence and magnitude (grading of the effect by a pathologist). However, calculation of an ED\textsubscript{10} taking both the incidence and the magnitude into account is not possible or at least more complex. The ED\textsubscript{10} should therefore be based on the incidence of the effect below or above a certain magnitude. The magnitude of the effects that will be selected as a starting point has to be chosen carefully. The ED\textsubscript{10} is then determined as the dose level at which the incidence, of effects with a magnitude above that of the starting point, is 10% above the incidence in the control group. In practice this means that the grading system is converted into a simplified system where only percentages of animals in each dose group with an effect with a magnitude above the starting point are regarded as positive. However, it is recognised that this approach uses only a part of the actual data and is imprecise, and it may be appropriate that other effects also be considered in determining the ED\textsubscript{10}.

Table 3.7.2.5.3 Example on the calculation of the ED\textsubscript{10} for testicular effects (N=10)

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Testicular degeneration (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>none</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>90</td>
<td>0</td>
</tr>
</tbody>
</table>

For the example in Table 3.7.2.5.3, the effects observed in the 10 mg/kg and 30 mg/kg dose groups have to be considered as equivalent to the effects of the control group so the NOAEL is 30 mg/kg. The magnitude of the testicular effect in the control group and the 10 and 30 mg/kg bw/day groups is slight or less. Because of the incidence observed in these three groups, the level of damage estimated as the starting point magnitude is ‘slight’. The ED\textsubscript{10} is then defined as a 10% increase of moderate effects or more above the control. In this example the incidences for moderate testicular degeneration or more are 10%, 0%, 10% and 100% at respectively 0, 10, 30 and 90 mg/kg bw/day. The ED\textsubscript{10} is then defined as the dose level with 20% (control plus 10%) of moderate testicular effects. The ED\textsubscript{10} would be 36.6 mg/kg bw/day based on interpolation between 30 and 90 mg/kg bw/day to a dose with 20% animals with moderate testicular degeneration or higher.

3.7.2.5.3.5 Specific data types

Non-oral studies
In most cases only oral studies will be available and used for determination of the potency. However, if the classification is based on the effects seen in non-oral studies or only non-oral studies are available, then these data should also be used to determine the potency. This requires route-to-route extrapolation of the external dermal or inhalatory dose to a corresponding oral dose. This should be done as described in the ECHA guidance on information requirements and chemical safety assessment in REACH (IR/CSA, section R.8).

Extrapolation from dermal exposure to oral exposure should only be done when there are sufficient kinetic data on dermal availability because assuming a high dermal availability is not a worst case assumption. In cases where such data are not available a direct comparison of the dermal dose with the oral potency ranges should be performed. However, such comparison should not result in moving the substance to a lower potency group (higher ED_{10}) – only moving the substance to a higher potency group (lower ED_{10}) should be considered.

Extrapolation from inhalatory exposure to oral exposure should only be done when there are sufficient kinetic data on inhaled availability because assuming a high inhaled availability is not a worst case assumption. If no inhalatory information on availability is available then it should be assumed that the inhalation and oral availability are comparable. However, such comparison should not result in moving the substance to a lower potency group (higher ED_{10}) – only moving the substance to a higher potency group (lower ED_{10}) should be considered.

**Human data**

The use of human data for ED_{10} calculation has several drawbacks including limited data on exposure, limited data on the size of the exposed population and limited information on whether the exposure included the window of sensitivity. For all these reasons, it is difficult to determine an ED_{10} based on human data. Therefore, and because in most instances animal data are also available for determining an ED_{10}, these data are evaluated together on a case by case basis. Guidance on the use of human data for the derivation of DNELs and DMELs has been developed by ECHA and is available at the ECHA website, see http://guidance.echa.europa.eu/guidance4_en.htm

**3.7.2.5.4 Provisional evaluation of the potency classification**

A preliminary potency evaluation applying the ED_{10} value is made at this stage.

ED_{10} values can be used to place substances classified as a reproductive toxicant into selected ranges that define potency groups. In this way, it is possible to identify reproductive toxicants of high and low potency. For the purpose of determining the preliminary potency group, the boundaries in Table 3.7.2.5.4 are used.

**Table 3.7.2.5.4 Boundaries of the potency groups.**

<table>
<thead>
<tr>
<th>Potency group</th>
<th>Boundaries</th>
</tr>
</thead>
<tbody>
<tr>
<td>High potency group</td>
<td>ED_{10} value ≤ 4 mg/kg bw/day</td>
</tr>
<tr>
<td>Medium potency group</td>
<td>4 mg/kg bw/day &lt; ED_{10} value ≤ 400 mg/kg bw/day</td>
</tr>
<tr>
<td>Low potency group</td>
<td>ED_{10} value &gt; 400 mg/kg bw/day</td>
</tr>
</tbody>
</table>

**3.7.2.5.5 Modifying factors**
Modifying factors may change the potency group for a substance. While some modifying factors should always be taken into account, other modifying factors could be more relevant when the potency is close to the boundary between two groups (see Table 3.7.2.5.4 above). It should be noted that several of the elements may be interrelated.

Some factors may have already been taken into account in deciding on the classification as a reproductive toxicant. Where such considerations have been made, care should be taken not to use that information again when determining the potency. For example, when the effects determining the ED$_{10}$ were observed at dose levels also causing maternal toxicity, this should already have been taken into consideration during the classification and should not be used again to set a higher SCL.

### 3.7.2.5.5.1 Type of effect / severity

The type of effect(s) resulting in a classification as reproductive toxicant differs between substances. Some effects could be considered as more severe than others. However, ranking different effects based on their severity is difficult. Further, the effects of a developmental toxicant can differ between dose levels from variations via malformations to death of the foetuses. The adverse effects on fertility and sexual function of a substance can differ between dose levels from small changes in testes histopathology through effects on fertility to an irreversible and complete absence of fertility. As the difference between the dose levels is often smaller than the proposed potency groups (factor 10-100) this will make no difference in most cases. Also classification is in most cases based on severe effects like malformations or death of the foetuses for developmental toxicants and effects on fertility or histopathological changes of the reproductive organs for fertility toxicants. For most classified substances such severe effects were already observed at the lowest dose with reproductive effects [(Muller et al, 2011)]. Therefore, differentiation between types of effect is considered to have limited added value. Exceptions can be dealt with on a case by case basis.

For example, if the ED$_{10}$ results in a preliminary conclusion for the medium potency group but is close to the border for the high potency group and the ED$_{10}$ is based on a severe effect like malformations or irreversible effects on sexual function and fertility then using the higher potency group (lower ED$_{10}$) for that substance should be considered.

### 3.7.2.5.5.2 Data availability

Where only limited data are available, such as a screening study (OECD 421 and 422), a 28-day repeated dose toxicity study or non-OECD studies which do not exclude the presence of reproductive effects at lower dose levels, the calculated ED$_{10}$ should not be used to set a SCL above the GCL. If there are only limited data which result in an ED$_{10}$ in the medium potency group but close to the border for the high potency group then using the higher potency group should be considered. If for example an ED$_{10}$ of 8 mg/kg bw/day is estimated based on a LOAEL at 12 mg/kg bw/day with 12% malformations using a BMD approach and no NOAEL, then the estimated ED$_{10}$ and resulting SCL is doubtful especially if the BMDL (Benchmark dose lower 95%-confidence limit) is below the border of 4 mg/kg bw/day for the high potency group. In such cases the high potency group should be used until additional data at lower dose levels is available.
3.7.2.5.5.3 Dose-response relationship

The ED_{10} is in most cases in the same range as the NOAEL and LOAEL. However, in cases of a shallow dose effect relationship, the LOAEL may for some effects be clearly below the ED_{10}. If a substance would fall into a lower potency group based on the ED_{10} but into a higher potency group based on the LOAEL then the higher potency group should be used for that substance when the dose effect relationship is shallow.

3.7.2.5.5.4 Mode or mechanism of action

It is assumed that effects observed in animal studies are relevant to humans. Where it is known that the mode or mechanism of action is not relevant for humans or is of doubtful relevance to humans, this should have been taken into account in the classification and should not be used again as a modifying factor for potency. However, quantitative differences in toxicodynamics can be taken into account when not already taken into account in the classification. In cases where mechanistic information shows a lower sensitivity in humans than in experimental animals, this may move substances which are close to the potency boundaries to a lower potency group. In cases where mechanistic information indicates a higher sensitivity in humans than in experimental animals, this may move substances near the potency boundaries to a higher potency group. In general, more conclusive evidence is required when moving a substance to a lower potency group than to a higher potency group.

3.7.2.5.5.5 Toxicokinetics

The toxicokinetics of a substance can differ between the tested animal species and humans. Where a difference is known this should be taken into account when determining the potency group of a substance. This should be based on a comprehensive knowledge of all involved toxicokinetic factors and not only on a single parameter. Also differences in kinetics between pregnant and non-pregnant animals and transport to the foetus should be taken into account. Substances close to the boundary of a potency group where a higher concentration at the site of action is expected in humans and thus a higher human ED_{10} compared to the studied species may be moved into a higher potency group (lower ED_{10}). Substances close to the boundary of a potency group where a lower concentration at the site of action is expected in humans and thus a higher human ED_{10} compared to the studied species may be moved into a lower potency group (higher ED_{10}). In general, more conclusive evidence is required when moving a substance to a lower potency group than to a higher potency group.

3.7.2.5.5.6 Bio-accumulation of substances

The study design of, for example, developmental studies is aimed at exposure only during development. For substances which bio-accumulate, the actual exposure in the time window of sensitivity for some developmental effects may therefore be much lower than when exposure at the same external dose level would have started long before the sensitivity window. Furthermore, human exposure may occur for a long period before the sensitive window. This should be taken into account when determining the potency group. Bio-accumulating substances with an ED_{10} just above the lower boundary of a potency group (see Table 3.7.2.5.4) should be considered to be moved into the higher potency group (lower ED_{10}).
For substances with an adverse effect on fertility and sexual function, the ED_{10} of a 28-day study or a screening study may be higher than the ED_{10} from a 90-day study or a 2-generation study for a bio-accumulating substance. When only a short exposure study is present for a bio-accumulating substance with for example an ED_{10} in the medium potency group but close to the boundary of the high potency group it should be considered for moving into the high potency group (lower ED_{10}).

3.7.2.5.6 Assigning specific concentration limits (SCLs)

Based upon the preliminary potency evaluation using only the ED_{10} and applying the modifying factors, a substance can be placed in the final potency group using the table below. The GCL or SCL of that substance can then be found in the same table.

<table>
<thead>
<tr>
<th>Category 1</th>
<th>Category 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td><strong>SCL</strong></td>
</tr>
<tr>
<td>Group 1 high potency</td>
<td>ED_{10} below 4 mg/kg bw/day</td>
</tr>
<tr>
<td>Group 2 medium potency</td>
<td></td>
</tr>
</tbody>
</table>
| Group 3 low potency | ED_{10} above 400 mg/kg bw/day | 3% | ED_{10} above 400 mg/kg bw/day | 3-10% ^

^ The limit of 10% may be considered in certain cases, such as for substances with a ED_{10} value above 1000 mg/kg bw/day and a NOAEL below 1000 mg/kg bw/day.

3.7.2.5.6.1 Assigning two SCLs to a substance

A substance toxic to reproduction is classified in one category for both effects on development and on sexual function and fertility. Within each category effects on development and on sexual function & fertility are considered separately. The potency and resulting concentration limits have to be determined separately for the two main types of reproductive toxic effects. In case the potency and resulting specific concentration limits are different for sexual function/fertility and development for a substance, the substance needs to be assigned one SCL for developmental toxicity and another SCL for effects on sexual function and fertility. These concentration limits will in all cases trigger different specifications of the hazard statements for the two main types of effects, to be applied to mixtures containing the substance (see also 3.7.4.1, Annex I, CLP)
### 3.7.6 Examples

#### 3.7.6.1 Examples of the determination of SCLs

**Example 1**

1. **Identification**

<table>
<thead>
<tr>
<th>Substance Name</th>
<th>Confidential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cas N°</td>
<td></td>
</tr>
<tr>
<td>EC N°</td>
<td></td>
</tr>
</tbody>
</table>

2. **EU CLP classification**

<table>
<thead>
<tr>
<th>Repro</th>
<th>1B</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>360D</td>
</tr>
</tbody>
</table>

3. **ED\(_{10}\) in animals**

**Brief summary**

OECD 414, Wistar rats, GD 6-19, 0, 20, 60, 180 mg/kg bw. The number of live foetuses per litter was significantly reduced and the postimplantation loss was 43 % at the high dose compared to only 8 % in the control being statistically significant.

The mean foetal body weight was reduced by 14 %. Further, the incidence of external malformations (anasarca and/or cleft palate) was significantly increased. About 10 % of the high dose foetuses were affected (13/132 foetuses; in 7/22 litters) while no such changes were observed in the control.

Skeletal malformations were also statistically significantly increased: 7.8 % affected foetuses per litter (7/73 foetuses in 5/21 litters) were noted in the high dose group compared to 1.1 % in the control. The incidences of shortened scapula (4/73 foetuses), bent radius/ulna (2/73 foetuses), malpositioned and bipartite sternebrae (2/73 foetuses) were statistically significantly increased. Soft tissue variations (dilated renal pelvis and ureter) were significantly increased in foetuses from high dose dams compared to controls (27.1 % vs. 6.4 %).

At 0, 20, 60, 180 mg/kg 7.9, 14.8, 9.6, 43 % postimplantation loss was found, respectively.

**Remarks on the study used for the determination of the ED\(_{10}\)**

<table>
<thead>
<tr>
<th>Species, strain, sex:</th>
<th>Female Wistar rat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study type:</td>
<td>OECD 414</td>
</tr>
<tr>
<td>Route of administration:</td>
<td>Oral gavage</td>
</tr>
<tr>
<td>Effect descriptor for LOAEL:</td>
<td>Post-implantation loss, anasarca, cleft palate</td>
</tr>
<tr>
<td>Mode of action:</td>
<td>Not known</td>
</tr>
<tr>
<td>Genotoxicity classification:</td>
<td>None</td>
</tr>
<tr>
<td>----------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Potential to accumulate:</td>
<td>No data, not known</td>
</tr>
</tbody>
</table>

## Determination of the ED\textsubscript{10} value

Control resorption rate (= postimplantation loss) is 7.9%. ED\textsubscript{10} rate would be 17.9%. Interpolation between NOAEL (classification) (9.6% at 60 mg/kg) and LOAEL (classification) (43% at 180 mg/kg) leads to an ED\textsubscript{10} of 89.8 mg/kg bw/d.

### Calculation:

\[
\frac{180 - 60}{43 - 9.6} = 3.593 \text{ mg/kg per % (steepness). Going from 9.6\% to 17.9\% requires addition of 8.3\%. This equals 8.3\% * 3.593 \text{ mg/kg per \%} = 29.8 \text{ plus 60 as the starting point = 89.8 mg/kg bw/day.}
\]

The ED\textsubscript{10} for other relevant effects was above 89.8 mg/kg bw/day.

### Preliminary potency group

**medium**

### 4. Elements that may modify the preliminary potency evaluation

#### 4.1. Dose-response relationship

Not relevant as ED\textsubscript{10} not borderline.

#### 4.2. Type of effect / severity

Not relevant as ED\textsubscript{10} not borderline.

#### 4.3. Data availability

Not relevant. Only one valid study available.

#### 4.4. Mode of action

No data.

#### 4.5. Toxicokinetics

No data.
4.6. **Bio-accumulation**

Little information, only environmental. Accumulation in organisms is not to be expected due to the calculated BCF at 3.16. The substance tends not to accumulate in biota due to the low calculated BCF (<500) and low measured log Kow (<4).

5. **Allocation of potency group and SCL**

Medium potency, GCL

6. **References**

Confidential
Example 2 (developmental part only):

1. **Identification**

<table>
<thead>
<tr>
<th>Substance Name</th>
<th>Confidential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cas N°</td>
<td></td>
</tr>
<tr>
<td>EC N°</td>
<td></td>
</tr>
</tbody>
</table>

2. **EU CLP classification**

<table>
<thead>
<tr>
<th>Repro</th>
<th>1B</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>360 FD</td>
</tr>
</tbody>
</table>

3. **ED_{10} in animals**

**Brief summary**

Study used for the determination of the ED_{10}:

Pregnant females received daily gavage doses of 0, 25, 50, 100 or 175 mg/kg during the gestation period (GD 6-19).

<table>
<thead>
<tr>
<th>LOAEL effect</th>
<th>0 mg/kg</th>
<th>25 mg/kg</th>
<th>50 mg/kg</th>
<th>100 mg/kg</th>
<th>175 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skeletal malformations</td>
<td>2/22 (9%)</td>
<td>2/17 (12%)</td>
<td>5/15 (33%)</td>
<td>10/19 (53%)</td>
<td>6/12 (50%)</td>
</tr>
</tbody>
</table>

Clear maternal toxicity was evident only at the highest dose level.

**Remarks on the study used for the determination of the ED_{10}**

<table>
<thead>
<tr>
<th>Species, strain, sex:</th>
<th>Rabbit, New Zealand White, female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study type:</td>
<td>Developmental 6-19</td>
</tr>
<tr>
<td>Route of administration:</td>
<td>Gavage</td>
</tr>
<tr>
<td>Effect descriptor for LOAEL:</td>
<td>Skeletal malformations (axial skeleton, ribs)</td>
</tr>
<tr>
<td>Mode of action:</td>
<td>Substance is metabolised to a substance which causes the developmental effect</td>
</tr>
<tr>
<td>Genotoxicity classification:</td>
<td>None</td>
</tr>
</tbody>
</table>
Potential to accumulate: Unknown

**Determination of the ED\textsubscript{10} value**

ED\textsubscript{10} was determined as 33 mg/kg.
Control skeletal malformations is 9%. ED\textsubscript{10} rate would be 19%. Interpolation between NOAEL (classification) (12% at 25 mg/kg) and LOAEL (classification) (33% at 50 mg/kg) leads to an ED\textsubscript{10} of 33.3 mg/kg bw/day.
Calculation:
\[
\frac{50 - 25}{33 - 12} = 1.19 \text{ mg/kg per } \% \text{ (steepness). Going from 12\% to 19\% requires addition of 7\%. This equals } 7\% \times 1.19 \text{ mg/kg per } \% = 8.3 \text{ plus 25 as the starting point = 33.3 mg/kg bw/day.}
\]

**Preliminary potency group**

Medium potency group.

**4. Elements that may modify the preliminary potency evaluation:**

**4.1 Dose-response relationship**
The effect on which the classification is based is the occurrence of malformations. As the lowest ED$_{10}$ was the ED$_{10}$ for skeletal malformations, this ED$_{10}$ was chosen as the basis for the SCL. The dose effect relationship is clear. The ED$_{10}$ (33 mg/kg) is not borderline with the LOAEL. There is no reason to consider the dose-response relationship to modify the potency of the substance.

<table>
<thead>
<tr>
<th>% malformations</th>
<th>mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>20</td>
<td>100</td>
</tr>
<tr>
<td>30</td>
<td>150</td>
</tr>
<tr>
<td>40</td>
<td>200</td>
</tr>
</tbody>
</table>

4.2 Type of effect / severity

The effect on which the classification is based is the occurrence of malformations, which is a severe effect. Moving the substance to a higher potency group should be considered.

4.3 Data availability

Not relevant. Different studies are available showing a developmental effect on different species (rat, mouse, rabbit).

4.4 Mode of action

The toxic metabolite has been extensively investigated and established as a strong embryotoxicant and teratogen. There is no mechanistic information showing a higher or a lesser sensitivity in humans than in experimental animals.
4.5 **Toxicokinetics**

Human and rat liver microsomal preparations have been shown to produce qualitatively and quantitatively similar oxidative metabolic products suggesting that the human pathways for this substance may be similar to those observed in experimental animals.

4.6 **Bio-accumulation**

Unknown

5. **Allocation of potency group and SCL**

The effect on which the classification is based is the occurrence of malformations. This is a severe effect.

Due to the fact that the ED$_{10}$ (33 mg/kg) is based on a severe effect like malformations, it is justified to move the substance to the highest potency group.

6. **References**

Confidential
Example 3 (limited to developmental toxicity)

1. Identification

<table>
<thead>
<tr>
<th>Substance Name</th>
<th>confidential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cas N°:</td>
<td></td>
</tr>
<tr>
<td>EC N°:</td>
<td></td>
</tr>
</tbody>
</table>

2. EU CLP classification

<table>
<thead>
<tr>
<th>Repro</th>
<th>1B</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>360</td>
</tr>
</tbody>
</table>

3. ED_{10} in animals

Brief summary

Several studies in rats were available for the evaluation of the developmental effect of this substance. These included 2-generation studies, developmental toxicity studies, and studies with exposure in sensitive periods during gestation. The most relevant study for the evaluation of potency was considered to be a two-generation study performed according to the revised OECD Test Guideline 416. In this study the substance was administered in the diet. Developmental toxicity was evident as reduced absolute and adjusted AGD in F1 and F2 offspring as well as and reduced foetal and testicular weight in offspring. The NOAEL was 50 mg/kg bw/day based on reduced AGD from 250 mg/kg bw/day. These effects were reported in the absence of marked maternal toxicity. Effects on the reproductive organs were also reported in male offspring in the developmental toxicity studies at higher doses.

Remarks on the study used for the determination of the ED_{10}

<table>
<thead>
<tr>
<th>Species, strain, sex:</th>
<th>CD(Sprague-Dawley) rats male and female:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study type:</td>
<td>2-generation according to OECD 416</td>
</tr>
<tr>
<td>Route of administration:</td>
<td>Oral in feed</td>
</tr>
<tr>
<td>Effect descriptor for LOAEL:</td>
<td>Overall: reduced anogenital distance</td>
</tr>
<tr>
<td></td>
<td>Classification: increase in areolae in males</td>
</tr>
<tr>
<td>Mode of action:</td>
<td>Antiandrogenic effect, mechanism relevant for humans</td>
</tr>
<tr>
<td>Genotoxicity classification:</td>
<td>Not classified for germ cell mutagenicity</td>
</tr>
<tr>
<td>Potential to accumulate:</td>
<td>No</td>
</tr>
</tbody>
</table>
**Determination of the ED\textsubscript{10} value**

Calculation of the ED\textsubscript{10} value: 416 mg/kg bw/day

<table>
<thead>
<tr>
<th>Dose (mg/kg bw/day)</th>
<th>% male F1 with areola</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2.63</td>
</tr>
<tr>
<td>50</td>
<td>0.0</td>
</tr>
<tr>
<td>250 (NOAEL)</td>
<td>0.76</td>
</tr>
<tr>
<td>750 (LOAEL)</td>
<td>32.3</td>
</tr>
</tbody>
</table>

The ED\textsubscript{10} is calculated by interpolation between 250 and 750 mg/kg bw/day to a dose level with 10% above control level. Roughly, an increase of 30% above control was found at 750 mg/kg bw/day. Interpolation between 250 and 750 mg/kg bw/day results in a dose of 16.67 mg/kg bw/day for each % of increase in areola. (750-250)/30. A 10% increase (ED\textsubscript{10}) is expected at 250 + 10 * 16.67 = 416 mg/kg bw/day.

**Preliminary potency group**

Low potency

**4. Elements that may modify the preliminary potency evaluation**

**4.1 Dose-response relationship**

A dose-response relationship on decreased AGD was evident for decrease in AGD in the two-generation study. (AGD was decreased in male offspring in a dose-related pattern from 250 mg/kg bw/day (1.89 mm at 250 mg/kg bw/day and 1.70 mm at 750 mg/kg bw/day (control: 2.06 mm)).

**4.2 Type of effect / severity**
Development: reduced anogenital distance (absolute and adjusted) from 250 mg/kg bw/day in F1 and F2 offspring. Weight changes in the reproductive organs in F1 and F2 male offspring, and macroscopic and microscopic lesions in the reproductive organs in male offspring at 750 mg/kg bw/day.

Maternal toxicity: organ weight changes, and histopathological lesions in the liver graded as minimal in females at 750 mg/kg bw/day.

NOAEL for developmental effects: 50 mg/kg bw/day based on reduced anogenital distance from 250 mg/kg bw/day in F1 and F2 offspring.

NOAEL for maternal toxicity: 250 mg/kg bw/day.

4.3 Data availability

A two-generation study is considered relevant for the assessment of development toxicity.

4.3 Mode of action

The mechanism (antiandrogen activity) is considered relevant for humans.

4.5 Toxicokinetics

When metabolites are measured in urine, they are related to the day before exposure. The metabolites of the substance in rats differ quantitatively from those in humans. In several studies the pattern of malformations induced by some of the metabolites were similar to that produced by the substance, suggesting that the metabolic products may be responsible for the developmental toxicity.

Although there is a difference in toxicokinetics between rats and humans, this difference is not expected to result in a difference in potency between rats and humans as the available data indicate comparable effects and potency of the metabolites.

4.6 Bio-accumulation

Low to medium bioaccumulation

6.7. Allocation of potency group and SCL

The ED_{10} was 416 mg/kg bw/day. The elements that may modify the potency evaluation were considered to not modify the potency. This substance is shown to have a low potency. Therefore an SCL of 3 % should be applied.
6. References

Confidential.

Example 4

1. Identification

<table>
<thead>
<tr>
<th>Substance Name</th>
<th>Confidential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cas N°</td>
<td></td>
</tr>
<tr>
<td>EC N°</td>
<td></td>
</tr>
</tbody>
</table>

2. EU CLP classification

<table>
<thead>
<tr>
<th>Repr</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>361f</td>
</tr>
</tbody>
</table>

3. ED_{10} in animals

Brief summary:

Only two repeated dose studies are available for this substance and no fertility studies. In the inhalatory repeated dose study testicular lesions were observed after exposure to 2.87 mg/l for 4 exposures of 16 to 20 hours per week during 11 weeks. Other dose levels were not tested. In the oral 90 day study, effects on the testes were observed after exposure to 660 mg/kg bw/day. Other dose levels were not tested.

Remarks on the study used for the determination of the ED_{10}

<table>
<thead>
<tr>
<th>Species, strain, sex:</th>
<th>Rats, CD(SD)BR males</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study type:</td>
<td>90 days, 5 days per week, 120 day observation period</td>
</tr>
<tr>
<td>Route of administration:</td>
<td>gavage</td>
</tr>
<tr>
<td>Effect descriptor for LOAEL:</td>
<td>testicular atrophy</td>
</tr>
<tr>
<td>Mode of action:</td>
<td>A metabolite is assumed to be causing the testicular effects. A direct effect of this metabolite on the Sertoli cells is postulated.</td>
</tr>
</tbody>
</table>
Genotoxicity classification: none
Potential to accumulate: unknown

### Determination of the ED_{10} value

A ED_{10} cannot be determined because only one dose level was tested. This dose level of 660 mg/kg bw/day is considered as the LOAEL but in the absence of a NOAEL.

### Preliminary potency group

**Low potency group**

### 4 Elements that may modify the preliminary potency evaluation

#### 4.1 Dose-response relationship

There is no data available on the dose response relationship.

#### 4.2 Type of effect / severity

There are clear testicular effects. It is unknown whether these effects will result in effects on fertility as this has not been tested.

#### 4.3 Data availability

There is only limited data available at one exposure level. This is insufficient for determining an ED_{10}. A LOAEL can be determined but in the absence of a NOAEL it cannot be excluded that effects on sexual organs occur at levels below the LOAEL. The available data are considered as limited.

#### 4.4 Mode of action

A metabolite is assumed to be the cause of the testicular effects. A direct effect of this metabolite on the Sertoli cells is postulated.

#### 4.5 Toxicokinetics

Unknown

### 4.6 Bio-accumulation
5 Allocation of potency group and SCL

An ED₁₀ cannot be determined. The LOAEL is above the boundary between the medium and low potency group indicating that this substance would be a low potency substance. However, there is only very limited data. As there is only an LOAEL and no NOAEL, it cannot be excluded that testicular effects can be induced at lower levels. Therefore this substance cannot be placed in the low potency group but should be placed in the medium potency group.

The available inhalatory study indicates that inhalatory exposure in rats to levels comparable to estimates of high or maximum human exposures to volatile substances in the workplace (Schneider et al., 2007)) can also induce testicular effects. This may provide additional support to place this substance in the medium potency group.

6 References

Confidential

Deleted: There is no detailed and accepted guidance developed for the setting of specific concentration limits (SCLs) for reproductive toxicity, as is the case for e.g. carcinogenic substances. Such guidance like the T₂₅ concept for carcinogens covering all relevant aspects would be needed to be able to derive SCLs for reproductive toxicants in a standardized manner. This is due to the fact that reproductive toxicity is a complex hazard class for which SCL setting is difficult. In conclusion, the possibility to set SCL for reproductive toxicity is therefore currently not considered possible in the process of self-classification as there is no standardized methodical approach available which adequately takes into account all relevant information. An EU expert group (linked to ECHA) is currently working on a concept for the setting of specific concentration limits (SCLs) for reproductive toxicity which will be added to this guidance when finalised.¶
3.7.2.6 Decision logic

The decision logic which follows is provided here as additional guidance. It is strongly recommended that the person responsible for classification study the criteria before and during use of the decision logic.

Classification of substances for fertility or developmental effects:

Does the substance have data on reproductive toxicity?

**NO**

Classification not possible

**YES**

According to the criteria, is the substance:
(a) **Known** human reproductive toxicant, or
(b) **Presumed** human reproductive toxicant?

Application of the criteria needs expert judgment in a weight of evidence approach.

**NO**

**YES**

Category 1

Danger

Classification of substances for effects via lactation:

Does the substance according to the criteria cause concern for the health of breastfed children?

**NO**

Not classified

**YES**

Additional category for effects on or via lactation
3.7.3 Classification of mixtures for reproductive toxicity

3.7.3.1 Classification criteria

Reproductive toxicity classification of mixtures is based on the presence of an ingredient classified for reproductive toxicity (see CLP Article 6(3) and Annex I, section 3.7.3). Only in case there is data available for the mixture itself which demonstrate effects not retrieved from the ingredients, this data might be used for classification. If such data is not available for the mixture itself, data on a similar mixture can be used in accordance to the bridging principle (see CLP Annex I, section 1.1.3).

Annex I: Table 3.7.2

Generic concentration limits of ingredients of a mixture classified as reproduction toxicants or for effects on or via lactation that trigger classification of the mixture

<table>
<thead>
<tr>
<th>Ingredient classified as:</th>
<th>Category 1A reproductive toxicant</th>
<th>Category 1B reproductive toxicant</th>
<th>Category 2 reproductive toxicant</th>
<th>Additional category for effects on or via lactation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1A reproductive toxicant</td>
<td>≥ 0.3 % [Note 1]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category 1B reproductive toxicant</td>
<td></td>
<td>≥ 0.3 % [Note 1]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category 2 reproductive toxicant</td>
<td></td>
<td></td>
<td>≥ 3.0 % [Note 1]</td>
<td></td>
</tr>
<tr>
<td>Additional category for effects on or via lactation</td>
<td></td>
<td></td>
<td></td>
<td>≥ 0.3 % [Note 1]</td>
</tr>
</tbody>
</table>

Note
The concentration limits in the table above apply to solids and liquids (w/w units) as well as gases (v/v units).

Note 1
If a Category 1 or Category 2 reproductive toxicant or a substance classified for effects on or via lactation is present in the mixture as an ingredient at a concentration above 0.1 %, a SDS shall be available for the mixture upon request.

3.7.3.1.1 When data are available for the individual ingredients

Annex I: 3.7.3.1.1. The mixture shall be classified as a reproductive toxicant when at least one ingredient has been classified as a Category 1A, Category 1B or Category 2 reproductive toxicant and is present at or above the appropriate generic concentration limit as shown in Table 3.7.2 below for Category 1A, Category 1B and Category 2 respectively.

3.7.3.1.2. The mixture shall be classified for effects on or via lactation when at least one ingredient...
has been classified for effects on or via lactation and is present at or above the appropriate generic concentration limit as shown in Table 3.7.2 for the additional category for effects on or via lactation.

3.7.3.1.2 When data are available for the complete mixture

**Annex I: 3.7.3.2.1** Classification of mixtures will be based on the available test data for the individual ingredients of the mixture using concentration limits for the ingredients of the mixture. On a case-by-case basis, test data on mixtures may be used for classification when demonstrating effects that have not been established from the evaluation based on the individual components. In such cases, the test results for the mixture as a whole must be shown to be conclusive taking into account dose and other factors such as duration, observations, sensitivity and statistical analysis of reproduction test systems. Adequate documentation supporting the classification shall be retained and made available for review upon request.

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

**Annex I: 3.7.3.3.1** Subject to the provisions of paragraph 3.7.3.2.1, where the mixture itself has not been tested to determine its reproductive toxicity, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterise the hazards of the mixture, these data shall be used in accordance with the applicable bridging rules set out in section 1.1.3.
3.7.3.2 Decision logic

The decision logic which follows is provided here as additional guidance. It is strongly recommended that the person responsible for classification study the criteria before and during use of the decision logic.

Classification of mixtures for fertility or developmental effects:

Classification based on individual ingredients of the mixture

1. Does the mixture contain one or more ingredients classified as a Category 1 reproductive toxicant at ≥ 0.3%?

   YES
   Category 1
   Danger

   NO

2. Does the mixture contain one or more ingredients classified as a Category 2 reproductive toxicant at ≥ 3%?

   YES
   Category 2
   Warning

   NO

   Not classified

Modified classification on a case-by-case basis

Test data on mixtures may be used for classification when demonstrating effects that have not been established from the evaluation based on the individual ingredients (CLP Annex I, 3.7.3.1.1, see also CLP Article 6(3)).

1. Are test data available for the mixture itself demonstrating a reproductive toxic effect not identified from the data on individual substances?

   YES

   Are the test results on the mixture conclusive taking into account dose and other factors such as duration, observations and analysis (e.g. statistical analysis, test sensitivity) of reproductive toxicity test systems?

   YES

   Classify in appropriate category
   Danger or Warning or No classification

   NO

   NO

2. Can bridging principles be applied?

   YES

   See above: Classification based on individual ingredients of the mixture.

   NO

   NO
Classification of mixtures for effects via lactation:

1. Classification based on individual ingredients of the mixture

Does the mixture contain one or more ingredients classified for effects on or via lactation at $\geq 0.3\%$?

- YES: Additional category for effects on or via lactation
- NO: Not classified

Modified classification on a case-by-case basis

Test data on mixtures may be used for classification when demonstrating effects that have not been established from the evaluation based on the individual ingredients (CLP Annex I, 3.7.3.1.1, see also CLP Article 6(3)).

- Are test data available for the mixture itself demonstrating effects on or via lactation not identified from the data on individual substances?
  - YES: The test results for the mixture as a whole must be shown to be conclusive taking into account dose and other factors such as duration, observations, sensitivity and statistical analysis of reproductive toxicity test systems.
  - NO: Can bridging principles be applied?
    - YES: See above: Classification based on individual ingredients of the mixture.
    - NO: Additional category for effects on or via lactation or No classification.
3.7.4 Hazard communication in form of labelling for reproductive toxicity

3.7.4.1 Pictograms, signal words, hazard statements and precautionary statements

Annex I: 3.7.4.1. Label elements shall be used for substances or mixtures meeting the criteria for classification in this hazard class in accordance with Table 3.7.3.

Table 3.7.3
Label elements for reproductive toxicity

<table>
<thead>
<tr>
<th>Classification</th>
<th>Category 1A or Category 1B</th>
<th>Category 2</th>
<th>Additional category for effects on or via lactation</th>
</tr>
</thead>
<tbody>
<tr>
<td>GHS Pictograms</td>
<td><img src="image" alt="Pictogram" /></td>
<td><img src="image" alt="Pictogram" /></td>
<td>No pictogram</td>
</tr>
<tr>
<td>Signal Word</td>
<td>Danger</td>
<td>Warning</td>
<td>No signal word</td>
</tr>
<tr>
<td>Hazard Statement</td>
<td>H360: May damage fertility or the unborn child (state specific effect if known)(state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)</td>
<td>H361: Suspected of damaging fertility or the unborn child (state specific effect if known) (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)</td>
<td>H362: May cause harm to breast-fed children</td>
</tr>
<tr>
<td>Precautionary Statement Prevention</td>
<td>P201</td>
<td>P202</td>
<td>P281</td>
</tr>
<tr>
<td>Precautionary Statement Response</td>
<td>P308 + P313</td>
<td>P308 + P313</td>
<td>P308 + P313</td>
</tr>
<tr>
<td>Precautionary Statement Storage</td>
<td>P405</td>
<td>P405</td>
<td></td>
</tr>
</tbody>
</table>

As shown in CLP Annex I, Table 3.7.3, a substance classified as reproductive toxicant in Category 1A or 1B shall be assigned the hazard statements H360 and a substance classified in Category 2 shall be assigned H361. Each of these two hazard statements includes the mention of the adverse effects on sexual function and fertility or adverse effects on development of the offspring.

Depending on the data available, the hazard statement H360 or H361 shall e.g. be assigned a reproductive toxic substance: in the case the criteria for Category 1A/1B or 2 are fulfilled, for either sexual function or fertility or developmental toxicity and when the other reproductive effect cannot be excluded.
In case reliable and adequate data are available on reproductive toxicity, (so that it is possible to ascribe one category for the fertility effects and one category for developmental toxic effects); it is possible to specify the hazard in the hazard statement. The resulting different variants of H360 and H361 are shown in the table below, which also provides some examples when they should be assigned a substance.

**Table 3.7.4.1: Hazard statements for reproductive toxicity: H360 and H361, and their specifications**

<table>
<thead>
<tr>
<th>Code</th>
<th>Hazard Statement</th>
<th>Examples</th>
</tr>
</thead>
</table>
| H360   | “May damage fertility or the unborn child”             | 1) a substance classified in Repr Cat 1A/B because of adverse effects on fertility and for which developmental toxic effects cannot be excluded  
       | Examples:                                             | 2) a substance classified in Repr Cat 1A/B but the effects cannot be specified with respect to fertility or developmental toxicity |
| H361   | “Suspected of damaging fertility or the unborn child” | 1) a substance classified in Repr. Cat 2 on the basis of effects on developmental toxicity and for which fertility effects cannot be excluded  
       | Example:                                              | 2) a substance classified in Repr. Cat 2 but the effects cannot be specified with respect to fertility or developmental toxicity |
| H360F  | “May damage fertility.”                                | Example: a substance classified in Repr Cat 1A/B on the basis of fertility effects and effects on developmental toxicity can be excluded according to reliable and adequate data |
| H360D  | “May damage the unborn child.”                         | Example: a substance classified in Repr Cat 1A/B on the basis of developmental toxicity and effects on fertility can be excluded according to reliable and adequate data |
| H361f  | “Suspected of damaging fertility”.                     | Example: a substance classified in Repr Cat 2 on the basis of fertility effects and effects on developmental toxicity can be excluded according to reliable and adequate data |
| H361d  | Suspected of damaging the unborn child.                | Example: a substance classified in Repr Cat 2 on the basis of fertility effects and effects on developmental toxicity can be excluded according to reliable and adequate data |
| H360FD | May damage fertility. May damage the unborn child.     | Example: a substance classified in Repr Cat 1A/B on the basis of fertility effects and developmental toxicity. |
| H361fd | Suspected of damaging fertility. Suspected of damaging the unborn child. | Example: a substance classified in Repr Cat 2 on the basis of fertility effects and developmental toxicity. |
| H360Fd | May damage fertility. Suspected of damaging the unborn child. | Example: a substance classified in Repr Cat 1A/B on the basis of fertility effects and in |
Repr Cat 2 on the basis of developmental toxicity.

| H360Df | May damage the unborn child. Suspected of damaging fertility. |

Example: a substance classified in Repr Cat 1A/B on the basis of developmental toxicity and classified in Repr Cat 2 on the basis of fertility effects.

According to CLP Annex I, section 3.7.4.1, the hazard statements shall be amended by specifying the route of exposure if it is conclusively proven that no other routes of exposure will lead to an adverse effect on sexual function or fertility or development of the offspring. When conclusively proven, it is meant that valid in vivo test data need to be available for all three exposure routes clearly indicating that only one exposure route has caused positive results i.e. adverse effects on the reproduction. Moreover, such a finding should be considered plausible with respect to the mechanism or mode of action. It is estimated that such a situation would rarely occur. Thus, amendment of the hazard statement with the route of exposure generally does not have to be considered.

3.7.4.2 Additional labelling provisions

There are no additional labelling provisions for reproductive toxic substances and mixtures in CLP, however there are provisions laid out in Annex XVII to REACH. The packaging of substances harmonised classified for reproductive toxicity category 1A or category 1B, and mixtures containing such substances, "must be marked visibly, legibly and indelibly as follows: ‘Restricted to professional users’." (REACH, Annex XVII, point 30).

3.7.5 Re-classification of substances and mixtures classified for reproductive toxicity according to DSD and DPD

3.7.5.1 Is direct “translation” of classification and labelling possible?

Generally yes. In case there is no re-evaluation of the data, the hazard statement specifying both 'damage to fertility' and 'damage to the unborn child' should be assigned. It is possible to omit the hazard statement specifying fertility or developmental effects; in case there are clearly negative results (see section 3.7.4.1).

However, in some very rare situations, a reproductive toxicant classified with Repr. Cat. 3; R62 may need classification with Repr. Cat. 1B H360 under CLP. According to Annex VI to DSD, for the classification of a substance into Category 2 for impaired fertility, there should normally be clear evidence in one animal species, with supporting evidence on mechanism of action or site of action, or chemical relationship to other known anti-fertility agents or other information from humans which would lead to the conclusion that effects would be likely to be seen in humans. According to CLP, such supporting evidence is not needed.

Classification for effects on or via lactation according to CLP is directly equivalent to assignment of R64 according to DSD as the criteria are essentially the same. Therefore, direct translation of R64 to H362 is possible.

3.8 SPECIFIC TARGET ORGAN TOXICITY – SINGLE EXPOSURE (STOT-SE)

3.8.1 Definitions and general considerations for STOT-SE

Annex 1: 3.8.1.1. Specific target organ toxicity (single exposure) is defined as specific, non lethal
target organ toxicity arising from a single exposure to a substance or mixture. All significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed and not specifically addressed in Chapters 3.1 to 3.7 and 3.10 are included (see also 3.8.1.6).

There are two hazard classes for single exposure toxicity: “Acute toxicity” and “STOT-SE”. These are independent of each other and both may be assigned to a substance or a mixture if the respective criteria are met. Acute toxicity refers to lethality and STOT-SE to non lethal effects. However, care should be taken not to assign both classes for the same toxic effect, essentially giving a “double classification”, even where the criteria for both classes are fulfilled. In such a case the most appropriate class should be assigned.

Acute toxicity classification is generally assigned on the basis of evident lethality (e.g. an LD$_{50}$/LC$_{50}$ value) or where the potential to cause lethality can be concluded from evident toxicity (e.g. from fixed dose procedure). STOT-SE should be considered where there is clear evidence of toxicity to a specific organ especially when it is observed in the absence of lethality.

Furthermore, specific toxic effects covered by other hazard classes are not included in STOT-SE. STOT-SE should only be assigned where the observed toxicity is not covered more appropriately by another hazard class. For example, specific effects caused after a single exposure like corrosion of skin or effects on the reproductive organs should be used for classification for skin corrosion or reproductive toxicity, respectively, but not for STOT-SE.

Annex 1: 3.8.1.4. Assessment shall take into consideration not only significant changes in a single organ or biological system but also generalised changes of a less severe nature involving several organs.

3.8.1.5. Specific target organ toxicity can occur by any route that is relevant for humans, i.e. principally oral, dermal or inhalation.

3.8.1.7. The hazard class Specific Target Organ Toxicity – Single Exposure is differentiated into:

Specific target organ toxicity – single exposure, Category 1 and 2;
Specific target organ toxicity – single exposure, Category 3.

The hazard class STOT-SE has 3 categories, with Categories 1 and 2 being distinct from Category 3 in terms of the toxicity they cover and the criteria. Categories 1 and 2 for non lethal “significant and/or severe toxic effects” are the basis for classification with the category reflecting the dose level required to cause the effect. Category 3 covers “transient effects” occurring after single exposure, specifically respiratory tract irritation (RTI) and narcotic effects (NE). The relationship between Categories 1/2 vs. Category 3 is discussed in section 3.8.2.4 of this document.

3.8.2 Classification of substances for STOT-SE

3.8.2.1 Identification of hazard information

Annex 1: 3.8.2.1.5. The information required to evaluate specific target organ toxicity comes either from single exposure in humans, such as: exposure at home, in the workplace or environmentally, or from studies conducted in experimental animals.

CLP does not require testing of substances or mixtures for classification purposes. The assessment is based on the respective criteria together with available adequate and robust test
data/information. Generally, information relevant to STOT-SE can be obtained from human experience or acute toxicity studies in animals.

### 3.8.2.1.1 Identification of human data

Relevant information with respect to toxicity after single exposure may be available from case reports, epidemiological studies, medical surveillance and reporting schemes and national poisons centres.

Data on sensory irritation of the airways may be available from volunteer studies including objective measurements of RTI such as electrophysiological responses, data from lateralization threshold testing, biomarkers of inflammation in nasal or bronchoalveolar lavage fluids (IR/CSA, section 7.2.3.2). For more details see IR/CSA, section 7.4.3.2 and R.7.2.

### 3.8.2.1.2 Identification of non human data

**Annex 1: 3.8.2.1.5** The standard animal studies in rats or mice that provide this information are acute toxicity studies which can include clinical observations and detailed macroscopic and microscopic examination to enable the toxic effects on target tissues/organs to be identified. Results of acute toxicity studies conducted in other species may also provide relevant information.

**Annex 1: 3.8.2.1.7.3.** Evidence from appropriate studies in experimental animals can furnish much more detail, in the form of clinical observations, and macroscopic and microscopic pathological examination, and this can often reveal hazards that may not be life-threatening but could indicate functional impairment. Consequently all available evidence, and relevance to human health, must be taken into consideration in the classification process, …

#### Non-testing data

**Physicochemical data**

Physicochemical properties, such as pH, physical form, solubility, vapour pressure, particle size, can be important parameters in evaluating toxicity studies and in determining the most appropriate classification especially with respect to inhalation where physical form and particle size can have a significant impact on toxicity.

**(Q)SAR models, Read across**

“Non-testing” data (i.e. data not obtained from experimental methods) can be provided by the use of techniques such as grouping/category formation, Quantitative and qualitative Structure Activity Relationship (Q)SAR models and expert systems, which generally relate physico-chemical properties and chemical structure to toxicity. The use of these methods is described in more detail in Section 2.3.2 and IR/CSA, section R.7.4.4.1.

The potential use of (Q)SAR models for predicting effects relevant to STOT-SE Categories 1/2 is currently quite limited and may only be applicable in specific cases. However, they may be somewhat more useful for STOT-SE Category 3 where there are some well established relationships between physicochemical properties or chemical structure and effects such as narcosis and respiratory tract irritation. For instance substances such as aldehydes, unsaturated carbonic esters and reactive inorganic compounds are generally found to be respiratory tract irritants.

In addition, there are systems which can predict the metabolism of substances. These can be useful in providing information on the potential for the substance to be metabolised to
substances with known toxicity. An example is certain esters, which after enzymatic cleavage to carbonic acids and alcohols in the nasal region, cause respiratory irritation.

For more details see IR/CSA, section 7.4.3.1.

**Testing data**

**Animal data**

The standard tests on acute toxicity are listed in IR/CSA, section R.7.4.3.1.

For **Category 1 and 2**, in general terms, most studies involving single exposure via any relevant route of exposure, such as acute toxicity studies, can be used for classification purposes. Older acute toxicity studies which tended to only measure lethality as an observational endpoint (e.g. to determine LD_{50}/LC_{50}) will generally not provide useful information for STOT-SE. However, newer acute toxicity test protocols, such as the fixed-dose and up-down procedures, have a wider range of observations on signs of toxicity and therefore may provide information relevant for STOT-SE. Other standard studies, e.g. neurotoxicity tests, or ad-hoc studies designed to investigate acute toxicity, can also provide valuable information for STOT-SE.

Care must be taken not to classify for STOT-SE for effects which are not yet lethal at a certain dose, but would lead to lethality within the numeric classification criteria. In other words, if lethality would occur at relevant doses then a classification for acute toxicity would take precedence and STOT-SE would not be assigned.

Although classification in **Category 3** is primarily based on human data, if available, animal data can be included in the evaluation. These animal data on RTI and NE will generally come from standard acute inhalation studies, although it is possible that narcosis could be observed in studies using other routes. Standard acute toxicity tests are often more useful for Category 3 than for STOT-SE Categories 1/2 because overt findings of narcosis and RTI are more often reported in clinical observations.

The Alarie test gives specific information on the potential for sensory irritation. Further, information on this test and its limitations can be found in IR/CSA, Section R.7.2.

Furthermore the Inhalation Hazard Test (Annex to OECD TG 403) might give information on the potential for RTI of volatile substances. Though the focus of STOT-SE is on effects caused by single exposure, data from studies with repeated exposure might give additional valuable information, especially with respect to the underlying mode of action of RTI.

**In vitro data**

Since there are currently no **in vitro** tests that have been officially adopted by the EU or OECD for assessment of acute toxicity, there are also no useful test systems for STOT-SE (see IR/CSA, section R.7.4.3.1). Any available studies should be assessed using expert judgement.

### 3.8.2.2 Classification criteria for Categories 1 and 2

**Annex I: 3.8.2.1.1.** Substances are classified for immediate or delayed effects separately, by the use of expert judgement (see 1.1.1) on the basis of the weight of all evidence available, including the use of recommended guidance values (see 3.8.2.1.9). Substances are then placed in Category 1 or 2, depending upon the nature and severity of the effect(s) observed (Table 3.8.1).

**Table 3.8.1**

<p>| Categories for specific target organ toxicity-single exposure |</p>
<table>
<thead>
<tr>
<th>Categories</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1</td>
<td>Substances that have produced significant toxicity in humans or that, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to produce significant toxicity in humans following single exposure. Substances are classified in Category 1 for specific target organ toxicity (single exposure) on the basis of: (a) reliable and good quality evidence from human cases or epidemiological studies; or (b) observations from appropriate studies in experimental animals in which significant and/or severe toxic effects of relevance to human health were produced at generally low exposure concentrations. Guidance dose/concentration values are provided below (see 3.8.2.1.9) to be used as part of weight-of-evidence evaluation.</td>
</tr>
<tr>
<td>Category 2</td>
<td>Substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following single exposure. Substances are classified in Category 2 for specific target organ toxicity (single exposure) on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations. Guidance dose/concentration values are provided below (see 3.8.2.1.9) in order to help in classification. In exceptional cases, human evidence can also be used to place a substance in Category 2 (see 3.8.2.1.6).</td>
</tr>
</tbody>
</table>

Note: Attempts shall be made to determine the primary target organ of toxicity and to classify for that purpose, such as hepatotoxicants, neurotoxicants. The data shall be carefully evaluated and, where possible, secondary effects should not be included (e.g. a hepatotoxicant can produce secondary effects in the nervous or gastro-intestinal systems).

3.8.2.1.2. The relevant route or routes of exposure by which the classified substance produces damage shall be identified (see 3.8.1.5).

STOT-SE Category 1 and 2 is assigned on the basis of findings of “significant” or “severe” toxicity. In this context “significant” means changes which clearly indicate functional disturbance or morphological changes which are toxicologically relevant. “Severe” effects are generally more profound or serious than “significant” effects and are of a considerably adverse nature with significant impact on health. Both factors have to be evaluated by weight of evidence and expert judgement.

3.8.2.2.1 Guidance values

Annex 1: 3.8.2.1.9.1 In order to help reach a decision about whether a substance shall be classified or not, and to what degree it shall be classified (Category I or Category 2), dose/concentration ‘guidance values’ are provided for consideration of the dose/concentration which has been shown to produce significant health effects.

Annex 1: 3.8.2.1.9.3. The guidance value (C) ranges for single-dose exposure which has produced a significant non-lethal toxic effect are those applicable to acute toxicity testing, as indicated in Table 3.8.2.
Table 3.8.2
Guidance value ranges for single-dose exposures

<table>
<thead>
<tr>
<th>Route of exposure</th>
<th>Units</th>
<th>Category 1</th>
<th>Category 2</th>
<th>Category 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral (rat)</td>
<td>mg/kg body weight</td>
<td>C ≤ 300</td>
<td>2000 ≥ C &gt; 300</td>
<td>Guidance values do not apply</td>
</tr>
<tr>
<td>Dermal (rat or rabbit)</td>
<td>mg/kg body weight</td>
<td>C ≤ 1000</td>
<td>2000 ≥ C &gt; 1000</td>
<td></td>
</tr>
<tr>
<td>Inhalation (rat) gas</td>
<td>ppmV/4h</td>
<td>C ≤ 2500</td>
<td>20000 ≥ C &gt; 2500</td>
<td></td>
</tr>
<tr>
<td>Inhalation (rat) vapour</td>
<td>mg/l/4h</td>
<td>C ≤ 10</td>
<td>20 ≥ C &gt; 10</td>
<td></td>
</tr>
<tr>
<td>Inhalation (rat) dust/mist/fume</td>
<td>mg/l/4h</td>
<td>C ≤ 1.0</td>
<td>5.0 ≥ C &gt; 1.0</td>
<td></td>
</tr>
</tbody>
</table>

Note

(a) The guidance values and ranges mentioned in Table 3.8.2 above are intended only for guidance purposes, i.e. to be used as part of the weight of evidence approach, and to assist with decision about classification. They are not intended as strict demarcation values.

(b) Guidance values are not provided for Category 3 substances since this classification is primarily based on human data. Animal data, if available, shall be included in the weight of evidence evaluation.

* Note: There is a misprint in Annex I, Table 3.8.2; the heading ‘Guidance value ranges for:’ should also belong to the column ‘Category 1’.

Where significant or severe toxicity has been observed in animal studies, the dose/exposure level causing these effects is compared to the guidance values provided to determine if classification in Category 1 or 2 is most appropriate.

In cases of inhalation studies with exposure times different to 4 hours an extrapolation can be performed similar to the one described in the section 3.1 for acute toxicity.

3.8.2.3 Classification criteria for Category 3: Transient target organ effects

Currently, the criteria for classification in category 3 only cover the transient effects of “respiratory tract irritation” and “narcotic effects”.

Annex I: Table 3.8.1 (continued)

Categories for specific target organ toxicity-single exposure

<table>
<thead>
<tr>
<th>Categories</th>
<th>Criteria</th>
</tr>
</thead>
</table>
| Category 3 | Transient target organ effects
This category only includes narcotic effects and respiratory tract irritation. These are target organ effects for which a substance does not meet the criteria to be classified in Categories 1 or 2 indicated above. These are effects which adversely alter human function for a short duration after exposure and from which humans may recover in a reasonable period without leaving significant alteration of structure or function. Substances are classified specifically for these effects as laid down in 3.8.2.2 |
Annex 1: 3.8.2.2.1 Criteria for respiratory tract irritation

The criteria for classifying substances as Category 3 for respiratory tract irritation are:

(a) respiratory irritant effects (characterized by localized redness, oedema, pruritis and/or pain) that impair function with symptoms such as cough, pain, choking, and breathing difficulties are included. This evaluation will be based primarily on human data.

(b) subjective human observations could be supported by objective measurements of clear respiratory tract irritation (RTI) (such as electrophysiological responses, biomarkers of inflammation in nasal or bronchoalveolar lavage fluids).

(c) the symptoms observed in humans shall also be typical of those that would be produced in the exposed population rather than being an isolated idiosyncratic reaction or response triggered only in individuals with hypersensitive airways. Ambiguous reports simply of “irritation” shall be excluded as this term is commonly used to describe a wide range of sensations including those such as smell, unpleasant taste, a tickling sensation, and dryness, which are outside the scope of classification for respiratory irritation.

(d) there are currently no validated animal tests that deal specifically with RTI, however, useful information may be obtained from the single and repeated inhalation toxicity tests. For example, animal studies may provide useful information in terms of clinical signs of toxicity (dyspnoea, rhinitis etc) and histopathology (e.g. hyperemia, edema, minimal inflammation, thickened mucous layer) which are reversible and may be reflective of the characteristic clinical symptoms described above. Such animal studies can be used as part of weight of evidence evaluation.

(e) this special classification would occur only when more severe organ effects including in the respiratory system are not observed.

It is clearly indicated in the CLP that there are currently no validated animal tests that deal specifically with RTI, but that animal studies can be used as a part of weight of evidence evaluation (3.8.2.2.1.2(d)). However when there are no data in human and animal data suggesting RTI effects, expert judgement is needed to estimate the severity of the effects observed in animals, the conditions of the test, the physical-chemical properties of the substance and whether those considerations alone might be sufficient for a classification in Category 3 for RTI.

The generic term RTI covers two different effects: “sensory irritation” and “local cytotoxic effects”. Classification in STOT-SE Category 3 for respiratory tract irritation is generally limited to local cytotoxic effects.

Sensory irritation refers to the local and central reflex interaction of a substance with the autonomic nerve receptors, which are widely distributed in the mucosal tissues of the eyes and upper respiratory tract. It helps to minimize exposure by decreasing the respiration-time-volume and inducing the exposed to leave the areas of irritant concentrations, if possible. Sensory irritation-related effects are fully reversible given that its biological function is to serve as a warning against substances that could damage the airways.

Local cytotoxic irritant effects induce tissue changes at the site of contact which can be detected by clinico-pathological or pathological methods. Such effects may induce long lasting functional impairment of the respiratory system.

The basic mechanisms underlying morphological changes comprise cytotoxicity and induction of inflammation. Based on the quality and severity of morphological changes, the function of the respiratory system will be impaired, which may lead to the development of
consequential systemic effects, i.e. there might be consequences on distal organs by a
diminution of the oxygen supply. As the functional impairment is seldom evaluated by
experimental inhalation studies in animals, data on functional changes will mainly be
available from experience in humans.

Further see IR/CSA, Section R.7.2.

**Annex 1: 3.8.2.2.2. Criteria for narcotic effects**
The criteria for classifying substances as Category 3 for narcotic effects are:

(a) central nervous system depression including narcotic effects in humans such as drowsiness, narcosis, reduced alertness, loss of reflexes, lack of coordination, and vertigo are included. These effects can also be manifested as severe headache or nausea, and can lead to reduced judgment, dizziness, irritability, fatigue, impaired memory function, deficits in perception and coordination, reaction time, or sleepiness.

(b) narcotic effects observed in animal studies may include lethargy, lack of coordination, loss of righting reflex, and ataxia. If these effects are not transient in nature, then they shall be considered to support classification for Category 1 or 2 specific target organ toxicity single exposure.

**3.8.2.4 Evaluation of hazard information on STOT-SE for substances**

**3.8.2.4.1 Evaluation of human data**

**Annex I: 3.8.2.1.6.** In exceptional cases, based on expert judgement, it is appropriate to place certain substances with human evidence of target organ toxicity in Category 2:

(a) when the weight of human evidence is not sufficiently convincing to warrant Category 1 classification, and/or

(b) based on the nature and severity of effects.

Dose/concentration levels in humans shall not be considered in the classification and any available evidence from animal studies shall be consistent with the Category 2 classification. In other words, if there are also animal data available on the substance that warrant Category 1 classification, the substance shall be classified as Category 1.

**Annex 1: 3.8.2.1.7.2.** Evidence from human experience/incidents is usually restricted to reports of adverse health consequence, often with uncertainty about exposure conditions, and may not provide the scientific detail that can be obtained from well-conducted studies in experimental animals.

**Annex 1: 3.8.2.1.10.2.** When well-substantiated human data are available showing a specific target organ toxic effect that can be reliably attributed to single exposure to a substance, the substance shall normally be classified. Positive human data, regardless of probable dose, predominates over animal data. Thus, if a substance is unclassified because specific target organ toxicity observed was considered not relevant or significant to humans, if subsequent human incident data become available showing a specific target organ toxic effect, the substance shall be classified.
Human data are potentially very valuable for determining an appropriate classification as they provide direct evidence on the effects of a substance in humans. However, the evaluation of human data is often made difficult by various limitations frequently found with the types of studies and data highlighted in section 3.8.2.4.1 of this document. These include uncertainties relating to exposure assessment (i.e., unreliable information on the amount of a substance the subjects were exposed to or ingested) and confounding exposures to other substances. As a result it should be acknowledged that human data often do not provide sufficiently robust evidence on their own to support classification but may contribute to a weight of evidence assessment with other available information such as animal studies.

**Categories 1 and 2**

In general, where reliable and robust human data are available showing that the substance causes significant target organ toxicity these take precedence over other data, and directly support classification in Category 1. Available animal data may support this conclusion but do not detract from it (e.g. if the same effect is not observed in animals).

In exceptional cases, where target organ toxicity is observed in humans but the data reported are not sufficiently convincing to support Category 1 because of the lack of details in the observations or in the exposure conditions, and/or with regard to the nature and the severity of the effects observed, then classification in Category 2 could be justified (CLP Annex I, 3.8.2.1.6). In this case, any animal data must also be consistent with Category 2 and not support Category 1 (see below). In this case, if the animal data support Category 1, they will take precedence over the human data. This is because the reliability of the human data in this case is probably lower than the reliability of data from standard well conducted animal studies and should accordingly have less weight in the assessment.

When using human data, there is no consideration of the human dose/exposure level that caused those effects.

**Category 3**

*Respiratory Tract Irritation*

Human evidence for RTI often comes from occupational case reports where exposure is associated with signs of RTI. Such reports should be interpreted carefully using expert judgement to ensure that they provide reliable information. For instance, there should be a clear relationship between exposure and the development of signs of RTI, with RTI appearing relatively soon after the start of exposure. A solid substance which causes RTI due to physical/mechanical irritation when inhaled as a dust should not be classified. For more details on RTI, see R7a.7.2.1, and example n° 3 for sulfur dioxide.

*Narcotic Effects*

Narcotic effects may range from slight dizziness to deep unconsciousness and may be caused by several mechanisms:

- pharmaceutical drugs (designed effect; often receptor-mediated; effective dose usually low; patient under professional observation; limited importance for industrial chemicals and their safety assessment.)

- unspecific effects of many organic industrial chemicals on CNS-membranes at high dose levels (often solvent vapours, ≥ 6000 ppm in respired air volume). Such effects can be expected at high exposure levels due to otherwise low toxicity.

- organic chemicals with similarities to and interference with CNS-transmitters; often metabolic transformation necessary; certain solvents, e.g. butandiol, butyrolactone,
methoxyethanol; medium levels of effective dose. Children may be considerably more susceptible than adults.

– chemicals with high specific CNS toxicity; narcotic effects usually close to near-lethal doses (example: H₂S).

Narcotic effects are usually readily reversible on cessation of exposure with no permanent damage or changes.

Human evidence relating to narcosis should be evaluated carefully. Often the reporting of clinical signs is relatively subjective and reports of effects such as severe headache and dizziness should be interpreted carefully to judge if they provide robust evidence of narcosis. Where relevant human data do not mirror realistic exposure conditions, for instance in case reports from accidental over-exposure situations, supportive information may be needed to corroborate the observed effects. A single case report from accidental or deliberate exposure (i.e. abuse) is unlikely to provide sufficiently robust evidence to support classification without other evidence. For more details on evaluation of available human information see also section 3.1.2.3.1 and IR/CSA, section R.7.4 (especially R.7.4.4.2). Example n° 4 for toluene illustrates the procedure.

3.8.2.4.2 Evaluation of non human data

Annex 1: 3.8.2.1.5. The standard animal studies in rats or mice that provide information are acute toxicity studies which can include clinical observations and detailed macroscopic and microscopic examination to enable the toxic effects on target tissues/ organs to be identified. Results of acute toxicity studies conducted in other species may also provide relevant information.

Annex 1: 3.8.2.1.10.1. When a substance is characterised only by use of animal data (typical of new substances, but also true for many existing substances), the classification process includes reference to dose/concentration guidance values as one of the elements that contribute to the weight of evidence approach.

Annex 1: 3.8.2.1.10.3. A substance that has not been tested for specific target organ toxicity may, where appropriate, be classified on the basis of data from a validated structure activity relationship and expert judgement-based extrapolation from a structural analogue that has previously been classified together with substantial support from consideration of other important factors such as formation of common significant metabolites.

The type of evidence mentioned in CLP Annex I, sections 3.8.2.1.7 and 3.8.2.1.8 to support or not to support classification (e.g. clinical biochemistry, changes in organ weights with no evidence of organ dysfunction) is rarely obtained from animal tests designed to measure acute lethality/toxicity (see section 3.8.2.1.2).

Categories 1 and 2

Generic guidance on data evaluation is presented in IR/CSA, Section R.7.4 and R.7.4.4.2. All available animal data which are of acceptable quality should be used in a weight of evidence approach based on a comparison with the classification criteria described above. The assessment should be done for each route of exposure.

For each study the effects seen in each sex at or around the guidance values (GV) for Category 1 and Category 2 should be compared with the effects warranting classification in Category 1 and 2. In general findings in the most sensitive sex would be used to determine the classification. If the NOAEL from the study is above the GV, the results of that study do
not indicate classification for that category (situations 1 and 2 in Figure 1). If the NOAEL is below the GV then the effective dose (ED) level, the lowest dose inducing significant/severe target organ toxicity as defined in section 3.8.2.2.1 should be determined based on the criteria described above. If the ED is below the GV then this study indicates that classification is warranted (situations 2 and 4 in Figure 1).

In a case where the ED is above a GV but the NOAEL is below the GV (situations 3 and 5) then interpolation between the ED and the NOAEL is required to determine whether the effects expected at or below the GV would warrant classification.

**Figure 3.8.2.4.2** Comparison between the NOAEL and the ED versus the guidance values

<table>
<thead>
<tr>
<th>Situation 1</th>
<th>Situation 2</th>
<th>Situation 3</th>
<th>Situation 4</th>
<th>Situation 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>- NOAEL 1</td>
<td>- ED 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- ED 2</td>
<td>- NOAEL 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- NOAEL 2</td>
<td></td>
<td></td>
<td>- ED 5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- NOAEL 4</td>
<td>- NOAEL 5</td>
<td></td>
</tr>
<tr>
<td>NC</td>
<td>Category 2</td>
<td>Interpolation</td>
<td>Category 1</td>
<td>Interpolation</td>
</tr>
</tbody>
</table>

Where a number of studies are available these should be assessed using a weight of evidence approach to determine the most appropriate classification. Where the findings from individual studies would lead to a different classification then the studies should be assessed in terms of their quality, species and strain used, nature of the tested substance (including the impurity profile and physical form) etc to choose the most appropriate study to support classification.

In general, the study giving the most severe classification will be used unless there are good reasons that it is not the most appropriate. If the effects observed in animals are not considered relevant for humans then these should not be used to support classification. Similarly, if there is robust evidence that humans differ in sensitivity or susceptibility to the effect observed in the study then this should be taken into account, possibly leading to an increase or decrease in the classification assigned. The final classification based on non human data will be the most severe classification of the three exposure routes.

**Category 3**

There are no similar guidance values for category 3. Therefore, if the study shows clear evidence for narcotic effects or respiratory tract irritation at any dose level then this could support classification with category 3.
In evaluating inhalation studies a differentiation of respiratory tract effects and systemic effects should always be attempted. In addition, the region in the respiratory tract and the qualitative nature of observed effects is pivotal. Often, the lesions observed are representing stages of a reaction pattern leading to severe and irreversible functional and structural alterations. Therefore reversibility of effects is a significant discriminator. For further details see also section 3.8.2.3.

### 3.8.2.4.3 Evaluation of non-testing and *in vitro* data

Non-testing and *in vitro* data can contribute to the weight of evidence supporting a classification. As described in Annex XI of REACH approaches such as (Q)SAR, grouping and read-across can provide information on the hazardous properties of substances in place of testing and can be used for classification purposes. Also see R7.4.4.1.

### 3.8.2.4.4 Conversions

The guidance values are given in mg/kg bodyweight. Where the doses in a study are given in different units they will need to be converted as appropriate. For instance, the dosages in feeding and drinking water studies are often expressed in ppm, mg test substance/ kg (feed) or mg (test substance)/l (drinking water).

The conversion from mg/l to ppm assuming an ambient pressure of 1 at 101.3 kPa and 25°C is

\[ \text{ppm} = 0.0245 \times \frac{\text{mg}}{\text{l}} \times \frac{1}{\text{MW}} \]

### 3.8.2.4.5 Weight of evidence

**Annex 1: 3.8.2.1.6.** In exceptional cases, based on expert judgement, it is appropriate to place certain substances with human evidence of target organ toxicity in Category 2:

1) when the weight of evidence is not sufficiently convincing to warrant Category 1 classification, and/or

2) based on the nature and severity of effects.

Dose/concentration levels in humans shall not be considered in the classification and any available evidence from animal studies shall be consistent with the Category 2 classification. In other words, if there are also animal data available on the substance that warrant Category 1 classification, the substance shall be classified as Category 1.

The available information should be considered using expert judgement and a weight of evidence assessment, as described in CLP Annex I, 1.1.1 and Module 1.

Valid human data generally take precedence over animal and other non-test data. If there are human data indicating no classification but there are also non-human data indicating classification then the classification is based on the non-human data unless it is shown that the human data cover the exposure range of the non-human data or that the non-human data are not relevant for humans. If the human and non-human data both indicate no classification then classification is not required.

If there are no human data then the classification is based on the non-human data.

### 3.8.2.5 Decision on classification of substances
Decision on classification for STOT-SE is based on the results of weight of evidence approach described in section 2.3.

STOT-SE and acute toxicity are independent of each other and both may be assigned to a substance if the respective criteria are met. However, care should be taken not to assign each class for the same effect, in other words a double classification for the same effect has to be avoided. STOT-SE will be considered where there is clear evidence for a specific organ toxicity especially in absence of lethality, see examples no 1 and no 3 (methanol and tricresylphosphate).

If no classification has been warranted for acute toxicity despite significant toxic effect, the substance should be considered for classification as STOT-SE.

Normally, the assignment of STOT-SE Category 1 or 2 is independent to the assignment of Category 3. Therefore, a substance may be classified in both Category 1/2 and Category 3 if the respective criteria are met, for instance, in the case of a neurotoxic substance that also causes transient narcotic effects. If category 1/2 is assigned on the basis of effects in the respiratory tract then Category 3 should not be assigned as this would provide no additional information.

Classification as acutely toxic and/or corrosive is considered to cover and communicate the specific toxicological effect(s) adequately. An additional classification as specific target organ toxicant (single exposure, category 1 or 2) is not indicated if the severe toxicological effect is the consequence of the local (i.e. corrosive) mode of action.

It is a reasonable assumption that corrosive substances may also cause respiratory tract irritation when inhaled at exposure concentrations below those causing frank respiratory tract corrosion. If there is evidence from animal studies or from human experience to support this then Category 3 may be appropriate. In general, a classification for corrosivity is considered to implicitly cover the potential to cause RTI and so the additional Category 3 is considered to be superfluous, although it can be assigned at the discretion of the classifier. The Category 3 classification would occur only when more severe effects in the respiratory system are not observed.

Category 3 effects should be confined to changes, whether functional or morphological, occurring in the upper respiratory tract (nasal passages, pharynx and larynx). Localized irritation with associated adaptive responses (e.g., inflammation, epithelial metaplasia, goblet cell hyperplasia, proliferative effects) may occur and are consistent with Category 3 responses. Injury of the olfactory epithelium should be distinguished in terms of irritation-related (non-specific) and metabolic/ non-irritant (specific).

### 3.8.2.6 Setting of specific concentration limits for STOT-SE

Specific concentration limits (SCLs) for STOT-SE may be set by the supplier in some situations according to Article 10 of CLP. For STOT-SE, this may only be done for substances inducing STOT-SE Category 1 at a dose level or concentration clearly (more than one magnitude) below the guidance values according to Table 3.8.2, e.g. below 30 mg/kg bodyweight from the oral single exposure study. This will be mainly based on data in experimental animals but can also be based on human data if reliable exposure data are available. The SCL for classification of a mixture in Category 1 (SCL Cat. 1) based on substances classified in Category 1 can be determined using the following formula:

\[
SCL_{Cat.1} = \frac{ED}{GV1} \times 100\% \quad \text{Equation 3.8.2.6(a)}
\]
SCL Cat 1: 0.7 mg/kg bw/300 mg/kg bw x 100% = 0.22% --> 0.2%

In this formula the ED is the dose inducing significant specific target organ toxicity and GV1 is the guidance value for Category 1 according to Table 3.8.2 of Annex I. The resulting SCL is rounded down to the nearest preferred value (1, 2 or 5).

Though classification of a mixture in Category 1 is not triggered if a Category 1 constituent is present in lower concentrations than the established SCL, a classification in Category 2 should be considered.

The SCL for classification of a mixture in Category 2 (SCL Cat. 2) based on substances classified in Category 1 can be determined using the following formula:

\[ SCL_{Cat.2} = \frac{ED}{GV2} \times 100\% \]  

Equation 3.8.2.6(b)

SCL Cat 2: 0.7 mg/kg bw/2000 mg/kg bw x 100% = 0.035% --> 0.02% (rounded down)

In this formula the ED is the dose inducing specific target organ toxicity and GV2 is the upper guidance value for Category 2 according to Table 3.8.2 of Annex I. The resulting SCL is rounded down to the nearest preferred values (1, 2 or 5). However, if the calculated SCL Category 2 mixture is above 1%, which is the Generic Concentration Limit, then this should be corrected to 1%.

For example, a substance inducing specific target organ toxicity at 0.7 mg/kg bw/day in an acute oral study would require a SCL for Category 1 mixture of 0.2% and for Category 2 mixture of 0.02%.

It is not appropriate to determine SCLs for substances classified in Category 2 since ingredients with a higher potency (i.e., lower effect doses than the lower guidance values of Category 2) will be classified in Category 1; substances with higher effect doses than the upper guidance value of Category 2 will generally not be classified.

Classification in STOT-SE Category 3 for RTI and narcotic effects does not take into account potency and consequently does not have any guidance values. A pragmatic default GCL of 20% is suggested, although a lower or higher SCL may be used where it can be justified. Therefore, an SCL can be determined on a case-by-case basis for substances classified as STOT-SE Category 3 and expert judgement shall be exercised.

Specific concentration limits for each of the hazard classes skin and eye irritation, and STOT-SE Category 3 for respiratory tract irritation need to be addressed separately, while unjustified read-across between these hazard categories is discouraged.

For narcotic effects, the factors to be taken into consideration in order to set lower or higher SCLs are the effective dose/concentration, and for liquids in addition the volatility (saturated vapour concentration) of the substance.
3.8.2.7 Decision logic

The decision logic is provided as additional guidance. It is strongly recommended that the person responsible for classification study the criteria for classification before and during use of the decision logic.

This decision logic deviates slightly from the original UNGHS in separating the connection between category 2 and category 3, since, different from the procedure in other hazard classes, they have to be regarded as independent.

Classification in Category 1 and Category 2

Has the substance data and/or information to evaluate specific target organ toxicity following single exposure?

**YES**

Following single exposure,
(a) Can the substance produce significant toxicity in humans, or
(b) Can it be presumed to have the potential to produce significant toxicity in humans on the basis of evidence from studies in experimental animals?

See CLP Annex I, 3.7.3 for criteria and guidance values. Application of the criteria needs expert judgment in a weight of evidence approach.

**YES**

Category 1
Danger

**NO**

Not classified

**NO**

Has the substance been presumed to have the potential to be harmful to human health on the basis of evidence from studies in experimental animals?

See CLP Annex I, 3.7.3 for criteria and guidance values. Application of the criteria needs expert judgment in a weight of evidence approach.

**YES**

Category 2
Warning

**NO**

Classification not possible
1 Classification in Category 3

Does the substance have data and/or information to evaluate specific target organ toxicity following single exposure with relevance for RTI or narcotic effects?

YES

Following single exposure,
Can the substance produce respiratory tract irritation or narcotic effects?

YES

Warning

NO

Classification not possible

Not classified
3.8.3 Classification of mixtures for STOT-SE

3.8.3.1 Identification of hazard information

Where toxicological information is available on a mixture this should be used to derive the appropriate classification. Such information may be available from the mixture manufacturer. Where such information on the mixture itself is not available information on similar mixtures and/or the component substances in the mixture must be used, as described below.

3.8.3.2 Classification criteria for mixtures

Annex 1: 3.8.3.1. Mixtures are classified using the same criteria as for substances, or alternatively as described below.

3.8.3.2.1 When data are available for the complete mixture

Annex 1: 3.8.3.2.1. When reliable and good quality evidence from human experience or appropriate studies in experimental animals, as described in the criteria for substances, is available for the mixture, then the mixture shall be classified by weight of evidence evaluation of these data (see 1.1.1.3). Care shall be exercised in evaluating data on mixtures, that the dose, duration, observation or analysis, do not render the results inconclusive.

In cases where test data for mixtures are available, the classification process is exactly the same as for substances.

3.8.3.2.2 When data are not available for the complete mixture: bridging principles

Annex 1: 3.8.3.3.1. Where the mixture itself has not been tested to determine its specific target organ toxicity, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterise the hazards of the mixture, these data shall be used in accordance with the bridging principles set out in section 1.1.3.

When there are no test data on the mixture as a whole, so called “Bridging principles” may be applied where there are data available on similar tested mixtures and on the individual hazardous ingredient substances within the mixture that are sufficient to adequately assess the hazards of the mixture.

3.8.3.2.3 When data are available for all components or only for some components of the mixture

Annex 1: 3.8.3.4.1. Where there is no reliable evidence or test data for the specific mixture itself, and the bridging principles cannot be used to enable classification, then classification of the mixture is based on the classification of the ingredient substances. In this case, the mixture shall be classified as a specific target organ toxicant (specific organ specified), following single exposure, when at least one ingredient has been classified as a Category 1 or Category 2 specific target organ toxicant and is present at or above the appropriate generic concentration limit as mentioned in Table 3.8.3 below for Category 1 and 2 respectively.

A mixture not classified as corrosive but containing a corrosive ingredient should be considered for classification in category 3 RTI on a case-by-case basis following the...
approach explained above (see section 3.8.2.3). More information on classification of mixtures into category 3 is provided below (section 3.8.3.3).

### 3.8.3.2.4 Components of a mixture that should be taken into account for the purpose of classification

Components with a concentration equal to or greater than the generic concentration limits (1% for category 1 components and 10% for category 2, see Table 3.8.3) or with a Specific Concentration Limit (see section 3.8.2.6) will be taken into account for classification purposes. For Category 3, the GCL is 20%. Specific concentration limits have preference over the generic ones.

### 3.8.3.3 Generic concentration limits for substances triggering classification of mixtures for STOT-SE

The STOT-SE hazard class does not foresee summation of category 1 or 2 substances in the classification process of a mixture. Furthermore, as category 1 and 2 depict different hazards than category 3 the assessment must be done independently from each other.

#### Annex 1: Table 3.8.3

<table>
<thead>
<tr>
<th>Ingredient classified as:</th>
<th>Generic concentration limits triggering classification of the mixture as:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1</td>
<td>Category 1: Concentration ≥ 10%</td>
</tr>
<tr>
<td>Specific Target Organ Toxicant</td>
<td>Category 2: 1.0% ≤ concentration &lt; 10%</td>
</tr>
</tbody>
</table>

**Note 1:**

If a Category 2 specific target organ toxicant is present in the mixture as an ingredient at a concentration ≥ 1.0% a SDS shall be available for the mixture upon request.

#### 3.8.3.4.4 Care shall be exercised when toxicants affecting more than one organ system are combined that the potentiation or synergistic interactions are considered, because certain substances can cause target organ toxicity at < 1% concentration when other ingredients in the mixture are known to potentiate its toxic effect.

#### 3.8.3.4.5 Care shall be exercised when extrapolating toxicity of a mixture that contains Category 3 ingredient(s). A generic concentration limit of 20% is appropriate; however, it shall be recognised that this concentration limit may be higher or lower depending on the Category 3 ingredient(s) and that some effects such as respiratory tract irritation may not occur below a certain concentration while other effects such as narcotic effects may occur below this 20% value. Expert judgement shall be exercised.

**Categories 1 and 2**
Each single classified component in a concentration range given in Table 3.8.3 triggers the classification of the mixture, i.e. additivity of the concentrations of the components is not applicable.

Category 3

When a mixture contains a number of substances classified with Category 3 and present at a concentration below the GCL (i.e. 20%), an additive approach to determine the classification of the mixture as a whole may be appropriate. In the additive approach the concentrations of the individual substances with the same hazard (i.e. RTI or narcotic effects) are totalled separately. If each individual total is greater than the GCL then the mixture should be classified as Category 3 for that hazard. A mixture may be classified either as STOT SE 3 (RTI) or STOT SE 3 (narcotic effects) or both.

Example

The following example shows whether or not additivity should be considered for Specific Target Organ Toxicity – Single Exposure (STOT-SE) Category 3 transient effects.

### Ingredient information:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Wt%</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingredient 1</td>
<td>0.5</td>
<td>-</td>
</tr>
<tr>
<td>Ingredient 2</td>
<td>3.5</td>
<td>Category 3 – Respiratory Tract Irritation</td>
</tr>
<tr>
<td>Ingredient 3</td>
<td>15</td>
<td>Category 3 - Narcotic effects</td>
</tr>
<tr>
<td>Ingredient 4</td>
<td>15</td>
<td>Category 3 - Narcotic effects</td>
</tr>
<tr>
<td>Ingredient 5</td>
<td>66</td>
<td>-</td>
</tr>
</tbody>
</table>

**Answer:**

Mixture is Category 3 – Narcotic effects

\[ \sum \% \text{Category 3 – Narcotic effects} = 15\% + 15\% = 30\% \text{ which is } > 20\% , \text{ therefore classify as Category 3 – Narcotic Effects} \]

\[ \sum \% \text{Category 3 – Respiratory Irritation} = 3.5\%, \text{ which is } < 20\%, \text{ not classified for Respiratory Irritation} \]

**Rationale:**

(a) Classification via application of substance criteria is not possible since test data was not provided for the mixture (paragraph 3.8.3.2);

(b) Classification via the application of bridging principles is not possible since data on a similar mixture was not provided (paragraph 3.8.3.3.1);

(c) Application of paragraph 3.8.3.4.5 is used for classification. Expert judgement is necessary when applying this paragraph. Paragraph 3.8.3.4.5 notes that a cut-off value/concentration limit of 20% has been suggested, but that the cut-off value/concentration limit at which effects occur may be higher or less depending on the Category 3 ingredient(s). In this case, the classifiers judged that 30% is sufficient to classify.
In the case where a specific concentration limit has been established for one or more ingredients these SCLs have precedence over the generic concentration limit.

3.8.3.4  Decision logic for mixtures

A mixture should be classified either in category 1 or in category 2, according to the criteria described above. The corresponding hazard statement (H370 for category 1 or H371 for category 2) should be used without specifying the target organs, except if the classification of the mixture is based on data available for the complete mixture, in which case the target organs may be given. In the same way, the route of exposure should not be specified, except if data are available for the complete mixture and it is conclusively demonstrated that no other routes of exposure cause the hazard. If the criteria are fulfilled to classify also the mixture in category 3 for respiratory irritation or narcotic effects, only the corresponding hazard statement (H335 and/or H336) will be added in hazard communication.

The decision logic is provided as additional guidance. It is strongly recommended that the person responsible for classification study the criteria for classification before and during use of the decision logic. This decision logic deviates slightly from the original UNGHS in separating the connection between category 2 and category 3, since different from the procedure in other hazard classes they have to be regarded as independent.
Classification in Category 1 or 2

Does the mixture as a whole have data/information to evaluate specific target organ toxicity following single exposure?

YES → See decision logics for substances

NO → Can bridging principles be applied?

YES → Classify in appropriate category

NO → Does the mixture contain one or more ingredients classified as a Category 1 specific target organ toxicant at a concentration of \( \geq 10\% \)?

YES → Category 1

NO → Does the mixture contain one or more ingredients classified as a Category 1 specific target organ toxicant at a concentration of \( \geq 1.0 \) and \( < 10\% \)? Or one or more ingredients classified as a Category 2 specific target organ toxicant at a concentration of \( \geq 10\% \)?

YES → Category 2

NO → Not classified
Classification in Category 3

Does the mixture as a whole have data and/or information to evaluate specific target organ toxicity following single exposure with relevance for RTI or narcotic effects?

YES → See decision logics for substances

NO → Can bridging principles be applied?

YES → Classify in appropriate category

NO → Does the mixture contain one or more ingredients classified as a Category 3 specific target organ toxicant at a concentration ≥ 20%?

YES → Category 3 Warning

NO → Not classified
3.8.4 Hazard communication in form of labelling for STOT-SE

3.8.4.1 Pictograms, signal words, hazard statements and precautionary statements

Annex I: 3.8.4.1. Label elements shall be used in accordance with Table 3.8.4., for substances or mixtures meeting the criteria for classification in this hazard class.

Table 3.8.4
Label elements for specific target organ toxicity after single exposure

<table>
<thead>
<tr>
<th>Classification</th>
<th>Category 1</th>
<th>Category 2</th>
<th>Category 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>GHS Pictograms</td>
<td>![Image]</td>
<td>![Image]</td>
<td>![Image]</td>
</tr>
<tr>
<td>Signal word</td>
<td>Danger</td>
<td>Warning</td>
<td>Warning</td>
</tr>
<tr>
<td>Hazard statement</td>
<td>H370: Causes damage to organs (or state all organs affected, if known) (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)</td>
<td>H371: May cause damage to organs (or state all organs affected, if known) (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)</td>
<td>H335: May cause respiratory irritation; or H336: May cause drowsiness and dizziness</td>
</tr>
<tr>
<td>Precautionary statement Prevention</td>
<td>P260 P264 P270</td>
<td>P260 P264 P270</td>
<td>P261 P271</td>
</tr>
<tr>
<td>Precautionary Statement Response</td>
<td>P307 + P311 P321</td>
<td>P309 + P311</td>
<td>P304 + P340 P312</td>
</tr>
<tr>
<td>Precautionary Statement Storage</td>
<td>P405</td>
<td>P405</td>
<td>P403 + P233 P405</td>
</tr>
<tr>
<td>Precautionary Statement Disposal</td>
<td>P501</td>
<td>P501</td>
<td>P501</td>
</tr>
</tbody>
</table>

The hazard statement should include the primary target organ(s) of toxicity. Organs in which secondary effects were observed should not be included. The route of exposure should not be specified, except if it is conclusively demonstrated that no other routes of exposure cause the hazard. When a mixture is classified for STOT-SE on basis of test data, the hazard statement will specify the target organs, in the same way as for a substance. If a mixture is classified on basis of the ingredients, the hazard statement (H370 for category 1 or H371 for category 2) may be used without specifying the target organs, as appropriate.

In the same way, the route of exposure should not be specified, except if data are available for the complete mixture and if it is conclusively demonstrated that no other routes of exposure cause the hazard. It is recommended to include no more than three primary target

Deleted: C
Deleted: C
organs for practical reasons and because the classification is for specific target organ toxicity. If more target organs are effected it is recommended that the overall systemic damage should be reflected by using the phrase “damage to organs”.

3.8.4.2 Additional labelling provisions

Annex I: 3.8.2.1.10.4
Saturated vapour concentration shall be considered, where appropriate, as an additional element to provide for specific health and safety protection.

According to CLP Annex I, section 3.8.2.1.10.4 the saturated vapour concentration shall be considered as an additional element for providing specific health and safety protection. Thus if a classified substance is highly volatile a supplementary precautionary advice (e.g., “Special/additional care should be taken due to the high saturated vapour pressure”) might be given in order to emphasize the hazard in case it is not already covered by the general precautionary statements. (As a rule substances for which the ratio of the effect concentration at <= 4h to the SVC at 20° C is <= 1/10).

Diluted corrosive substances (may) exhibit an irritation potential with respect to the respiratory tract if they have a sufficient saturated vapour concentration. Expert judgement is needed for a decision with respect to a classification in STOT-SE Category 3. In these cases a switch from one hazard class (skin corrosion/irritation) to another (STOT-SE) would be justified.

3.8.5 Re-classification of substances and mixtures classified for STOT-SE according to DSD and DPD

Classification with STOT–SE 1 and 2 according to CLP is comparable to the classification with R39/X and R68/X according to DSD. Classification with R39 – 41 has been used occasionally for substances inducing mortality in eye irritation studies. This classification should not be translated to STOT SE but will result in additional labelling with EUH070. Classification with STOT–SE 3 according to CLP is comparable to the classification with R37 and R67 according to DSD.

3.8.5.1 Is direct “translation” of Classification and Labelling possible for STOT-SE substances?

Direct translation of substances or mixtures classified with R39/X is possible but the category may change. All substances or mixtures classified with R39/24, R39/25, R39/27, R38/28 and/or vapours and dusts/mists/fumes classified with R39/26 or R39/23 shall be classified as STOT SE 1 because less adverse effects and higher guidance values are required for classification according to CLP compared to DSD. Setting of SCLs may be considered for substances showing STOT SE at levels clearly below the guidance values (see section 3.8.2.6).

All substances or mixtures classified with R68/22, R68/21 and/or R68/20 (for vapours) shall be classified at least as STOT SE 2. However, due to the higher guidance values, the requirement for less severe effects, and because STOT SE in humans always leads to classification in category 1, this is a minimal classification and may not adequately convey the seriousness of the toxicity. Therefore, classification in category 1 should be considered. Dusts/mists/fumes classified with R68/20 can be directly translated into STOT SE 2 because the guidance values are the same. Gasses classified with R68/20 should be re-evaluated because of the change from guidance values in mg/L into ppm.
If translation results in a classification in STOT SE 1 for one route and in STOT SE 2 for another route only classification in Category 1 is required (for both routes).

Classification as STOT SE is not route specific as it was for classification with R39/X and R68/X. The route specificity of STOT SE is included in the hazard statement and includes route-to-route extrapolation by default unless conclusively shown otherwise. Therefore, the route specific data on STOT SE should be re-evaluated. A re-evaluation is also necessary because the primary target organs for STOT SE should be stated in the hazard statement.

All substances or mixtures classified with R67 shall be classified as STOT SE Category 3 H336.

All substances or mixtures classified with R37 shall be classified as STOT SE Category 3 H335. Also additional labelling with EUH071 (Corrosive to the respiratory tract) shall be considered.

3.8.5.2 Re-evaluation of the STOT-SE data

Gasses classified with R39/23 or R39/26 should be re-evaluated because of the change from guidance values in mg/L into ppm.

Substances or mixtures not classified for STOT-SE, should be considered for re-evaluation because less adverse effects and higher guidance values are required for classification according to CLP compared to DSD. Also, effects in humans are now considered for classification without restrictions to the exposure level.

3.8.6 Examples of classification for STOT-SE

3.8.6.1 Examples of substances fulfilling the criteria for classification

3.8.6.1.1 Example 1: Methanol
### Application

Use of adequate and reliable human data, where animal data are not appropriate. Independent classification for STOT-SE and Acute toxicity due to different effects.

<table>
<thead>
<tr>
<th>Available information</th>
<th>Test Data</th>
<th>Classification</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Animal data:</strong></td>
<td>LD₅₀ rat &gt; 5,000 (mg/kg)</td>
<td>Classification not possible</td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td>No specific target organ toxicity (impairment of seeing ability) observed in rats, even in high doses.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Human experience:</strong></td>
<td></td>
<td>STOT-SE Category 1</td>
<td>The classification criteria for Category 1 are fulfilled: clear human evidence of a specific target organ toxicity effect which is not covered by Acute toxicity.</td>
</tr>
<tr>
<td></td>
<td>Broad human experience from many case reports about blindness following oral intake. Methanol is known to cause lethal intoxications in humans (mostly via ingestion) in relatively low doses: “…minimal lethal dose in the absence of medical treatment is between 300 and 1000 mg/kg” (IPCS)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Remarks

The standard animal species for single exposure (acute) tests, the rat, is not sensitive, i.e. no appropriate species for this specific target organ effect. Methanol is classified independently for acute toxicity, since the impairment of vision is not causal for the lethality, i.e. there are different effects.

Labelling:

- Pictogram GHS 08; Signal word: Danger; Hazard statement: H370 Causes damage to the eye.
### 3.8.6.1.2 Example 2: Tricresyl phosphate

<table>
<thead>
<tr>
<th>Application</th>
<th>Use of valid human evidence supported by animal data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test Data</strong></td>
<td><strong>Classification</strong></td>
</tr>
<tr>
<td>Available information</td>
<td>Human experience: There are well documented case reports about severe neurotoxic effects</td>
</tr>
</tbody>
</table>

**Animal experiments:**
Severe neurotoxic effects (Paralysis) were observed after single exposure of doses < 200 mg/kg

LD$_{50}$ rat oral: 3000 - 3900 mg/kg

**Remarks Labelling:**
Pictogram GHS 08; Signal word: Danger; Hazard Statement: H370 Causes damage to the central nervous system.

### 3.8.6.1.3 Example 3: Sulfur dioxide

<table>
<thead>
<tr>
<th>Application</th>
<th>Use of valid human evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test Data</strong></td>
<td><strong>Classification</strong></td>
</tr>
<tr>
<td>Available information</td>
<td>Human experience: Broad, well documented human experience on irritating effect to respiratory system.</td>
</tr>
</tbody>
</table>

**Remarks Labelling:**
Pictogram GHS 07; Signal word: Warning; Hazard statement: H335 May cause respiratory irritation

### 3.8.6.1.4 Example 4: Toluene

<table>
<thead>
<tr>
<th>Application</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test Data</strong></td>
<td><strong>Classification</strong></td>
</tr>
<tr>
<td>Available information</td>
<td>Animal data: In valid animal experiments narcotic effects (transient effect on nervous system) at $\geq$ 8 mg/l were observed.</td>
</tr>
</tbody>
</table>

**Remarks Labelling:**
Pictogram GHS 07; Signal word: Warning; Hazard statement: H336 May cause drowsiness and dizziness
### 3.8.6.2 Examples of substances not fulfilling the criteria for classification

#### 3.8.6.2.1 Example 5: ABC

<table>
<thead>
<tr>
<th>Application</th>
<th>Test Data</th>
<th>Classification</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Available information</td>
<td>Animal data: In a study in rats after single exposure at 2,000mg/kg severe damage in liver (macroscopic examination) and mortality in 6/10 animals were observed</td>
<td>No classification in STOT-SE</td>
<td>Though a specific organ is damaged, the substance will be classified in Acute Toxicity (Category 4), since lethality was observed which was due to the liver impairment. It is assumed that the LD$_{50}$=ATE is $\leq$ 2,000 mg/kg. There should be no double classification for the same effect/mechanism causing lethality by impairment of a specific organ, thus no classification for STOT-SE</td>
</tr>
</tbody>
</table>

#### 3.8.6.2.2 Example 6: N,N-Dimethylaniline
**Application**

No classification for STOT-SE in case same effect leading to Acute toxicity classification

<table>
<thead>
<tr>
<th>Test Data</th>
<th>Classification</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Available information</strong></td>
<td><strong>No classification in STOT-SE</strong></td>
<td>The criteria for STOT-SE classification are not fulfilled despite a clear specific target organ effect in humans and in a relevant animal species. The substance is classified in Category 3 Acute Toxicity since the Met HB formation is causative for the lethality in humans and in animals (cats) in low doses.</td>
</tr>
</tbody>
</table>

**Human experience:**

Broad human experience from many case reports about lethal intoxications caused by methemoglobinemia following oral/dermal/inhalation exposure to aromatic amines

| Remarks | The standard animal species for single exposure (acute) tests, the rat, is not sensitive, i.e. no appropriate species for this specific effect. |

### 3.9 SPECIFIC TARGET ORGAN TOXICITY – REPEATED EXPOSURE (STOT-RE)

#### 3.9.1 Definitions and general considerations for STOT-RE

Annex I: 3.9.1.1. Specific target organ toxicity (repeated exposure) means specific, target organ toxicity arising from a repeated exposure to a substance or mixture. All significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed are included. However, other specific toxic effects that are specifically addressed in Chapters 3.1 to 3.8 and Chapter 3.10 are not included here.

According to CLP Annex I, section 3.9.1.1, specific toxic effects covered by other hazard classes are not included in STOT-RE. STOT-RE should only be assigned where the observed toxicity is not covered more appropriately by another hazard class. For example specific effects like tumours or effects on the reproductive organs should be used for classification for carcinogenicity or reproductive toxicity, respectively, but not for STOT-RE.
Annex I: 3.9.1.3. These adverse health effects include consistent and identifiable toxic effects in humans, or, in experimental animals, toxicologically significant changes which have affected the function or morphology of a tissue/organ, or have produced serious changes to the biochemistry or haematology of the organism and these changes are relevant for human health.

3.9.1.4. Assessment shall take into consideration not only significant changes in a single organ or biological system but also generalised changes of a less severe nature involving several organs.

3.9.1.5. Specific target organ toxicity can occur by any route that is relevant for humans, i.e. principally oral, dermal or inhalation.

Annex I: 3.9.2.2. The relevant route or routes of exposure by which the classified substance produces damage shall be identified.

The purpose of STOT-RE is to identify the primary target organ(s) of toxicity (CLP Annex I, section 3.9.1.4) for inclusion in the hazard statement. Where possible secondary effects are observed in other organs, they should be carefully considered for the classification. The STOT-RE classification should identify those routes by which the substance causes the target organ toxicity (CLP Annex I, sections 3.9.1.5 and 3.9.2.2). This is usually based on the available evidence for each route. There are no compelling reasons to do routine to route extrapolation to attempt to assess the toxicity by other routes of exposure for which there are no data.

Annex I: 3.9.1.6. Non-lethal toxic effects observed after a single-event exposure are classified as described in Specific target organ toxicity — Single exposure (section 3.8) and are therefore excluded from section 3.9.

Where the same target organ toxicity of similar severity is observed after single and repeated exposure to a similar dose, it may be concluded that the toxicity is essentially an acute (i.e. single exposure) effect with no accumulation or exacerbation of the toxicity with repeated exposure. In such a case classification with STOT-SE only would be appropriate.

3.9.2 Classification of substances for STOT-RE

3.9.2.1 Identification of hazard information

Annex I: 3.9.2.5. The information required to evaluate specific target organ toxicity comes either from repeated exposure in humans, such as exposure at home, in the workplace or environmentally, or from studies conducted in experimental animals.

CLP does not require testing of substances and mixtures for classification purposes. The assessment is based on the respective criteria and consideration of all available adequate and reliable information, primarily such relating to repeated-dose exposures but also taking into account the general physico-chemical nature of the substance. The most useful information is generally from human epidemiology, case studies and animal studies, but information obtained using read-across from similar substances and from appropriate in vitro models can also be used, where appropriate.

3.9.2.1.1 Identification of human data

Relevant information with respect to repeated dose toxicity may be available from case reports, epidemiological studies, medical surveillance and reporting schemes, and national poison centres.
Details are given in IR/CSA, Section 7.5.3.2.

### 3.9.2.1.2 Identification of non human data

**Annex 1: 3.9.2.5.** … The standard animal studies in rats or mice that provide this information are 28 day, 90 day or lifetime studies (up to 2 years) that include haematological, clinicochemical and detailed macroscopic and microscopic examination to enable the toxic effects on target tissues/organisms to be identified. Data from repeat dose studies performed in other species shall also be used, if available. Other long-term exposure studies, such as on carcinogenicity, neurotoxicity or reproductive toxicity, may also provide evidence of specific target organ toxicity that could be used in the assessment of classification.

#### Non-testing data

**Physico-chemical data**

Physicochemical properties, such as pH, physical form, solubility, vapour pressure, and particle size, can be important parameters in evaluating toxicity studies and in determining the most appropriate classification especially with respect to inhalation where physical form and particle size can have a significant impact on toxicity.

**(Q)SAR models**

Structurally or mechanistically related substance(s), read-across/grouping/chemical category and metabolic pathway approach: A (Q)SAR analysis for a substance may give indications for a specific mechanism of action and identify possible organ or systemic toxicity upon repeated exposure. Overall, (Q)SAR approaches are currently not well validated for repeated dose toxicity. (IR/CSA, section R7.5.4.1). Data on structurally analogous substances may be available and add to the toxicity profile of the substance under investigation. The concept of grouping, including both read-across and the related chemical category concept have been developed under the OECD HPV program. For certain substances without test data the formation of common significant metabolites or information with those of tested substances or information from precursors may be valuable information. (For more details see IR/CSA, sections R.6.1 and R.6.2.5.2 and OECD (2004)). OECD Principles for the Validation, for Regulatory Purposes, of (Quantitative) Structure-Activity Relationship Models

#### Testing data

**Animal data**

"The most appropriate data on repeated dose toxicity for use in hazard characterisation and risk assessment are primarily obtained from studies in experimental animals conforming to internationally agreed test guidelines. In some circumstances repeated dose toxicity studies not conforming to conventional test guidelines may also provide relevant information for this endpoint” (IR/CSA, section R.7.5.3.1). Studies not performed according to Standard Test Guidelines and/or GLP have to be evaluated on case by case basis by expert judgement and in the context of a total weight of evidence assessment if there are more data (for more information see section 3.9.2.3.4 of this document and IR/CSA, section R.7.5.4.1.

The standard test guidelines are described in IR/CSA, section R.7.5.4.1. There may also be studies employing different species and routes of exposure. In addition, special toxicity studies investigating further the nature, mechanism and/or dose relationship of a critical effect in a target organ or tissue may also have been performed for some substances. Other studies providing information on repeated dose toxicity: although not aiming at investigating repeated dose toxicity per se and other available EU/OECD test guideline studies involving repeated exposure of experimental animals may provide useful information on repeated dose...
toxicity, e.g. reproduction toxicity or carcinogenicity studies. For more details see IR/CSA, section R.7.5.4.1 (ECHA, 2008).

**In vitro data**

At present available *in vitro* data is not useful on its own for regulatory decisions such as classification and labelling. However, such data may be helpful in the assessment of repeated dose toxicity, for instance to detect local target organ effects and/or to clarify the mechanisms of action. Since, at present, there are no validated and regulatory accepted *in vitro* methods, the quality of each of these studies and the adequacy of the data provided should be carefully evaluated” (IR/CSA, section R.7.5.4.1).

### 3.9.2.2 Classification criteria for substances

**Annex 1: 3.9.2.1.** Substances are classified as specific target organ toxicants following repeated exposure by the use of expert judgement (see 1.1.1), on the basis of the weight of all evidence available, including the use of recommended guidance values which take into account the duration of exposure and the dose/concentration which produced the effect(s), (see 3.9.2.9), and are placed in one of two categories, depending upon the nature and severity of the effect(s) observed (Table 3.9.1).

**Table 3.9.1**

<table>
<thead>
<tr>
<th>Categories for specific target organ toxicity-repeated exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Categories</td>
</tr>
</tbody>
</table>

Deleted: S
Category 1: Substances that have produced significant toxicity in humans or that, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to produce significant toxicity in humans following repeated exposure. Substances are classified in Category 1 for target organ toxicity (repeat exposure) on the basis of:

- reliable and good quality evidence from human cases or epidemiological studies; or
- observations from appropriate studies in experimental animals in which significant and/or severe toxic effects, of relevance to human health, were produced at generally low exposure concentrations. Guidance dose/concentration values are provided below (see 3.9.2.9), to be used as part of a weight-of-evidence evaluation.

Category 2: Substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following repeated exposure. Substances are classified in Category 2 for target organ toxicity (repeat exposure) on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations. Guidance dose/concentration values are provided below (see 3.9.2.9) in order to help in classification.

In exceptional cases human evidence can also be used to place a substance in Category 2 (see 3.9.2.6).

Note

Attempts shall be made to determine the primary target organ of toxicity and classify for that purpose, such as hepatotoxicants, neurotoxicants. One shall carefully evaluate the data and, where possible, not include secondary effects (a hepatotoxicant can produce secondary effects in the nervous or gastro-intestinal systems).

In the Note above "classify" would mean to identify the primary target organ.

STOT-RE is assigned on the basis of findings of “significant” or “severe” toxicity. In this context “significant” means changes which clearly indicate functional disturbance or morphological changes which are toxicologically relevant. “Severe” effects are generally more profound or serious than “significant” effects and are of a considerably adverse nature which significantly impact on health. Both factors have to be evaluated by weight of evidence and expert judgement.

Annex 1: 3.9.2.9.4. The decision to classify at all can be influenced by reference to the dose/concentration guidance values at or below which a significant toxic effect has been observed.

Annex 1: 3.9.2.9.6. Thus classification in Category 1 is applicable, when significant toxic effects observed in a 90-day repeated-dose study conducted in experimental animals are seen to occur at or below the guidance values (C) as indicated in Table 3.9.2 below:

<table>
<thead>
<tr>
<th>Route of exposure</th>
<th>Units</th>
<th>Guidance values (dose/concentration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral (rat)</td>
<td>mg/kg body weight/day</td>
<td>C ≤ 10</td>
</tr>
</tbody>
</table>
Annex 3.9.2.9.7. Classification in Category 2 is applicable, when significant toxic effects observed in a 90-day repeated-dose study conducted in experimental animals are seen to occur within the guidance value ranges as indicated in Table 3.9.3 below:

<table>
<thead>
<tr>
<th>Route of Exposure</th>
<th>Units</th>
<th>Guidance</th>
<th>Value Ranges: (dose/concentration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral (rat)</td>
<td>mg/kg body weight/day</td>
<td></td>
<td>10 &lt; C ≤ 100</td>
</tr>
<tr>
<td>Dermal (rat or rabbit)</td>
<td>mg/kg body weight/day</td>
<td></td>
<td>20 &lt; C ≤ 200</td>
</tr>
<tr>
<td>Inhalation (rat) gas</td>
<td>ppmV/6h/day</td>
<td></td>
<td>50 &lt; C ≤ 250</td>
</tr>
<tr>
<td>Inhalation (rat) vapour</td>
<td>mg/litre/6h/day</td>
<td></td>
<td>0.2 &lt; C ≤ 1.0</td>
</tr>
<tr>
<td>Inhalation (rat) dust/mist/fume</td>
<td>mg/litre/6h/day</td>
<td></td>
<td>0.02 &lt; C ≤ 0.2</td>
</tr>
</tbody>
</table>

Annex 1 3.9.2.9.8. The guidance values and ranges mentioned in paragraphs 3.9.2.9.6 and 3.9.2.9.7 are intended only for guidance purposes, i.e., to be used as part of the weight of evidence approach, and to assist with decisions about classification. They are not intended as strict demarcation values.

Annex 1 3.9.2.9.5. The guidance values refer to effects seen in a standard 90-day toxicity study conducted in rats. They can be used as a basis to extrapolate equivalent guidance values for toxicity studies of greater or lesser duration, using dose/exposure time extrapolation similar to Haber’s rule for inhalation, which states essentially that the effective dose is directly proportional to the exposure concentration and the duration of exposure. The assessment shall be done on a case-by-case basis; for a 28-day study the guidance values below is increased by a factor of three.

Haber’s rule is used to adjust the standard guidance values, which are for studies of 90-day duration, for studies of longer or shorter durations. It should be used cautiously with due consideration of the nature of the substance in question and the resulting value produced.

In particular, care should be taken when using Haber’s rule to assess inhalation data on substances which are corrosive or local active or have the potential to accumulate with repeated exposure.

One particular problem to note is that when adjusting the guidance value for very short study durations this can lead to very high guidance values which are not appropriate. For instance, for a 4 day exposure a guidance value of 2250 mg/kg bw/day for classification as STOT RE category 2 could potentially be produced. This is above the limit for acute toxicity of 2000 mg/kg bw and it does not make sense to have a guidance value for repeated dose toxicity that is above the guidance value for mortality after acute exposure. To address this problem a
A pragmatic approach is proposed. For studies with exposure durations shorter than 9 days (i.e. 10% of the 90 days to which the default general guidance value applies) the guidance value used should be no greater than 10 times the default guidance value. For example, the effects in an oral range-finding study of 9 days or less should be compared with a guidance value of 1000 mg/kg bw/day for STOT-RE Category 2.

Expert judgement is needed for the establishment of equivalent guidance values because one needs to know about the limitations of the applicability of the proportionality. In the following table the equivalents for 28-day and 90-day studies according to Haber's rule are given:

**Table 3.9.2.2 Equivalent guidance values for 28-day and 90-day studies**

<table>
<thead>
<tr>
<th>Study type</th>
<th>Species</th>
<th>Unit</th>
<th>Category 1 90-day</th>
<th>Category 1 28-day</th>
<th>Category 2 90-day</th>
<th>Category 2 28-day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Rat</td>
<td>mg/kg bw/d</td>
<td>≤ 10</td>
<td>≤ 30</td>
<td>≤ 100</td>
<td>≤ 300</td>
</tr>
<tr>
<td>Dermal</td>
<td>Rat</td>
<td>mg/kg bw/d</td>
<td>≤ 20</td>
<td>≤ 60</td>
<td>≤ 200</td>
<td>≤ 600</td>
</tr>
<tr>
<td>Inhalation, gas</td>
<td>Rat</td>
<td>ppmV/6 h/d</td>
<td>≤ 50</td>
<td>≤ 150</td>
<td>≤ 250</td>
<td>≤ 750</td>
</tr>
<tr>
<td>Inhalation, vapor</td>
<td>Rat</td>
<td>mg/l/6 h/d</td>
<td>≤ 0.2</td>
<td>≤ 0.6</td>
<td>≤ 1</td>
<td>≤ 3</td>
</tr>
<tr>
<td>Inhalation, dust/mist/fume</td>
<td>Rat</td>
<td>mg/l/6 h/d</td>
<td>≤ 0.02</td>
<td>≤ 0.06</td>
<td>≤ 0.2</td>
<td>≤ 0.6</td>
</tr>
</tbody>
</table>

Annex 1: 3.9.2.9.9. Thus it is feasible that a specific profile of toxicity occurs in repeat-dose animal studies at a dose/concentration below the guidance value, such as < 100 mg/kg bw/day by the oral route, however the nature of the effect, such as nephrotoxicity seen only in male rats of a particular strain known to be susceptible to this effect may result in the decision not to classify. Conversely, a specific profile of toxicity may be seen in animal studies occurring at above a guidance value, such as ≥ 100 mg/kg bw/day by the oral route, and in addition there is supplementary information from other sources, such as other long-term administration studies, or human case experience, which supports a conclusion that, in view of the weight of evidence, classification is the prudent action to take.

3.9.2.3 Evaluation of hazard information

Annex 1: 3.9.2.4. Evaluation shall be based on all existing data, including peer-reviewed published studies and additional acceptable data.

3.9.2.3.1 Evaluation of human data
Annex 1: 1.1.1.4. For the purpose of classification for health hazards (Part 3) established hazardous effects seen in appropriate animal studies or from human experience that are consistent with the criteria for classification shall normally justify classification. Where evidence is available from both humans and animals and there is a conflict between the findings, the quality and reliability of the evidence from both sources shall be evaluated in order to resolve the question of classification. Generally, adequate, reliable and representative data on humans (including epidemiological studies, scientifically valid case studies as specified in this Annex or statistically backed experience) shall have precedence over other data. However, even well-designed and conducted epidemiological studies may lack a sufficient number of subjects to detect relatively rare but still significant effects, to assess potentially confounding factors. Therefore, positive results from well-conducted animal studies are not necessarily negated by the lack of positive human experience but require an assessment of the robustness, quality and statistical power of both the human and animal data.

1

Annex 1 3.9.2.7.2. Evidence from human experience/incidents is usually restricted to reports of adverse health consequence, often with uncertainty about exposure conditions, and may not provide the scientific detail that can be obtained from well-conducted studies in experimental animals.

Where relevant human data do not mirror realistic exposure conditions, supportive information may be needed to corroborate the observed effects. A single case report from deliberate exposure (i.e. abuse) is unlikely to provide sufficiently robust evidence to support classification without other evidence.

IR/CSA, Section R.7.5.4.2 gives a detailed description on the use of human hazard information

3.9.2.3.2 Evaluation of non human data

Annex 1 3.9.2.7.3. Evidence from appropriate studies in experimental animals can furnish much more detail, in the form of clinical observations, haematology, clinical chemistry, and macroscopic and microscopic pathological examination, and this can often reveal hazards that may not be life-threatening but could indicate functional impairment.

All available animal data which are of acceptable quality should be used in a weight of evidence approach based on a comparison with the classification criteria described above. This should be done separately for each route for which data are available.

For each study the effects seen in each sex at or around the guidance values for Category 1 and Category 2 should be compared with the effects warranting classification in Category 1 and 2. In general findings in the most sensitive sex would be used to determine the classification. If the NOAEL from the study is above the guidance value (GV), the results of that study do not indicate classification for that category (situations 1 and 2 in Figure 3.9.2.3.2). If the NOAEL is below the GV then the effective dose level (ED), i.e. the lowest dose inducing significant/severe target organ toxicity as defined in Section 3.9.2.2, should be determined based on the criteria described above. If the ED is below the GV then this study indicates that classification is warranted (situations 2 and 4 in Figure 1).

In a case where the ED is above a GV but the NOAEL is below the GV (situations 3 and 5) then interpolation between the ED and the NOAEL is required to determine whether the effects expected at or below the GV would warrant classification.

Figure 3.9.2.3.2 Comparison between the NOAEL and the ED versus the guidance values
Where a number of studies are available these should be assessed using a weight of evidence approach to determine the most appropriate classification. Where the findings from individual studies would lead to a different classification then the studies should be assessed in terms of their quality, species and strain used, nature of the tested substance (including the impurity profile and physical form) etc to choose the most appropriate study to support classification. In general, the study giving the most severe classification will be used unless there are good reasons that it is not the most appropriate. If the effects observed in animals are not considered relevant for humans then these should not be used to support classification. Similarly, if there is robust evidence that humans differ in sensitivity or susceptibility to the effect observed in the study then this should be taken into account, possibly leading to an increase or decrease in the classification assigned.

If there are differences in effects at the GV between studies with different duration then more weight is usually given to studies of a longer duration (28 days or more). This is because animals may not have fully adapted to the exposure in studies of shorter durations and also because longer duration studies tend to include more thorough and extensive investigations (e.g. in terms of detailed pathology and haematological effects etc) which can generally give more substantial information compared to shorter duration studies. If a 90-day as well as a 28-day study are available expert judgement has to be used and not just Haber's rule.

If there are differences in effects between good quality data in the same sex, species and strain then other variables such as particle size, vehicle, substance purity and impurities and concentration should be considered. If the results are considered to be depending on a specific impurity then different classifications depending on the concentration of the impurity could be considered.

Any information pertaining to the relevance of findings in animals to humans must be taken into account and may be used to modify the classification from how it would be if based on the available animal data. For instance, it may be shown that the findings in animals are not relevant for humans, for example if the toxicity in animals is mediated by a mode of action.
that does not occur in humans. This would potentially provide a supporting case for no
classification. Similarly, evidence may suggest that the potency of the substance may be
higher or lower in humans than in animals, for example because of differences in
toxicokinetics/toxicodynamics between the species. Such evidence could be used to increase
or decrease the severity of the classification as appropriate. It should be noted that such
arguments for modifying the classification must be robust and transparent (see section
3.9.2.3.4).

The final classification based on non human data will be the most severe classification of the
three routes. If it is shown that classification for this endpoint is not required for a specific
route then this can be included in the hazard statement. Evaluation of non human data can
result in no classification, STOT RE 1 or STOT RE 2. The results of the evaluation in non
human data should be used in combination with the results of the evaluation of human data.

If it is shown that classification for this endpoint is not required for a specific route then this
can be included in the hazard statement according to the table below.

<table>
<thead>
<tr>
<th>Route 1</th>
<th>Route 2</th>
<th>Route 3</th>
<th>H-statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1</td>
<td>Category 2</td>
<td>unknown</td>
<td>Causes damage to organs through prolonged or repeated exposure</td>
</tr>
<tr>
<td>Category 1</td>
<td>Category 2</td>
<td>NC</td>
<td>Causes damage to organs via route 1 and 2</td>
</tr>
<tr>
<td>Category 1</td>
<td>NC</td>
<td>unknown</td>
<td>Causes damage to organs through prolonged or repeated exposure</td>
</tr>
<tr>
<td>Category 1</td>
<td>unknown</td>
<td>unknown</td>
<td>Causes damage to organs through prolonged or repeated exposure</td>
</tr>
<tr>
<td>Category 1</td>
<td>NC</td>
<td>NC</td>
<td>Causes damage to organs via route 1</td>
</tr>
</tbody>
</table>

3.9.2.3.3 Conversions

The guidance values are giving in mg/kg bodyweight. Where the doses in a study are given in
different units they will need to be converted as appropriate. For instance the dosages in
feeding and drinking water studies are often expressed in ppm, mg test substance/ kg (feed)
or mg (test substance)/l (drinking water).

Where insufficient information is reported in the study to perform the conversion, Table
3.9.2.3.3.1 and Table 3.9.2.3.3.2 can be used as “Approximate relations”. These tables are
derived from the following documents: IR/CSA, Chapter 8, Table 17; and OECD
ENV/JM/MONO (2002)19, 04-Sep-2002, Table 1; L.R. Arrington (Introductory Laboratory

Table 3.9.2.4.2(a) Food conversion
Guidance to Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of substances and mixtures

<table>
<thead>
<tr>
<th>Animal</th>
<th>Weight (kg)</th>
<th>Food consumed per day (g)</th>
<th>Factor 1 mg/kgbw/d equivalent to ppm in diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat, young</td>
<td>0.10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Rat, older</td>
<td>0.40</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Mouse</td>
<td>0.02</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Dog</td>
<td>10</td>
<td>250</td>
<td>40</td>
</tr>
</tbody>
</table>

Table 3.9.2.4.2(b) Conversion drinking water

<table>
<thead>
<tr>
<th>Animal</th>
<th>Weight (kg)</th>
<th>Drinking water consumed per day (g)</th>
<th>Factor 1 mg/kgbw/d equivalent to ppm in drinking water</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat, young</td>
<td>0.25</td>
<td>28 (25-30)</td>
<td>9</td>
</tr>
<tr>
<td>Rat, older</td>
<td>0.40</td>
<td>28 (25-30)</td>
<td>14</td>
</tr>
<tr>
<td>Mouse</td>
<td>0.025</td>
<td>5 (4-7)</td>
<td>8</td>
</tr>
<tr>
<td>Dog</td>
<td>13</td>
<td>350</td>
<td>37</td>
</tr>
</tbody>
</table>

The conversion is performed according to the following simple equation:

\[ \text{mg/kgbw} = \text{ppm/factor} \]

Example: In a 4 week study rats received the 1000 ppm test substance in feed

\[ \text{Dosage (mg/kg bw)}: 1000:10 = 100 \text{ mg/kgbw}. \]

In any case a calculation of the average substance intake based on measured bodyweight and consumption data is preferable and should be performed where possible.

Gases: mg/l into ppm:

Effect doses from gases given in the unit mg/l have to be converted into the unit ppm as used by the CLP via the following simplified formula assuming values for ambient pressure of 1 atm = 101.3 kPa and 25 °C:

\[ \text{mg/l} = \text{ppm} \times \text{MW/0.02445} \]

3.9.2.3.4 Weight of evidence

Annex 1: 3.9.2.3. Classification is determined by expert judgment (see section 1.1.1), on the basis of the weight of all evidence available including the guidance presented below.

3.9.2.4. Weight of evidence of all data (see section 1.1.1), including human incidents, epidemiology, and studies conducted in experimental animals, is used to substantiate specific target organ toxic effects that merit classification. This taps the considerable body of industrial toxicology data collected over the years. Evaluation shall be based on all existing data, including peer-reviewed published studies and additional acceptable data.
Annex 1: 3.9.2.10.2. When well-substantiated human data are available showing a specific target organ toxic effect that can be reliably attributed to repeated or prolonged exposure to a substance, the substance shall normally be classified. Positive human data, regardless of probable dose, predominates over animal data. Thus, if a substance is unclassified because no specific target organ toxicity was seen at or below the dose/concentration guidance value for animal testing, if subsequent human incident data become available showing a specific target organ toxic effect, the substance shall be classified.

3.9.2.10.3. A substance that has not been tested for specific target organ toxicity may, where appropriate, be classified on the basis of data from a validated structure activity relationship and expert judgment-based extrapolation from a structural analogue that has previously been classified together with substantial support from consideration of other important factors such as formation of common significant metabolites.

In cases where there is sufficient human evidence that meets the criteria given in CLP Annex I, Table 3.9.1 to support classification then this will normally lead to classification in Category 1, irrespective of other information available.

Where human evidence does not meet this criterion, for example when the weight of evidence is not sufficiently convincing (limited number of cases or doubt on causal relationship) or because of the nature and severity of the effects (CLP Annex I, sections 3.9.2.7.3 and 3.9.2.8.1), then classification is based primarily on the non-human data.

If there are no human data then the classification is based on the non-human data. If there is human data indicating no classification but there is also non-human data indicating classification then the classification is based on the non-human data unless it is shown that the human data cover the exposure range of the non-human data and that the non-human data are not relevant for humans. If the human and non-human data both indicate no classification then classification is not required.

3.9.2.4 Decision on classification

Annex 1: 3.9.2.7.1. Reliable evidence associating repeated exposure to the substance with a consistent and identifiable toxic effect demonstrates support for the classification.
Annex 1: 3.9.2.7.3. Evidence from appropriate studies in experimental animals can furnish much more detail, in the form of clinical observations, haematology, clinical chemistry, and macroscopic and microscopic pathological examination, and this can often reveal hazards that may not be life-threatening but could indicate functional impairment. Consequently all available evidence, and relevance to human health, shall be taken into consideration in the classification process, including but not limited to the following toxic effects in humans and/or animals:

(a) morbidity or death resulting from repeated or long-term exposure. Morbidity or death may result from repeated exposure, even to relatively low doses/concentrations, due to bioaccumulation of the substance or its metabolites, and/or due to the overwhelming of the de-toxification process by repeated exposure to the substance or its metabolites.

(b) significant functional changes in the central or peripheral nervous systems or other organ systems, including signs of central nervous system depression and effects on special senses (e.g., sight, hearing and sense of smell).

(c) any consistent and significant adverse change in clinical biochemistry, haematology, or urinalysis parameters.

(d) significant organ damage noted at necropsy and/or subsequently seen or confirmed at microscopic examination.

(e) multi-focal or diffuse necrosis, fibrosis or granuloma formation in vital organs with regenerative capacity.

(f) morphological changes that are potentially reversible but provide clear evidence of marked organ dysfunction (e.g., severe fatty change in the liver).

(g) evidence of appreciable cell death (including cell degeneration and reduced cell number) in vital organs incapable of regeneration.

Annex 1: 3.9.2.8. Effects considered not to support classification for specific target organ toxicity following repeated exposure

3.9.2.8.1. It is recognised that effects may be seen in humans and/or animals that do not justify classification. Such effects include, but are not limited to:

(a) Clinical observations or small changes in bodyweight gain, food consumption or water intake that have toxicological importance but that do not, by themselves, indicate “significant” toxicity.

(b) Small changes in clinical biochemistry, haematology or urinalysis parameters and/or transient effects, when such changes or effects are of doubtful or minimal toxicological importance

(c) Changes in organ weights with no evidence of organ dysfunction.

(d) Adaptive responses that are not considered toxicologically relevant.

(e) Substance-induced species-specific mechanisms of toxicity, i.e. demonstrated with reasonable certainty to be not relevant for human health, shall not justify classification.

If the evaluation of available data on a substance shows that the criteria for classification in a category are fulfilled than the substance shall be classified in that category for STOT-RE.

If the data show that classification is warranted in Category 1 for one route and in Category 2 for another route then the substance shall only be classified in Category 1. The corresponding hazard statements are provided in Section 3.9.4.1.
If only data is available for one route showing that classification is warranted than no route should be stated in the hazard statement. If the data conclusively show that no classification for STOT-RE is warranted for a specific route then the remaining routes should be stated. If the data show that classification is warranted in Category 1 for one route and in Category 2 for another route then the hazard statement for Category 1 should include both routes because substances are placed in one of two categories.

3.9.2.5 Additional considerations

In the following sections some special aspects in the decision process on classification are described in more detail.

3.9.2.5.1 Irritating/corrosive substances

Substances (or mixtures) classified as corrosive may cause severe toxicological effects following repeated exposure, especially in the lungs following inhalation exposure. In such cases, it has to be evaluated whether the severe effect is a reflection of true repeated exposure toxicity or whether it is in fact just acute toxicity (i.e. corrosivity). One way to distinguish between these possibilities is to consider the dose level which causes the toxicity. If the dose is more than half an order of magnitude lower than that mediating the evident acute toxicity (corrosivity) then it could be considered to be a repeated-dose effect distinct from the acute toxicity. In this case, classification as specific target organ toxicant (repeated exposure) would be warranted even if the substance (or mixture) is also classified as acutely toxic and/or corrosive.

In assessing non systemic effects caused by irritating/corrosive substances it should be kept in mind, that the guidance values /criteria for R48 in the DSD and later on those for STOT-RE of the CLP were derived from acute toxicity criteria (lethality based) assuming that systemic effects show a time dependent increase of severity due to accumulation of toxicity and taking also adaptive and detoxification processes into account. The effect considered in this context was lethality. This indicates that classification was intended for the presence of severe health damage, only. (see ECBI/67/00)

3.9.2.5.2 Hematotoxicity

Methaemoglobin generating agents

Methaemoglobinemia has often been regarded as an acute clinical symptom resulting from the action of methemoglobin-generating agents. If lethality is observed in humans or in animals or can be predicted (QSAR), methemoglobin generating substances should be classified in the Acute Toxicity Hazard Class. Since this effect is difficult to detect in rodents, expert judgement should be used (cf. Guidance on Acute toxicity, Example2). If methaemoglobinemia does not result in lethality but exposure to methaemoglobin generating agents results in signs of damage to the erythrocytes and haemolysis, anaemia or hypoxemia, the formation of methaemoglobin shall be classified accordingly either in STOT-SE or STOT-RE. (Muller A. et al., 2006).

Haemolytic anaemia

The guidance developed for classification of substances inducing haemolytic anaemia according to 67/548/EEC (Muller A. et al., 2006) cannot directly be used under CLP because

---

43 Observation of lethality following methemoglobin formation is not usual, as several animals are more tolerant to it. Extrapolation to the human situation must be the critical decision key.
of the changes in criteria (see CLP Annex I, 3.9.2.7.3 c and 3.9.2.8.b, d ). The major criterion
for haemolytic anaemia changed:

- From “Any consistent changes in haematology which indicate severe organ
dysfunction.”
- To “Any consistent and significant adverse changes in haematology.”

This indicates that less adverse effects are considered for classification according to CLP.
This is consistent with the changes in the other criteria for classification for repeated
exposure.

Adaptation towards the criteria according to CLP results in the following guidance:

It is evident that anaemia describes a continuum of effects, from sub-clinical to potentially
lethal in severity. Overall, the interpretation of study findings requires an assessment of the
totality of findings, to judge whether they constitute an adaptive response or an adverse
toxicologically significant effect. If a haemolytic substance induces one or more of the
serious health effects listed as examples below within the critical range of doses,
classification is warranted. It is sufficient for classification that only one of these criteria is
fulfilled.

Annex I: 3.9.2.7.3.

(a) morbidity or death resulting from repeated or long-term exposure. Morbidity or death may
result from repeated exposure, even to relatively low doses/concentrations, due to bioaccumulation
of the substance or its metabolites, and/or due to the overwhelming of the de-toxification process by
repeated exposure to the substance or its metabolites;

Example:
- Premature deaths in anaemic animals that are not limited to the first three days of
treatment in the repeated dose study. (Mortality during days 0–3 may be relevant for
acute toxicity.)
- Clinical signs of hypoxia, e.g. cyanosis, dyspnoea, pallor, in anaemic animals that
are not limited to the first three days of treatment in the repeated dose study.

(b) significant functional changes in the central or peripheral nervous systems or other organ
systems, including signs of central nervous system depression and effects on special senses (e.g.
sight, hearing and sense of smell);

(c) any consistent and significant adverse effect in clinical biochemistry, haematology or urinalysis
parameters;

Examples:
- Reduction in Hb at ≥20%.
- Reduction in functional Hb at ≥20% due to a combination of Hb reduction and
MetHb increase.
- Haemoglobinuria that is not limited to the first three days of treatment in the
repeated dose study in combination with other changes indicating significant
haemolytic anaemia (e.g. a reduction in Hb at ≥10%).
- Haemosiderinuria supported by relevant histopathological findings in the kidney in
combination with other changes indicating significant haemolytic anaemia (e.g. a
reduction in Hb at ≥10%).

(d) significant organ damage noted at necropsy and/or subsequently seen or confirmed at
Guidance to Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of substances and mixtures

297

microscopic examination;

(e) multifocal or diffuse necrosis, fibrosis or granuloma formation in vital organs with regenerative capacity;

Example:

- Multifocal or diffuse fibrosis in the spleen, liver or kidney.

(f) morphological changes that are potentially reversible but are clear evidence of marked organ dysfunction (e.g. severe fatty change in the liver)

Example:

- Tubular nephrosis

(g) evidence of appreciable cell death (including cell degeneration and reduced cell number) in vital organs incapable of regeneration.

In the case where multiple less severe effects with regenerative capacity were observed, the classification should apply as

“Assessment shall take into consideration not only significant changes in a single organ or biological system but also generalised changes of a less severe nature involving several organs.”

Example:

- Marked increase of haemosiderosis in the spleen, liver or kidney in combination with other changes indicating significant haemolytic anaemia (e.g. a reduction in Hb at ≥10%) in a 28 day study.

- Significant increase in haemosiderosis in the spleen, liver or kidney in combination with microscopic effects like necrosis, fibrosis or cirrhosis.

Annex I: 3.9.2.8.1. It is recognised that effects may be seen in humans and/or animals that do not justify classification. Such effects include, but are not limited to:

(a) clinical observations or small changes in bodyweight gain, food consumption or water intake that have toxicological importance but that do not, by themselves, indicate ‘significant’ toxicity;

(b) small changes in clinical biochemistry, haematology or urinalysis parameters and/or transient effects, when such changes or effects are of doubtful or minimal toxicological importance;

Example:

- Significant decrease in Hb without any other significant indicators of haemolytic anaemia.

- Minimal to slight increase in MetHb formation without any other indications of significant haemolytic anaemia.

(c) changes in organ weights with no evidence of organ dysfunction;

(d) adaptive responses that are not considered toxicologically relevant.

Example:

- Only adaptive or compensating effects without significant signs of haemolytic anaemia.

(e) substance-induced species-specific mechanisms of toxicity, i.e. demonstrated with reasonable...
3.9.2.5.3 Mechanisms not relevant to humans (CLP Annex I, 3.9.2.8.1. (e))

In general, valid data from animal experiments are considered relevant for humans and are used for hazard assessment/classification. However, it is acknowledged that there are cases where animal data are not relevant for humans and should not be used for that purpose. This is the case when there is clear evidence that a substance – induced effect is due to a species-specific mechanism which is not relevant for humans. Examples for such species differences are described in this section.

α-2-µ globulin nephropathy in male rats

The protein α-2-µ globulin, which is primarily synthesized in male rats, has the capability to bind to certain chemicals. The resultant adducts accumulate as droplets in the kidneys and causes progressive renal toxicity within a few weeks which can ultimately lead to kidney tumours. This specific mechanism is unique to male rats and has no relevance for humans. Examples of chemicals causing α-2-µ globulin nephropathy are: unleaded gasoline, chlorinated paraffins, isophorone, d-limonene.

Specific thyroid toxicity via liver enzyme induction

Certain chemicals cause induction of liver enzymes and are interfering with the regulation of thyroid hormones. An increase in the activity of hepatic UDPG-transferase results in increased glucuronidation of thyroid hormones and increased excretion. It is known that rodents are highly sensitive to a reduction in thyroid hormone levels (T4), resulting in thyroid toxicity (e.g. hypertrophy, hyperplasia) after repeated stimulation / exposure of this organ. This in turn is related to an increase in the activity of hepatic UDPG-transferase. Humans, unlike rodents, possess a T4 binding protein that greatly reduces susceptibility to plasma T4 depletion and thyroid stimulation. Thus, such a mechanism/effect cannot be directly extrapolated to humans, i.e. these thyroid effects observed in rodents caused by an increase in hepatic UDPG-transferase are therefore considered of insufficient concern for classification (see ECBI/22/98-Add1).

Peroxisome induction/proliferation

Peroxisomes are cell-organelles which can be induced to a specifically high level in rats and mice under certain conditions, e.g. by repeated exposure to long chain and branched fatty acids. Peroxisome proliferation which is especially occurring in the liver causes liver toxicity (e.g. hyperplasia, oxidative stress) and can ultimately after longterm exposure also may lead to tumours. There is no evidence of e.g. hepatomegaly from clinical studies in humans treated with peroxisome proliferators (I.H.F.Purchase, Human & Experimental Toxicology (1994), 13, Suppl.2 S47-S48). Examples are Clofibrat and Diethylhexylphthalate (DEHP).

Lung Overload

The relevance of lung overload in animals to humans is currently not clear and is subject to continued scientific debate.

3.9.2.5.4 Adaptive responses (CLP Annex I, 3.9.2.8.1. (d))

Adaptive (compensatory) changes generally constitute a normal biochemical or physiological response to a substance or to the effect of the substance (e.g. in response to methaemoglobin formation), usually manifested as an increase in background processes such as metabolism or erythropoiesis etc, which are generally reversible with no adverse consequences on cessation of exposure. In some cases the adaptive response may also be associated with pathological
changes which reflect the normal response of the target tissue to substances. For example, liver hypertrophy in response to enzyme induction, the increase in alveolar macrophages following inhalation of insoluble particles that must be cleared from the lungs, and the development of epithelial hyperplasia and metaplasia in the rat larynx in response to inhalation of irritants.

Determination of whether adaptive changes support a classification requires a holistic assessment of the nature and severity of the observations and their dose-response relationship using expert judgement. Exposure to a substance can lead to a spectrum of effects which vary in incidence and severity with dose. At lower doses there may be adaptive changes which are not considered to be toxicologically significant or adverse, whereas at higher doses these changes may become more severe and/or other effects may occur which together constitute frank toxicity. Also, sometimes the adaptive effect is observed but the primary effect is not because the relevant parameter is not determined or not determined at the right time. For example, irritation of the larynx after inhalation of irritants is not observed at the end of a repeated dose study because of the quick response. The adaptive effect can then be used as an indication of the primary effect. It is often difficult to clearly distinguish between changes which are adaptive in nature and those which represent clear overt toxicity and this assessment requires expert judgement. Where the response to a substance is considered to be purely adaptive at dose levels relevant for classification then no classification would be appropriate.

3.9.2.5 Post-observation periods in 28 day and 90 day studies

For subacute/subchronic testing protocols, the usual guideline procedure is to sacrifice the exposed animals immediately after the end of the exposure period (d 29 or 91).

Japanese agencies often require a 14 days postobservation period for 28 day studies (OECD 407). This means that 10 more animals in the top dose and 10 more animals as an additional control group are then necessary.

The reversibility of organotoxic effects can in most cases be estimated by the pathologist from histologic findings without a post-observation period.

- Certain effects are entirely reversible such as simple irritation or many forms of liver, testicular and hematotoxicity.
- Other effects may be reversible in morphological terms but the reserve capacity of the organism may be irreversibly compromised (such as in the case of kidney toxicity with a persistent loss in kidney nephrons).
- Some forms of tissue toxicity may be fundamentally irreversible, such as CNS- and neuro-toxicity with specific histological findings, cardiac toxicity and lung toxicity. Often, such effects do not return to normal morphology and may deteriorate even after the end of exposure.

3.9.2.6 Setting of specific concentration limits

Specific concentration limits (SCLs) for STOT-RE may be set by the supplier in some situations according to Article 10 of CLP. For STOT-RE, this may only be done for substances inducing target organ toxicity at a dose level or concentration clearly (more than one magnitude) below the guidance values according to CLP Annex I, Table 3.9.2, that corresponds to ED below 1 mg/kg bodyweight from the 90-day oral study. Where the exposure duration is not 90 days the ED has to be adjusted to an equivalent for 90 days using Haber’s law and expert judgement (as described above). This will be mainly based on data in experimental animals but can also be used for human data if reliable exposure data are
available. Setting of SCLs above the GCL is not applicable for STOT-RE because classification for STOT-RE is based on potency. Substances with a low potency do not require classification for this hazard class and substances with a medium or high potency are classified in a category defined by the GV.

The SCL for a Category 1 substance \( (SCL_{Cat.1}) \) can be determined using the following formula:

\[
SCL_{Cat.1} = \frac{ED}{GV} \times 100\% \\
\text{Equation 3.9.2.6(a)}
\]

SCL Cat 1: \( \frac{0.12 \text{ mg/kgbw}}{10 \text{ mg/kgbw}} \times 100\% = 1.2\% \rightarrow 1\% \)

ED (effective dose) is the dose inducing specific target organ toxicity and GV1 is the guidance value for Category 1 according to CLP Annex I, Table 3.9.2 of Annex I corrected for the exposure duration. The resulting SCL is rounded down to the nearest preferred value \( (1, 2 \text{ or } 5) \).

Though classification of a mixture in Category 1 is not triggered if a Category 1 constituent is present in lower concentrations than the established SCL, a classification in Category 2 should be considered. The SCL for classification of a mixture in Category 2 \( (SCL_{Cat.2}) \) based on substances classified in Category 1 can be determined using the following formula:

\[
SCL_{Cat.2} = \frac{ED}{GV} \times 100\% \\
\text{Equation 3.9.2.6(b)}
\]

SCL Cat 2: \( \frac{0.12 \text{ mg/kgbw}}{100 \text{ mg/kgbw}} \times 100\% = 0.12\% \rightarrow 0.1\% \)

In this formula the ED (effective dose) is the dose inducing specific target organ toxicity and GV2 is the upper guidance value for Category 2 according to CLP Annex I, Table 3.9.3 corrected for the exposure duration. The resulting SCL is rounded down to the nearest preferred values \( (1, 2 \text{ or } 5) \).

It is not appropriate to determine SCLs for substances classified in Category 2 since ingredients with a higher potency (i.e. lower effect doses than the guidance values of Category 2) will be classified in Category 1 and substances with respective higher effect doses will generally not be classified. For example, a substance inducing significant specific target organ toxicity at \( 0.12 \text{ mg/kg bw/day} \) in a 90-day oral study would require a SCL for Category 1 of \( 1\% \) and for Category 2 of \( 0.1\% \).
3.9.2.7 Decision logic for classification of substances

The decision logic which follows is provided as additional guidance to the criteria. It is strongly recommended that the person responsible for classification, study the criteria for classification before and during use of the decision logic.

Does the substance have data and/or information to evaluate specific target organ toxicity following repeated exposure?

No  Classification not possible

Yes

Following repeated exposure,
Can the substance produce significant toxicity in humans, or
Can it be presumed to have the potential to produce significant toxicity in humans on the basis of evidence from studies in experimental animals?

Yes  Category 1  Danger

No

Following repeated exposure,
Can the substance be presumed to have the potential to be harmful to human health on the basis of evidence from studies in experimental animals?

Yes  Category 2  Warning

No

Not classified
3.9.3 Classification of mixtures for STOT-RE

3.9.3.1 Identification of hazard information

Where toxicological information is available on a mixture this should be used to derive the appropriate classification. Such information may be available from the mixture manufacturer. Where such information on the mixture itself is not available information on similar mixtures and/or the component substances in the mixture must be used, as described below.

Further, the hazard information on all individual components in the mixture could be identified as described in section 3.9.3.3.

3.9.3.2 Classification criteria for mixtures

Annex 1: 3.9.3.1. Mixtures are classified using the same criteria as for substances, or alternatively as described below. As with substances, mixtures shall be classified for specific target organ toxicity following repeated exposure.

3.9.3.3 When data are available for the complete mixture

Annex 1: 3.9.3.2.1. When reliable and good quality evidence from human experience or appropriate studies in experimental animals, as described in the criteria for substances, is available for the mixture (see 1.1.1.3), then the mixture shall be classified by weight of evidence evaluation of these data. Care shall be exercised in evaluating data on mixtures, that the dose, duration, observation or analysis, do not render the results inconclusive.

In cases where test data for mixtures are available, the classification process is exactly the same as for substances.

3.9.3.3.1 When data are not available for the complete mixture: bridging principles

Annex 1: 3.9.3.3.1. Where the mixture itself has not been tested to determine its specific target organ toxicity, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterise the hazards of the mixture, these data shall be used in accordance with the bridging principles set out in section 1.1.3.

When there are no test data on the mixture as a whole, so called “Bridging principles” may be applied where there are data available on similar tested mixtures and on the individual hazardous ingredient substances within the mixture that are sufficient to adequately assess the hazards of the mixture.

3.9.3.3.2 When data are available for all components or only for some components of the mixture

Annex 1: 3.9.3.4.1. Where there is no reliable evidence or test data for the specific mixture itself, and the bridging principles cannot be used to enable classification, then classification of the mixture is based on the classification of the ingredient substances. In this case, the mixture shall be classified as a specific target organ toxicant (specific organ specified), when at least one ingredient has been classified as a Category 1 or Category 2 specific target organ toxicant and is present at or above the appropriate generic concentration limit as laid out in Table 3.9.4 below for Category 1 and 2 respectively.

3.9.3.3.3 Components of a mixture that should be taken into account for the purpose of classification
Components with a concentration equal to or greater than the generic concentration limits (1% for category 1 components and 10% for category 2; see CLP Annex I, Table 3.9.4) or with a specific concentration limit (see also section 3.9.3.5 of this document) will be taken into account for classification purposes. Specific concentration limits have preference over the generic concentration limits.

### 3.9.3.4 Generic concentration limits for substances triggering classification of mixtures

<table>
<thead>
<tr>
<th>Ingredient classified as:</th>
<th>Category 1</th>
<th>Category 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1 Specific Target Organ Toxicant</td>
<td>Concentration $\geq$ 10%</td>
<td>1.0% $\leq$ concentration $&lt;$ 10%</td>
</tr>
<tr>
<td>Category 2 Specific Target Organ Toxicant</td>
<td>Concentration $\geq$ 10% (Note 1)</td>
<td></td>
</tr>
</tbody>
</table>

**Note 1**
If a Category 2 specific target organ toxicant is present in the mixture as an ingredient at a concentration $\geq$ 1.0% a SDS shall be available for the mixture upon request.

### Annex 1: 3.9.3.4.4
Care shall be exercised when toxicants affecting more than one organ system are combined that the potentiation or synergistic interactions are considered, because certain substances can cause target organ toxicity at $< 1\%$ concentration when other ingredients in the mixture are known to potentiate its toxic effect.

In the case a specific concentration limit has been established for one or more ingredients these SCLs have precedence over the respective generic concentration limit.

When classifying a mixture for STOT-RE the additive approach, where the concentrations of individual components with the same hazards are summed, is not used. If any individual component is present at a concentration higher than the relevant generic or specific concentration limit then the mixture will be classified.
### 3.9.3.5 Decision logic for mixtures

A mixture should be classified either in category 1 or in category 2, according to the criteria described above. When a mixture is classified for STOT-SE on basis of test data, the hazard statement will specify the target organs, in the same way as for a substance. If a mixture is classified on basis of the ingredients, the hazard statement (H372 for category 1 or H373 for category 2) may be used without specifying the target organs, as appropriate. In the same way, the route of exposure should not be specified, except if data are available for the complete mixture and if it is conclusively demonstrated that no other routes of exposure cause the hazard.

The decision logic which follows is provided as additional guidance to the criteria. It is strongly recommended that the person responsible for classification study the criteria for classification before and during use of the decision logic.

#### Decision Logic Diagram

- **Does the mixture have data and/or information to evaluate?**
  - Yes → See Substances
  - No → Can bridging principles be applied?
    - Yes → Classify in appropriate category
    - No → Does mixture contain one or more ingredients classified as a Category 1 specific target organ toxicant at a concentration of:
      - $\geq 10\%$?
        - Yes → Category 1
          - Danger
        - No → Does mixture contain one or more ingredients classified as a Category 2 specific target organ toxicant at a concentration of:
          - $\geq 10\%$
            - Yes → Category 2
              - Warning
            - No → Not classified

(A SDS is required if a cat 2 substance is present at or above 1%)
3.9.4 Hazard communication in form of labelling for STOT RE

3.9.4.1 Pictograms, signal words, hazard statements and precautionary statements

**Annex I: 3.9.4.1.** Label elements shall be used in accordance with Table 3.9.5 for substances or mixtures meeting the criteria for classification in this hazard class.

**Table 3.9.5**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Category 1</th>
<th>Category 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>GHS Pictograms</td>
<td><img src="image" alt="Pictogram" /></td>
<td><img src="image" alt="Pictogram" /></td>
</tr>
<tr>
<td>Signal word</td>
<td>Danger</td>
<td>Warning</td>
</tr>
<tr>
<td>Hazard statement</td>
<td>H372: Causes damage to organs (state all organs affected, if known) through prolonged or repeated exposure (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)</td>
<td>H373: May cause damage to organs (state all organs affected, if known) through prolonged or repeated exposure (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)</td>
</tr>
<tr>
<td>Precautionary statement prevention</td>
<td>P260, P264, P270</td>
<td>P260</td>
</tr>
<tr>
<td>Precautionary statement response</td>
<td>P314</td>
<td>P314</td>
</tr>
<tr>
<td>Precautionary statement storage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precautionary statement disposal</td>
<td>P501</td>
<td>P501</td>
</tr>
</tbody>
</table>

The hazard statement should include the primary target organ(s) of toxicity. Organs in which secondary effects were observed should not be included. The route of exposure should not be specified, except if it is conclusively demonstrated that no other routes of exposure cause the hazard.

When a mixture is classified for STOT-RE on basis of test data, the hazard statement will specify the target organs, in the same way as for a substance. If a mixture is classified on basis of the ingredients, the hazard statement (H372 for category 1 or H373 for category 2) may be used without specifying the target organs, as appropriate.

In the same way, the route of exposure should not be specified, except if data are available for the complete mixture and if it is conclusively demonstrated that no other routes of exposure cause the hazard.

It is recommended to include no more than three primary target organs for practical reasons and because the classification is for specific target organ toxicity. If more target organs are affected it is recommended that the overall systemic damage should be reflected by using the more general term “damage of organs”.

305
3.9.4.2 Additional labelling provisions

Annex 1: 3.9.2.10.4 Saturated vapour concentration shall be considered, where appropriate, as an additional element to provide for specific health and safety protection

According to CLP Annex I, 3.9.2.10.4 the saturated vapour concentration shall be considered as an additional element for providing specific health and safety protection. Thus if a classified substance is highly volatile a supplementary precautionary advice (e.g., “Special/additional care should be taken due to the high saturated vapour pressure”) might be given in order to emphasize the hazard in case it is not already covered by the general P statements. (As a rule substances for which the ratio of the effect concentration at ≤ 4h to the SVC at 20° C is ≤ 1/10).

Although not according to the criteria of STOT-RE, the following EU-special hazard statement “Repeated exposure” may be used when appropriate:

EUH066- “Repeated exposure may cause skin dryness or cracking” (see section 3.2 on Skin Corrosion/Irritation).

3.9.5 Re-classification of substances and mixtures classified for STOT-RE according to DSD and DPD

Classification with STOT–RE according to CLP is comparable to the classification with R48/X according to DSD. Also substances and mixtures currently classified with R33 should be considered because there is no corresponding classification in CLP. However, differences are present regarding the approach to route-to-route extrapolation.

3.9.5.1 Is direct “translation” of classification and labelling possible for STOT-RE substances?

Direct translation of substances or mixtures classified with R48/X is possible because classification criteria are based on the dose and the severity of a toxic effect and are comparable in both, CLP and DSD. However, in some cases a change in the category may result by reviewing the data.

Substances or mixtures classified with R48/23, R48/20 (for vapour), R48/24 and/or R48/25 shall be classified as STOT-RE Category 1 because less adverse effects and higher guidance values are required for classification according to CLP compared to DSD. Notable, there is one exception: dust/mist/fume with an ED > 0.02 and ≤ 0.025 mg/l/6h which are classified according to DSD with R48/23 might not be classified in Category 1 according to CLP. Setting of SCL may be considered for substances showing STOT-RE at levels clearly below the guidance values (see section 3.9.2.6).

All substances or mixtures classified with R48/20 (for dust/mist/fume), R48/21 and/or R48/22 shall be classified generally at least as STOT-RE Cat 2. Again, dust/mist/fume with an ED > 0.2 and ≤ 0.25 mg/l/6h which are classified according to DSD with R48/20 might not be classified according to CLP. However, due to the general increase in guidance values, the requirement for less severe effects classification in category 2 should also be considered but.

If translation results in a classification in STOT-RE Category 1 for one route and in STOT-RE Category 2 for another route only classification in Category 1 is required (for both routes).

In contrast to DSD where the route of exposure is included in the classification and correlates with the routes tested (or extrapolated), according to CLP the exposure route should be specified only when it is conclusively proven that no other routes of exposure cause the
hazard. Therefore, the route specific data on STOT-RE should be re-evaluated. A re-evaluation is also necessary because the primary target organs for STOT-RE should be stated in the hazard statement.

3.9.5.2 Re-evaluation of the STOT-RE data

Gasses classified with R48/20 or R48/23 should be re-evaluated because the guidance values changed from general guidance values in mg/L for aerosols, vapours and gasses to a specific guidance value for gasses in ppm.

Substances or mixtures not classified for, STOT-RE including substances or mixtures classified with R33, should be re-evaluated because less adverse effects and higher guidance values are required for classification according to CLP compared to DSD. Also, effects in humans are now considered for classification generally without restrictions to the exposure level.

3.9.6 Examples of classification for STOT-RE

Remarks:

The classification proposals for the examples refer only to STOT-RE.

Labelling is done only with respect to hazard statements (statement with respect of organs affected = target organs).

3.9.6.1 Examples of substances fulfilling the criteria for classification

3.9.6.1.1 Example 1: Hydroxylamine / Hydroxylamonium salts (CAS no. 7803-49-8)

Application of criteria for evaluation/classification and decision on classification: Use of studies with different duration; Haber’s rule; Expert judgement

Available information:

1) Human experience: No information available

2) Animal data:

Background:

Hydroxylamine and its salts are direct MetHb producers in contrast to aromatic amines, which require metabolic activation (XI/484/92).

Several studies are available for the assessment of the toxicity after repeated administration:

- 4-week drinking water study (BASF, 1989)
- 3-month drinking water study (BASF, 1989)
- Combined chronic/carcinogenicity study in drinking water in rats (BASF, 2001)

Though not explicitly stated in the criteria the "... study with the longest duration should normally be used".

- In the 3-month-study at the dose level of 21 mg/kg bw only “slight to moderate hematotoxic effects” were observed. Thus this dose would not be a sufficient ED causing ”significant/severe” effects, but it can be concluded that via interpolation an ED would result within the Guidance Value Range for Cat 2 (10-100 mg/kg bw).

- A classification in category 2 would be warranted based on the 3-month-study.
In the combined chronic/carcinogenicity study (BASF, 2001), the effects observed after 12 and 24 months are to be considered separately:

12 month study:

- 0 ppm (control): hemosiderin storage of low degree in males and females (spleen)
- 5 ppm (males 0.3 mg and females 0.4 mg/kg bw/day): No substance-induced effects; hemosiderin storage of low degree in males and females, comparable to controls.
- 20 ppm (males 1.1 mg and females 1.6 mg/kg b.w./day): Here, hemosiderin deposits with the gradation of moderate was observed in the spleens of the males; hemosiderin storage of low degree in females comparable to controls. This effect is not to be regarded as serious since hematology did not reveal any findings whatsoever with regard to anemia. This is supported by the fact that no substantial (1/10 moderate, but 1/10 severe in the male control group) extramedullary hematopoiesis was observed in this group. In the histopathological examination, the spleen was not found to be impaired morphologically. Thus, this dose is to be regarded as the NOAEL for males whereas it is the NOEL for females.
- 80 ppm (males 4.5 mg and females 6.2 mg/kg b.w./day): The clinicochemical findings are assessed as mild anemia in the males (e.g. decrease of RBC, HB and HT (< 10%); MCV increased at the beginning and compensatory normalization later) and, also as mild anemia in the females (decrease in RBC ≤ 12%, HB < 10% and HT < 10%). The increase of MCV, PLT and RET and of Howell-Jolly bodies is regarded as a compensatory effect, and the bone marrow still reacts, i.e. it does not demonstrate "... decreased bone marrow production of red blood cells" within the meaning of the criteria. The only slight increase of the Heinz bodies is considered to be a sign of a weak hematotoxic effect. From the point of view of histopathology, the effects (hemosiderin storage, extramedullary hematopoiesis) can be regarded as signs of anemia, but not within the meaning of "serious" (the effect was more pronounced in the females than in the males). The extramedullary hematopoiesis observed is thus again compensatory in the sense of a functional counterreaction.

Assessment:

For a 12-month study, cut-off values of 25 and 2.5 mg/kg bw/day (100 mg/kg/day : 4) have to be regarded for STOT-RE Category 1 vs. Category 2 respectively. At the dose level of 1.1 (m) or 1.6 mg/kg bw/day (f), no hematotoxic effects whatsoever or extramedullary hematopoiesis were observed, nor substantial hemosiderin deposits. The effects at 4.5 (f) and 6.2 (m) mg/kg bw/day are regarded as mild anemia; however, more distinct effects may be expected to occur up to the cut-off value (25 mg/kg/day). Therefore, a classification in Category 2 seems justified.

24-month study:

In contrast to the 12-month study, no complete hematological examination was carried out, i.e. only morphological parameters were evaluated, yet full histopathology. The following findings relevant to classification – with the exception of the neoplasias – were obtained:

- 5 ppm (males 0.2 mg and females 0.4 mg/kg b.w./day): No nonneoplastic effects
- 20 ppm (males 1 mg and females 1.6 mg/kg b.w./day): Increased proportion of hemosiderin deposits in the spleens of the females, but no extramedullary hematopoiesis, which demonstrates that there was no clear anemia before.
Remark:
The fact that, at this dose level, hemosiderin was detected only in the males in the 12-month study and an increased proportion of it only in the females in the 24-month study shows that this effect was only borderline.

- 80 ppm (males 3.7 mg and females 6.2 mg/kg b.w./day): Again hemosiderin storage and extramedullary hematopoiesis were observed, yet no serious effects in hematology nor histopathology. Furthermore, the results of the study do not indicate that any animal died prematurely on account of the anemia.

Remark:
No effects at all were observed in kidneys nor in liver in the 12-month study. In the 3 month study only in the highest dose the relative liver weights were increased in the males; in the 3 month as well as in the 24-month study only marginal effects (diffuse hemosiderin storage in the liver) in both sexes was observed in the highest dose.

Assessment:
The results of the 24 month study show that effects as seen after 12 month exposure are not substantially increased.

Classification:
Based on the evaluation of the 3-month study and the more relevant 12-month study by expert judgement a classification in category 2 is warranted.

Labelling:
Hazard statement: H373 May cause damage to blood system through prolonged or repeated exposure
(See also ECBI/14/3/Add 3 (2003) and ECBI/56/04 Rev 1)

3.9.6.1.2 Example 2: But-2-yn-1,4-diol (EC No 203-788-6; CAS No 110-65-6)
Current classification according to DSD: Xn; R48/22
Application of criteria for evaluation/classification and allocation of hazard statements with respect to specific target organs and route of exposure

Available information:
1) Human experience: no information available
2) Animal data:
- 28 d oral study
- 28 d inhalation study
- Acute oral toxicity: LD50 rat 132 (males) and 176 (females) mg/kg -> Category 3
- Acute dermal toxicity: LD50 424 (males) and 983 (female) mg/kg -> Category 3
- Acute inhalation toxicity: LC50 rat 0.69 mg/l -> Category 2
- Corrosivity in animal experiments (Category 1)

STOT-RE oral:
28 d rat oral (gavage): doses 0; 1; 10; 50 mg/kg bw/d
- 1 mg/kg: NOEL
- 10-mg/kg: LOEL
- Increased liver weight (not statistically significant)
- Hepatic and splenic changes (no clear description of severity given)
- Diminished RBC counts in females, yet no other changes in blood chemistry
- Histopathology: in 2/10 males and 3/10 females swelling of parenchymal cells and increased polymorphism of the hepatocyte nuclei and the nuclear cells. These effects are regarded as not “significant/severe toxic effects”
- 50 mg/kg: mortality (3/8 males; 3/8 females); hepatoad nephrotoxicity responsible for mortality; no distinct hepatoad nephrotoxicity described for survivors
- Hematology: Decrease in RBC count ca. 20% and 21% in HB both in females; decrease in Hematocrite 11%. These effects are regarded as “moderate hematotoxicity”.

Conclusion for the highest dose group: severe effects.

Assessment:
The substance has a high acute toxicity (s. a.). Since the factor between the acute LD50 and the subacute lethal dose (20 applications) is only 2-3, it can be assumed that the substance has a low cumulative potential. On the other hand there is a steep dose response in the 4 week study, thus it can be concluded by interpolation that at 30 mg/kg moderate but no “significant/severe” toxicity could be expected; 30 mg/kg is the guidance value for category 1 in a 4 week study according to Haber’s rule: 10 mg/kg x 3).

STOT-RE inhalation
In a valid 4 week inhalation study (vapour) rats were exposed to 0.5; 5; and 25 mg/m3/6h/d.

- 0.5 mg/m3: NOAEC for local effects in the respiratory tract
- 5 mg/m3: minimal –slight focal squamous metaplasia and inflammation in the larynx
- 25 mg/m3: minimal –slight focal squamous metaplasia and inflammation in the larynx
- 25 mg/m3: NOAEC for systemic effects including hematology, clinical chemistry, histopathology and neuropathology examinations

Assessment:
Up to the highest concentration tested there were no systemic effects. Since the substance is classified as corrosive an irritation of the respiratory tract by the vapour could be expected and has been observed in minimal –slight degree at 5-25 mg/m3. It is assumed that the irritation would increase with higher concentrations. The corrosive/irritation potential is covered by the classification as “corrosive” Category 1, thus no classification as STOT-RE with respect to the inhalation route would result.

Classification:
Category 2 for the oral route is proposed since within the guidance values of 30-300 mg/kg in a 4 week study serious effect occurred. According to a total weight of evidence approach it is concluded that these significant effects would not be observed below 30 mg/kg, the concentration limit for category 1.

Classification via the inhalation route is not warranted, since at the highest concentration tested only local effects, but no systemic effects were observed. The local effects (corrosivity/irritancy) are covered by the respective classification.

Labelling:
HAZARD STATEMENT: H373 MAY CAUSE DAMAGE TO LIVER AND KIDNEY THROUGH PROLONGED OR REPEATED EXPOSURE

Remark. Since the substance is classified as STOT-RE via the oral route and specific toxicity has not been conclusively excluded for the dermal route (rather it can be expected due to high dermal absorption in acute toxicity, category 3) the Hazard statement for STOT-RE in total without specifying a route has to be applied based on the classification via the oral route. (See also Risk assessment report BUT-2YNE-1,4-DIOL; EC 2005)

3.9.6.1.3 Example 3: XYZ

Application of criteria for evaluation/classification and allocation of hazard statements with respect to specific target organs and route of exposure

Available information:

1) Human experience: No information available
2) Animal data:

<table>
<thead>
<tr>
<th>Key chronic toxicity data (underlined for EU classification)</th>
<th>NOAEL ppm (mg/kg/d)</th>
<th>LOAEL ppm (mg/kg/d)</th>
<th>CLP Repeated Exposure (STOT) classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>mouse, oral 28 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0, 300, 600, 1200 ppm (M: 0, 51-58, 101-115, 177-226</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mg/kg/d, F: 0, 59-66, 111-127, 221-281 mg/kg/d)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hematological changes in M (↓ RBC count, Hb, Ht)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M: no NOAEL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F: 300 (59-66)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M: 300 (51-58)</td>
<td></td>
<td></td>
<td>Category 2 based on the effects on blood</td>
</tr>
<tr>
<td>F: 600 (111-127)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rat, oral 13 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0, 50, 500, 1000 ppm (M: 0, 3.5, 38, 67 mg/kg/d, F: 0, 4,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>38, 80 mg/kg/d)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hematological changes in F (↓ RBC count, Hb, Ht)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 (M: 3.5, F: 4)</td>
<td></td>
<td></td>
<td>Category 2 based on the effects on blood</td>
</tr>
<tr>
<td>500 (M: 38, F: 38)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>male rat, oral 30, 60, 90 days</td>
<td></td>
<td></td>
<td>No classification is proposed on basis of this study because the death observed in the 3 groups are in contradiction with the other relevant experiments in this species. (death no dose related, some animals (2/6) are already dead after 30 days at 5 mg/kg)</td>
</tr>
<tr>
<td>0, 5, 10, 25 mg/kg/d (by gavage) (open literature)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mortality at 5 (5/25), 10 (7/25) &amp; 25 (8/25) mg/kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Species</td>
<td>Duration</td>
<td>Dose Levels</td>
<td>Effects</td>
</tr>
<tr>
<td>-------------</td>
<td>----------</td>
<td>-------------</td>
<td>---------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Rat, Oral 2-years</td>
<td>0, 150, 300 ppm</td>
<td>(M: 0, 1.46, 7.31, 14.66 mg/kg/d, F: 0, 1.8, 8.86, 18.57 mg/kg/d)</td>
<td>Eyelid masses: 1 F/50 at 150 ppm, 5 M/50 &amp; 3 F/49 at 300 ppm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 (M: 1.46, F: 1.8)</td>
<td>Changes in erythroid parameters (↓RBC count, ↑MC Hb, ↑MCV in F at 300 ppm)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>150 (M: 7.31, F: 8.86)</td>
<td>Extramedullary hemopoiesis in liver (M: 150 &amp; 300 ppm, F: 300 ppm), spleens ↑myeloid hyperplasia in BM in femur &amp; sternum of F at 300 ppm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑i. hemorrhages w/i mesenteric lymph nodes at 150 &amp; 300 ppm</td>
</tr>
<tr>
<td>Rat, Oral 80 weeks</td>
<td>M: 0, 5, 20, 52 mg/kg/d</td>
<td>F: 0, 6, 26, 67 mg/kg/d</td>
<td>Ataxic syndrome in F at 67 mg/kg/d (unusual gait). The condition of these rats worsened, leading to paralysis posterior to the lumbar region atrophy of the hing legs. No specific histopathological lesion of CNS or PNS.</td>
</tr>
<tr>
<td>Rat, Oral 104 weeks</td>
<td>0, 3, 30, 300 ppm</td>
<td>(M: 0, 0.1, 1.2, 11.6 mg/kg/d, F: 0, 0.1, 1.4, 13.8 mg/kg/d)</td>
<td>Anemia in 300 ppm (F) (not in 30 ppm)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Regressive changes of sciatic nerve (degeneration) + atrophy of calf muscle in F at 300 ppm, but no neurological signs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Progression of myocardial lesions at 300 ppm</td>
</tr>
<tr>
<td>Mouse, Oral 97/98 weeks</td>
<td>M: 0, 15, 150, 300 ppm</td>
<td>(0, 3, 24, 50 mg/kg/d)</td>
<td>Category 2 based on the effects on blood</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F: 0, 15, 300, 600 ppm (0, 3, 57, 115 mg/kg/d)</td>
<td>15 (M: 5.2, F: 3.1)</td>
</tr>
</tbody>
</table>
Guidance to Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of substances and mixtures

112 mg/kg/d) retinal atrophy at ≥ 150 ppm (↓ or absence of outer nuclear cell layer of retina) ↑ turnover of erythrocytes

Classification for XYZ: STOT-RE Category 2

Labelling:

Symbol: GHS08
Signal word: Warning
Hazard statement: H373 May cause damage to the blood and nervous systems through prolonged or repeated exposure.

Justification:
The effects on blood are reported in the 2 species (mouse, rat), at doses low enough to justify category 2. The effects on NS are reported in the rat at doses low enough to justify category 2.

3.9.6.2 Examples of substances not fulfilling the criteria for classification

3.9.6.2.1 Example 4: MCCPs (Medium Chain Chlorinated Paraffins) = Alkanes, C_{14-17}, Chloro- (EC No 287-477-0; CAS No 85535-85-9)

Application of criteria for evaluation/classification with regard to mechanisms not relevant to humans (see section 3.9.2.5.3)

Available information:
1) Human experience: No information available
2) Animal data: see summary

Key chronic toxicity data: Summary of data for repeated exposure

The only available data relate to a number of oral dosing studies (up to 90 days duration) that have investigated the repeated dose toxicity of MCCPs (C_{14-17}, 40% or 52% chlorinated paraffins) in rodents. However, only two studies emerge as providing helpful dose-response information in respect of classification and labelling (IRDC 1984, Poon et al 1995). The others, all presented in more detail in the ESR RAR, were generally mechanistic studies on the interplay between liver and thyroid and the relevance of effects on these organs to human health, conducted at relatively high exposure levels.

In rats, the liver, thyroid and kidney are the target organs for repeated dose toxicity of MCCPs.

For the liver, increases in weight and changes in enzyme activity are seen in rats at exposure levels of 36 mg/kg/day or more (Poon et al 1995). These effects are considered part of an adaptive response to an increase in metabolic demand. There is also the possibility that peroxisome proliferation plays a role. These findings were not considered to justify classification. At higher exposure levels (around 360 mg/kg/day), single cell necrosis was observed in rats (Poon et al 1995), but this is above the cut-off level for classification.

Increased thyroid weight was observed in a 90-day study only at the highest exposure level tested, 625 mg/kg/day (IRDC 1984). Histopathologically, lesions such as hyperplasia have been observed down to the lowest exposure levels tested (eg. 0.4 mg/kg/day by Poon et al 1995) with an exposure-related increase in severity. However, the severity only ranged from “mild” to “moderate” even...
with an increase in exposure of 3 orders of magnitude. The thyroid changes (increased weight and follicular hypertrophy and hyperplasia) are considered to occur as a result of repeated stimulation of this organ caused by the well-characterised negative feedback control effect arising from plasma T4 depletion. This in turn is related to an increase in the activity of hepatic UDPG-transferase. Humans, unlike rodents, possess a T4 binding protein that greatly reduces susceptibility to plasma T4 depletion and thyroid stimulation. The thyroid effects observed in rats are therefore considered of insufficient concern for classification.

No adverse renal effects were seen in males and female rats at 0.4 mg/kg/day in a 90-day study (Poon et al., 1995). Inner medullary tubular dilatation was seen at 4 mg/kg/day in the kidneys of females only. These lesions were slight, with changes increasing only marginally in severity and incidence at higher levels (up to 420 mg/kg/day for females). An exposure-related increase in the incidence and severity of a mixed population of interstitial inflammatory cells, tubular regeneration and minimal degenerative changes in the tubular epithelium was seen in treated males and females at 10 mg/kg/day or more. At 10 mg/kg/day the severity of these changes was graded as ‘trace’, and even at the highest exposure level, 625 mg/kg/day it was only ‘mild’. As the effects observed in the highest dose group do not seem to be severe, no classification is proposed for repeated-exposure effects.

Mechanistic studies conducted using short-chain chlorinated paraffins (SCCPs, C10-13) indicate deposition of β2µ globulin in proximal convoluted tubules and this may be the primary mechanism for renal toxicity in male rats.

Classification for MCCP’s: No classification for STOT-RE

Justification:

Effects on the liver: the effects justifying the classification (necrosis) are above the cut-off limit values.
Effects on the thyroid: the effects observed are specific for the rat and do not justify classification.
Effects on the kidneys: the data are not detailed enough to have an idea what are effectively the effects around the cut-off values (10-100 mg/kg) instead of 50 mg/kg (DSD cut-off value) but probably we could come to the same conclusion, i.e. the effect is not enough to justify the classification in any category.

3.9.6.3 Examples of mixtures fulfilling the criteria for classification

3.9.6.3.1 Example 5:

Application of criteria for mixture classification: ‘When data are available for the complete mixture’ (see section 3.9.3.3).

Available information:

A mixture with a suspect ingredient (8%) has been tested in a valid 90-day oral study according to TG OECD 408 and GLP. At the dose of 90 mg/kg bw/day severe liver damage (necrosis) has been observed, at 30 mg/kg bw/day slight-moderate liver impairment. The NOAEL was 9 mg/kg bw/day.

Classification: STOT-RE Category 2

Justification:

The classification is based on data of a valid, appropriate animal study for the complete mixture. Therefore the criteria for substances (CLP Annex I, Table 3.9.3) are applied.
### 3.9.6.3.2 Example 6

Application of criteria for mixture classification: 'When data are available for all components' (Section 3.9.3.3). Components of a mixture that should be taken into account are listed below together with their concentrations. Generic concentration limits should be used, non-additivity is applied.

**Available information:**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>% w/w</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>39</td>
<td>NC</td>
</tr>
<tr>
<td>2</td>
<td>5.5</td>
<td>STOT-RE Category 1</td>
</tr>
<tr>
<td>3</td>
<td>54</td>
<td>NC</td>
</tr>
<tr>
<td>4</td>
<td>1.5</td>
<td>STOT-RE Category 2</td>
</tr>
</tbody>
</table>

**Classification of the mixture:** STOT-RE Category 2

**Justification:**

No test data with respect to STOT-RE are available for the complete mixture. Bridging principles can not be applied since no respective test data on a similar mixture are available. The classification of the mixture will be based on the classified ingredients (CLP Annex I, Table 3.9.4).

There is one category 1 ingredient in a concentration of <10%. Therefore the mixture is not classified in category 1. There is one category 1 ingredient in a concentration of ≥1% and <10%, therefore category 2 is warranted. The category 2 ingredient with 1.5% is not taken into account at all, since the concentration is <10%.

### 3.9.6.3.3 Example 7

Application of criteria for mixture classification 'When data are available for all components' (see section 3.9.3.3). Components of a mixture that should be taken into account are listed below together with their concentrations. Generic concentration limits should be used besides when specific concentration limits are indicated, non-additivity applies.

**Available information:**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Classification</th>
<th>Concentration (% w/w)</th>
<th>Mixture Classification</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Category 1</td>
<td>0.1</td>
<td>SCL 0.2%</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Category 1</td>
<td>9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Classification of the mixture:** Category 2 based on 9% of B, which is ≥1% and <10%; A does not contribute to the classification of the mixture, as the concentration of A is <0.2% (the SCL) and additivity of the two ingredients is not foreseen.

### 3.9.6.3.4 Example 8

Application of criteria for mixture classification 'When data are available for all components' (see section 3.9.3.3). Components of a mixture that should be taken into account are listed...
below together with their concentrations. Generic concentration limits should be used besides when specific concentration limits are indicated, non-additivity applies.

Available information:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Classification</th>
<th>Concentration (% w/w)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Cat 1</td>
<td>0.3</td>
<td>SCL 0.2%</td>
</tr>
<tr>
<td>C</td>
<td>Cat 2</td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>

Classification of the mixture: Category 1 since the concentration of A, even if being lower than the generic concentration limit, is higher than the SCL; C does not contribute to the classification.

3.9.6.4 Example of mixtures not fulfilling the criteria for classification

3.9.6.4.1 Example 9

Application of criteria for mixture classification: 'When data are available for all components' (section 3.9.3.3); components of a mixture that should be taken into account are listed below together with their concentrations. Generic concentration limits should be used, non-additivity is applied:

Available information:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Concentration (% w/w)</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>39</td>
<td>NC</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>STOT-RE Category 2</td>
</tr>
<tr>
<td>3</td>
<td>49.5</td>
<td>NC</td>
</tr>
<tr>
<td>4</td>
<td>2.5</td>
<td>STOT-RE Category 2</td>
</tr>
</tbody>
</table>

Classification of the mixture: NC (no classification).

Justification:

No test data with respect to STOT-RE are available for the mixture as a whole. Bridging principles cannot be applied, since no respective test data on a similar mixture are available (CLP Annex I, Table 3.9.4).

The classification of the mixture is based on the classified ingredients. No ingredient is classified in category 1. Therefore the mixture cannot be classified in category 1. Though the sum of the category 2 ingredients (11.5%) is above the generic concentration limit of 10%, the mixture is not classified. This is because for STOT-RE the no additivity approach applies and no individual ingredient ≥ 10% is present in the mixture.

3.9.7 References

PART 4: ENVIRONMENTAL HAZARDS

HAZARDOUS TO THE AQUATIC ENVIRONMENT

Introduction

Scope

Classification of substances hazardous to the aquatic environment

Information applicable for classification of substances hazardous to the aquatic environment

Substance properties used for classification

Information sources and data availability

Evaluation of available information

General considerations

Substances difficult to test

Interpretation of data for aquatic toxicity, degradation and bioaccumulation

Aquatic toxicity

Degradation

Bioaccumulation

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

General aspects of weight of evidence

Guidance on WoE for data deficient substances

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

Outliers

Weight of evidence in degradation

Weight of evidence in bioaccumulation

Classification categories and criteria

Outline of the core classification system

The “Safety net”

Setting M-factor for highly toxic substances

Decision on classification: examples for substances

Example A: Simple substance, straightforward classification based on data
4.1.3.4.2 Example B: Substance with several toxicity data for a trophic level

4.1.3.4.3 Example C: Use of the “escape clause” - NOECs > 1 mg/l for declassification

4.1.3.4.4 Example E: Application of QSAR

4.1.3.4.5 Example F: Application of “weight of evidence” in case of data of questionable / incomprehensible quality

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

4.1.3.4.7 Example H: Polymeric substance, data obtained by read across

4.1.4 Classification of mixtures hazardous to the aquatic environment

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

4.1.4.2 Information requirements

4.1.4.3 When data are available for some or all the components of the mixture

4.1.4.4 Classification criteria for mixtures hazardous to the aquatic environment based on test data

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

4.1.4.6 When toxicity data are available for all components or only for some components of the mixture – use of the Additivity Formula

4.1.4.7 Decision on classification: examples for mixtures

4.1.4.7.1 Example A: When classification data is available for some or all the components of the mixture

4.1.4.7.2 Example B: When test data on the mixture and classification data on the components are available

4.1.4.7.3 Example C: When experimental data are not available for the complete mixture, but there are sufficient data on the individual components and similar tested mixtures: bridging principles

4.1.4.7.4 Example D: When toxicity data are available on components which have not yet been classified – use of the additivity formula
4.1.5 Metal and metal compounds

4.1.6 Hazard communication for hazards to the aquatic environment

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

4.1.8 References
ANNEXES

I  ANNEX I: AQUATIC TOXICITY

I.1 Introduction

I.2 Description of tests

I.2.1 Fish tests

I.2.1.1 Acute testing

I.2.1.2 Chronic testing

I.2.2 Tests with Crustacea

I.2.2.1 Acute testing

I.2.2.2 Chronic testing

I.2.3 Algae / other aquatic plant tests

I.2.3.1 Tests with aquatic macrophytes

I.3 Aquatic toxicity concepts

I.3.1 Acute toxicity

I.3.2 Chronic toxicity

I.3.3 Exposure regimes

I.3.4 Use of QSARs

I.4 Substances which are difficult to test

I.4.1 Unstable substances

I.4.2 Poorly soluble substances

I.4.3 Other factors contributing to concentration loss

I.4.4 Perturbation of the test media

I.4.5 Complex substances

I.5 References
ANNEX II: RAPID DEGRADATION

II.1 Introduction

II.2 Interpretation of degradability data

II.2.1 Ready biodegradability

II.2.1.1 Concentration of test substance

II.2.1.2 Time window

II.2.2 BOD₅/COD

II.2.3 Other convincing scientific evidence

II.2.3.1 Aquatic simulation tests

II.2.3.2 Field investigations

II.2.3.3 Monitoring data

II.2.3.4 Inherent and Enhanced Ready Biodegradability tests

II.2.3.5 Sewage treatment plant simulation tests

II.2.3.6 Soil and sediment degradation data

II.2.3.7 Anaerobic degradation data

II.2.3.8 Hydrolysis

II.2.3.9 Photochemical degradation

II.2.3.10 Estimation of degradation

II.2.3.11 Volatilisation

II.2.4 No degradation data available

II.3 General interpretation problems

II.3.1 Complex substances

II.3.2 Availability of the substance

II.3.3 Test duration less than 28 days

II.3.4 Primary biodegradation

II.3.5 Conflicting results from screening tests
1. II.3.6 Variation in simulation test data
2. II.4 Decision scheme
3. II.5 Reference
III ANNEX III: BIOACCUMULATION

III.1 Introduction

III.2 Interpretation of bioconcentration data

III.2.1 Bioconcentration factor (BCF)

III.2.1.1 BCF in different test species

III.2.1.2 Use of radio-labelled substances

III.2.2 Octanol-water-partitioning coefficient (K\textsubscript{ow})

III.2.2.1 Experimental determination of K\textsubscript{ow}

III.2.2.2 Use of QSARs for determination of log K\textsubscript{ow}

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

III.3.1 Substances difficult to test

III.3.2 Poorly soluble and complex substances

III.3.3 High molecular weight substances

III.3.4 Surface-active substances (surfactants)

III.3.4.1 Octanol-water-partition coefficient (K\textsubscript{ow})

III.4 Conflicting data and lack of data

III.4.1 Conflicting BCF data

III.4.2 Conflicting log K\textsubscript{ow} data

III.4.3 Expert judgement

III.5 Decision scheme

III.6 References

IV ANNEX IV: METALS AND INORGANIC METAL COMPOUNDS

IV.1 Introduction
<table>
<thead>
<tr>
<th>Page</th>
<th>Section</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IV.2</td>
<td>Application of aquatic toxicity data and solubility data for classification</td>
</tr>
<tr>
<td>2</td>
<td>IV.2.1</td>
<td>Interpretation of aquatic toxicity data</td>
</tr>
<tr>
<td>3</td>
<td>IV.2.1.1</td>
<td>Metal complexation and speciation</td>
</tr>
<tr>
<td>4</td>
<td>IV.2.2</td>
<td>Interpretation of solubility data</td>
</tr>
<tr>
<td>5</td>
<td>IV.2.2.1</td>
<td>Assessment of existing data</td>
</tr>
<tr>
<td>6</td>
<td>IV.2.2.2</td>
<td>Screening test for assessing solubility of metal compounds</td>
</tr>
<tr>
<td>7</td>
<td>IV.2.2.3</td>
<td>Full test for assessing solubility of metals and metal compounds</td>
</tr>
<tr>
<td>8</td>
<td>IV.2.3</td>
<td>Comparison of aquatic toxicity data and solubility data</td>
</tr>
<tr>
<td>9</td>
<td>IV.3</td>
<td>Assessment of environmental transformation</td>
</tr>
<tr>
<td>10</td>
<td>IV.4</td>
<td>Bioaccumulation</td>
</tr>
<tr>
<td>11</td>
<td>IV.5</td>
<td>Application of classification criteria to metals and metal compounds</td>
</tr>
<tr>
<td>12</td>
<td>IV.5.1</td>
<td>Introduction to the classification strategy for metals and metal compounds</td>
</tr>
<tr>
<td>13</td>
<td>IV.5.2</td>
<td>Classification strategy for metals</td>
</tr>
<tr>
<td>14</td>
<td>IV.5.2.1</td>
<td>7 day and 28 day Transformation Test</td>
</tr>
<tr>
<td>15</td>
<td>IV.5.3</td>
<td>Classification strategy for metal compounds</td>
</tr>
<tr>
<td>16</td>
<td>IV.5.3.1</td>
<td>7 day and 28 day Transformation Test</td>
</tr>
<tr>
<td>17</td>
<td>IV.5.4</td>
<td>Particle size and surface area</td>
</tr>
<tr>
<td>18</td>
<td>IV.5.5</td>
<td>Classification of mixtures of metal compounds</td>
</tr>
<tr>
<td>19</td>
<td>IV.5.5.1</td>
<td>Classification of alloys and complex metal containing materials</td>
</tr>
<tr>
<td>20</td>
<td>IV.6</td>
<td>Examples of classification of metal and metal compounds</td>
</tr>
<tr>
<td>21</td>
<td>IV.6.1</td>
<td>Example 1: Environmental Classification of a Metal in Powder and Massive form</td>
</tr>
<tr>
<td>22</td>
<td>IV.6.1.1</td>
<td>Transformation-Dissolution Data</td>
</tr>
<tr>
<td>23</td>
<td>IV.6.1.2</td>
<td>Acute Toxicity Reference Value</td>
</tr>
<tr>
<td>24</td>
<td>IV.6.1.3</td>
<td>Chronic Toxicity Reference Value</td>
</tr>
<tr>
<td>25</td>
<td>IV.6.1.4</td>
<td>Comparison of aquatic toxicity data and solubility data</td>
</tr>
<tr>
<td>26</td>
<td>IV.6.1.5</td>
<td>Critical Surface Area (CSA) Approach</td>
</tr>
</tbody>
</table>
Executive summary

Regulation (EC) No 1272/2008 on the classification, labelling and packaging of substances and mixtures (CLP Regulation or CLP) contains rules including criteria for the classification of substances and mixtures. While the classification of substances for human health hazards is based on specific criteria for each hazard class, the classification of mixtures is mainly based on the concentration and the classification of the substances contained in the mixture. CLP includes generic concentration limits (GCLs) which are specific for a hazard class and category and which indicate a threshold above which the presence of a substance in a mixture leads to classification of the mixture. However, under certain conditions specific concentration limits (SCLs) must or may be used. As the Regulation itself does not provide any further guidance on when and how to set SCLs, guidance has been developed for certain hazard classes (see the respective chapters on setting SCLs in Part 3 of the Guidance on the Application of the CLP Criteria).

This Annex provides a background to the method for the determination of SCLs for substances classified as reproductive toxicants as outlined in the guidance in Part 3.

The potency, expressed as the dose for the induction of reproductive effects was identified as the best determinant for setting SCLs. The ED_{10} for effects warranting classification was selected as the most appropriate parameter for estimating the potency. The ED_{10} is the dose level which induces reproductive effects in 10% of the animals above the control group or a change of 10% in the effect compared to the control group. Based on the ED_{10} the substance is placed in a potency group. However, modifying factors can alter the potency group, especially when the potency estimate is close to the boundary between two groups.

The distribution of the potency of a large number of substances classified in Annex VI to CLP as developmental toxicants and/or substances affecting sexual function and fertility was determined by means of establishing two databases. In line with other methods for setting SCLs for other hazard classes, it is proposed to define three potency groups. The boundaries for the potency groups were determined based on the provisions outlined in Article 10(1) of CLP, the results of the database analyses and policy considerations. Most substances are foreseen to fall into the medium potency group which is linked to the GCL. For substances in the high and low potency group, the SCLs included in the table below are proposed.
<table>
<thead>
<tr>
<th>Category 1</th>
<th>Category 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>Dose</td>
</tr>
<tr>
<td>SCL</td>
<td>SCL</td>
</tr>
<tr>
<td>High potency group</td>
<td></td>
</tr>
<tr>
<td>ED$_{10}$ below 4 mg/kg bw/day</td>
<td>0.03% (factors of 10 lower for extremely potent substances)</td>
</tr>
<tr>
<td>Medium potency group</td>
<td></td>
</tr>
<tr>
<td>0.3% (GCL)</td>
<td>3% (GCL)</td>
</tr>
<tr>
<td>Low potency group</td>
<td></td>
</tr>
<tr>
<td>ED$_{10}$ above 400 mg/kg bw/day</td>
<td>3%</td>
</tr>
<tr>
<td>ED$_{10}$ above 400 mg/kg bw/day</td>
<td>3-10%$^\wedge$</td>
</tr>
</tbody>
</table>

$^\wedge$The limit of 10% may be considered in certain cases, such as for substances with a ED$_{10}$ value above 1000 mg/kg bw/day and a NOAEL below 1000 mg/kg bw/day

2 Introduction

2.1 General description of the classification system for reprotoxic substances and mixtures

Regulation (EC) No 1272/2008 (CLP) contains rules for the classification of substances and mixtures. In chapter 3.7 of Annex I to this Regulation, criteria are given for the classification of substances as reprotoxicants in one of the following categories:

Category 1: Known or presumed human reprotoxicant

Substances are classified in Category 1 for reproductive toxicity when they are known to have produced an adverse effect on sexual function and fertility, or on development in humans or when there is evidence from animal studies, possibly supplemented with other information, to provide a strong presumption that the substance has the capacity to interfere with reproduction in humans. The classification of a substance is further distinguished on the basis of whether the evidence for classification is primarily from human data (Category 1A) or from animal data (Category 1B).

Category 1A: Known human reprotoxicant

The classification of a substance in Category 1A is largely based on evidence from humans.

Category 1B: Presumed human reprotoxicant

The classification of a substance in Category 1B is largely based on data from animal studies. Such data must provide clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic
effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate.

Category 2: Suspected human reproductive toxicant

Substances are classified in Category 2 for reproductive toxicity when there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development, and where the evidence is not sufficiently convincing to place the substance in Category 1. If deficiencies in the study make the quality of evidence less convincing, Category 2 could be the more appropriate classification. Such effects shall have been observed in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects.

Effects on or via lactation are also part of the hazard class reproductive toxicity. Classification for these effects is independent of the classification in the classes 1A, 1B or 2 as described above. Development of a method for the determination of SCLs for substances with effects on or via lactation is outside the scope of this document. Therefore, these effects and this classification are not further considered in this document.

The classification of mixtures containing substances classified for reproductive toxicity and of substances containing impurities, additives or constituents classified for reproductive toxicity is based on the concentration of the reproductive toxic component(s). Table 3.7.2 of Annex I to CLP contains GCLs above which classification for reproductive toxicity is required. The GCL is 0.3% for reprotoxicants Category 1A and 1B and 3.0% for Category 2. However, a GCL for all substances may not be protective for high potency substances and may be overprotective for substances with a low potency. Therefore, SCLs may be needed for such substances.

According to CLP Article 10, SCLs shall be set where adequate and reliable scientific information shows that the hazard of a substance is evident at a level below the GCL. This results in SCLs below the GCLs. SCLs above the GCLs may be set in exceptional circumstances where adequate, reliable and conclusive scientific information shows that a hazard of a substance is not evident at a concentration above the GCL. Normally, substances that fulfil the criteria for reproductive toxicity are subject to a harmonised classification and labelling and included in Annex VI to CLP. In such cases, SCLs are set via the procedure for harmonisation of classification and labelling of substances in line with CLP Article 37. When there is no such harmonised entry in Annex VI to CLP, a manufacturer, importer or downstream user must self-classify reproductive toxic substances and must set lower or may set higher SCLs than the GCLs if justified according to CLP Article 10(1). He may also provide a proposal for a harmonised classification (CLP Article 37(2)), including an SCL where appropriate.
2.2 Description of the process for the development of a method to set SCLs for reproductive toxic substances

There are no hazard specific criteria for the setting of SCLs in CLP. According to CLP Article 10 (7), the European Chemicals Agency (ECHA) is required to provide further guidance on the setting of SCLs. A working group was established to develop such guidance for the hazard class reproductive toxicity, with the exception of the effects on or via lactation.

The work on the proposal for guidance on the determination of SCLs for reproductive toxicants was initiated by an EU working group of the TC C&L (Technical Committee on Classification and Labelling of Dangerous Substances), continued under the REACH Implementation Project (RIP) 3.6 and subsequently under the auspices of ECHA.

To get an impression of the possible parameters for potency and their distribution, two databases were compiled, containing several parameters for a large number of substances classified for developmental toxicity and impaired fertility. Based on the compiled data choices were made for the most appropriate parameter, the boundaries of the potency groups and the associated SCLs.

In the course of the guidance development, three documents have been produced. The first document is the actual guidance chapter included in the Guidance on the Application of the CLP Criteria. The second document is this annexed background document, describing the process and considerations and providing the rationale for the proposed guidance. The third document is a publication of the databases of parameters for developmental toxicants and substances with an effect on sexual function or fertility and the analyses of the databases [(Muller et al., 2011)](Muller et al., 2011).

Chapter 2 of this document contains a number of theoretical considerations on the determination of the most appropriate parameter and the SCLs. A description of the databases and the analyses is also provided in this chapter. The general procedure for determining the SCLs and guidance on the determination of the ED_{10} (dose producing 10% of effects) are provided in Chapter 3. Chapter 4 is dedicated to the modifying factors. Chapter 5 describes and justifies the potency boundaries and corresponding SCLs.

2.3 Considering potency in setting specific concentration limits for various health hazards

The criteria for classification for reproductive toxicity are based on the strength of scientific evidence that the substance can cause reproductive toxicity. In general, no specific considerations are given to the potency of the substance to induce reproductive toxicity.

On the other hand, classification for several other health hazard classes is based on potency. Substances with different potency are classified in different categories within the hazard class. The classification of mixtures for that hazard class is then based on the concentration of the substance in the mixture and the hazard category or the potency (for acute toxicity) of the substance.

For acute toxicity, the potency is based on the acute toxicity estimate (ATE). The ATE is the dose level which induces 50% mortality in a acute toxicity study (LD_{50} or LC_{50}) or the estimated LD_{50} or LC_{50} using fixed dose procedure or the acute toxic class method. This value is used to classify a substance into one of several categories. For mixtures, the ATE
value is used to estimate the potency of a mixture by calculation. The estimated potency is then used to classify the mixture into a hazard category.

For specific target organ toxicity (STOT) after single and repeated exposure, the potency is defined as the dose at which the substance shows significant toxic effects in a study. Based on the potency, a substance is either classified for STOT into one of two hazard categories or not classified. The classification of a mixture containing a substance classified for STOT depends on the percentage of the substance in the mixture and the hazard category of the substance. A minimal percentage is included in the criteria. SCLs have to be determined for substances with a very high potency.

Classification for carcinogenicity is, as for reproductive toxicity, based on the strength of scientific evidence and again no specific consideration is given to the potency. The classification of mixtures containing a carcinogenic substance is based on the GCL unless a SCL has been allocated for that substance as outlined in Annex VI to CLP. SCLs for carcinogenic substances are determined based on the potency for carcinogenic effects based on the T25. The T25 is defined as the daily dose (in mg/kg bw) inducing a tumour incidence of 25% upon lifetime exposure after correction for the spontaneous incidence. This is mainly based on animal studies. Substances are divided into 3 groups based on the T25. High potency substances have a T25 < 1mg/kg bw/ day, medium potency substances have a T25 between 1 -100 mg/kg bw/day, and T25> 100 mg/kg bw/day for low potency substances. Besides the T25, other elements were included that modify the potency evaluation (Commission Working Group, date unknown). This method has been included in the Guidance on the Application of the CLP Criteria.

The use of potency for the classification into different categories for several other hazard classes and the use of the potency to set SCLs for carcinogenic substances, justifies the use of potency as a first approach also for setting SCLs for reproductive toxic substances. As no definition of potency for reproductive toxicants was available, the following definition is used as a working definition:

**Reproductive toxicity potency is defined as the dose which induces reproductive toxic effects with a specific type, incidence and magnitude, considering the study design in terms of species and strain, exposure route, exposure duration, exposure window in the life cycle, and possible concomitant parental toxicity.**

According to this definition ‘Potency’ is primarily based on applied dose and can be modified by consideration of ‘severity’. Within this definition the dose is defined as the amount of substance to which the animals or humans that showed the effect (meaning type, incidence and magnitude) were exposed on an mg/kg bw/day basis. The incidence is the proportion of animals or humans that showed the effect. The type of effect describes which property of an organ or system of the animal or human is affected and the magnitude describes the level of change compared to the control. Together, the incidence, type and magnitude describe the ‘severity’ of the effect, meaning how adverse the effect or combination of effects is. With specific incidence, type and magnitude (together specific severity) a comparable level of severity is indicated for different effects.

The working definition above allows potency to be defined at different levels of specific severity, for example at the ED_{10} and the LOAEL (Lowest Observed Adverse Effect Level), and for different type of effects. Therefore, several possible estimates for potency were investigated.
2.4 Parameters for potency for reproductive toxicity

A consistent database to derive potency estimates for reproductive toxicity was lacking. Therefore, data on substances classified for effects on reproduction were collected and analysed. This was done separately for substances with an effect on development and substances with an effect on sexual function and fertility because the types of effects clearly differ between these two main types of reproductive effects. Therefore, this chapter falls into two parts, namely one for parameters for potency of substances with developmental effects (chapter 2.3.1) and one for parameters for potency of substances with effects on sexual function and fertility (chapter 2.3.2). As potency is primarily based on the dose in mg/kg bw/day at which different adverse effects are observed, a number of parameters/dose descriptors (e.g. NOAEL, LOAEL, ED10 etc.) exist for each type of adverse effect. The collected data included the NOAEL, LOAEL and ED10 (effective dose with a 10% incidence or effect level above the background) as parameters for the effect on reproduction of each substance. They were further divided into effects fulfilling the criteria for classification (named “LOAEL (classification)” for example) and any effects on reproduction (named “NOAEL (overall)” for example). Together, this sub-division results in 6 different potency parameters, see Table 1. Other data, e.g. a mutagenicity classification of a substance, the type of effect at the LOAEL and species used in the test, were also collected. These parameters were analysed and the results tabulated and plotted graphically. The results were published by Muller et al., 2011, available as an Annex to this document until publication. As the data for these two main types of reproductive toxicity were analysed separately, the results are provided separately.

2.4.1 Potency parameters for developmental toxicants

Data for one or more of the parameters for development were available for 99 substances classified for developmental toxicity when the work on this guidance development started. For almost all substances a LOAEL is available but a NOAEL and ED10 were sometimes missing. The absence of a NOAEL is mostly caused by the absence of a dose level without an effect in the study or database of a substance. The absence of an ED10 value is mainly caused by the absence of a NOAEL and in most of those cases an ED10 could only be derived by a benchmark dose (BMD) approach to avoid interpolation between the LOAEL and the vehicle control. Another cause for the absence of ED10 values is the limited reporting of effect levels in the consulted study summaries or study reports.

The difference in the average value between the highest and lowest of the 6 parameters for potency is a factor of 4 or less. This is very small compared to the difference in potency between substances for each parameter of up to 1,000,000 fold (Table 1). The potency difference is more pronounced for a NOAEL or LOAEL compared to an ED10 mainly because for most potent substances only a NOAEL and/or a LOAEL was available but not an ED10. The available data indicate that there is a close relation between the NOAEL, LOAEL and ED10 for most substances. The average LOAEL is between a factor of 2 and 3 above the average NOAEL. The fact that it is not closer to the factor of 3 to 4 that is normally used between dose levels is probably due to the absence of a NOAEL for a number of substances.

---

44 NOAEL means No Observed Adverse Effect Level
45 LOAEL means Lowest Observed Adverse Effect Level
The average \( ED_{10} \) (classification), is slightly higher than the average \( LOAEL \) (classification). The difference is more pronounced for the “overall” values, namely approximately a factor of 2. These findings are caused by both the dose spacing in the studies and the limited discriminative power of the \( NOAEL \) approach.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N</th>
<th>Average</th>
<th>Standard deviation</th>
<th>Lowest value</th>
<th>Highest value</th>
<th>Potency difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>( NOAEL ) (overall)</td>
<td>68</td>
<td>12</td>
<td>10</td>
<td>0.002</td>
<td>684</td>
<td>342000</td>
</tr>
<tr>
<td>( LOAEL ) (overall)</td>
<td>98</td>
<td>25</td>
<td>13</td>
<td>0.002</td>
<td>2281</td>
<td>1140500</td>
</tr>
<tr>
<td>( ED_{10} ) (overall)</td>
<td>59</td>
<td>43</td>
<td>6</td>
<td>0.3</td>
<td>785</td>
<td>2617</td>
</tr>
<tr>
<td>( NOAEL ) (classification)</td>
<td>76</td>
<td>18</td>
<td>11</td>
<td>0.002</td>
<td>1100</td>
<td>550000</td>
</tr>
<tr>
<td>( LOAEL ) (classification)</td>
<td>97</td>
<td>40</td>
<td>13</td>
<td>0.002</td>
<td>2281</td>
<td>1140500</td>
</tr>
<tr>
<td>( ED_{10} ) (classification)</td>
<td>63</td>
<td>48</td>
<td>6</td>
<td>0.3</td>
<td>933</td>
<td>3110</td>
</tr>
</tbody>
</table>

A part of the differences in average values and potency between the different parameters in Table 1 is probably caused by the difference in the number of substances for which a particular variable is present. When only substances are used for which all 6 parameters were present, this reduces the database to 44 substances (Table 2). A part of the difference between the parameters in potency difference can be explained by the unusual dose levels (\( NOAEL 0.026 \) mg/kg bw/day and \( LOAEL 0.26 \) mg/kg bw/day) used in the study for the substance that had the lowest values for all parameters (cadmium oxide).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Average</th>
<th>Standard deviation</th>
<th>Lowest value</th>
<th>Highest value</th>
<th>Potency difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>( NOAEL ) (overall)</td>
<td>19</td>
<td>7</td>
<td>0.026</td>
<td>684</td>
<td>26308</td>
</tr>
<tr>
<td>( LOAEL ) (overall)</td>
<td>58</td>
<td>7</td>
<td>0.260</td>
<td>2281</td>
<td>8773</td>
</tr>
<tr>
<td>( ED_{10} ) (overall)</td>
<td>44</td>
<td>5</td>
<td>0.300</td>
<td>570</td>
<td>1900</td>
</tr>
<tr>
<td>( NOAEL ) (classification)</td>
<td>25</td>
<td>7</td>
<td>0.026</td>
<td>684</td>
<td>26308</td>
</tr>
<tr>
<td>( LOAEL ) (classification)</td>
<td>71</td>
<td>6</td>
<td>0.260</td>
<td>2281</td>
<td>8773</td>
</tr>
<tr>
<td>( ED_{10} ) (classification)</td>
<td>49</td>
<td>6</td>
<td>0.300</td>
<td>933</td>
<td>3110</td>
</tr>
</tbody>
</table>

Comparing Tables 1 and 2 indicates no major changes in average, standard deviation and highest value for each parameter. However, the lowest value changes for several parameters. The resulting potency difference becomes much more comparable between the parameters. This indicates that the difference between the parameters in potency difference in Table 1 is mainly due to the absence of an \( ED_{10} \) for some very potent substances.
2.4.2 Potency parameters for substances with an adverse effect on sexual function and fertility

Data for one or more of the potency parameters were available for 93 substances classified for adverse effects on sexual function and fertility (hereafter called fertility toxicants) when the work with the guidance development started. For all substances, an LOAEL was available but a NOAEL and an ED_{10} were sometimes missing. The absence of a NOAEL is mostly caused by the absence of a dose level without an effect in the study or database of a substance. The absence of an ED_{10} value is mainly caused by the absence of a NOAEL and in most of those cases an ED_{10} could only be derived by a Benchmark Dose (BMD) approach to avoid interpolation between the LOAEL and the vehicle control. Another cause for the absence of an ED_{10} values is the limited reporting of effect levels in the consulted study summaries or study reports.

The difference in the average values between the highest and lowest of the 6 parameters for potency is less than a factor of 4. This is small compared to the difference in potency between substances for each parameter of up to 30,000 (Table 3). The difference in potency within the parameters is more pronounced for the NOAEL values than for the values of LOAEL and ED_{10}, which is mainly due to one substance with a NOAEL of 0.032 mg/kg bw/day but an LOAEL of 10 mg/kg bw/day. The available data indicate that there is a close relation between the NOAEL, LOAEL and ED_{10} for most substances. The average LOAEL is between a factor 2 and 3 above the average NOAEL. The fact that it is not closer to the factor of 3 to 4 that is normally used between dose levels is probably due to the absence of an NOAEL for a number of substances. The average ED_{10} is between the average NOAEL and LOAEL.

Table 3. Average values (assuming log/normal distribution) (in mg/kg bw/day) and potency differences for parameters for all fertility toxicants of the database

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N</th>
<th>Average</th>
<th>Standard deviation</th>
<th>Lowest value</th>
<th>Highest value</th>
<th>Potency difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOAEL (overall)</td>
<td>68</td>
<td>20</td>
<td>7</td>
<td>0.032</td>
<td>635</td>
<td>19844</td>
</tr>
<tr>
<td>LOAEL (overall)</td>
<td>93</td>
<td>54</td>
<td>7</td>
<td>0.25</td>
<td>2060</td>
<td>8240</td>
</tr>
<tr>
<td>ED_{10} (overall)</td>
<td>37</td>
<td>31</td>
<td>5</td>
<td>0.6</td>
<td>1065</td>
<td>1775</td>
</tr>
<tr>
<td>NOAEL (classification)</td>
<td>70</td>
<td>24</td>
<td>7</td>
<td>0.032</td>
<td>940</td>
<td>29375</td>
</tr>
<tr>
<td>LOAEL (classification)</td>
<td>93</td>
<td>62</td>
<td>7</td>
<td>0.33</td>
<td>2060</td>
<td>6242</td>
</tr>
<tr>
<td>ED_{10} (classification)</td>
<td>37</td>
<td>33</td>
<td>6</td>
<td>0.6</td>
<td>1065</td>
<td>1775</td>
</tr>
</tbody>
</table>

A part of the differences in the average values and in potency between the different parameters in Table 3 is probably caused by the difference in the number of substances for which a particular parameter is present. When only substances are used for which all 6 parameters were present, this reduces the database to 34 substances (Table 4).
Table 4. Average values (assuming log/normal distribution) (in mg/kg bw/day) and potency differences for parameters for fertility toxicants (N=34) with all 6 parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Average</th>
<th>Standard deviation</th>
<th>Lowest value</th>
<th>Highest value</th>
<th>Potency difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOAEL (overall)</td>
<td>19</td>
<td>6</td>
<td>0.3</td>
<td>250</td>
<td>833</td>
</tr>
<tr>
<td>LOAEL (overall)</td>
<td>72</td>
<td>6</td>
<td>0.7</td>
<td>1000</td>
<td>1429</td>
</tr>
<tr>
<td>ED_{10} (overall)</td>
<td>35</td>
<td>5</td>
<td>1.3</td>
<td>1065</td>
<td>819</td>
</tr>
<tr>
<td>NOAEL (classification)</td>
<td>24</td>
<td>6</td>
<td>0.3</td>
<td>940</td>
<td>3133</td>
</tr>
<tr>
<td>LOAEL (classification)</td>
<td>89</td>
<td>6</td>
<td>0.7</td>
<td>1580</td>
<td>2257</td>
</tr>
<tr>
<td>ED_{10} (classification)</td>
<td>39</td>
<td>5</td>
<td>1.3</td>
<td>1065</td>
<td>819</td>
</tr>
</tbody>
</table>

Comparing Tables 3 and 4 indicates no major changes in average, standard deviation and highest value for each parameter. However, the lowest value changes for some parameters. The resulting potency difference becomes much more comparable between the parameters. This indicates that part of the differences between the parameters in potency difference in Table 3 is due to the absence of an ED_{10} for some very potent substances.

2.4.3 Conclusions on the most appropriate parameter for potency

As LOAELs are available for almost all substances, this could be considered the most useful informed parameter on which to base potency. However, in the absence of a NOAEL, a LOAEL is not a suitable parameter for potency because there is no indication to what extent the real LOAEL could be lower than the LOAEL observed. The lower number of substances for which an ED_{10} is available is probably due to the limitations of the available study summaries for several substances. Use of the ED_{10} requires access to a detailed summary of the study or the study report itself which was not available for several substances in the database.

However, this guidance will be applied by both industry and Member State Competent Authorities when preparing proposals for harmonised classification and labelling, and by industry in case of self-classification of a reproductive toxic substance for which there is no entry in Annex VI to CLP.

Companies have access to their own studies. It is expected that by the completion of the REACH registration deadlines, more detailed information including ED_{10} will be available for more substances than in this database used to develop this guidance.

Member States will have access to the study summaries in the registrations. The full studies could be requested by ECHA or by a Member State Competent Authority, according to CLP Article 49(3).

It should be noted that in the absence of a NOAEL, an ED_{10} cannot be determined by interpolation, in case the size of the effect at the LOAEL is more than 10%. However, an ED_{10} can be estimated using benchmark dose (BMD) software when sufficient data are
available. A NOAEL and LOAEL cannot be estimated using the BMD approach. In addition, 
a fixed level of effect of e.g. 10% (ED_{10}) is considered to be more representative for the 
potency and facilitates comparisons of relative potency between substances to a greater 
extent, than a LOAEL which is a chosen dose level.

For most other hazard classes, the SCLs are based on effect levels. For carcinogenicity the 
T25 is used, and for skin sensitisation the EC_{3} value or the dose level with a certain level of 
responders is used. Therefore, the LOAEL or ED_{10} is considered a more appropriate 
parameter for determination of an SCL than the NOAEL.

For substances where there is a difference in the LOAEL overall (lowest dose with any effect 
on reproduction) versus the LOAEL classification (lowest dose with an effect on 
reproduction fulfilling the classification criteria), this is in most cases due to non-significant 
increases in lethalities or malformations or decreases in foetal body weight at the LOAEL 
overall versus significant increases in lethalities or malformations at the LOAEL 
classification. The difference between significant and non-significant effects will disappear if 
the ED_{10} is used as parameter for potency.

The difference in parameters between “overall” and “classification” was sometimes due to 
limited effects that normally do not warrant classification such as a small increase in 
variations at the LOAEL and to more severe effects warranting classification at a higher dose 
level. To have a more consistent parameter for potency, it was preferred to use the parameters 
for effects warranting classification.

Overall, the use of the ED_{10} for effects warranting classification is proposed as the most 
appropriate estimate for the potency. The advantage of this parameter is that it is a dose level 
with a specified level of effects of at least a certain severity. This is in line with most 
classification criteria and with other methods for the determination of SCLs.

Furthermore, not all aspects included in the working definition of reproductive potency are 
fully taken into account in the ED_{10}. Therefore, certain additional parameters should be 
considered which can change the potency group as determined by using the ED_{10}, resulting in 
the setting of lower or higher concentration limits. See chapter 4 for such modifying factors.

### 3 Determination of the potency for reproductive toxicity

#### 3.1 Procedure for setting SCL for reproductive toxicity

When the reproductive toxicity hazard of a substance is assessed, consideration should also 
be given to the potency if there is reason for concern (see section 2.1 above). The available 
data from animal and human studies are evaluated to establish the reproductive toxicity dose 
descriptor, ED_{10}, as described in this chapter. A preliminary conclusion as to whether the 
substance shows high, medium or low potency is taken based on the ED_{10} data. In some 
cases, such a potency evaluation will not be appropriate (see section 3.2).

The preliminary potency evaluation may be modified after due consideration of a number of 
other elements (modifying factors) as described in Chapter 4. Each final potency group 
results in a GCL or an SCL. In this way specific concentration limits are then set by taking 
into account all relevant factors.
3.2 Cases where potency evaluation is difficult or unfeasible

The process for evaluating potency assumes the availability of certain types of data. However, these data may not always be available. Also the classification of substances as reproductive toxicants may be based on information such as grouping, read-across and the use of QSARs. In such cases, no direct estimate of the reproductive toxicity potency based on an ED$_{10}$ value is possible. While there are often good reasons for extrapolation of the hazardous properties from one or more substances to another, the expected potency of the individual substances within the group may vary. In these cases a potency evaluation may be difficult or impossible. However, determination of the classification and the potency using non-testing methods is possible in some cases. These cases could include interpolation of an ED$_{10}$ within a group of substances with comparable structures and effects or correction for molecular weight in case of extrapolation between different salts with comparable availability. If the classification of a substance in Category 2 is done on the basis of “limited evidence”, the quality of the available data will in such cases determine whether a potency assessment is possible. In cases where no further evaluation is possible, the generic concentration limits of CLP apply. In general, more conclusive evidence is required when moving a substance to a lower potency group than to a higher potency group.

3.3 Determination of the ED$_{10}$ value

Based on the above discussion, reproductive toxicity potency (ED$_{10}$) is defined as the lowest dose which induces reproductive toxic effects which fulfil the criteria for classification for reproductive toxicity with an incidence or magnitude of 10% after correction for the spontaneous incidence.

Determining exactly which effect or combination of effects that fulfils the classification criteria may seem difficult. However, for the majority of substances in the database, the developmental effect(s) evident at the lowest dose level for which developmental effects could be observed was/were an increase in malformations and/or lethalities of the offspring. The ED$_{10}$ for effects on sexual function and fertility is mainly based on effects on fertility and histopathological changes of the reproductive organs. These effects clearly fulfil the classification requirements. Also, allocation to the final SCLs is based on a limited number of potency groups and not on the exact ED$_{10}$ value. Therefore, in practice, it is likely that the ED$_{10}$ values for several different effects fall into the same potency grouping resulting in the same SCL.

The ED$_{10}$ may either be obtained directly or by linear interpolation from experimental data, or estimated using BMD software. The use of BMD software will result in a more precise estimate of the ED$_{10}$ because all data of the dose-response curve are used. The use of BMD software is needed when an ED$_{10}$ cannot be determined using linear interpolation due to the absence of a NOAEL when the LOAEL has an effect size above 10%. In general, however, the use of BMD software is not required because of the wide potency groups used for setting the SCLs. However, it could be important for substances which are close to the boundary of a potency group. When an ED$_{10}$ cannot be calculated by linear interpolation or by the use of BMD software, the LOAEL should be used instead of the ED$_{10}$. However, in such cases, only SCLs below the GCL can be determined and not above the GCL, if no other reliable information is available, because it may be difficult in these cases to prove the absence of effects at lower dose levels.
3.3.1 Determination in practice

Often, in practice, often several effects on reproduction are observed in various studies, and the classification is based on the weight of evidence of all results. As a first step, it must be determined whether the classification is for effects on development, for effects on sexual function and fertility or both. The effects used for classification for developmental toxicity must only be used to determine the potency for developmental toxicity only. The same applies to effects on sexual function and fertility. This means that for substances fulfilling the criteria for classification for both developmental effects and effects on sexual function and fertility, two ED$_{10}$ values are derived which may differ. The lowest ED$_{10}$ of the effect(s) that fulfil the criteria for classification in the different studies is then used as the ED$_{10}$ that determines the potency of that substance. Where there are doubts as to whether a specific effect fulfils the classification criteria, ED$_{10}$ values for different effects could be taken forward to the next step to see the impact.

The calculation of the ED$_{10}$ by linear interpolation requires a different approach depending on whether the effect is measured as an incidence (quantal data, non-parametric data), a magnitude (continuous data, parametric data) or both.

3.3.2 Quantal or non-parametric data

For effects that are measured as changes in incidence, such as an increase in the number of malformations or resorptions, the ED$_{10}$ is defined as the dose level at which 10% of the test population above the incidence in the concurrent control shows the effect. There may be occasions where the historical control data have to be taken into account. In the example in Table 5, the ED$_{10}$ is 90 mg/kg bw/day because at this dose level 12% - 2% (control) = 10% of the test population shows the effect.

Table 5. Example on the calculation of the ED$_{10}$

<table>
<thead>
<tr>
<th>Dose</th>
<th>0 mg/kg</th>
<th>10 mg/kg</th>
<th>30 mg/kg</th>
<th>90 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malformations</td>
<td>2%</td>
<td>3%</td>
<td>7%</td>
<td>12%</td>
</tr>
</tbody>
</table>

For some effects the results of the calculation of the ED$_{10}$ based on the incidence in pups may be different from that based on the incidence in litters. Mechanism of action studies may indicate which parameter is more appropriate, but in the absence of such information it is not possible to estimate which ED$_{10}$ is more appropriate for a specific effect. In such cases, both the incidence in offspring and the incidence in litters should be calculated, and the lowest ED$_{10}$ value should be used.
3.3.3 Continuous or parametric data

For effects that are measured as changes in magnitude such as pup weight or testis weight, the ED\textsubscript{10} is defined as the dose at which a change of 10% compared to the control group is observed. In the example in Table 6, the ED\textsubscript{10} is 19.3 mg/kg bw/day because at this dose level the mean foetal bodyweight is calculated to be 90% of the control value. A 10% reduction of the control value of 6.2 g gives 5.58 g. Interpolation between 10 and 30 mg/kg bw/day to a dose level which would be expected to result in a foetal bodyweight of 5.58 g gives a value of 19.3 mg/kg bw/day.

Table 6. Example on the calculation of the ED\textsubscript{10}

<table>
<thead>
<tr>
<th>dose (mg/kg)</th>
<th>0 mg/kg</th>
<th>10 mg/kg</th>
<th>30 mg/kg</th>
<th>90 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>foetal bodyweight (g)</td>
<td>6.2</td>
<td>6.0</td>
<td>5.1</td>
<td>4.5</td>
</tr>
</tbody>
</table>
| (NOAEL) | (LOAEL) |}

3.3.4 Data combining incidence and magnitude

Some effects such as histopathological changes in the testis are a combination of effects on incidence and magnitude (grading of the effect by a pathologist). However, calculation of an ED\textsubscript{10} taking both the incidence and the magnitude into account is not possible or at least more complex. The ED\textsubscript{10} should therefore be based on the incidence of the effect below or above a certain magnitude. The magnitude of the effects that will be selected as a starting point has to be chosen carefully. The ED\textsubscript{10} is then determined as the dose level at which the incidence, of effects with a magnitude above that of the starting point, is 10% above the incidence in the control group. In practice this means that the grading system is converted into a simplified system where only percentages of animals in each dose group with an effect with a magnitude above the starting point are regarded as positive. However, it is recognised that this approach uses only a part of the actual data and is imprecise, and it may be appropriate that other effects should also be considered in determining the ED\textsubscript{10}.

Table 7. Example of the calculation of the ED\textsubscript{10} for testicular effects (N=10)

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Testicular degeneration (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>none</td>
</tr>
<tr>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>NOAEL</td>
<td>10</td>
</tr>
<tr>
<td>LOAEL</td>
<td>30</td>
</tr>
</tbody>
</table>

For the example in Table 7, the effects observed in the 10 mg/kg and 30 mg/kg dose groups have to be considered as equivalent to the effects of the control group so the NOAEL is 30 mg/kg. The magnitude of the testicular effect in the control group and the 10 and 30 mg/kg bw/day groups is slight or less. Because of the incidence observed in these three groups, the level of damage estimated as the starting point magnitude is ‘slight’. The ED\textsubscript{10} was then
defined as a 10% increase of moderate effects or more above the control. In this example the incidences for moderate testicular degeneration or more are 10%, 0%, 10% and 100% at respectively 0, 10, 30 and 90 mg/kg bw/day. The ED$_{10}$ is then defined as the dose level with 20% (control plus 10%) of moderate testicular effects. The ED$_{10}$ would be 36.6 mg/kg bw/day based on interpolation between 30 and 90 mg/kg bw/day to a dose with 20% animals with moderate testicular degeneration or higher.

3.3.5 Specific data types

Non-oral studies

In most cases only oral studies will be available and used for the determination of the potency. However, if the classification is based on the effects seen in non-oral studies or only non-oral studies are available, then these data should also be used to determine the potency. This requires route-to-route extrapolation of the external dermal or inhalatory dose to a corresponding oral dose. This should be done as described in the ECHA guidance on information requirements and chemical safety assessment (IR/CSA, section R.8).

Extrapolation from dermal exposure to oral exposure should only be done when there are sufficient kinetic data on dermal availability because assuming a high dermal availability is not a worst case assumption. In cases where such data are not available a direct comparison of the dermal dose with the oral potency ranges should be performed. However, such comparison should not result in moving the substance to a lower potency group (higher ED$_{10}$) – only moving the substance to a higher potency group (lower ED$_{10}$) should be considered.

Extrapolation from inhalatory exposure to oral exposure should only be done when there are sufficient kinetic data on inhaled availability because assuming a high inhaled availability is not a worst case assumption. If no inhalatory information on availability is available then it should be assumed that the inhalation and oral availability are comparable. However, such comparison should not result in moving the substance to a lower potency group (higher ED$_{10}$) – only moving the substance to a higher potency group (lower ED$_{10}$) should be considered.

Human data

The use of human data for ED$_{10}$ calculation has several drawbacks including limited data on exposure, limited data on the size of the exposed population and limited information as to whether the exposure included the window of sensitivity. For all these reasons, it is difficult to determine an ED$_{10}$ based on human data. Therefore, and because in most instances animal data are also available for determining an ED$_{10}$, these data are evaluated together on a case by case basis. Guidance on the use of human data for the derivation of DNELs and DMELs has been developed by ECHA and is available at the ECHA website, see http://guidance.echa.europa.eu/guidance4_en.htm

3.4 Provisional allocation of a substance to a potency group

A preliminary potency evaluation applying the ED$_{10}$ value is made at this stage.

ED$_{10}$ values can be used to place substances classified as a reproductive toxicant into selected ranges that define potency groups. As such, it is possible to identify reproductive toxicants of
high and low potency. For the purpose of determining the preliminary potency group, the following groups are proposed:

Table 8 Boundaries of the potency groups.

<table>
<thead>
<tr>
<th>Potency group</th>
<th>Boundaries</th>
</tr>
</thead>
<tbody>
<tr>
<td>High potency group</td>
<td>$ED_{10}$ value $\leq 4$ mg/kg bw/day</td>
</tr>
<tr>
<td>Medium potency group</td>
<td>$4$ mg/kg bw/day $&lt; ED_{10}$ value $\leq 400$ mg/kg bw/day</td>
</tr>
<tr>
<td>Low potency group</td>
<td>$ED_{10}$ value $&gt; 400$ mg/kg bw/day</td>
</tr>
</tbody>
</table>

The justification of these boundaries is provided in chapter 5.

4 Modifying factors

Several possible elements of reproductive toxicity were considered as elements which should also be taken into account when determining the potency group for reproductive toxicity of a substance (modifying factors). Modifying factors may change the potency group for a substance. While some modifying factors should always be taken into account, other modifying factors could be more relevant when the potency is close to the boundary between two groups (see Table 8 above). It should be noted that several of the elements may be interrelated.

Some factors may have already been taken into account in deciding on the classification as a reproductive toxicant. Where such considerations have been made, care should be taken not to use that information again when determining the potency. For example, when the effects determining the $ED_{10}$ were observed at dose levels also causing maternal toxicity, this should already have been taken into consideration during the classification and should not be used again to set a higher SCL. Factors considered not to be used as modifying factors are included in section 4.7 of this Annex. The following factors are used as modifying factors:

- Type of effect / severity
- Data availability
- Dose-response relationship
- Mode or mechanism of action
- Toxicokinetics
- Bio-accumulation of substances

Comment ECHA: The draft guidance text originally included reference to volatility as a modifying factor and limit dose calculations for the derivation of a correction factor for the $ED_{10}$ for volatile substances.

The ECHA Secretariat did not include the pertinent texts in the draft guidance for the following reasons:

- ECHA considers volatility as being a physical property which is rather related to exposure than to potency of a substance causing reproductive toxicity effects (see also the definition of potency in this annex);
• Volatility has not been considered in the guidance on how to set SCLs for hazard classes related to systemic toxicity, such as carcinogenicity. Nevertheless, it is suggested to be a factor to take into consideration when setting SCLs for narcotic effects (STOT-SE 3);

• Volatility is not specifically mentioned in the criteria for classification for any other hazard class other than STOT-SE and -RE (3.8.2.1.10.4 and 3.9.2.10.4) for which the guidance recommends a specific precautionary statement on the label for highly volatile substances.

Thus, the ECHA Secretariat believes that the introduction of volatility as a modifying factor only for the derivation of SCL for reprotoxic effects would lead to inconsistencies. If there should be a preference for introducing volatility as a general factor when deriving the C&L of mixtures, it appears to be more appropriate to agree first on the principle and then apply it in a consistent manner to all relevant concentration limits (not only SCLs).

As this change to the draft guidance text was made at a late stage, the other members of the drafting expert group did not have the opportunity to discuss this issue. ECHA would therefore invite the PEG members’ opinions on the appropriateness of the changes highlighted.

4.1 Type of effect / severity

The type of effect(s) resulting in a classification as reproductive toxicant differs between substances. Some effects could be considered as more severe than others. However, ranking different effects based on their severity is difficult. Further, the effects of a developmental toxicant can differ between dose levels from variations via malformations to death of the foetuses. The adverse effects on fertility and sexual function of a substance can differ between dose levels from small changes in testes histopathology through effects on fertility to an irreversible and complete absence of fertility. As the difference between the dose levels is often smaller than the proposed potency groups (factor 10-100) this will make no difference in most cases. Also classification is in most cases based on severe effects like malformations or death of the foetuses for developmental toxicants and effects on fertility or histopathological changes of the reproductive organs for fertility toxicants. For most classified substances such severe effects were already observed at the lowest dose with reproductive effects [(Muller et al, 2011)]. Therefore, differentiation between types of effect is considered to have limited added value. Exceptions can be dealt with on a case by case basis.

For example, if the ED$_{10}$ results in a preliminary conclusion for the medium potency group but is close to the boundary for the high potency group and the ED$_{10}$ is based on a severe effect like malformations or irreversible effects on sexual function and fertility then using the higher potency group (lower ED$_{10}$) for that substance should be considered.

4.2 Data availability

Where only limited data are available, such as a screening study (OECD 421 and 422), a 28-day repeated dose toxicity study or non-OECD studies which do not exclude the presence of reproductive effects at lower dose levels, the calculated ED$_{10}$ should not be used to set a SCL above the GCL. If there are only limited data which results in an ED$_{10}$ in the medium potency group but close to the boundary for the high potency group then using the higher potency group should be considered. If for example an ED$_{10}$ of 8 mg/kg bw/day is estimated based on a LOAEL at 12 mg/kg bw/day with 12% malformations using a BMD approach and no NOAEL, then the estimated ED$_{10}$ and resulting SCL is doubtful especially if the BMDL (Benchmark dose lower 95%-confidence bound) is below the boundary of 4 mg/kg bw/day
for the high potency group. In such cases the high potency group should be used until additional data at lower dose levels is available.

4.3 Dose-response relationship

The ED$_{10}$ is in most cases in the same range as the NOAEL and LOAEL. However, in cases of a shallow dose-effect relationship, the LOAEL may for some effects be clearly below the ED$_{10}$. If a substance would fall into a lower potency group based on the ED$_{10}$ but into a higher potency group based on the LOAEL then the higher potency group should be used for that substance when the dose effect relationship is shallow.

4.4 Mode or mechanism of action

It is assumed that effects observed in animal studies are relevant to humans. Where it is known that the mode or mechanism of action is not relevant for humans or is of doubtful relevance to humans, this should have been taken into account in the classification and should not be used again as a modifying factor for potency. However, quantitative differences in toxicodynamics could be taken into account when not already taken into account in the classification. In cases where mechanistic information shows a lower sensitivity in humans than in experimental animals, this may move substances which are close to the potency boundaries, to a lower potency group. In cases where mechanistic information indicates a higher sensitivity in humans than in experimental animals, this may move substances near the potency boundaries to a higher potency group. In general, more conclusive evidence is required when moving a substance to a lower potency group than to a higher potency group.

4.5 Toxicokinetics

The toxicokinetics of a substance can differ between the tested animal species and humans. Where a difference is known this should be taken into account when determining the potency group of a substance. This should be based on comprehensive knowledge of all involved toxicokinetic factors and not only on a single parameter. Differences in kinetics between pregnant and non-pregnant animals and transport to the foetus should also be taken into account. Substances close to the boundary of a potency group where a higher concentration at the site of action is expected in humans and thus a lower human ED$_{10}$ compared to the studied species may be moved into a higher potency group (lower ED$_{10}$). Substances close to the boundary of a potency group where a lower concentration at the site of action is expected in humans and thus a higher human ED$_{10}$ compared to the studied species may be moved into a lower potency group (higher ED$_{10}$). In general, more conclusive evidence is required when moving a substance to a lower potency group than to a higher potency group.

4.6 Bio-accumulation of substances

The study design of, for example, developmental studies is aimed at exposure only during development. For substances which bio-accumulate, the actual exposure in the time window of sensitivity for some developmental effects may therefore be much lower than when exposure at the same external dose level would have started long before the sensitive window. Furthermore, human exposure may occur for a long period before the sensitive
window. This should be taken into account when determining the potency group. Bio-
accumulating substances with an ED<sub>10</sub> just above the lower boundary of a potency group (see Table 8) should be considered for moving into the higher potency group (lower ED<sub>10</sub>).

For substances with an adverse effect on fertility and sexual function, the ED<sub>10</sub> of a 28-day study or a screening study may be higher than the ED<sub>10</sub> from a 90-day study or a 2-generation study for a bio-accumulating substance. When only a short exposure study is present for a bio-accumulating substance with for example an ED<sub>10</sub> in the medium potency group but close to the boundary of the high potency group it should be considered for moving into the high potency group (lower ED<sub>10</sub>).

4.7 Non-modifying factors

A wide range of parameters were considered as possible modifying factors for the determination of reproductive potency. Parameters selected as modifying factors are included above. Parameters or factors considered but not included as modifying factors are listed below:

4.7.1 Species and strains

The species used to determine the ED<sub>10</sub> could be considered as a modifying factor if it is shown that a certain species is generally more sensitive to reproductive toxicants, meaning showing effects at a lower exposure level, and this can be considered relevant to humans. However, comparison of the different parameters between the two most used species for developmental effects, rats and rabbits, did not indicate a difference in average NOAEL, LOAEL or ED<sub>10</sub> in this analysis. Furthermore, almost all studies that were determinative for the classification for fertility were studies in rats. Therefore, species is not regarded as a modifying factor. The most sensitive species for each substance has to be used to determine the potency parameter unless there is clear evidence that the observed effects are not relevant to humans or when there is good evidence for a difference in sensitivity between humans and the test species. This also applies to different strains.

4.7.2 Systemic or maternal toxicity

Adverse effects on fertility and sexual function may be caused as a secondary effect of systemic toxicity to other organs. Developmental effects may be caused as a secondary effect of maternal toxicity. However, this should have already been taken into account for classifying a substance in a specific category. Therefore, this should not also be used for modifying the concentration limit.

4.7.3 Mutagenicity

Analyses of the databases [(Muller et al., 2011)] indicate that substances classified both for reproductive toxicity and mutagenicity have a higher potency (lower ED<sub>10</sub>) than substances classified for reproductive toxicity only. However, as this higher potency is already included in the lower ED<sub>10</sub>, there is no need to use mutagenicity as a modifying factor.
4.7.4 Volatility

Volatility is a physical property related to exposure rather than to the intrinsic hazardous potency of a substance and is not included as a modifying factor of potency of reproductive toxicity in similarity with the line taken for other hazard classes where guidance on how to set SCLs have been provided, such as carcinogenicity.

5. Potency groups and specific concentration limits

5.1 Justification of the proposed potency boundaries and specific concentration limits

In the following some general considerations on potency groups are first provided, followed by justifications for the approach taken and for the suggested boundaries of the potency groups and the corresponding concentration limits.

5.1.1 General considerations on potency groups

5.1.1.1 Legal requirements

According to the second subparagraph of CLP Article 10(1) “Specific concentration limits shall be set by the manufacturer, importer or downstream user where adequate and reliable scientific information shows that the hazard of a substance is evident when the substance is present at a level below the concentrations set for any hazard class in Part 2 of Annex I or below the generic concentration limits set for any hazard class in Parts 3, 4 and 5 of Annex I.”

According to the third subparagraph of CLP Article 10(1) “In exceptional circumstances specific concentration limits may be set by the manufacturer, importer or downstream user where he has adequate, reliable and conclusive scientific information that a hazard of a substance classified as hazardous is not evident at a level above the concentrations set for the relevant hazard class in Part 2 of Annex I or above the generic concentration limits set for the relevant hazard class in Parts 3, 4 and 5 of that Annex.”.

5.1.1.2 Scientific results of the database analysis

The databases with ED_{10} values for substances (Category 1 and 2) with an effect on development and with an effect on sexual function and fertility were compared to determine whether there is a difference in potency between Category 1 and Category 2 substances [(Muller et al, 2011)]. The results should be carefully interpreted because of the limitations of the database: the database is based on a limited number of substances and the available data per substance is reduced to a single number (ED_{10}) and some modifying factors. Reducing the data in the database would have included removal of differences in effects and doubts between Category 1 and Category 2. In any case, the comparisons indicate that the average potency of substances with an effect on development and with an effect on sexual function and fertility are comparable and that also the average potencies of Category 1 and 2 substances are comparable and certainly do not differ by a factor of 10.
5.1.1.3 Policy related considerations and proposed method

Data derived from an insensitive test method could in some cases not be regarded as adequate, reliable and conclusive evidence, as mentioned in Article 10 (1) (3rd para). For example, a screening assay which only uses a limited number of animals and studied endpoints, cannot be used to set higher SCLs (but can be used to set lower SCLs). Also a study resulting in an LOAEL without an NOAEL cannot be used to set higher SCLs.

Determination of the boundaries of the potency groups (see Table 8) and the SCL or GCL for each group is a policy related issue. CLP Article 10, the criteria in Annex I to CLP and the available data do not give a clear direction. Therefore, a simple system was developed. Furthermore, the approach taken is similar to the one developed for other hazard classes such as skin sensitization and carcinogenicity, which should be an appropriate justification for the current method.

Determination of the potency for reproductive toxicity will in most cases be based on limited data from one or a few studies. It was recognised that an exact SCL for each substance that also differs for each substance would indicate a precision that is not realistic or scientifically justified. Also, Janer (2007) has shown that the variation in the NOAELs of 2-generation studies for one substance is considerable. Therefore, it is proposed to divide the substances into large potency groups with associated SCLs as it is done for other hazard classes. Three potency groups are proposed. As shown in Table 10 below, substances with the lowest potency (highest ED_{10}) fall in a group with an SCL above the GCL. Most substances should fall in the group with the GCL. Only substances with a very high potency (low ED_{10}) should fall in the group with a SCL below the GCL. It is proposed to include approximately 70 – 80% in the GCL potency group and 5 to 15% in the low and high potency groups. Further, as the average potency of developmental toxicants and substances affecting sexual function and fertility are comparable, it is proposed to use the same boundaries for both types of effect. Also, the database shows there is no difference in potency between substances in Category 1 and Category 2. Therefore it is proposed to use the same boundaries for Category 1 and 2 substances.

5.1.1.4 Other methods considered

Several other options for a method for determining SCLs were discussed including a method that was used by the TC C&L in a limited number of cases in the past. This method is based on the limit dose of 1000 mg/kg bw/day, as described in the test guideline OECD 414 and 416.

The concentration limit expressed as a % in preparations is derived by dividing the NOAEL by the limit dose followed by multiplication by 100 (see ECBI/47/02 Add.7). This method would result in an individual SCL for each substance. This would indicate a precision that cannot be expected from standard reproduction studies. Also this would result in an SCL for most substances and in a GCL for only some substances. Therefore, this method was not considered. Potency groups are used in the proposed method because this does not give the impression of a high precision and allow the placing of many substances in the medium potency group with the connected GCL.

5.1.2 Justification of the boundaries between the three potency groups.
The estimated percentages of already classified substances in each group for both Category 1 and 2 substances with an effect on development or an adverse effect on fertility and sexual function are provided in the tables below. They are based on the distribution of potencies of known developmental toxicants and of known fertility toxicants ([Muller et al., 2011]). Several possible values of the boundaries between the three groups are tested. The estimations are based on counting the number of substances above or below a number of possible boundaries and applying some of the modifying factors such as the presence of a NOAEL and considering also the saturated vapour concentration for substances in the low potency group. However, the saturated vapour concentration, reflecting volatility, is not proposed as a modifying factor in the guidance.

Taking into account all modifying factors for all substances would imply a full assessment of the potency for all substances. This was not possible within the available resources. As most modifying factors result in a shift from the low potency group into the medium potency group and from the medium potency group into the high potency group, it is likely that the percentages in the low potency group may decrease and the percentages in the high potency group may increase. (Thus, the effect of volatility on the frequencies in Table 9 should be marginal.)

Based on the ED_{10} distribution a rough estimate was made by the Working group of the optimal boundaries using a range of a factor of 100 for the medium potency group. Then the number of substances falling into several combinations of boundaries was estimated.

Table 9. Percentages of substances in the three potency groups using the ED_{10} and some of the modifying factors for different boundaries of the potency groups and considering the saturated vapour concentration of low potency substances.

<table>
<thead>
<tr>
<th>Type of effect</th>
<th>Classification</th>
<th>Potency group</th>
<th>Boundaries of the high and low potency groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>High potency</td>
<td>&lt;2 mg/kg</td>
</tr>
<tr>
<td>Development</td>
<td>Cat 1A/1B</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>H360D</td>
<td>High potency</td>
<td>12.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medium potency</td>
<td>75.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low potency</td>
<td>12.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% with SCL</td>
<td>24.1</td>
</tr>
<tr>
<td></td>
<td>Cat 2</td>
<td>High potency</td>
<td>10.3</td>
</tr>
<tr>
<td></td>
<td>H361d</td>
<td>Medium potency</td>
<td>72.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low potency</td>
<td>17.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% with SCL</td>
<td>27.6</td>
</tr>
<tr>
<td>Fertility</td>
<td>Cat 1A/1B</td>
<td>High potency</td>
<td>3.4</td>
</tr>
<tr>
<td></td>
<td>H360F</td>
<td>Medium potency</td>
<td>89.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low potency</td>
<td>6.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% with SCL</td>
<td>10.3</td>
</tr>
</tbody>
</table>
As shown in Table 9 boundaries of 4 to 400 mg/kg bw/day would result in the maximum number of substances being included in the medium potency range for most types of effects and classifications and for both type of effects and classifications combined. For developmental effects Category 1 and 2 the percentage of substances in the medium potency group is within the target of ca. 70-80%. For effects on sexual function and fertility Category 2 this is almost the case. Only for Category 1 is this not the case. The percentage of substances in the medium potency group could be reduced by reducing the factor of 100 between the boundaries. However, because of the large difference in potency of the substances classified for reproductive toxicity of up to a million, this was not considered necessary. The percentage of substances in the high potency group is higher than the percentage in the lower potency group for the boundaries of 4 to 400 mg/kg bw/day. However, the percentage of substances in the high potency group was above 15% for substances classified for an effect on development in Category 1.

5.1.3 Concentration limits for Category 1 and Category 2 substances

The generic concentration limit (GCL) from the respective categories will be used for medium potency substances (group 2). As mentioned earlier the GCL is 0.3% for reproductive toxicants Category 1A and 1B and 3.0% for Category 2.

Category 1A and 1B

Different concentration limits have to be used for the different potency groups. Substances classified in Category 1 in the low potency group (group 3) can have a SCL above the GCL of 0.3%. We propose to use an SCL of 3% which is tenfold of the GCL. A factor of 10 is used often in CLP as difference in GCL between hazard categories. This factor is also used in the guidance for setting SCLs for carcinogens. For substances in group 1 (high potency), it is proposed to use a SCL of 0.03%. For extremely potent reproductive toxicants with an ED$_{10}$ (classification) of more than 10 fold below the boundary limit of 4 mg/kg bw/day it is proposed to use even lower SCLs. For every factor of 10 below the upper limit the SCL is reduced with a factor of 10.

Category 2

Substances classified in Category 2 in the low potency group (group 3) can have a SCL above the GCL of 3%. We propose to use an SCL of 3-10% which is one to 3-fold of the GCL. An SCL above 10% was considered too high. The upper SCL of 10% can only be used in exceptional cases (NOAEL below 1000 mg/kg bw/day but ED$_{10}$ above 1000 mg/kg bw/day). This would account for none of the substances in the database. For high potency substances (group 1), it is proposed to use an SCL of 0.3%. For extremely potent reproductive toxicants
with an ED$_{10}$ (classification) of more than 10-fold below the boundary limit of 4 mg/kg bw/day it is proposed to use even lower SCLs. For every factor of 10 below the upper limit, the SCL is reduced by a factor of 10.

The resulting SCLs for each potency group are presented in Table 10.

### Table 10. SCLs for substances in each potency group and classification category

<table>
<thead>
<tr>
<th>Category 1</th>
<th>Category 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose</td>
</tr>
<tr>
<td>Group 1 high potency</td>
<td>ED$_{10}$ (classification) below 4 mg/kg bw/day</td>
</tr>
<tr>
<td>Group 2 medium potency</td>
<td></td>
</tr>
<tr>
<td>Group 3 low potency</td>
<td>ED$_{10}$ (classification) above 400 mg/kg bw/day</td>
</tr>
</tbody>
</table>

^ The limit of 10% may be considered in certain cases, such as for substances with an ED$_{10}$ value above 1000 mg/kg bw/day and a NOAEL below 1000 mg/kg bw/day.

### Assigning two SCLs to a substance

A reproductive toxic substance is classified in one category for both effects on development and on sexual function and fertility. Within each category effects on development and on sexual function & fertility are considered separately. The potency and resulting concentration limits have to be determined separately for the two main types of reproductive toxic effects. In case the potency and resulting specific concentration limits are different for sexual function/fertility and development for a substance, the substance needs to be assigned one SCL for developmental toxicity and another SCL for effects on sexual function and fertility. These concentration limits will in all cases trigger different specifications of the hazard statements for the two main types of effects, to be applied to mixtures containing the substance (see also 3.7.4.1, Annex I, CLP).

### 5.2 Assigning SCLs

The SCL or GCL for each substance can be determined using the final potency group of the substance using Table 9.

### 6 References
Gemma Janer, Betty C. Hakkert, Aldert H. Piersma, Theo Vermeire and Wout Slob (2007) A retrospective analysis of the added value of the rat two-generation reproductive toxicity study versus the rat subchronic toxicity study. Reproductive Toxicology 24,103-123.


Whenever adequate and reliable scientific information shows that the hazard of a substance is present in a mixture below the generic concentration limit, this information should be used to establish a specific concentration limit (SCL) for the substance. This limit overrules the generic concentration limit detailed in CLP Tables 3.2.3 and 3.2.4.

It is more difficult to prove the lack of a hazardous property. Therefore, only in exceptional circumstances, where adequate, reliable and conclusive scientific information is available, a specific concentration limit which is higher than the generic one may be set.

Note that an SCL is substance specific and should be applicable on all mixtures containing the substance.

Confirmation is also needed that the dilutions of the test substance were made using a suitable vehicle to ensure the test substance was actually dissolved and was not a sole dispersion.

The following example illustrates that, based on the results from tests using different concentrations of the test substance a threshold can be determined where classification as Skin Irritant Category 2 is no longer necessary. However it should be noted that such additional animal testing is not encouraged and should only take place if there are no alternatives providing adequate reliability and quality of data, but the classification can be based on the individual components using general concentration limits."

Example: Setting of SCL

Results for a substance tested in OECD TG 404 test where all requirements mentioned are met:

<table>
<thead>
<tr>
<th>Concentration [%]</th>
<th>Positive response (=2.3 mean score)</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>3/3</td>
<td>Irritant Category 2</td>
</tr>
<tr>
<td>50</td>
<td>2/3</td>
<td>Irritant Category 2</td>
</tr>
<tr>
<td>30</td>
<td>1/3</td>
<td>Not irritant</td>
</tr>
</tbody>
</table>

30 % is the SCL for this substance.

Mixtures containing concentrations of substance A exceeding 30 % will carry a Skin Irritant Category 2 classification.