

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

Extracts of the document in this consultation:

Revision of Part 1, section 1.5.1 – SCLs p. 9

NOTE: Since this consultation started, this section has been agreed in the separate consultation exercise for Part 1 Introduction and Part 4 Environment and is published on the ECHA website.

Update of Part 3 - Health Hazards p. 12

Inclusion of new Annex VI p. 129

Relevant sections in Part 3 Health Hazards for this consultation:

3.2 Skin Corrosion/Irritation p. 12

3.3 Serious Eye Damage/Eye Irritation p. 36

3.7 Reproductive Toxicity p. 61

3.8 STOT-SE p. 99

Note that the page numbers above are only correct in this document.

Note that the numbering and headings of the sections that are displayed in this document are the original numbering of the sections as shown in the original Guidance. This will facilitate the comparison of the revised parts with the original.

Note that this consultation is specifically focused on the last revisions of the “Further development of the RIP 3.6 guidance – Human health hazards”. All revisions relating to the 2nd ATP to the CLP Regulation will be updated in 2013: this will be a separate consultation that will start later this year (2012) and be completed in 2013. Please reserve all comments relating to the 2nd ATP for this consultation.

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

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1 LIST OF ABBREVIATIONS

2

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

2 1.1 INTRODUCTION

3 1.2 THE SIGNIFICANCE OF

4 1.3 SPECIFIC CASES

5 1.4 USE OF

6 1.5 SPECIFIC CONCENTRATION LIMITS AND M-FACTORS

7

8 **NOTE TO RAC and Forum on Part 1 section 1.5.1: *For Your Information.***
9 Since the PEG consultation started, this section has been agreed in the separate
10 consultation exercise for Part 1 Introduction and Part 4 Environment: the proposed
11 text for the PEG was deleted, so there were no changes to this section and
12 therefore the ECHA Secretariat took this forward with the separate consultation
13 on Part 1 and Part 4 which is now finished. This section is published on the
14 ECHA website.

15 1.5.1 Specific concentration limits

16

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.

17

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.

18 The specific concentration limit (SCL) concept allows a fine tuning of the contribution of
19 certain hazardous substances to the classification of mixtures based on the potency of the

1 substances, as well as a classification of other substances containing these substances as
 2 impurities, additives or individual constituents. The SCL concept is only applicable to health
 3 hazards. For physical hazards, classification shall be established on the basis of test data for
 4 the respective mixture, where applicable.

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

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

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

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

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

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

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

18 **1.5.2 Multiplying factors (M-factors)**

1	1.6	MIXTURES
2	1.7	THE APPLICATION OF ANNEX VII
3	2	PART 2: PHYSICAL HAZARDS
4		

1 **3 PART 3 HEALTH HAZARDS**

2 **3.1 ACUTE TOXICITY**

3 **3.2 SKIN CORROSION/IRRITATION**

4 **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.

5 **3.2.2 Classification of substances for skin corrosion/irritation**

6 **3.2.2.1 Identification of hazard information**

7 **3.2.2.1.1 Identification of human data**

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

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

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

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

24 **3.2.2.1.2 Identification of non human data**

25 Non human data include physico-chemical properties, results from (Q)SARs and expert
26 systems, and results from *in vitro* and *in vivo* tests. Available skin corrosion/irritation
27 information on substances may include existing data generated by the test methods in the Test
28 Methods Regulation or by methods based on internationally recognised scientific principles.

1 Several of the following non-testing methods and *in vitro* methods have been validated
2 against the DSD criteria but not against CLP criteria for classification. As the criteria differ
3 slightly between DSD and CLP, it should be checked whether the method is sufficiently
4 validated for classification according to CLP.

5 **3.2.2.1.2.1 Consideration of physico-chemical properties**

6 Substances with oxidising properties can give rise to highly exothermic reactions in contact
7 with other substances and human tissue. High temperatures thus generated may
8 damage/destroy biological materials. This applies, for example, to organic peroxides, which
9 can be assumed to be skin irritants, unless evidence suggests otherwise (IR/CSA Section
10 R.7.2.3.1).

11 For a hydro peroxide classification as Skin Corrosive Category 1B should be considered,
12 whereas Skin Irritation Category 2 should be considered for peroxides. Appropriate evidence
13 must be provided in order to consider non-classification of substances with oxidising
14 properties.

15 **3.2.2.1.2.2 Non-testing methods: (Q)SARs and expert systems**

16 Non-testing methods such as (Q)SARs and expert systems may be considered on a case-by-
17 case basis. (Q)SAR systems that also account for skin effects are for example TOPKAT,
18 TerraQSAR, and the BfR-DSS. These systems go beyond the structural similarity
19 considerations encompassing also other parameters such as topology, geometry and surface
20 properties. For full guidance consult IR/CSA, sections R.6 and R.7.2.3.1.

21 The BfR-DSS has been recommended in IR/CSA, section R.7.2.4 since there is no other
22 model that sufficiently describes the absence of effects. The BfR rules to predict skin
23 irritation and corrosion have been integrated in the internet tool “toxtree”,
24 <http://ecb.jrc.ec.europa.eu/qsar>.

25 Conclusion on no classification can be made if the (Q)SAR or expert system has been shown
26 to adequately predict the absence of the classified effect (IR/CSA, Figure R.7.2-2, footnote f).

27 Since a formal adoption procedure for those non-testing methods is not foreseen and no
28 formal validation process is in place, appropriate documentation is very important. In order to
29 achieve acceptance under REACH the documentation must conform the so-called QSAR
30 Model Reporting Format (QMRF). For more details consult the IR/CSA, section R.6.1.

31 **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 $\geq 11,5$ 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.

32 The acid/alkaline reserve is a measure of the buffering capacity of chemicals. For details of
33 the methodology, see Young *et al*, 1988, and Young and How, 1994.

34 **3.2.2.1.2.4 Testing methods: *in vitro* methods**

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

37 *In vitro* methods for skin corrosion

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

5 The transcutaneous electrical resistance (TER; using rat skin) test (TM B.40; OECD TG 430)

6 Human skin model (HSM) tests (TM B.40 bis; OECD TG 431)

7 The *in vitro* membrane barrier test method (OECD TG 435)

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

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

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

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

21 *In vitro* methods for skin irritation

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

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

42 *Other suitable in vitro methods*

43 Positive data from other suitable *in vitro* methods may be used in a weight of evidence
44 approach to determine classification as irritant, while negative data are not conclusive for a

1 non-classification. In this context 'suitable' means sufficiently well developed according to
2 internationally agreed development criteria (see REACH Annex XI, section 1.4).

3 **3.2.2.1.2.5 Testing methods: *In vivo* data**

4 The *in vivo* test in rabbits according to TM B.4 (OECD TG 404) is the standard test for the
5 hazard assessment and classification required under the REACH Annex VIII provisions (10
6 tons per year and more). However it should be noted that according to REACH (Annexes VII
7 to X) *in vivo* testing of corrosive substances at concentration/dose levels causing corrosivity
8 shall be avoided.

9 Until 1987 the OECD standard protocol used occlusive patching for the application of the test
10 substance, which resulted in more rigorous test conditions compared to the semi-occlusive
11 patching used today. Especially in borderline cases of classification the method of application
12 should be accounted for in the evaluation of effects.

13 Studies performed according to the USA Federal Hazardous Substances Act (US-FHSA) may
14 be used for classification purposes although they deviate in their study protocol from the
15 OECD TG 404. They do not include a 48-hour observation time and involve a 24-hour test
16 material exposure followed by observations at 24 hour and 72 hours. Moreover, the test
17 material is patched both on abraded and on intact skin of six rabbits. Studies usually are
18 terminated after 72 hours. In case of no or minimal responses persisting until the 72 hours
19 time points it is feasible to use such data for classification by calculating the mean values for
20 erythema and oedema on the basis of only the 24 and 72 hours time points. Calculation of
21 mean scores should normally be restricted to the results obtained from intact skin. In case of
22 pronounced responses at the 72 hours time point an expert judgement is needed as to whether
23 the data is appropriate for classification.

24 Data on skin effects on animals may be available from tests that were conducted for other
25 primary purposes than the investigation of skin corrosion / irritation. Such information may
26 be gained from acute or repeated dose dermal toxicity studies on rabbits or rats (TM B.3,
27 OECD TG 402; TM B.9, OECD TG 410), guinea pig skin sensitisation studies (TM B.6,
28 OECD guideline 406) and from irritation studies in hairless mice.

29 **3.2.2.2 Classification criteria**

Annex I: 3.2.2.6. Corrosion

3.2.2.6.1. On the basis of the results of animal testing a substance is classified as corrosive, as shown in Table 3.2.1. A corrosive substance is a substance that produces destruction of skin tissue, namely, visible necrosis through the epidermis and into the dermis, in at least 1 tested animal after exposure up to a 4 hour duration. Corrosive reactions are typified by ulcers, bleeding, bloody scabs and, by the end of observation at 14 days, by discoloration due to blanching of the skin, complete areas of alopecia and scars. Histopathology shall be considered to discern questionable lesions.

3.2.2.6.2. Three subcategories are provided within the corrosive category: subcategory 1A – where responses are noted following up to 3 minutes exposure and up to 1 hour observation; subcategory 1B – where responses are described following exposure between 3 minutes and 1 hour and observations up to 14 days; and subcategory 1C – where responses occur after exposures between 1 hour and 4 hours and observations up to 14 days.

3.2.2.6.3. The use of human data is discussed in paragraphs 3.2.2.1 and 3.2.2.4 and also in paragraphs 1.1.1.3, 1.1.1.4 and 1.1.1.5.

Table 3.2.1

Skin Corrosive category and subcategories

		Corrosive in ≥ 1 of 3 animals*	
	Corrosive subcategory	Exposure	Observation
Category 1: Corrosive	1A	≤ 3 minutes	≤ 1 hour
	1B	> 3 minutes - ≤ 1 hour	≤ 14 days
	1C	> 1 hour - ≤ 4 hours	≤ 14 days

3.2.2.7. Irritation

3.2.2.7.1. Using the results of animal testing a single irritant category (Category 2) is presented in Table 3.2.2. The use of human data is discussed in paragraphs 3.2.2.1 and 3.2.2.4 and also in paragraphs 1.1.1.3, 1.1.1.4 and 1.1.1.5. The major criterion for the irritant category is that at least 2 of 3 tested animals have a mean score of $\geq 2,3 - \leq 4,0$.

Table 3.2.2

Skin irritation category

Category	Criteria
Category 2: Irritant	<p>(1) Mean value of $\geq 2,3 - \leq 4,0$ 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</p> <p>(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</p> <p>(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.</p>

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.

1 * 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,
2 EN, LV, PT, and RO versions of CLP published in the Official Journal 31.12.2008.

3 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.

1 **3.2.2.3.1 Evaluation of human data**

2 The usefulness of human data for classification purposes will depend on the extent to which
3 the effect, and its magnitude, can be reliably attributed to the substance of interest. Further
4 guidance on evaluation of human data for skin corrosion/irritation can be found in IR/CSA
5 Section R.7.2.4.2.

6 The criteria in Annex I, Table 3.2.2 are not applicable to human data.

7 **3.2.2.3.2 Evaluation of non human data**

8 **3.2.2.3.2.1 *In vitro* data**

9 In evaluation of data from *in vitro* tests the applicability domain has to be taken into account.
10 The *in vitro* membrane barrier test method e.g. is mainly applicable for acids and bases and is
11 not applicable for solutions with pH values between 4.5 and 8.

12 **3.2.2.3.2.2 *In vivo* data**

13 Tests in albino rabbits (OECD TG 404)

14 Evaluation criteria for local effects on the skin are *severity* of the damage and *reversibility*.

15 For the *severity* of damage the responses are evaluated according to the Draize score ranking
16 from “0” (no response”) up to “4” (severe response”). Evaluation takes place separately for
17 erythema and oedema.

18 *Reversibility* of skin lesions is the other decisive factor in evaluating responses in the animal
19 test. The criteria are fulfilled if, for

20 – *corrosion*

21 – the full thickness of the skin is destroyed resulting in ulcers, bleeding, bloody scabs
22 discoloration, complete areas of alopecia and scars. In questionable cases a pathologist
23 should be consulted. One animal showing this response at the end of the observation
24 period is sufficient for the classification as corrosive.

25 – *irritation*

26 – a limited degree of alopecia, hyperkeratosis, hyperplasia and scaling occurs. Two
27 animals showing this response are sufficient for the classification as irritant.

28 – very elevated mean scores throughout the study are revealed, including lesions
29 persisting at the end of an observation period of normally 14 days. One animal showing
30 this response throughout and at the end of the observation period is sufficient for the
31 classification as irritant (In cases of suspected corrosives, existing test data may only be
32 available for one animal due to testing restrictions, see Example 2.).

1 With regard to severity the main criterion for classification of a substance as irritant to skin,
2 is the mean score per animal for either erythema/eschar or oedema. During the observation
3 period following the removal of the patch each animal is scored on erythema and oedema.
4 For each of the three test animals the average scores for three consecutive days (usually 24,
5 48 and 72 hours) are calculated separately for oedema and erythema. If 2/3 animals exceed
6 the cut-off-values defined in CLP, the classification has to be done accordingly.

7 With regard to reversibility the test report must prove that these effects are transient i.e. the
8 affected sites are repaired within the observation period of the test (see Example 1).

9 Non-classification as corrosive can be only justified, if the test was performed with at least
10 three animals and the test results were negative for all three animals.

11 *Tests that have been conducted with more than three animals*

12 Current guidelines foresee a sequential testing of rabbits until a response is confirmed.
13 Typically, up to 3 rabbits may be used. The basis for a positive response is the individual
14 rabbit value averaged over days 1, 2, and 3. The mean score for each individual animal is
15 used as a criterion for classification. The Skin Irritant Category 2 is used if at least 2 of 3
16 animals show a mean score of 2.3 or above. Other test methods, however, have been using up
17 to 6 rabbits. This is also the case for the studies performed according to the US-FSHA.

18 For existing test data with more than three animals, specific provisions need to be applied.
19 For the sake of flexibility basically two approaches can be accepted for evaluation:

- 20 – the overall average over all animals will be used (see Example 3a). This has been
21 common practice under the DSD.
- 22 – According to the second approach the average score is determined per animal (see
23 Example 3b). In this case Skin Irritant Category 2 is assigned if 4 of 6 rabbits show a
24 mean score of 2.3 or above. Likewise, if the test was performed with 4 or 5 animals, for at
25 least 3 individuals the mean score must exceed the value of 2.3 to classify as Skin Irritant
26 Category 2.

27 The more stringent result has to be used if the evaluation according to the method shown
28 under Example 3a is different to that under Example 3b.

29 Other dermal tests in animals

30 Relevant data may also be available from animal studies that were conducted for other
31 primary purposes than the investigation of skin corrosion/irritation. However, due to the
32 different protocols and the interspecies differences in sensitivity, the use of such data in
33 general needs to be evaluated on a case-by-case basis. These are considered significant if the
34 effects seen are comparable to those described above. For further guidance how to evaluate
35 data from studies on dermal toxicity or skin sensitisation, see IR/CSA, Figure R.7.2-2
36 footnotes d) and e), respectively.

37 **3.2.2.3.3 Weight of evidence**

38 Where the criteria cannot be applied directly to available identified information, a weight of
39 the evidence determination using expert judgement shall be applied in accordance with CLP
40 Article 9(3).

41 A weight of the evidence determination means that all available and scientifically justified
42 information bearing on the determination of hazard is considered together, such as physico-
43 chemical parameters (e.g., pH, reserve alkalinity/acidity), information from the application of
44 the category approach (grouping, read-across), (Q)SAR results, the results of suitable *in vitro*

1 tests, relevant animal data, skin irritation information/data on other similar mixtures, human
2 experience such as occupational data and data from accident databases, epidemiological and
3 clinical studies and well-documented case reports and observations. The quality and
4 consistency of the data shall be given appropriate weight. Both positive and negative results
5 shall be assembled together in a single weight of evidence determination.

6 Evaluation must be performed on a case-by-case basis and with expert judgement. However,
7 normally positive results that are adequate for classification should not be overruled by
8 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.

9 For further guidance, if both human and animal data are available, see IR/CSA Section
10 R.7.2.3.2.

11 **3.2.2.4 Decision on classification**

12 Where the substance is classified as a skin corrosive but the data used for classification does
13 not allow differentiation between the skin corrosion subcategories 1A/1B/1C, then the
14 substance should be assigned Skin Corrosive Category 1.

15 **3.2.2.5 Setting of specific concentration limits**

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

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

16 It is more difficult to prove the absence of a hazardous property; the legal text states that:

Article 10(1)

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

17

18

1 An SCL set in accordance with the above mentioned provisions shall take precedence over
2 the GCL set out in Tables 3.2.3 and 3.2.4 of Annex I to CLP (Article 10(6)). Furthermore, an
3 SCL is substance-specific and should be applicable to all mixtures containing the substance,
4 instead of any GCL that otherwise would apply to a mixture containing the substance.

5
6 **NOTE TO RAC and Forum on Skin Corrosion/Irritation & Serious Eye**
7 **Damage/Eye Irritation Sections**

8 A particular issue arose regarding the draft text presented to the PEG consultation
9 relating to the “*What type of information may be the basis for setting a SCL*”. There
10 were some 20 comments submitted raising issues relating to test data already existing
11 for mixtures and dilutions of substances, derived from OECD TG 404 and 405 and
12 also the use of *in vitro* methodology, particularly for skin tests. Following an
13 exhaustive and controversial discussion at the PEG meeting, there was some
14 agreement to revise the text and the revised proposed text, has been further discussed
15 at length internally at ECHA and endeavours to find a compromise of the differing
16 views.

17 Members are asked to consider this text (in these two sections) in light of the above
18 controversial discussions and comment on its acceptability.

19
20 *What type of information may be the basis for setting a specific concentration limit?*

21 Existing human data may in certain cases (especially if dose-response information is
22 available) indicate that the threshold for the irritation hazard in humans, for a substance in a
23 mixture, would be higher or lower than the GCL. A careful evaluation of the usefulness and
24 the validity of such human data as well as their representativeness and predictive value
25 (IR/CSA, sections R.4.3.3. and R.7.2.4.2) should be performed. As pointed out in 1.1.1.4
26 (Annex I to CLP), positive results from well-conducted animal studies are not necessarily
27 negated by the lack of positive human experience but require an assessment of robustness,
28 quality and a degree of statistical certainty of both the human and animal data.

29 The aim of the standard test method for “Acute Dermal Irritation/Corrosion” TM B.4/OECD
30 TG 404¹ is to **identify** potential skin corrosives or irritants. The test material is generally
31 administered undiluted, thus, no dose-response relationship can be obtained from an
32 individual test. However, if there are test data from already performed animal studies for a
33 corrosive or irritant substance in an appropriate series of tests on dilutions of the substance, a
34 concentration can be derived, but this would not lead to a classification. , Subject to the test
35 data being “adequate, reliable and conclusive”, as required to set a lower and in “exceptional
36 cases” a higher SCL than the GCL, these data can be used for testing dilutions in order to
37 demonstrate non-irritating thresholds.

38 If adequate, relevant and conclusive data exists from other already performed animal studies
39 with a sufficient number of animals tested to ensure a high degree of certainty, and with
40 information on dose-response relationships, such data may be considered for setting a lower
41 or, in exceptional cases, a higher SCL on a case-by-case basis.

¹ TO NOTE: In OECD TG 404 is called the term test substance refers to the test material, test article or test item. The term substance may be used differently from the REACH/CLP definition.

1 However, it should be noted that any additional animal testing (of dilutions) of substances
 2 already classified as a skin corrosive or skin irritant, is not encouraged and may only take
 3 place on a case-by-case basis if there are no alternatives providing adequate reliability and
 4 quality of data (see CLP Articles 7(1) and 8(1)). The possibilities to use *in vitro* test methods
 5 as a basis for setting SCLs have not yet been explored. However, this does not exclude that a
 6 method to set SCLs based on *in vitro* tests could be developed, as they provide a promising
 7 option for SCL setting in the future. Annex VI Part 3 (Table 3.2) to CLP includes examples of
 8 substances for which a higher or lower SCL was set under Directive 67/548/EEC (old DSD
 9 system).

10 3.2.2.6 Decision logic for classification of substances

11 The decision logic, which is based on IR/CSA, Figure R.7.2-2 has been revised to meet CLP
 12 requirements. It is strongly recommended that the person responsible for classification, study
 13 the criteria for classification, as well as the guidance above, before and during use of the
 14 decision logic.

Step		
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 <i>in vitro</i> 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 <i>on irritation and corrosion</i> in laboratory animals, which provide sound conclusive evidence that the substance is a corrosive, irritant or non-irritant? YES → NO ↓	Classify accordingly (either Skin Corr. 1A/1B/1C or Skin Irrit. 2 or no classification).
4a	Has the substance proven to be a corrosive, irritant or non-irritant in a suitable acute dermal toxicity test? YES → NO ↓	If test conditions are consistent with OECD TG 404, classify accordingly (Skin Corr. 1A/ 1B/1C or Skin Irrit. 2 or no classification) If test conditions are not consistent with OECD TG 404, use this information in the WoE determination (step 7) and proceed to step 4b
4b	Has the substance proven to be a corrosive or an irritant in sensitisation studies or after repeated exposure? YES → NO ↓	Classification cannot be considered directly. Use this information for WoE determination (step 7). Proceed to step 5a
5a	Are there structurally related substances (suitable “read-across” or grouping), which are classified as corrosive (Skin Cat. 1) on the skin, or do suitable (Q)SAR methods indicate corrosive potential of the substance? YES → NO ↓	Consider to classify as Skin Corr. 1. Proceed to step 5b
5b	Are there structurally related substances (suitable “read-across” or grouping), which are classified as irritant on the skin (Skin Cat. 2), or do suitable (Q)SAR methods indicate the presence of irritating potential of the substance? YES → NO ↓	Consider to classify as Skin Irrit. 2. Proceed to step 6a
6a	Has the substance demonstrated corrosive properties in an OECD adopted <i>in vitro</i> test? YES → NO ↓	Classify as corrosive. If discrimination between Skin Corr. 1A/1B/1C is not possible, Skin Corr. 1 must be chosen.
6b	Are there acceptable data from a validated <i>in</i>	Consider to classify accordingly (Skin Irrit.

	<i>in vitro</i> test (adopted by OECD or not), which provide evidence that the substance is an irritant or non-irritant? YES → NO ↓	2 or no classification). Proceed to step 6c
6c	Are there data from a suitable <i>in vitro</i> test, which provide sound conclusive evidence that the substance is an irritant? YES → NO ↓	Consider to classify as Skin Irrit. 2 Proceed to step 7
7	Taking all existing and relevant data (steps 1-6) into account, is there sufficient information to make a decision on classification? YES → NO ↓	Classify accordingly (Skin Corr. 1A or Skin Corr. 1B or Skin Corr. 1C or Skin Irrit. 2 or no classification)
Unable to classify substance for skin corrosion/irritation		Decision to undertake generation of new test data should be made in compliance with REACH and Article 8 of CLP. It is recommended that IR/CSA R.7.2.6 should also be considered.

1 3.2.3 Classification of mixtures for skin corrosion/irritation

2 3.2.3.1 Identification of hazard information

3 The procedure for classifying mixtures is a tiered, i.e. a stepwise, approach based on a
4 hierarchy principle and depending on the type and amount of available data/information
5 starting from evaluating existing human data on the mixture, followed by a thorough
6 examination of the existing *in vivo* data, physico-chemical properties, and finally *in vitro* data
7 available on the mixture. For mixtures that have been on the market for a long time, human
8 data and experience may exist that may provide useful information on the skin irritation
9 potential of the respective mixtures. See [section 3.2.2.1.1](#) for further information on the
10 identification of human data.

11 If valid test data are available for the whole mixture they have precedence. If no such data
12 exist, the so called bridging principles have to be applied if possible. If the bridging
13 principles are not applicable an assessment on the basis of data for the components of the
14 mixture will be applied.

15 Where it is decided to base the classification of a mixture upon consideration of pH alone,
16 Skin corrosion Category 1A should be applied. In this case no further retrieval of information
17 on the mixture itself is needed.

18 3.2.3.2 Classification criteria

19 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.

1 There are a range of available *in vitro* test systems that have been validated for their
 2 suitability in assessing skin corrosion/irritation potential of substances. Some but not all test
 3 systems have been validated for mixtures and not all available *in vitro* test systems work
 4 equally well for all types of mixtures. Prior to testing a mixture in a specific *in vitro* assay for
 5 classification purposes, it has to be assured that the respective test has been previously shown
 6 to be suitable for the prediction of skin corrosion/irritation properties for the type of mixture
 7 to be evaluated.

8 **3.2.3.2.1.1 Mixtures with extreme pH**

9 As a general rule, mixtures with a pH of ≤ 2 or ≥ 11.5 should be considered as corrosive.
 10 However, assessment of the buffering capacity of the mixture indicated by its acid or alkali
 11 reserve should be considered. If the additional consideration of the acid/alkaline reserve
 12 according to Young *et al.* (1987, 1994) suggests that classification for corrosion or even
 13 irritation may not be warranted, then further *in vitro* testing to confirm final (or no)
 14 classification shall be carried out. The consideration of acid/alkali reserve should not be used
 15 alone to exonerate mixtures from classification.

16 Where the mixture has an extreme pH value but the only corrosive/irritant ingredient present
 17 in the mixture is an acid or base with an assigned SCL (either in CLP Annex VI or set by
 18 supplier), then the mixture should be classified according to the SCL. In this instance, pH of
 19 the mixture should not be considered a second time since it would have already been taken
 20 into account when deriving the SCL for the substance.

21 If this is not the case, then the steps to be taken into consideration when classifying a mixture
 22 with $\text{pH} \leq 2$ or ≥ 11.5 are described in the following decision logic:

Mixture without <i>in vivo</i> data on skin corrosion or relevant data from similar tested mixtures, pH is ≤ 2 or ≥ 11.5	
Does the acid alkaline reserve indicate that the mixture may not be corrosive? NO → YES ↓	Classify as corrosive, Skin Corr. Cat. 1A.
Is the mixture tested in an OECD adopted <i>in vitro</i> test for skin corrosion? NO → YES ↓	Classify as corrosive, Skin Corr. Cat. 1A.
Does the mixture demonstrate corrosive properties in an OECD adopted <i>in vitro</i> test? YES → NO	Classify as corrosive. If discrimination between Skin Corr. 1A/1B/1C is not possible, Skin Corr. 1 must be chosen.

↓	
Apply methods in Annex I, sections 3.2.3.3.2 (Table 3.2.3) / 3.2.3.3.4 (Table 3.2.4) → (When validated <i>in vitro</i> skin irritation test methods are available, these may be used to generate data to classify the mixture instead of using the summation method.)	Classify accordingly.

1 The mixture must be classified as Skin corrosion Category 1 should the supplier decide not to
2 carry out the required confirmatory testing.

3 It is also important to note that the pH-acid/alkali reserve to change classification from
4 corrosive to irritant or from irritant to not classified assumes that the potential corrosivity or
5 irritancy is due to the effect of the ionic entities. When this is not the case, especially when
6 the mixture contains non-ionic (non-ionisable) substances themselves classified as corrosive
7 or irritant, then the pH-reserve method cannot be a basis for modifying the classification but
8 should be considered in a weight of evidence analysis.

9 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.

10 In order to apply bridging principles, there needs to be sufficient data on similar tested
11 mixtures as well as the components of the mixture.

12 When the available identified information is inappropriate for the application of the bridging
13 principles then the mixture should be classified using the methods described in **section**
14 **1.6.3.4.**

15 3.2.3.2.3 When data are available for all components or only for some components

16 3.2.3.2.3.1 Components that should be taken into account for the purpose of 17 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.

18 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.

1 When the supplier is unable to derive the classification using either data on the mixture itself
 2 or bridging principles, he must determine the skin corrosion/irritation properties of the
 3 mixture using data on the individual ingredients. The supplier must ascertain whether the
 4 additivity approach is applicable, the first step in the process being to identify all the
 5 ingredients in the mixture (i.e. their name, chemical type, concentration level, hazard
 6 classification and any SCLs) and the pH of the mixture. In addition to for example surfactant
 7 interaction, neutralisation of acids/bases could also occur in a mixture, which also makes it
 8 important to consider effects of the entire mixture (i.e. pH and the acid/alkaline reserve)
 9 rather than considering contributions of individual ingredients. Additivity may not apply
 10 where the mixture contains substances mentioned in Annex I, 3.2.3.3.4, see **section**
 11 **3.2.3.2.3.3.**

12 *Application of SCLs when applying the additivity approach*

13 The generic concentration limits (GCLs) are specified in Annex I, Table 3.2.3. However,
 14 according to CLP Article 10(5) SCLs take precedence over GCLs. Thus, if a given substance
 15 has a SCL, then this limit has to be taken into account when applying the summation
 16 (additivity) method for skin corrosion/irritation (see Examples 5 and 6).

17 In cases where additivity applies for skin corrosion/irritation to a mixture with two or more
 18 substances some of which may have SCLs assigned, then the following formula should be
 19 used:

20 The mixture is classified for skin corrosion/irritation if the

21 $\text{Sum of } (\text{ConcA} / \text{clA}) + (\text{ConcB} / \text{clB}) + \dots + (\text{ConcZ} / \text{clZ}) \text{ is } \geq 1$

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

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

24 ConcB = the concentration of substance B in the mixture;

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

26 This approach is similar to that used in the DPD where a substance SCL replaces the default
 27 limits in the conventional method equations.

28 **3.2.3.2.3.3 The additivity approach is not applicable**

Annex I: 3.2.3.3.4.1. Particular care must be taken when classifying certain types of mixtures containing substances such as acids and bases, inorganic salts, aldehydes, phenols, and surfactants. The approach explained in paragraphs 3.2.3.3.1 and 3.2.3.3.2 may not be applicable given that many of such substances are corrosive or irritant at concentrations < 1%.

3.2.3.3.4.2. For mixtures containing strong acids or bases the pH shall be used as a classification criterion (see paragraph 3.2.3.1.2) since pH is a better indicator of corrosion than the concentration limits of Table 3.2.3.

3.2.3.3.4.3. A mixture containing ingredients that are corrosive or irritant to the skin and that cannot be classified on the basis of the additivity approach (Table 3.2.3), due to chemical characteristics that make this approach unworkable, shall be classified as Skin Corrosive Category 1A, 1B or 1C if it contains $\geq 1\%$ of an ingredient classified in Category 1A, 1B or 1C respectively or as Category 2 when it contains $\geq 3\%$ 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.

1 **3.2.3.3 Generic concentration limits for substances triggering classification of**
 2 **mixtures**

3 **3.2.3.3.1 When the additivity approach is applicable**

Annex I: Table 3.2.3		
Generic concentration limits of ingredients classified for skin corrosive/irritant hazard (Category 1 or 2) that trigger classification of the mixture as corrosive/irritant to skin		
Sum of ingredients classified as:	Concentration triggering classification of a mixture as:	
	Skin Corrosive	Skin Irritant
	Category 1 (see note below)	Category 2
Skin corrosive Categories 1A, 1B, 1C	≥ 5%	≥ 1% but < 5%
Skin irritant Category 2		≥ 10%
(10 x Skin corrosive Category 1A, 1B, 1C) + Skin irritant Category 2		≥ 10%
<i>Note</i>		
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.		

4 **3.2.3.3.2 When the additivity approach is not applicable**

Annex I: Table 3.2.4		
Generic concentration limits of ingredients of a mixture for which the additivity approach does not apply, that trigger classification of the mixture as corrosive/irritant to skin		
Ingredient:	Concentration:	Mixture classified as: Skin
Acid with pH ≤ 2	≥ 1%	Category 1
Base with pH ≥ 11,5	≥ 1%	Category 1

Other corrosive (Categories 1A, 1B, 1C) ingredients for which additivity does not apply	≥ 1%	Category 1
Other irritant (Category 2) ingredients for which additivity does not apply, including acids and bases	≥ 3%	Category 2

1 **3.2.3.4 Decision logic for classification of mixtures**

2 The decision logic, which is based on IR/CSA, Figure R.7.2-2, is revised to meet CLP
 3 requirements. It is strongly recommended that the person responsible for classification, study
 4 the criteria for classification, as well as the guidance above, before and during use of the
 5 decision logic.

1. When data are available for the complete mixture		
1a	Is the pH of the mixture ≤ 2 or ≥ 11.5? YES → NO ↓	Consider to classify as corrosive. – Where classification is based upon consideration of pH alone (i.e. buffering capacity is not known), Skin Corr. 1A should be applied. – Where consideration of alkali/acid reserve suggests that the substance is not corrosive, this has to be confirmed (preferably by use of an appropriate <i>in vitro</i> 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 <i>on irritation and corrosion</i> in laboratory animals, which provide sound conclusive evidence that the mixture is corrosive, irritant or non-irritant? YES → NO ↓	Classify accordingly (Skin Corr. 1A or Skin Corr. 1B or Skin Corr. 1C or Skin Irrit. 2 or no classification).
4a	Has the mixture proven to be a corrosive, irritant or non-irritant in a suitable acute dermal toxicity test? YES → NO	– If test conditions are consistent with OECD TG 404, classify accordingly (Skin Corr. 1A/1B/1C or Skin Irrit. 2 or no classification).

	↓	– If test conditions are not consistent with OECD TG 404, use this information in the WoE determination (step 6) and proceed to step 4b
4b	Has the mixture proven to be a corrosive or an irritant in sensitisation studies or after repeated exposure? YES → NO ↓	Classification cannot be considered directly. Use this information for WoE determination (step 6). Proceed to step 5a
5a	Has the mixture demonstrated corrosive properties in an OECD adopted <i>in vitro</i> test? YES → NO ↓	Classify as corrosive. If discrimination between Skin Corr. 1A/1B/1C is not possible, Skin Corr. 1 must be chosen.
5b	Are there acceptable data from a validated <i>in vitro</i> test (adopted by OECD or not), which provide evidence that the mixture is an irritant or non-irritant? YES → NO ↓	Consider to classify accordingly (Skin Irrit. 2 or no classification). Proceed to step 5c
5c	Are there data from a suitable <i>in vitro</i> test, which provide sound conclusive evidence that the mixture is an irritant? YES → NO ↓	Consider to classify as Skin Irrit. 2. Proceed to step 6
6	Taking all existing and relevant data (steps 1-5) into account including potential synergistic/antagonistic effects and bioavailability, is there sufficient information to make a decision on classification? YES → NO ↓	Classify accordingly (Skin Corr. 1A or Skin Corr. 1B or Skin Corr. 1C or Skin Irrit. 2 or no classification)
2. When data are not available for the complete mixture: bridging principles		
7a	Are existing sufficient skin corrosion/irritation data available on similar tested mixtures and on the individual ingredients? NO → YES ↓	Proceed to step 8
7b	Can bridging principles be applied? YES → NO ↓	Classify in appropriate category (Skin Corr. 1A or Skin Corr. 1B or Skin Corr. 1C or Skin Irrit. 2 or no classification)



3. When data are available for all components or only for some components of the mixture		
8a	Is pH of the mixture ≤ 2 or ≥ 11.5 ? YES → NO ↓	Follow decision logic in Section 3.2.3.2.1.1 and classify accordingly.
8b	Is there any indication that the additivity principle does not apply? YES → NO ↓	Annex I, section. 3.2.3.3.4 and Table 3.2.4 may apply. Take into account relevant ingredients (Annex I, 3.2.3.3.1. and SCLs as appropriate. Classify in appropriate category (Skin Corr. 1A/1B/1C or Skin Irrit. 2 or no classification)
	Annex I, section 3.2.3.3.2 and Table 3.2.3 applies. Take into account relevant ingredients (Annex I, 3.2.3.3.1. and SCLs as appropriate. Classify in appropriate category (Skin Corr. 1A/1B/1C or Skin Irrit. 2 or no classification)	Where the mixture is classified as corrosive but the data used for classification does not allow differentiation between the skin corrosion subcategories 1A/1B/1C, then the mixture should be assigned Skin corrosion Category 1.

1 **3.2.4 Hazard communication in form of labelling for skin corrosion/irritation**

2 **3.2.4.1 Pictograms, signal words, hazard statements and precautionary statements**

Annex I: 3.2.4.1. Label elements shall be used for substances or mixtures meeting the criteria for classification in this hazard class in accordance with Table 3.2.5.

Table 3.2.5
Label elements for skin corrosion/irritation

Classification	Category 1A / 1B / 1C	Category 2
GHS Pictograms		
Signal Word	Danger	Warning
Hazard Statement	H314: Causes severe skin burns and eye damage	H315: Causes skin irritation
Precautionary Statement Prevention	P260 P264 P280	P264 P280
Precautionary Statement Response	P301 + P330 + P331 P303 + P361 + P353 P363 P304 + P340 P310 P321 P305 + P351 + P338	P302 + P352 P321 P332 + P313 P362

Precautionary Statement Storage	P405	
Precautionary Statement Disposal	P501	

1 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.

2 Corrosive substances (and mixtures) may be acutely toxic after inhalation to a varying
3 degree, which is only occasionally proved by testing. In case no acute inhalation study is
4 available for a corrosive substance (or mixture) and such substance (or mixture) may be
5 inhaled, a hazard of respiratory tract corrosion may exist. As a consequence, substances and
6 mixtures have to be supplementary labelled with EUH071. Moreover, in such a case it is
7 strongly recommended to apply the precautionary statement P260: “Do not breathe
8 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.

9 3.2.5 Re-classification of substances and mixtures classified for skin 10 corrosion/irritation according to DSD and DPD

11 3.2.5.1 Is direct “translation” of classification and labelling possible?

12 A direct translation as indicated in the translation table in Annex VII to CLP is generally
13 possible. Translation from classification according to DSD or DPD to the classification
14 according to CLP is as follows:

- 15 – C; R35 is translated into Skin Corr. 1A; H314. The criteria in CLP and in DSD are
16 identical.
- 17 – C; R34 is translated into Skin Corr. 1B; H 314 with the following note:

Annex VII: Table 1.1

Note 2

It is recommended to classify in Category 1B even if it also could be possible that 1C could be applicable for certain cases. Going back to original data, may not result in a possibility to distinguish between Category 1B or 1C, since the exposure period has normally been up to 4 hours according to Regulation (EC) No 440/2008. However, for the future, when data are derived from tests following a sequential approach as foreseen in the Regulation (EC) No 440/2008, Category 1C should be considered.

- 18 – Xi; R38 is translated into Skin Irrit. 2; H315. The criteria in CLP and DSD are almost
19 identical.

1 It should be noted that where mixtures containing substances with risk phrase R34 have been
 2 classified on basis of the hazards of individual ingredients, the use of the translation table
 3 may lead to an under-classification of the mixture. This is because the general concentration
 4 limits, to be applied for mixtures, are lowered under CLP compared to DPD. For mixtures
 5 containing substances with this classification the use of the translation table may therefore
 6 not be appropriate and re-classification done by using the existing data would be more
 7 correct. For more details see section 1.7.

8 3.2.5.2 Re-evaluation of data

9 If there is new information which might be relevant with respect to classification a re-
 10 evaluation has to be performed.

11 3.2.6 Examples of classification for skin corrosion/irritation

12 3.2.6.1 Examples of substances fulfilling the criteria for classification

13 3.2.6.1.1 Example 1: Standard test according to OECD TG 404 with three animals

14 In a guideline test according to OECD TG 404 the test substance was applied for three minutes
 15 and 1 hour. No scars or other irreversible effects were found. The scoring results obtained after 4
 16 hours application time are listed in the following table:

Animal Nr.	Degree of erythema after ...[observation time]						Degree of oedema after ...[observation time]						<u>Ø 24/48/72 h</u> <u>≥2.3 ?</u>		
	1h	24h	48 h	72 h	7d	14d	1h	24h	48 h	72 h	7d	14d	Erythe- ma	Oede- ma	
1	3	3	3	2	0		1	2	2	2	0		Yes	No	
		<u>Ø 24/48/72 h = 2.7</u>						<u>Ø 24/48/72 h = 2.0</u>						=>"positive Responder"	
2	3	3	3	3	0		1	2	2	1	0		Yes	No	
		<u>Ø 24/48/72 h = 3</u>						<u>Ø 24/48/72 h = 1.7</u>						=>"positive Responder"	
3	1	1	1	0	0		1	1	1	1	0		No	No	
		<u>Ø 24/48/72 h = 0,66</u>						<u>Ø 24/48/72 h = 1</u>							

17 Classification: Skin Irritant Category 2

18 The classification is made on basis of 2/3 "positive responder" exceeding 2.3 mean score for
 19 erythema.

20 3.2.6.1.2 Example 2: Test carried out with one animal with a test substance which is 21 suspected as corrosive

22 Due to the unprecedented structure the biological effects of the substance cannot be
 23 anticipated. Therefore, the test according to OECD TG 404 was started with one animal only

1 in line with testing restrictions. Exposure times were 3 min and 1h. The following
 2 scores/effects were observed:

Exposure time	Degree of erythema after[observation time]					Degree of oedema after[observation time]					Visible necrosis, irreversible skin damage After 14d
	1h	24h	48h	72h	...	1h	24h	48h	72h	...	
3 min	0	0	0	0		0	0	0	0		No
1h	0	1	2	3		0	2	2	3		Yes

3 Classification: Skin Corrosion Category 1B

4 Rationale for the classification is destruction of the tissue within 1 hour exposure.

5 **3.2.6.1.3 Example 3a: Test carried out with more than three animals**

6 A substance was tested on acute skin irritation / corrosion according to OECD TG 404.

7 Contact time was 4 hours. No effects were seen after a contact time of 3 min and one hour.

8 The following scores were obtained:

Animal Nr	Degree of erythema after ...[observation time]						Degree of oedema after ...[observation time]					
	1h	24h	48h	72h	7d	14d	1h	24h	48h	72h	7d	14d
1	3	3	2	2	1	0	2	3	2	2	1	0
2	3	2	2	2	1	0	2	2	2	2	1	0
3	2	2	1	1	1	0	2	2	2	2	1	0
4	2	2	1	1	1	0	2	2	2	2	1	0

9 Evaluation was made based on the arithmetic mean of all animals.

10 The arithmetic mean after 24/48/72 hours for erythema $M_E = 21:12 = 1.8$; and for oedema M_O
 11 $= 25:12 = 2.1$. Both values are below 2.3, i.e. no classification warranted for skin irritation.

12 **3.2.6.1.4 Example 3b: Test carried out with more than three animals**

13 A substance was tested on acute skin irritation / corrosion according to OECD TG 404. Contact

14 time was 4 hours. No effects were seen after a contact time of 3 min and one hour. The

15 following scores were obtained after a contact time of 4 hours:

Animal Nr	Observation time												Pos responder	
	1h	24h	48h	72h	7d	14d	1h	24h	48h	72h	7d	14d	Erythema	Oedema
1	3	3	2	2	1	0	2	3	2	2	1	0	Yes	Yes
2	3	2	2	2	1	0	2	2	2	2	1	0	No	No
3	2	2	1	1	1	0	2	2	2	2	1	0	No	No

4	2	2	1	1	1	0	2	2	2	2	1	0	No	No
---	---	---	---	---	---	---	---	---	---	---	---	---	----	----

- 1 Evaluation was made based on the average score per animal.
 2 Only 1/4 of the animals reached the cut-off value of 2.3, i.e. only animal No 1 is a positive
 3 responder. No classification is warranted with regard to skin irritation.

4 3.2.6.2 Examples of mixtures fulfilling the criteria for classification

5 Where the mixture is made up of ingredients with no assigned SCLs, then the appropriate
 6 summation(s) and generic concentration limits from CLP Annex I, Table 3.2.3 should be
 7 used.

8 3.2.6.2.1 Example 4

Ingredient	Skin corrosion / irritation classification	Concentration (% w/w)	SCL
Surfactant A	Skin Cat 2	1,8	Not assigned
Substance B	Not classified	0,5	
Substance C	Skin Cat 2	5,4	Not assigned
Substance D	Not classified	4	
Acid	Skin Cat 1A	2	Not assigned
Water	Not classified	86.3	

9 pH of the mixture is 9.0 – 10.0, thus extreme pH provisions do not apply. The mixture
 10 contains a surfactant and an acid but neither are corrosive/irritant below 1% (as identified by
 11 the absence of SCLs in either CLP Annex VI or the Classification and Labelling Inventory).
 12 Additivity is considered to apply.

13 Substance B, substance D and water can be disregarded as they are not classified for skin
 14 corrosion/irritation.

15 The mixture contains 2% acid, the only ingredient classified as Skin Corr. Cat 1. As this is
 16 below the 5% GCL, the mixture is not classified Skin Corr. Cat. 1 but is classified Skin Irrit.
 17 Cat. 2 ($\geq 1\% < 5\%$).

18 3.2.6.2.2 Example 5

Ingredient	Skin corrosion / irritation classification	Concentration (% w/w)	SCL
Surfactant A	Skin Cat 2	3,8	Not assigned
Substance B	Not classified	0,5	
Base E	Skin Cat 1B	5,4	$C \geq 10\%$: Skin Cat 1B $5\% \leq C < 10\%$: Skin Cat 2
Substance D	Not classified	4	
Substance F	Skin Cat 1B	2	Not assigned
Water	Not classified	84.3	

19 pH of the mixture is 10.5 – 11.0, thus extreme pH provisions do not apply. The mixture
 20 contains a surfactant and a base but none are corrosive/irritant below 1% (as identified by

1 absence of specific concentration limits in either CLP Annex VI or the Classification and
2 Labelling Inventory). Additivity is considered to apply.

3 Substance B, substances D and water can be disregarded as they are not classified for skin
4 corrosion/irritation.

5 SCLs are neither assigned to substance F nor surfactant A, thus GCLs apply for these
6 ingredients. SCLs are assigned to Base E (see section 3.2.3.2.3.2 under *Application of SCLs*
7 *when applying the additivity approach*).

8 Skin Cat 1:

9 $(\% \text{ substance F/GCL}) + (\% \text{ base E/SCL}) = (2/5) + (5.4/10) = 0.94 \Rightarrow < 1$, thus mixture is not
10 classified as Skin Corr. Cat 1

11 Skin Cat 2:

12 $(\% \text{ substance F/GCL}) + (\% \text{ base E/SCL}) + (\% \text{ surfactant A/GCL}) = (2/1) + (5.4/5) + (3.8/10)$
13 $= 3.46$ which is > 1 , thus the mixture is classified Skin Irrit. Cat. 2

14 3.2.6.3 Examples of mixtures not fulfilling the criteria for classification

15 3.2.6.3.1 Example 6

Ingredient	Skin corrosion / irritation classification	Concentration (% w/w)	SCL
Surfactant C	Skin Cat 2	0,4	Not assigned
Surfactant G	Skin Cat 2	3.0	Not assigned
Surfactant A	Skin Cat 2	0,7	Not assigned
Substance H	Skin Cat 1A	3,0	$C \geq 70 \%$: Skin Cat 1A $50 \% \leq C < 70 \%$: Skin Cat 1B $35 \% \leq C < 50 \%$: Skin Cat 2
Substance D	Not classified	2	
Water	Not classified	90.9	

16 pH of the mixture is: 2.5 – 3.0, thus extreme pH provisions do not apply. The mixture
17 contains three surfactants but none are corrosive/irritant below 1% (as identified by the
18 absence of specific concentration limits in either CLP Annex VI or the Classification and
19 Labelling Inventory). Additivity is considered to apply.

20 Substance D and water can be disregarded as they are not classified for skin
21 corrosion/irritation. Also surfactant C and surfactant A can be disregarded as both are present
22 below 1%.

23 A SCL is not assigned to surfactant G, thus GCL apply for this ingredient.

24 Skin Cat 1:

25 The mixture contains 3% substance H, the only ingredient classified as Skin Corr. Cat. 1. As
26 this is below the 50% SCL for substance H, the mixture is not classified as Skin Corr. Cat. 1.

27 Skin Cat 2:

28 $(\% \text{ substance H/SCL}) + (\% \text{ surfactant G/GCL}) = (3/35) + (3/10) = 0.39$ which is < 1 , thus the
29 mixture is not classified Skin Irrit. Cat. 2.

1 3.2.7 References

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24 3.3 SERIOUS EYE DAMAGE/EYE IRRITATION

25 It should be noted that if a substance or mixture is classified as skin corrosive category 1 then
26 serious damage to eyes is implicit and there is no need to proceed with classification for eye
27 effects.

28 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.

29 3.3.2 Classification of substances for serious eye damage/eye irritation

30 3.3.2.1 Identification of hazard information

31 3.3.2.1.1 Identification of human data

32 Existing data on eye effects in humans may include well-documented epidemiological
33 studies, clinical studies, case reports, and data from poison information units and accident
34 databases or occupational experience. Their quality and relevance for hazard assessment

1 should be thoroughly reviewed. A critical review of the value of human studies is provided in
2 IR/CSA, section R.4.3.3 and more specific considerations for eye damage/irritation are given
3 in IR/CSA, section R.7.2.4.2.

4 **3.3.2.1.2 Identification of non human data**

5 Available serious eye damage/eye irritation information on substances may include existing
6 data generated by the test methods in the Test Methods Regulation or by methods based on
7 internationally recognised scientific principles.

8 Several of the following non-testing and *in vitro* methods have been validated against the
9 DSD criteria but not against the CLP criteria for classification. Therefore it should be
10 checked whether the method is sufficiently validated for classification according to CLP.

11 **3.3.2.1.2.1 Consideration of physico-chemical properties**

12 Substances with oxidising properties can give rise to highly exothermic reactions in contact
13 with other substances and human tissue. High temperatures thus generated may
14 damage/destroy biological materials. This applies, for example, to organic peroxides, which
15 can be assumed to be eye irritants, unless evidence suggests otherwise (IR/CSA Section
16 R.7.2.3.1).

17 For a hydro peroxide classification as eye damage category 1 should be considered, whereas
18 eye irritation Category 2 should be considered for peroxides. Appropriate evidence must be
19 provided in order to consider non-classification of substances with oxidising properties.

20 **3.3.2.1.2.2 Non-testing methods: (Q)SARs and expert systems**

21 Non-testing methods such as (Q)SARs and expert systems may be considered on a case-by-
22 case basis. (Q)SARs are in general not very specific for eye irritancy. In many cases rules are
23 used in a similar manner to those used for skin irritation and corrosion. (Q)SAR systems that
24 also account for eye effects are for example TOPKAT, Derek for Windows, and SICRET.
25 For full guidance, consult the IR/CSA Section R.6 (“QSAR and grouping of chemicals”), in
26 which also the many shortcomings of the existing systems are discussed.

27 Since a formal adoption procedure for those non-testing methods is not foreseen and no
28 formal validation process is in place, appropriate documentation is crucial. In order to
29 achieve acceptance under REACH, the documentation must conform to the so-called QSAR
30 Model Reporting Format (QMRF). For more details consult the IR/CSA Section R.6.1.

31 **3.3.2.1.2.3 Testing-methods: pH and the acid/alkaline reserve**

Annex I: 3.3.2.3. ...Likewise, pH extremes like ≤ 2 and $\geq 11,5$ may produce serious eye damage, especially when associated with significant buffering capacity. Such substances are expected to produce significant effects on the eyes. Possible skin corrosion has to be evaluated prior to consideration of serious eye damage/eye irritation in order to avoid testing for local effects on eyes with skin corrosive substances...

32 Substances can be predicted to be corrosive, if the pH is ≤ 2 or ≥ 11.5 . Where extreme pH is
33 the only basis for classification as serious eye damage, it is important to take into
34 consideration the acid/alkaline reserve, a measure of the buffering capacity (Young *et al*,
35 1988, and Young and How, 1994). However, lack of buffering capacity should not be used
36 alone to exonerate from classification as corrosive.

37 If pH is < 3.2 or > 8.6 , then consider the substance for severe eye damage/eye irritation
38 (IR/CSA Section R.7.2.4.1). Further information and/or reasoning is needed to conclude

1 whether the substance is causing severe eye damage or eye irritation. This model is not
2 recommended for the stand-alone discrimination between eye irritants and non-irritants.
3 However, it could be used in the context of a tiered testing strategy to identify eye irritants
4 (due to its very low false positive rate) but not for non-irritants (due to its relatively high false
5 negative rate).

6 **3.3.2.1.2.4 Testing methods: *in vitro* methods**

7 Two *in vitro* test methods, the Bovine Corneal Opacity and Permeability (BCOP) test and the
8 Isolated Chicken Eye (ICE) test, have been accepted by the OECD in September 2009 (TG
9 437 and 438) and included in the EU Test Method Regulation in December 2010 (B.47 and
10 B.48) as test methods able to distinguish seriously eye damaging substances (Serious eye
11 damage Category 1). Furthermore, there is regulatory acceptance in the EU that a substance
12 can be considered as seriously damaging the eye (Serious eye damage Category 1) based on
13 positive results in the Isolated Rabbit Eye (IRE) test or the Hen's Egg Test on Chorio-
14 allantoic Membrane (HET-CAM) test. Negative *in vitro* corrosivity responses in these tests
15 must be followed by further testing (IR/CSA Section R.7.2.4.1)

16 There are no *in vitro* tests with regulatory acceptance for eye irritation at present, but the two
17 human corneal epithelium models, EpiOcular™ and SkinEthic™, have been submitted to
18 ECVAM for validation.

19 **3.3.2.1.2.5 Testing methods: *In vivo* data**

20 Testing for eye irritation would not be carried out on substances known or predicted to be
21 corrosive to skin. Such substances are automatically considered to be severely damaging to
22 the eye. A parallel classification with serious eye damage in addition to skin corrosion is not
23 required.

24 The *in vivo* test in rabbits according to OECD TG 405 (B.5 in the Test Methods Regulation)
25 is the standard test for the hazard assessment under the REACH.

26 The Low Volume Eye Test (LVET; Griffith *et al* 1980) is a modification of the standard
27 OECD TG 405 test method, the differences being:

- 28 - the test material is placed directly on the cornea instead of introducing it in the
29 conjunctival sac inside the lower lid;
- 30 - a reduction in the volume of test material applied (0.01 ml (or corresponding weight for
31 solids) compared with the standard 0.1 ml).

32 Data from the LVET should be considered but must be carefully evaluated. The applicability
33 domain up to now is limited to detergent and cleaning products. It is stated that positive data
34 are a trigger for appropriate classification, but that negative data are not conclusive for a non-
35 classification (IR/CSA R.7.2.4.1). However, they should be considered in a weight of
36 evidence determination.

37 **3.3.2.2 Classification criteria**

Annex I: 3.3.2.6. Irreversible effects on the eye/serious damage to eyes (Category 1)

3.3.2.6.1. Substances that have the potential to seriously damage the eyes are classified in Category 1 (irreversible effects on the eye). Substances are classified in this hazard category on the basis of the results of animal testing, in accordance with the criteria listed in Table 3.3.1. These observations include animals with grade 4 cornea lesions and other severe reactions (e.g., destruction of cornea) observed at any time during the test, as well as persistent corneal opacity, discoloration of the cornea by a dye substance, adhesion, pannus, and interference with the function of the iris or other effects that impair sight. In this context, persistent lesions are considered those

which are not fully reversible within an observation period of normally 21 days. Substances are also classified in Category 1 if they fulfil the criteria of corneal opacity ≥ 3 or iritis $> 1,5$ detected in a Draize eye test with rabbits, recognising that such severe lesions usually do not reverse within a 21 days observation period.

Table 3.3.1
Category for irreversible eye effects

Category	Criteria
Irreversible effects on the eye (Category 1)	If, when applied to the eye of an animal, a substance produces: <ul style="list-style-type: none"> – at least in one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days; and/or – at least in 2 of 3 tested animals, a positive response of: <ul style="list-style-type: none"> – corneal opacity ≥ 3 and/or – iritis > 1.5 calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material.

1

Annex I: 3.3.2.7. Reversible effects on the eye (Category 2)

3.3.2.7.1. Substances that have the potential to induce reversible eye irritation are classified in Category 2 (irritating to eyes).

Table 3.3.2
Category for reversible eye effects

Category	Criteria
Irritating to eyes (Category 2)	if, when applied to the eye of an animal, a substance produces: <ul style="list-style-type: none"> – at least in 2 of 3 tested animals, a positive response of: <ul style="list-style-type: none"> – corneal opacity ≥ 1 and/or – iritis ≥ 1, and/or – conjunctival redness ≥ 2 and/or – conjunctival oedema (chemosis) ≥ 2 – calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material, and which fully reverses within an observation period of 21 days

3.3.2.7.2. For those substances where there is pronounced variability among animal responses, this information shall be taken into account in determining the classification

2 The classification criteria apply to the results of the OECD TG 405 and to the results of the
 3 LVET. Negative data from the LVET are not conclusive for non-classification, but should be
 4 considered in a weight of evidence determination.

5 **3.3.2.3 Evaluation of hazard information**

Annex I: 3.3.2.5. A tiered approach to the evaluation of initial information shall be considered where applicable, while recognising that all elements may not be relevant in certain cases.

3.3.2.4. ...Although information may be gained from the evaluation of single parameters within a tier (e.g. caustic alkalis with extreme pH shall be considered as local corrosives), the totality of existing information shall be considered in making an overall weight of evidence determination, particularly when there is information available on some but not all parameters. Generally, primary

emphasis shall be placed upon expert judgement, considering human experience with the substance, followed by the outcome of skin irritation testing and of well-validated alternative methods.

3.3.2.3.1 Evaluation of human data

Quality data on substance-induced eye irritation in humans are likely to be rare. Where human data are available, the usefulness of such data for classification purposes will depend on the extent to which the effect, and its magnitude, can be reliably attributed to the substance of interest. The quality and relevance of such data for hazard assessment should be critically reviewed.

If a substance is diagnostically confirmed by a physician to be the cause for decay in vision with the effects not being transient but persistent this should lead to the most serious eye classification, i.e. Eye Damage Category 1.

Further information on the evaluation of human data for eye irritation can be found in IR/CSA Section R7.2.4.2.

3.3.2.3.2 Evaluation of non-human data

The results of the non-testing methods fulfilling the criteria of REACH Annex XI paragraphs 1.3 and 1.5 should be used instead of testing or as part of the weight of evidence approach.

3.3.2.3.2.1 *In vitro* data

Only positive results in the BCOP, ICE, IRE and HET-CAM *in vitro* assays can be used for classification as severe eye irritants. Negative results are not conclusive for a non-classification.

There are currently no validated *in vitro* eye irritation test methods available. However, two reconstituted human tissue models (the EpiOcularTM and SkinEthicTM 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.

1 According to OECD TG 405, in cases of suspected serious eye damage, the test is started
2 with one animal only. If effects in this animal are irreversible until the end of the observation
3 period, sufficient information is available to classify the substance for serious eye damage.
4 For a decision on no classification for serious eye damage and/or irritation or for a decision
5 on classification as irritant, two additional animals have to be tested.

6 For each of the three test animals the average scores for three consecutive days (usually 24,
7 48 and 72 hours) are calculated separately for the cornea, iris and conjunctiva (erythema and
8 swelling). If the mean scores for 2 out of 3 animals exceed the values in Tables 3.3.1 / 3.3.2,
9 classification has to be assigned accordingly.

10 Tests that have been conducted with more than three animals

11 Older test methods, however, have been using up to six rabbits. The CLP does not provide
12 criteria for the evaluation of such studies. The current US EPA/UN Recommendation may be
13 considered (see Example 2):

14 *In case of 6 rabbits the following applies:*

15 Classification as serious eye damage – Category 1 if at least in one animal effects on the cornea,
16 iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation
17 period of normally 21 days; and/or

18 at least 4 out of 6 rabbits show a mean score of

19 ≥ 3 for the cornea and/or

20 ≥ 1.5 for the iris

21 Classification as eye irritation – Category 2 if at least 4 out of 6 rabbits show a mean score of

22 ≥ 1 for the cornea and/or

23 ≥ 1 for the iris and/or

24 ≥ 2 conjunctival erythema and/or

25 ≥ 2 conjunctival swelling

26 *In case of 5 rabbits the following applies:*

27 Classification as serious eye damage – Category 1 if at least in one animal effects on the cornea,
28 iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation
29 period of normally 21 days; and/or

30 at least 3 out of 5 rabbits show a mean score of

31 ≥ 3 for the cornea and/or

32 ≥ 1.5 for the iris

33 Classification as eye irritation – Category 2 if at least 3 out of 5 rabbits show a mean score of

34 ≥ 1 for the cornea and/or

35 ≥ 1 for the iris and/or

36 ≥ 2 conjunctival erythema and/or

37 ≥ 2 conjunctival swelling

38 *In case of 4 rabbits the following applies:*

1 Classification as serious eye damage – Category 1 if at least in one animal effects on the cornea,
2 iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation
3 period of normally 21 days; and/or

4 at least 3 out of 4 rabbits show a mean score of

5 ≥ 3 for the cornea and/or

6 ≥ 1.5 for the iris

7 Classification as eye irritation – Category 2 if at least 3 out of 4 rabbits show a mean score of

8 ≥ 1 for the cornea and/or

9 ≥ 1 for the iris and/or

10 ≥ 2 conjunctival erythema and/or

11 ≥ 2 conjunctival swelling

12 In this case the irritant categories 1 and 2 are used if 4 of 6 rabbits show a mean score as
13 outlined in the criteria. Likewise, if the test was performed with 4 or 5 animals, for at least 3
14 individuals the mean score must exceed the values laid down in the classification criteria. A
15 single animal showing irreversible or otherwise serious effects consistent with corrosion will
16 necessitate classification as serious eye damage Category 1 irrespective of the number of
17 animals used in the test.

18 Other animal tests

19 The LVET uses the same scoring system as for results from the OECD TG 405, but data from
20 the test is not conclusive for a non-classification. However, they can be included in a weight
21 of evidence determination.

22 Note that in case there are test data that originate from non-OECD tests and scoring has not
23 been performed according to the Draize system, the values in Annex I, Tables 3.3.1 / 3.3.2
24 are no longer applicable for classification purposes. However these data from non-OECD
25 tests should be considered in a weight of evidence determination.

26 **3.3.2.3.3 Weight of evidence**

27 Where the criteria cannot be applied directly to available identified information, a weight of
28 the evidence determination using expert judgement shall be applied in accordance with CLP
29 Article 9(3).

30 A weight of the evidence determination means that all available and scientifically justified
31 information bearing on the determination of hazard is considered together, such as human
32 experience (including occupational data and data from accident databases, epidemiological
33 and clinical studies, and well-documented case reports and observations), relevant animal
34 data, skin irritation information/data, physico-chemical parameters (e.g., pH, reserve
35 alkalinity/acidity), the results of suitable *in vitro* tests, information from the application of the
36 category approach (grouping, read-across), QSAR results. The quality and consistency of the
37 data shall be given appropriate weight. Both positive and negative results shall be assembled
38 together in a single weight of evidence determination. Evaluation must be performed on a
39 case-by-case basis and with expert judgement. However, normally positive results that are
40 adequate for classification should not be overruled by negative findings.

Annex I: 1.1.1.4. For the purpose of classification for health hazards (Part 3) established hazardous effects seen in appropriate animal studies or from human experience that are consistent with the

criteria for classification shall normally justify classification. Where evidence is available from both humans and animals and there is a conflict between the findings, the quality and reliability of the evidence from both sources shall be evaluated in order to resolve the question of classification. Generally, adequate, reliable and representative data on humans (including epidemiological studies, scientifically valid case studies as specified in this Annex or statistically backed experience) shall have precedence over other data. However, even well-designed and conducted epidemiological studies may lack a sufficient number of subjects to detect relatively rare but still significant effects, to assess potentially confounding factors. Therefore, positive results from well-conducted animal studies are not necessarily negated by the lack of positive human experience but require an assessment of the robustness, quality and statistical power of both the human animal data.

1 For further guidance, if both human and animal data are available, see IR/CSA Section
2 R.7.2.3.2.

3 **3.3.2.4 Decision on classification**

4 A skin corrosive substance is considered to also cause serious eye damage which is indicated
5 in the hazard statement for skin corrosion (H 314: Causes severe skin burns and eye damage).
6 Thus, in case a substance has to be classified for skin corrosion an additional classification
7 with H318 “Causes serious eye damage” is not indicated.

8 **3.3.2.5 Setting of specific concentration limits**

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

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

9 It is more difficult to prove the absence of a hazardous property, the legal text states that:

Article 10(1)

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

10

11 An SCL set in accordance with the above mentioned provisions shall take precedence over
12 the GCL set out in Tables 3.2.3 and 3.2.4 of Annex I to CLP (Article 10(6)). Furthermore, an
13 SCL is substance-specific and should be applicable to all mixtures containing the substance,
14 instead of any GCL that otherwise would apply to a mixture containing the substance.

NOTE TO RAC and Forum on Skin Corrosion/Irritation & Serious Eye Damage/Eye Irritation Sections

A particular issue arose regarding the draft text presented to the PEG consultation relating to the “*What type of information may be the basis for setting a SCL*”. There were some 20 comments submitted raising issues relating to test data already existing for mixtures and dilutions of substances, derived from OECD TG 404 and 405 and also the use of *in vitro* methodology, particularly for skin tests. Following an exhaustive and controversial discussion at the PEG meeting, there was some agreement to revise the text and the revised proposed text, has been further discussed at length internally at ECHA and endeavours to find a compromise of the differing views.

Members are asked to consider this text (in these two sections) in light of the above controversial discussions and comment on its acceptability.

What type of information may be the basis for setting a specific concentration limit?

Existing human data may in certain cases (especially if dose-response information is available) indicate that the threshold for the irritation hazard in humans, for a substance in a mixture, would be higher or lower than the GCL. A careful evaluation of the usefulness and the validity of such human data as well as their representativeness and predictive value (IR/CSA, sections R.4.3.3. and R.7.2.4.2) should be performed. As pointed out in Section 1.1.1.4 of Annex I, CLP, positive results from well-conducted animal studies are not necessarily negated by the lack of positive human experience but require an assessment of robustness, quality and a degree of statistical certainty of both the human and animal data.

The aim of the standard test method for “Acute Eye Irritation/Corrosion” TM B.5/OECD TG 405² is to **identify** potential serious eye damage or eye irritants. The test material is generally administered undiluted. Thus, no dose-response relationship can be obtained from an individual test. However, if there are test data from already performed animal studies for a corrosive or irritant substance in an appropriate series of dilutions, a concentration can be derived that would not lead to a classification. Subject to the test data being “adequate, reliable and conclusive”, as required by Art.10(1) CLP to set a higher SCL than the GCL, these data can be used for testing dilutions in order to demonstrate non-irritating thresholds.

If adequate, relevant and conclusive data exist from other already performed animal studies with a sufficient number of animals tested to ensure a high degree of certainty, and with information of dose-response relationships, such data may be considered for setting a lower or, in exceptional cases, a higher SCL on a case-by-case basis.

However, it should be noted that any additional animal testing (of dilutions) of substances already classified as a serious eye irritant or eye irritant, 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)). The possibilities to use *in vitro* test methods as a basis for setting SCLs have not yet been explored. However, this does not exclude that a method to set SCLs based on *in vitro* tests could be developed, and these tests may provide a promising option for SCL setting in the future.

² TO NOTE: In OECD TG 404 is called the term test substance refers to the test material, test article or test item. The term substance may be used differently from the REACH/CLP definition.

1 Annex VI Part 3 (Table 3.2) to CLP Regulation includes examples of substances for which a
 2 higher or lower SCL was set under Directive 67/548/EEC (old Dangerous Substances
 3 Directive (DSD) system).-

4 **3.3.2.6 Decision logic**

5 The decision logic which is based on IR/CSA, Figure R.7.2-3 is revised to meet CLP
 6 requirements. It is strongly recommended that the person responsible for classification, study
 7 the criteria for classification before and during use of the decision logic.

Step		
0	Is the substance classified as a skin corrosive? YES → NO ↓	When classified as Skin Corr. 1, the risk of severe damage to eyes is considered implicit. No need to proceed.
1a	Is the substance an organic hydro peroxide or an organic peroxide? YES → NO ↓	– Consider to classify as serious eye damage (Eye Dam. 1) if the substance is a hydro peroxide, or – eye irritating (Eye Irrit. 2) if the substance is a peroxide. OR Provide evidence for the contrary and proceed to step 1b
1b	Is the pH of the substance ≤ 2 or ≥ 11.5 ? YES → NO ↓	– Where classification is based upon consideration of pH alone (i.e. buffering capacity not known), Eye Dam. 1 should be applied. When assigned Skin Corr. 1, the risk of severe damage to eyes is considered implicit. – Where consideration of the alkali/alkaline reserve suggests that the substance is not corrosive, this has to be confirmed (preferably by use of an appropriate <i>in vitro</i> test). Proceed to step 1c
1c	Are there other physical or chemical properties that indicate that the substance has the potential to cause serious eye damage or is irritating to the eye? YES → NO ↓	Use this information for weight of evidence (WoE) determination (step 6). Proceed to step 2
2	Is there adequate existing human experience which provides evidence that the substance has the potential to cause serious eye damage or is irritating to the eye? YES → NO ↓	Classify accordingly (Eye Dam. 1 or Eye Irrit. 2).

3	<p>Are there data from existing studies <i>on eye irritation</i> 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 →</p> <p>NO ↓</p>	<p>Classify accordingly (Eye Dam. 1 or Eye Irrit. 2 or no classification).</p>
4	<p>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 →</p> <p>NO ↓</p>	<p>Consider to classify accordingly (Eye Dam. 1 or Eye Irrit. 2). If discrimination between Eye Dam. 1 and Eye Irrit. 2 is not possible, Eye Dam. 1 must be chosen.</p> <p>Proceed to step 5a</p>
5a	<p>Are there data from a validated <i>in vitro</i> test (adopted by OECD or not), which provide evidence that the substance is an eye irritant or non-irritant? YES →</p> <p>NO ↓</p>	<p>Consider to classify accordingly (Eye Dam. 1 or Eye Irrit. 2 or no classification). If discrimination between Eye Dam. 1 and Eye Irrit. 2 is not possible, Eye Cat. 1 must be chosen.</p> <p>Proceed to step 5b</p>
5b	<p>Are there acceptable data from a suitable <i>in vitro</i> test, which provide evidence that the substance is a severe eye irritant? YES →</p> <p>NO ↓</p>	<p>Consider to classify as Eye Dam. 1.</p> <p>Proceed to step 6</p>
6	<p>Taking all existing and relevant data) into account, is there sufficient information to make a decision on classification? YES →</p> <p>NO ↓</p>	<p>Classify accordingly (Eye Dam. 1 or Eye Irrit. 2 or no classification).</p>
	<p>Unable to classify substance for serious eye damage/eye irritation</p>	<p>Decision to undertake generation of new test data should be made in compliance with REACH and Article 8 of the CLP.</p> <p>It is recommended that ECHA guidance R.7.2.6 should also be considered.</p>

1 3.3.3 Classification of mixtures for serious eye damage/eye irritation

2 3.3.3.1 Identification of hazard information

3 The procedure for classifying mixtures is a tiered i.e. a stepwise approach based on a
 4 hierarchy principle and depending on the type and amount of available data/information

1 starting from evaluating existing human data on the mixture, followed by a thorough
2 examination of the existing *in vivo* data, physico-chemical properties, and finally *in vitro* data
3 available on the mixture. If valid test data are available for the whole mixture they have
4 precedence. If no such data exist, the so called bridging principles have to be applied if
5 possible. If the bridging principles are not applicable an assessment on the basis of data for
6 the components of the mixture will be applied.

7 Where it is decided to base the classification of a mixture upon consideration of pH alone,
8 Eye Damage Category 1 should be applied. In this case no further retrieval of information on
9 the mixture itself is needed.

10 **3.3.3.1.1 Identification of existing human data**

11 For mixtures that have been on the market for a long time, some human data and experience
12 may exist that could provide useful information on the eye irritation potential of the
13 respective mixtures. However, lack of data on effects in humans may be due to, for example,
14 poor reporting or adequate preventive measures. Therefore, lack of data cannot be taken as
15 evidence of the mixture being non-hazardous. See **section 3.3.2.1.1** for further information on
16 the identification of human data.

17 **3.3.3.2 Classification criteria**

18 **3.3.3.2.1 When data are available for the complete mixture**

Annex I: 3.3.3.1.1. The mixture will be classified using the criteria for substances, and taking into account the testing and evaluation strategies used to develop data for these hazard classes.

Unlike other hazard classes, there are alternative tests available for skin corrosivity of certain types of mixtures that give an accurate result for classification purposes, as well as being simple and relatively inexpensive to perform. When considering testing of the mixture classifiers are encouraged to use a tiered weight of evidence strategy as included in the criteria for classification of substances for skin corrosion and serious eye damage and eye irritation to help ensure an accurate classification, as well as avoid unnecessary animal testing. A mixture is considered to cause serious eye damage (Category 1) if it has a pH ≤ 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 *in vitro* test.

19 Where the criteria cannot be applied directly to available identified information, a weight of
20 evidence determination using expert judgement shall be applied in accordance with CLP
21 Article 9(3). A weight of the evidence determination means that all available and
22 scientifically justified information bearing on the determination of hazard is considered
23 together, such as physico-chemical parameters, the results of suitable *in vitro* tests, relevant
24 animal data, and human experience. The quality and consistency of the data shall be given
25 appropriate weight. Both positive and negative results shall be assembled together in a single
26 weight of evidence determination.

27 The integration of all information to come to a final hazard assessment based on weight of
28 evidence in general requires in-depth toxicological expertise.

29 There are a number of available *in vitro* test systems that currently being validated for their
30 suitability in assessing serious eye damage/eye irritation potential of substances and mixtures.
31 When validated *in vitro* eye irritation test methods are available in the future the results from
32 such tests can be used for classification. Then these results can also be used to classify the
33 mixture. However, not all available *in vitro* test systems work equally well for all types of

1 mixtures. Prior to testing a mixture in a specific *in vitro* assay for classification purposes, it
 2 has to be assured that the respective test has been previously shown to be suitable for the
 3 prediction of serious eye damage/eye irritation properties for the type of mixture to be
 4 evaluated.

5 3.3.3.2.1.1 Mixtures with extreme pH

6 Where the mixture has an extreme pH value but the only corrosive/irritant ingredient present
 7 in the mixture is an acid or base with an assigned SCL (either CLP Annex VI or set by
 8 supplier), then the mixture should be classified accordingly. In this instance, pH of the
 9 mixture should not be considered a second time since it would have already been taken into
 10 account when deriving the SCL for the substance.

11 If this is not the case, then the steps to be taken into consideration when classifying a mixture
 12 with $\text{pH} \leq 2$ or ≥ 11.5 are described in the following decision logic:

Mixture not classified as Skin Corr. 1 and without <i>in vivo</i> data on serious eye damage/eye irritation or relevant data from similar tested mixtures. pH is ≤ 2 or ≥ 11.5	
Does the acid/alkaline reserve indicate that the mixture may not be corrosive? NO → YES ↓	Classify as serious eye damaging, Eye Dam. 1.
Is the mixture tested for serious eye damaging properties in an accepted <i>in vitro</i> test? NO → YES ↓	Classify as serious eye damaging, Eye Dam. 1.
Does the mixture demonstrate serious eye damaging properties in an accepted <i>in vitro</i> test? YES → NO ↓	Classify as serious eye damaging, Eye Dam. 1.
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 <i>in vitro</i> 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.

13 If consideration of extreme pH and acid/alkaline reserve indicates the mixture may not have
 14 the potential to cause serious eye damage, then the supplier should carry out further testing to
 15 confirm this (Annex I, section 3.3.3.2.1). The mixture must be classified as Serious eye
 16 damage Category 1 if the supplier decide not to carry out the required confirmatory testing.

17 If further testing confirms that the mixture should not be classified for serious eye damage
 18 effects, then the supplier should assess the mixture for eye irritation either using *in vitro* eye
 19 irritation test methods when available or the summation method.

20 It must be note that the pH-acid/alkali reserve method assumes that the potential corrosivity
 21 or irritancy is due to the effect of the ionic entities. When this is not the case, especially when
 22 the mixture contains non-ionic (non-ionisable) substances themselves classified as corrosive
 23 or irritant, then the pH-reserve method cannot be a basis for modifying the classification.

1 Where the mixture has an extreme pH value and contains some other corrosive/irritant
2 ingredients (some of which may have SCLs assigned) in addition to an acid or base with or
3 without an assigned SCL, then the mixture shall follow the procedure described in the
4 decision logic.

5 **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.

6 In order to apply bridging principles, there needs to be sufficient data on similar tested
7 mixtures as well as the components of the mixture.

8 When the available identified information is inappropriate for the application of the bridging
9 principles then the mixture should be classified using the methods described in Section
10 1.6.3.4

11 **3.3.3.2.3 When data are available for all components or only for some components** 12 **of the mixture**

13 **3.3.3.2.3.1 Components that should be taken into account for the purpose of** 14 **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.

15 **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.

16 When the supplier is unable to derive the classification using either data on the mixture itself
17 or bridging principles, he must determine the serious eye damage/ eye irritation properties of
18 his mixture using data on the individual ingredients. The supplier must ascertain whether the
19 additivity approach is applicable, the first step in the process being to identify all the
20 ingredients in the mixture (i.e. their name, chemical type, concentration level, hazard
21 classification and any SCLs) and the pH of the mixture. In addition, for example surfactant
22 interaction or neutralisation of acids/bases could occur in a mixture, which makes it important
23 to consider not only the contribution of individual ingredients but also the effects of the entire
24 mixture

1 Additivity may not apply where the mixture contains substances mentioned in Annex I,
2 3.3.3.3.4.1 which may be corrosive/irritant at concentrations below 1%, see **section**
3 **3.3.3.2.3.3.**

4 *Application of SCLs when applying the additivity approach*

5 The generic concentration limits are specified in Table 3.3.3. However, Article 10.5 indicates
6 that specific concentration limits (SCLs) take precedence over generic concentration limits.
7 Thus, if a given substance has a SCL, then this specific concentration limit has to be taken
8 into account when applying the summation (additivity) method for serious eye damage/eye
9 irritation (see Examples 4 and 5).

10 In cases where additivity applies for serious eye damage/eye irritation to a mixture with two
11 or more substances some of which may have SCLs assigned, then the following formula
12 should be used:

13 The mixture is classified for serious eye damage/eye irritation if the

14 $\text{Sum of } (\text{ConcA} / \text{clA}) + (\text{ConcB} / \text{clB}) + \dots + (\text{ConcZ} / \text{clZ}) \text{ is } \geq 1$

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

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

17 ConcB = the concentration of substance B in the mixture;

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

19 This approach is similar to that used in the DPD where a substance SCL can replace the
20 default limits in the conventional method equations.

21 **3.3.3.2.3.3 The additivity approach is not applicable**

Annex I; 3.3.3.3.4.1. Particular care must be taken when classifying certain types of mixtures containing substances such as acids and bases, inorganic salts, aldehydes, phenols, and surfactants. The approach explained in paragraphs 3.3.3.3.1 and 3.3.3.3.2 might not work given that many of such substances are corrosive or irritant at concentrations < 1 %.

3.3.3.3.4.2. For mixtures containing strong acids or bases the pH shall be used as classification criteria (see paragraph 3.3.2.3) since pH will be a better indicator of serious eye damage than the generic concentration limits of Table 3.3.3.

3.3.3.3.4.3. A mixture containing corrosive or irritant ingredients that cannot be classified based on the additivity approach (Table 3.3.3), due to chemical characteristics that make this approach unworkable, shall be classified as Category 1 for effects on the eye if it contains ≥ 1 % of a corrosive ingredient and as Category 2 when it contains ≥ 3 % of an irritant ingredient. Classification of mixtures with ingredients for which the approach in Table 3.3.3 does not apply is summarised in Table 3.3.4.

3.3.3.3.5. On occasion, reliable data may show that the reversible/irreversible eye effects of an ingredient will not be evident when present at a level above the generic concentration limits mentioned in Tables 3.3.3 and 3.3.4. In these cases the mixture shall be classified according to those data. On other occasions, when it is expected that the skin corrosion/irritation hazards or the reversible/irreversible eye effects of an ingredient will not be evident when present at a level above the generic concentration limits mentioned in Tables 3.3.3 and 3.3.4, testing of the mixture shall be considered. In those cases, the tiered weight of evidence strategy shall be applied.

3.3.3.3.6. If there are data showing that (an) ingredient(s) may be corrosive or irritant at a concentration of < 1 % (corrosive) or < 3 % (irritant), the mixture shall be classified accordingly.

1 **3.3.3.3 Generic concentration limits for substances triggering classification of**
 2 **mixtures**

3 **3.3.3.3.1 When the additivity approach is applicable**

Annex I: Table 3.3.3		
Generic concentration limits of ingredients of a mixture classified as Skin corrosive Category 1 and/or eye Category 1 or 2 for effects on the eye that trigger classification of the mixture for effects on the eye (Category 1 or 2)		
Sum of ingredients classified as:	Concentration triggering classification of a mixture as:	
	Irreversible Eye Effects	Reversible Eye Effects
	Category 1	Category 2
Eye effects Category 1 or Skin corrosive Category 1A, 1B, 1C	≥ 3 %	≥ 1 % but < 3 %
Eye Effects Category 2		≥ 10 %
(10 x Eye Effects Category 1) + Eye effects Category 2		≥ 10 %
Skin Corrosive Category 1A, 1B, 1C + Eye effects Category 1	≥ 3 %	≥ 1 % but < 3 %
10 x (Skin corrosive Category 1A, 1B, 1C + Eye Effects Category 1) + Eye Effects Category 2		≥ 10 %

4 **3.3.3.3.2 When the additivity approach is not applicable**

Annex I: Table 3.3.4		
Generic concentration limits of ingredients of a mixture for which the additivity approach does not apply, that trigger classification of the mixture as hazardous to the eye		
Ingredient	Concentration	Mixture classified as: Eye
Acid with pH ≤ 2	≥ 1%	Category 1
Base with pH ≥ 11,5	≥ 1%	Category 1
Other corrosive (Categories 1) ingredients for which additivity does not apply	≥ 1%	Category 1
Other irritant (Category 2) ingredients for which additivity does not apply, including acids and bases	≥ 3%	Category 2

5 There are ongoing discussions at UN level whether 'Other irritant (Category 2) ingredients' in
 6 Table 3.3.4 (last row) include skin and eye irritants or only eye irritants.

7 **3.3.3.4 Decision logic**

8 The decision logic which is based on IR/CSA, Figure R.7.2-3 is revised to meet CLP
 9 requirements. It is strongly recommended that the person responsible for classification, study
 10 the criteria for classification before and during use of the decision logic.



1. When data are available for the complete mixture		
0	Is the mixture classified as a skin corrosive? YES → NO ↓	When assigned Skin Corr. 1, the risk of severe damage to eyes is considered implicit. No need to proceed.
1a	Is the pH of the mixture ≤ 2 or ≥ 11.5 ? YES → NO ↓	– Where classification is based upon consideration of pH alone (i.e. buffering capacity not known), Eye Dam. 1 should be applied. When assigned Skin Corr. 1, the risk of severe damage to eyes is considered implicit. – Where consideration of the acid/alkaline reserve suggests that the substance is not corrosive, this has to be confirmed (preferably by use of an appropriate <i>in vitro</i> test). Proceed to step 1b.
1b	Are there other physical or chemical properties that indicate that the mixture has the potential to cause serious eye damage or is irritating to the eye? YES → NO ↓	Use this information for weight of evidence (WoE) determination (step 6). Proceed to step 2.
2	Are there adequate existing human experience data which provide evidence that the mixture has the potential to cause serious eye damage or is irritating to the eye? YES → NO ↓	Classify accordingly (Eye Dam. 1 or Skin Irrit. 2).
3	Are there data from existing studies <i>on eye irritation</i> in laboratory animals, which provide sound conclusive evidence that the mixture has the potential to cause serious eye damage, is an eye irritant or non-irritant? YES → NO ↓	Classify accordingly (Eye Dam. 1 or Eye Irrit. 2 or no classification).
4a	Are there data from a validated <i>in vitro</i> or <i>ex vivo</i> test (adopted by OECD or not), which provide evidence that the mixture is an eye irritant or non-irritant? YES → NO ↓	Consider to classify accordingly (Eye Dam. 1 or Eye Irrit. 2 or no classification). If discrimination between Eye Dam. 1 and Eye Irrit. 2 is not possible, Eye Dam. 1 must be chosen. Proceed to step 4b
4b	Are there acceptable data from a suitable <i>in vitro</i> test, which provide evidence that the mixture is an irritant to the eye? YES →	Consider to classify accordingly (Eye Dam. 1 or Eye Irrit. 2). If discrimination between Eye Dam. 1 and Eye Irrit. 2 is not possible,

	NO ↓	Eye Dam. 1 must be chosen. Proceed to step 5
5	Taking all existing and relevant data (steps 1-4) into account including potential synergistic/antagonistic effects and bioavailability, is there sufficient information to make a decision on classification? YES → NO ↓	Classify accordingly (Eye Dam. 1 or Eye Irrit. 2 or no classification)
2. When data are not available for the complete mixture: bridging principles		
6a	Are existing eye irritation data available on similar tested mixtures and on the individual ingredients? NO → YES ↓	Proceed to step 7a
6b	Can bridging principles be applied? YES → NO ↓	Classify in appropriate category (Eye Dam. 1 or Eye Irrit. 2 or no classification)
3. When data are available for all components or only for some components of the mixture		
7a	Is pH of the mixture ≤ 2 or ≥ 11.5 ? YES → NO ↓	Follow decision logic in Section 3.3.3.2.1.1 and classify accordingly.
7b	Is there any indication that the additivity principle does not apply? YES → NO ↓	Section 3.3.3.4 and Table 3.3.4 may apply. Take relevant ingredients (Annex I, 3.2.3.3.1) and SCLs into account, as appropriate. Classify in appropriate category (Eye Dam. 1 or Eye Irrit. 2 or no classification)
	Section. 3.3.3.3.2 and Table 3.3.3 applies. Take relevant ingredients (Annex I, 3.2.3.3.1) and SCLs into account, as appropriate. Classify in appropriate category (Eye Dam. 1 or Eye Irrit. 2 or no classification).	

1 **3.3.4 Hazard communication in form of labelling for serious eye damage/eye**
2 **irritation**

3 **3.3.4.1 Pictograms, signal words, hazard statements and precautionary statements**

Annex I; 3.3.4.1 Label elements shall be used for substances or mixtures meeting the criteria for classification in this hazard class in accordance with Table 3.3.5.

Table 3.3.5 Label elements for serious eye damage/eye irritation		
Classification	Category 1	Category 2
GHS Pictograms		
Signal Word	Danger	Warning
Hazard Statement	H318: Causes serious eye damage	H319: Causes serious eye irritation
Precautionary Statement Prevention	P280	P264 P280
Precautionary Statement Response	P305 + P351 + P338 P310	P305 + P351 + P338 P337 + P313
Precautionary Statement Storage		
Precautionary Statement Disposal		

1 A skin corrosive mixture is considered to also cause serious eye damage which is indicated in
 2 the hazard statement for skin corrosion, H 314: Causes severe skin burns and eye damage.
 3 Thus, in case a mixture has to be classified for skin corrosion an additional classification with
 4 H318: Causes serious eye damage is not indicated.

5 3.3.5 Re-classification of substances and mixtures classified for serious eye 6 damage/eye irritation according to DSD and DPD

7 3.3.5.1 Is direct “translation” of classification and labelling possible?

8 A direct translation as indicated in the translation table in Annex VII to CLP is generally
 9 possible. However, an evaluation and classification must be carried out in accordance with
 10 CLP Articles 9 – 13 when data for the mixture are available. Translation from classification
 11 according to DSD to the classification according to CLP is as follows:

- 12 – Xi; R41 is translated into Eye Dam. 1; H318. The criteria in DSD are completely covered
 13 by the criteria in CLP.
- 14 – Xi; R36 is translated into Eye Irrit. 2; H 319. The criteria in DSD are completely covered
 15 by the criteria in CLP.

16 It should be noted that CLP eye irritation Category 2 will include more substances which are
 17 currently not classified under the DSD, but with values of cornea opacity >1 and <2 or values
 18 of conjunctival redness >2 and < 2.5, will be classified as eye irritants under CLP.

19 It should be noted that where mixtures containing substances with risk phrase R41 have been
 20 classified on basis of the hazards of individual ingredients, the use of the translation table
 21 may lead to an under-classification of the mixture. This is because the general concentration
 22 limits, to be applied for mixtures, are lowered under CLP compared to DPD. For mixtures
 23 containing substances with this classification the use of the translation table may therefore
 24 not be appropriate and re-classification done by using the existing data would be more
 25 correct. For more details see Chapter 1.7.

1 **3.3.5.2 Re-evaluation of data**

2 If there is new information which might be relevant with respect to classification a re-
3 evaluation has to be performed.

4 **3.3.6 Examples of classification for serious eye damage/eye irritation**

5 **3.3.6.1 Examples of substances fulfilling the criteria for classification**

6 **3.3.6.1.1 Example 1: Standard test according to OECD TG 405 with three animals**

7 In a study according to OECD 405 the test substance was applied on the eyes of three rabbits.
8 The scoring results obtained are listed in the following table:

9 Cornea:

Animal Nr	Evaluation after ...					<u>Positive responder?</u>	
	1 hr	24 hrs	48 hrs	72 hrs	21 days	∅ Score ...	∅ Score ...
1	0	2	2	2	0		
	<u>∅ 24/48/72 h animal 1 is 2</u>					Yes	No
2	2	2	2	2	0		
	<u>∅ 24/48/72 h animal 2 is 2</u>					Yes	No
3	2	2	1	1	0		
	<u>∅ 24/48/72 h animal 3 is 1.3</u>					Yes	No

10

11

Effects are reversible

12 Iris:

Animal Nr	Evaluation after ...					<u>Positive responder?</u>	
	1 hr	24 hrs	48 hrs	72 hrs	21 days	∅ Score ...	∅ Score ...
1	0	1	1	1	0		
	<u>∅ 24/48/72 h animal 1 is 1</u>					Yes	No
2	1	1	1	1	0		
	<u>∅ 24/48/72 h animal 2 is 1</u>					Yes	No
3	1	1	1	1	0		
	<u>∅ 24/48/72 h animal 3 is 1</u>					Yes	No

13

14

Effects are reversible

15 Conjunctiva – Erythema:

Animal #	Evaluation after ...					<u>Positive responder?</u>	
	1 hr	24 hrs	48 hrs	72 hrs	21 days	∅ Score ...	∅ Score ...

	1 hr	24 hrs	48 hrs	72 hrs	21 days	≥ 2	
1	2	2	2	2	0		
	<u>Ø 24/48/72 h animal 1 is 2</u>						Yes
2	1	1	1	1	0		
	<u>Ø 24/48/72 h animal 2 is 1</u>						No
3	1	1	1	1	0		
	<u>Ø 24/48/72 h animal 3 is 1</u>						No

1

2

Effects are reversible

3

Conjunctiva – Swelling:

Animal #	Evaluation after ...					<u>Positive responder?</u>	
	1 hr	24 hrs	48 hrs	72 hrs	21 days	Ø Score ...	
1	0	3	3	3	0		
	<u>Ø 24/48/72 h animal 1 is 3</u>						Yes
2	2	2	2	1	0		
	<u>Ø 24/48/72 h animal 2 is 1.7</u>						No
3	2	3	2	2	0		
	<u>Ø 24/48/72 h animal 3 is 2.3</u>						Yes

4

5

Effects are reversible

6

Classification according to CLP: Eye irritant Category 2

7

Rationale: Cornea and Conjunctiva "positive responder" ≥ 2: 2/3 animals

8

Iris "positive responder" ≥ 1: 3/3 animals

9

3.3.6.1.2 Example 2: Test carried out with more than 3 rabbits

10

Cornea:

Animal No.	Evaluation after ...							<u>Positive responder?</u>	
	1h	24h	48h	72h	7d	14d	21d	≥ 3	≥ 1
1	1	2	3	3	1	1	0		
	<u>Ø 24/48/72h = 2.7</u>							no	yes
2	1	2	2	3	1	1	0		
	<u>Ø 24/48/72h = 2.3</u>							no	yes
3	1	2	3	3	2	1	0		

		$\bar{\varnothing} 24/48/72h = 2.7$						no	yes
4	1	2	4	4	2	1	0		
		$\bar{\varnothing} 24/48/72h = 3.3$						yes	yes

1 **Effects are reversible**

2 Iris:

3

Animal No.	Evaluation after ...							Positive responder?	
	1h	24h	48h	72h	7d	14d	21d	$\bar{\varnothing}$ Score ≥ 1.5	≥ 1
1	0	0	0	0	0	0	0		
	$\bar{\varnothing} 24/48/72h = 0$							no	no
2	0	0	0	0	0	0	0		
	$\bar{\varnothing} 24/48/72h = 0$							no	no
3	0	1	1	1	1	0	0		
	$\bar{\varnothing} 24/48/72h = 1$							no	yes
4	0	0	0	0	0	0	0		
	$\bar{\varnothing} 24/48/72h = 0$							no	no

4 **Effects are reversible**

5 Conjunctiva – Erythema:

Animal No.	Evaluation after ...							Positive responder?	
	1h	24h	48h	72h	7d	14d	21d	≥ 2	
1	2	2	2	1	1	1	0		
	$\bar{\varnothing} 24/48/72h = 1.7$							no	
2	2	2	2	1	1	0	0		
	$\bar{\varnothing} 24/48/72h = 1.7$							no	
3	2	2	2	1	1	1	1		
	$\bar{\varnothing} 24/48/72h = 1.7$							no	
4	2	2	2	1	0	0	0		
	$\bar{\varnothing} 24/48/72h = 1.7$							no	

6 **Effects are NON-reversible**

7 Conjunctiva – Swelling:

Animal No.	Evaluation after ...							Positive responder?	
	1h	24h	48h	72h	7d	14d	21d	≥ 2	Score ...
1	2	2	2	1	1	1	0		
	<u>Ø 24/48/72h = 1.7</u>								no
2	2	2	1	1	1	0	0		
	<u>Ø 24/48/72h = 1.3</u>								no
3	2	2	2	1	1	1	1		
	<u>Ø 24/48/72h = 1.7</u>								no
4	2	2	2	1	1	1	1		
	<u>Ø 24/48/72h = 1.7</u>								no

1 **Effects are NON-reversible**

2 Classification according to CLP: Serious eye damage Category 1

3 Rationale: Conjunctiva with irreversible effects

4 **3.3.6.2 Examples of mixtures fulfilling the criteria for classification**

5 **3.3.6.2.1 Example 3: Application of the additivity approach for mixtures containing**
 6 **ingredients without SCLs**

7 Where the mixture is made up of ingredients with no assigned SCLs, then the appropriate
 8 summation(s) from Table 3.3.3 should be used.

Ingredient	Skin / eye classification	Concentration (% w/w)	SCL
Surfactant A	Eye Cat 1	1.8	Not assigned
Substance B	Eye Cat 2	0.5	Not assigned
Substance C	Eye Cat 1	5.4	Not assigned
Substance D	Not classified	4.0	
Acid E	Skin Cat 1A	2.0	Not assigned
Water	Not classified	86.3	

9 pH of the mixture is 9.0 – 10.0, thus extreme pH provisions do not apply. The mixture
 10 contains a surfactant and an acid but neither are corrosive/irritant below 1% (as identified by
 11 the absence of specific concentration limits in either CLP Annex VI or the Classification and
 12 Labelling Inventory). Additivity is considered to apply.

13 Substance D and water can be disregarded as they are not classified for serious eye
 14 damage/eye irritation. Substance B can also be disregarded as present below 1%.

15 Mixture contains 7.2% Eye Cat 1 ingredients as well as 2% acid E so the summation {Skin
 16 corrosion Cat 1A, 1B, 1C + Eye Cat 1} applies and is > 3%, thus mixture is classified Eye
 17 Cat 1.

1 **3.3.6.2.2 Example 4: Application of the additivity approach for mixtures containing**
 2 **ingredients which may have SCLs**

Ingredient	Skin / eye classification	Concentration (% w/w)	SCL
Surfactant A	Eye Cat 1	2.0	Not assigned
Substance B	Eye Cat 2	0.5	Not assigned
Substance C	Skin Cat 1B	5.4	C ≥ 10 %: Skin Cat 1B 5 % ≤ C < 10 %: Eye Cat 2
Substance D	Not classified	4.0	
Substance E	Skin Cat 1B	2.0	Not assigned
Water	Not classified	86.1	

3 pH of the mixture is 10.5 – 11.0, thus extreme pH provisions do not apply. The mixture
 4 contains a surfactant, an acid and a base but none are corrosive/irritant below 1% (as
 5 identified by the absence of specific concentration limits in either CLP Annex VI or the
 6 Classification and Labelling Inventory). Additivity is considered to apply.

7 Substance D and water can be disregarded as they are not classified for serious eye
 8 damage/eye irritation. Substance B can also be disregarded as present below 1%.

9 SCLs are not assigned to substance E or surfactant A, thus generic concentration limits
 10 (GCL) apply for these ingredients

11 Eye Cat 1

12 $(\% \text{ surfactant A} / \text{GCL}) + (\% \text{ Substance C} / \text{SCL}) + (\% \text{ Substance E} / \text{GCL}) = (2/3) +$
 13 $(5.4/10) + (2/3) = 1.9 \Rightarrow > 1$ thus mixture is classified Eye Cat. 1

14 **3.3.6.2.3 Example 5: Application of the additivity approach for mixtures containing**
 15 **ingredients which may have SCLs**

Ingredient	Serious eye damage/ eye irritation classification	Concentration (% w/w)	SCL
Surfactant B	Eye Cat 1	0.7	Not assigned
Substance C	Eye Cat 2	74.9	Not assigned
Substance D	Eye Cat 1	8.5	C ≥ 25 %: Eye Cat 1 10 % ≤ C < 25 %: Eye Cat 2
Substance E	Not classified	15.9	

16 pH of the mixture is 10.0 – 10.5 (10% solution), thus extreme pH provisions do not apply.
 17 The mixture contains a surfactant which is not corrosive/irritant below 1% (as identified by
 18 the absence of specific concentration limits in either CLP Annex VI or the Classification and
 19 Labelling Inventory). Additivity is considered to apply.

20 Substance E can be disregarded as it is not classified for serious eye damage/eye irritation.
 21 Surfactant B can also be disregarded as present below 1%.

22 SCLs are not assigned to substance C, thus GCL apply for this ingredient

23 Eye Cat. 1

1 Mixture contains 8.5% substance D, the only 'relevant' ingredient classified as Eye Cat. 1. As
2 this is below the 25% SCL for substance D, the mixture is not classified Eye Cat. 1

3 Eye Cat. 2

4 $(\% \text{substance D} / \text{SCL}) + (\% \text{substance C} / \text{GCL}) = (8.5/10) + (74.9/10)$ which is > 1 thus
5 mixture is classified Eye Cat. 2

6 3.3.7 References

7 Griffith J.F., Nixon G.A., Bruce R.D., Reer P.J., Bannan E.A. (1980): Dose-response studies
8 with chemical irritants in the albino rabbit eye as a basis for selecting optimum testing
9 conditions for predicting hazard to the human eye. *Toxicol Appl Pharmacol* **55**, 501-513.

10 Young J.R., How M.J., Walker A.P., Worth W.M.H. (1988): Classification as corrosive or
11 irritant to skin of preparations containing acidic or alkaline substances, without test on
12 animals. *Toxicology in Vitro* **2**, 19-26.

13 Young J.R., How M.J. (1994), Product classification as corrosive or irritant by measuring pH
14 and acid / alkali reserve. In *Alternative Methods in Toxicology* vol. 10 - *In Vitro* Skin
15 Toxicology: Irritation, Phototoxicity, Sensitization, eds. A.Rougier, A.M. Goldberg and H.I
16 Maibach, Mary Ann Liebert, Inc. 23-27.

17 3.4 RESPIRATORY OR SKIN SENSITISATION

18 **The guidance provided in this chapter is based on the classification criteria of the**
19 **original version of the CLP Regulation. Guidance relating to the revised criteria for**
20 **respiratory and skin sensitization that are based on the 2nd ATP to the CLP Regulation**
21 **will be updated in 2012/2013.**

22 3.5 GERM CELL MUTAGENICITY

23 3.6 CARCINOGENICITY

1 **3.7 REPRODUCTIVE TOXICITY**

2 **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 **3.7.1.1 Special considerations on effects on or via lactation**

- 4 This classification is intended to indicate when a substance may cause harm due to its effects
5 on or via lactation. This can be due to the substance being absorbed by women and adversely

1 affecting milk production or quality, or due to the substance (or its metabolites) being present
2 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.

3 Therefore, if the adverse effects that lead to impaired development in the offspring also occur
4 after *in utero* exposure then the substance would also be classified for developmental toxicity.
5 In other words, the classification for effects on or via lactation is independent of
6 consideration of the reproductive toxicity of the substance, and a substance can be classified
7 for effects on or via lactation whether or not the substance is also classified for reproductive
8 toxicity.

9 Classification for effects on or via lactation alone is not sufficient for a substance to be
10 subject to harmonised classification and labelling in accordance with CLP Article 36.

11 **3.7.2 Classification of substances for reproductive toxicity**

12 **3.7.2.1 Identification of hazard information**

13 **3.7.2.1.1 Identification of human data**

14 Epidemiological studies as well as clinical data and case reports may be available as stated in
15 CLP, Annex I, 3.7.2.2.3 and further under IR/CSA, Section R.7.6.3.2.

16 **3.7.2.1.2 Identification of non human data**

17 *In vitro*, animal data and non-testing information used for classification is outlined in CLP
18 Annex I, section 3.7.2.5. and further specific references to different testing methods are listed
19 in IR/CSA, section R.7.6.3.1.

20 **3.7.2.2 Classification criteria**

Annex I: 3.7.2.1.1. For the purpose of classification for reproductive toxicity, substances are allocated to one of two categories. Within each category, effects on sexual function and fertility, and on development, are considered separately. In addition, effects on lactation are allocated to a separate hazard category.

Table 3.7.1 (a)

Hazard categories for reproductive toxicants

Categories	Criteria
CATEGORY 1	<p>Known or presumed human reproductive toxicant</p> <p>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).</p>

Category 1A	<p>Known human reproductive toxicant</p> <p>The classification of a substance in this Category 1A is largely based on evidence from humans.</p>
Category 1B	<p>Presumed human reproductive toxicant</p> <p>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.</p>
CATEGORY 2	<p>Suspected human reproductive toxicant</p> <p>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.</p> <p>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.</p>

1 **3.7.2.2.1 Classification in the presence of parental toxicity**

2 **3.7.2.2.1.1 Effects to be considered in the presence of marked systemic effects**

3 In general all findings on reproductive toxicity should be considered for classification
4 purposes irrespective of the level of parental toxicity. A comparison between the severity of
5 the effects on fertility/development and the severity of other toxicological findings must be
6 performed.

7 Fertility effects

8 Adverse effects on fertility and reproductive performance seen only at dose levels causing
9 marked systemic toxicity (e.g. lethality, dramatic reduction in absolute body weight, coma)
10 are not relevant for classification purposes.

11 There is no established relationship between fertility effects and less marked systemic
12 toxicity. Therefore it should be assumed that effects on fertility seen at dose levels causing
13 less marked systemic toxicity are not a secondary consequence of this toxicity. However,
14 mating behaviour can be influenced by parental effects not directly related to reproduction
15 (e.g. sedation, paralysis), and such effects on mating behaviour may not warrant
16 classification.

1 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.

2 Adverse effects on postnatal survival and growth seen only at dose levels causing maternal
 3 toxicity may be due to lack of maternal care or other causes such as adverse effects on or via
 4 lactation or developmental toxicity. In case post-natal effects are caused by lack of maternal
 5 care classification for developmental effects may not be warranted.

6 **3.7.2.2.1.2 Relevance of specific effects in the parent**

7 All types of reproductive toxic effects may be considered as secondary to parental toxicity.
 8 With current knowledge it is not possible to identify specific effects indicating toxicity in
 9 parental animals which do not have any relevance to reproductive toxicity (e.g. peroxisome
 10 proliferation). However parental toxicity that is less than marked should not influence the
 11 classification for reproductive toxicity independent of the specific parental effects observed.

12 In general it is very difficult to prove a causal relationship between a parentally mediated
 13 mechanism and adverse effects in the offspring. Usually data are insufficient to conclude if
 14 an effect on the offspring is a direct effect or secondary to parental toxicity. In order to
 15 determine whether a reproductive toxic effect is independent or secondary to a parental

- 1 effect, it would be most appropriate to correlate individual data for offspring and their
2 parents. Nevertheless, associations between parental and offspring effects do not by default
3 prove a causal relationship.
- 4 In cases where a causal relationship is established between reproductive and parental toxicity
5 and the effects on the offspring can be proved to be secondary to maternal toxicity, they may
6 still be relevant for developmental classification, dependent on the severity of the effects.
- 7 A comparison between the severity of the maternal toxicity and the severity of the findings in
8 the offspring must be performed. There are several examples showing that the developing
9 organism can be more susceptible and the long-term consequences can be more severe than in
10 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 fetuses), 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.

1 3.7.2.2.2 Substances causing effects on or via lactation

Annex I: Table 3.7.1 (b)

Hazard category for lactation effects

EFFECTS ON OR VIA LACTATION

Effects on or via lactation are allocated to a separate single category. It is recognised that for many substances there is no information on the potential to cause adverse effects on the offspring via lactation. However, substances which are absorbed by women and have been shown to interfere with lactation, or which may be present (including metabolites) in breast milk in amounts sufficient to cause concern for the health of a breastfed child, shall be classified and labelled to indicate this property hazardous to breastfed babies. This classification can be assigned on the:

- (a) human evidence indicating a hazard to babies during the lactation period; and/or
- (b) results of one or two generation studies in animals which provide clear evidence of adverse effect in the offspring due to transfer in the milk or adverse effect on the quality of the milk; and/or
- (c) absorption, metabolism, distribution and excretion studies that indicate the likelihood that the substance is present in potentially toxic levels in breast milk.

2 There are the two general criteria for this classification.

3 (i) ...are absorbed by women and have been shown to interfere with lactation.

4 This relates to effects in the mother that impact adversely on the breast milk, either in terms
 5 of the quantity produced or the quality of the milk produced (i.e. the composition). Any effect
 6 on the quantity or quality of the breast milk is likely to be due to systemic effects in the
 7 mother. However, overt maternal toxicity may not be seen (e.g. the substance may just affect
 8 the transfer of a nutrient into the milk with no consequence for the mother). The type and
 9 magnitude of the maternal effects and their potential influence on lactation/milk production
 10 need to be considered on a case-by-case basis to determine whether classification for effects
 11 on or via lactation is necessary.

12 If a substance causes marked overt systemic toxicity in the mother at the same dose level then
 13 it is possible that this may indirectly impair milk production or impair maternal care as a non-
 14 specific secondary effect. The type and magnitude of the maternal effects and their potential
 15 influence on lactation/milk production needs to be considered on a case-by-case basis using
 16 expert judgment. If there is robust evidence to indicate that the effects on lactation are not
 17 caused directly by the substance then it should not be classified as such.

1 A substance which does not cause overt toxicity in the mother but which interferes with milk
2 production or quality will normally be classified for effects on or via lactation because in this
3 case the effect on lactation is most likely a direct substance-related effect.

4 (ii) ... may be present (including metabolites) in breast milk in amounts sufficient to cause
5 concern for the health of a breastfed child.

6 This relates to the ability of the substance (including metabolites), to enter the breast milk in
7 amounts sufficient to cause a concern. When the effect on the offspring is caused by the
8 substance (or metabolite) after transport through the milk then the maternal toxicity has no
9 relevance for classification. In general, positive data should usually be available to show that
10 a substance leads to an adverse effect in offspring due to effects on lactation to support
11 classification. However, in exceptional circumstances, if there are substantiated grounds for
12 concern that the substance may have an adverse effect via lactation then it may be classified
13 as such in the absence of direct evidence. This should be based on a quantitative comparison
14 of the estimated transfer via the milk and the threshold for toxicity in the pups. This might
15 apply in cases where the substance has the capacity to bioaccumulate which would lead to a
16 potentially higher burden in the offspring, or where there is evidence that the offspring may
17 be more sensitive to the substance's toxicity than adult.

18 The mere presence of the substance in the milk alone, without a strong justification for a
19 concern to offspring, would normally not support classification for effects on or via lactation.

20 **3.7.2.3 Evaluation of hazard information**

21 Appropriate classification will always depend on an integrated assessment of all available
22 data and their interrelationship using a weight of evidence approach. Individual datasets
23 should be analysed case by case using expert judgment.

24 **3.7.2.3.1 Use of data from standard repeat dose tests**

25 Fertility effects:

26 Toxicological effects, including marked effects, observed in a standard repeat dose study
27 could be considered valid for the pre-mating phase for adult females and the pre- and post-
28 mating phase for adult males. However in case of contradictions between the standard repeat
29 dose studies and reproductive studies, the result from the latter should be considered more
30 relevant.

31 For pregnant and lactating females and juveniles data from standard repeat dose studies
32 cannot easily be extrapolated.

33 Developmental effects:

34 A detailed assessment of toxicity in pregnant animals cannot be extrapolated from studies
35 with non-pregnant animals. However information from general toxicity studies might give an
36 indication of the maternal toxicity that could be anticipated in a subsequent developmental
37 toxicity study.

38 **3.7.2.3.2 Study design**

39 Assessment of the dose-response relationships of parental and reproductive toxicity end
40 points and their possible interrelationship require study designs where the dose intervals are
41 not too far apart. This will improve dose-response assessment and will also reduce the chance
42 of masking malformations by severe toxicity (e.g. resorptions, lethality) at high dose levels.
43 This may lead to experimental designs in which more than the standard three dose groups and

1 a control are tested. Endpoints from repeat dose toxicity studies may be considered useful for
2 inclusion in subsequent reproductive toxicity studies. These endpoints should be evaluated
3 both in parental animals and in offspring.

4 **3.7.2.3.3 Evaluation of evidence relating to effects on or via lactation**

5 (a) Human evidence indicating a hazard to babies during the lactation period:

6 This criterion acknowledges that human data, e.g. from epidemiological studies or case
7 reports, indicating a hazard to babies during the lactation period can also be used to support
8 classification for effects on or via lactation. The use of human data is self-explanatory and
9 any study should be assessed on its merits for which expert judgment may be required.
10 Observations in humans that give evidence of adverse effects in breastfed babies of mothers
11 exposed to the chemical in question should be taken to provide clear evidence supporting
12 classification. Such studies which do not show an adverse effect need to be considered
13 carefully. Human studies investigate the risk under the specific conditions of exposure, and a
14 negative finding may just reflect inadequate methods to detect effects or insufficient
15 exposures rather than prove the absence of a hazard.

16 In practice, useful human data are likely to be rare due to the nature of the endpoint. More
17 likely are survey type studies which measure the levels of the chemical in breast milk. Such
18 studies may provide useful information on the potential for maternal exposure to lead to the
19 presence of the chemical in the breast milk and so they may be of use in assessing the need
20 for classification for effects on or via lactation.

21 (b) Results of one or two generation studies in animals which provide clear evidence of 22 adverse effect in the offspring due to transfer in the milk or adverse effect on the quality of 23 the milk;

24 Ideally, studies will be available which inform directly on whether the substance causes
25 adverse effects in the offspring due to an adverse effect on lactation. One generation or multi-
26 generation reproductive toxicity studies, which involve direct exposure or exposure via the
27 milk of the offspring postnatally, usually provide information on this. The most common
28 study performed today is the two-generation study, but one-generation studies with new study
29 designs, like the screening study OECD TG421/422 or the developmental neurotoxicity study
30 OECD TG426, also exist. The value of these studies is that they directly observe the pups
31 during lactation and any adverse effects, such as deaths, decreased viability, clinical signs
32 such as reduced bodyweight gain etc, can be directly observed and quantified. However,
33 expert judgement is required to decide whether these effects in pups are due to a direct
34 adverse effect on lactation, or are due to impaired nursing behaviour which is a non specific
35 secondary consequence of maternal toxicity. If the impaired nursing behaviour is proven to
36 be a substance related specific effect on behaviour, then classification for effects on or via
37 lactation may be appropriate. It should also be noted that some developmental effects
38 resulting from exposure in utero would only manifest post-natally and those should not be
39 used for classification for effects on or via lactation. Cross-fostering studies, where available,
40 may help establish whether effects are due to in utero or lactational exposure. If there is
41 sufficient data that animal results are not relevant to humans, they should not be taken into
42 account.

43 (c) Absorption, metabolism, distribution and excretion studies that indicate the likelihood that 44 the substance is present in potentially toxic levels in breast milk;

45 The criterion indicates that toxicokinetic studies showing that the substance can be present at
46 potentially toxic levels in breast milk can support classification. The implicit assumption

1 behind this clause is that the pups may receive a body burden of the toxic entity through
2 suckling that is sufficient to cause toxicity when the level of the toxic entity in the milk is
3 above a certain threshold level (“a level to cause concern”). There is no robust way to
4 estimate what this threshold is, although the likely body burden expected in the breastfed
5 child may be compared to the toxicity data in adults (e.g. an appropriate NOAEL or BMD) to
6 indicate whether toxicity is likely. The mere presence of a substance in the milk, without a
7 robust argument that these levels may be potentially toxic to offspring would not normally
8 support classification.

9 The toxicokinetics of a substance and the likelihood that it will enter the breast milk may be
10 predicted on the basis of the physico-chemical properties of the chemical (e.g. using pKa,
11 logP, water solubility, and molecular weight etc) and this information could be used as part of
12 the argumentation outlined above. The potential of a substance to bioaccumulate following
13 repeated exposure may also be an important factor to consider as this may contribute to the
14 body burden reaching a potentially toxic level in the offspring. Studies where the
15 offspring/neonates have extended exposure, such as multi-generation studies, implicitly allow
16 for bioaccumulation and so findings from these studies can, in themselves, be taken to
17 provide information on the potential effects of bioaccumulation. Where these types of studies
18 are not available, potential bioaccumulation can be taken into consideration as part of the
19 toxicokinetic assessment using expert judgement.

20 There may be toxicokinetic and toxicodynamic reasons why neonates may potentially be
21 more or less vulnerable to a particular adverse effect than adults due to the fact that certain
22 systems (e.g. the immune and metabolic systems) and tissues/organs are immature and are
23 still developing. Whether the neonate is more or less vulnerable than adults will depend on
24 the specific chemical and will be determined by factors such as the hazardous properties of
25 the chemical, its’ physico-chemical properties and how it is metabolised. Therefore, the
26 relative sensitivity of neonates and adults to a substance must be judged on a case by case
27 basis using expert judgement. In the absence of any reliable and robust information to inform
28 on this, it should be assumed that neonates and adults are equivalent in terms of sensitivity to
29 the substance.

30 Overall, classification for effects on or via lactation can be assigned on the basis of
31 toxicokinetic data or a well substantiated estimate of the exposure through the milk alone
32 provided that it is supported by an argument clearly justifying that the level present in the
33 breast milk would be likely to harm developing offspring.

34 **3.7.2.4 Decision on classification**

35 According to CLP Annex I, section 3.7.2.1.1, reproductive toxic substances are allocated to
36 either Category 1A, 1B or 2. Effects on lactation are allocated to a separate hazard category
37 and should be ascribed to a substance irrespective if it classified in any other category for
38 reproductive toxicity or not.

39 **3.7.2.5 Setting of specific concentration limits**

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

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

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

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

NOTE TO RAC and Forum on Reprotoxicity Section

A particular issue arose regarding the concept of setting SCLs for reprotoxicity, based on potency and using the ED₁₀ to estimate the potency. This concept was considered to be the best approach by the Expert Working Group, and is the basis of the guidance proposed. It is acknowledged that there are other methods and concepts and such views were expressed by one PEG member in particular during the consultation and explained and discussed at length at the PEG meeting. However, the overall majority view remained in support of the proposed concept, but it was agreed to highlight this for the RAC and Forum consultation, to ensure due consideration of the concept.

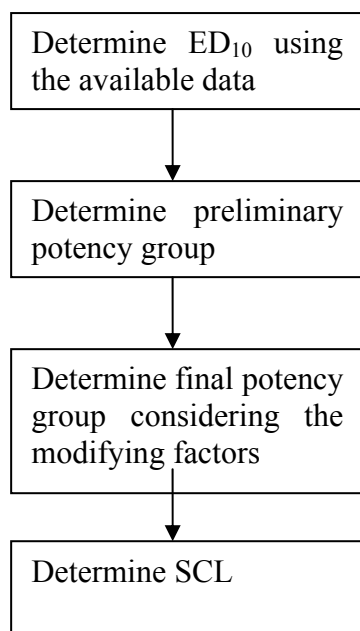
Members are asked to consider if they support the concept presented in the draft revised guidance. If, in the event of not supporting this concept, please submit scientific justification for why such a concept is not scientifically acceptable with a proposal for an alternative concept and way forward for providing guidance on this issue.

Members should note that should the concept not be supported, then this section of the Guidance would not be revised for the publication due in December 2012, and a new drafting and consultation exercise would need to be started in 2013 with an estimated publication date of 2014. For Members who have concerns over the scientific concept, they may also consider that the guidance could be reviewed and revised in the future.

3.7.2.5.1 Procedure

The available data from animal and human studies are evaluated to establish the reproductive toxicity dose descriptor, ED₁₀ (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 ED₁₀ 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



1

2 **3.7.2.5.2 Cases where potency evaluation is difficult or unfeasible**

3 The process for evaluating potency assumes the availability of certain types of data.
4 However, these data may not always be available. Also, the classification of substances as
5 reproductive toxicants may be based on information such as grouping, read-across and the
6 use of QSARs (Guidance IR/CSA, sections R.6 and R.7.2.3.1). In such cases, no direct
7 estimate of the reproductive toxicity potency based on an ED₁₀ value is possible. While there
8 are often good reasons for extrapolation of the hazardous properties from one or more
9 substances to another, the expected potency of the individual substances within the group
10 may vary. In these cases a potency evaluation may be difficult or impossible. However,
11 determination of the classification and the potency using non-testing methods is possible in
12 some cases. These cases could include interpolation of an ED₁₀ within a group of substances
13 with comparable structures and effects or correction for molecular weight in case of
14 extrapolation between different salts with comparable availability. If the classification of a
15 substance in Category 2 is done on the basis of "limited evidence", the quality of the
16 available data will in such cases determine whether a potency assessment is possible. In cases
17 where no further evaluation is possible, the generic concentration limits of CLP apply. In
18 general, more conclusive evidence is required when moving a substance to a lower potency
19 group than to a higher potency group.

20 **3.7.2.5.3 Determination of the ED₁₀ value**

21 The ED₁₀ value (as used for reprotoxicity SCLs) is the lowest dose which induces
22 reproductive toxic effects which fulfil the criteria for classification for reproductive toxicity
23 with an incidence or magnitude of 10% after correction for the spontaneous incidence (see in
24 3.7.2.5.3.2).

25 Determining exactly which effect or combination of effects is the one that fulfils the
26 classification criteria may seem difficult. However, for the majority of substances in the
27 database, the developmental effect(s) observed at the lowest dose level was(/were) an
28 increase in malformations and/or lethalties of the offspring. The ED₁₀ for effects on sexual
29 function and fertility is mainly based on effects on fertility and histopathological changes of
30 the reproductive organs. These effects clearly fulfil the classification requirements. Also,

1 allocation to the final SCLs is based on a limited number of potency groups and not on the
 2 exact ED₁₀ value. Therefore, in practice, it is likely that the ED₁₀ values for several different
 3 effects fall into the same potency grouping, resulting in the same SCL.

4 The ED₁₀ may be obtained either directly or by linear interpolation from experimental data or
 5 estimated using Bench Mark Dose (BMD) software. The use of BMD software will result in a
 6 more precise estimate of the ED₁₀ because all data from the dose-response curve are used.
 7 The use of BMD software is needed when an ED₁₀ cannot be determined using linear
 8 interpolation due to the absence of a NOAEL when the LOAEL has an effect size above
 9 10%. In general, however, the use of BMD software is not required because of the wide
 10 potency groups used for setting the SCLs. However, it could be important for substances
 11 which are close to the boundary of a potency group. When an ED₁₀ cannot be calculated by
 12 direct or linear interpolation or by the use of BMD software, the extrapolation between the
 13 control group and the LOAEL should be used instead of the ED₁₀. In such cases, only SCLs
 14 below the GCL can be determined and not those above the GCL, if no other reliable
 15 information is available, because it may be difficult in these cases to prove the absence of
 16 effects at lower dose levels.

17 3.7.2.5.3.1 Determination in practice

18 In practice, often several effects on reproduction are observed in various studies, and the
 19 classification is based on the weight of evidence of all results. As a first step, it should be
 20 determined whether the classification is for effects on development, for effects on sexual
 21 function and fertility or both. The effects used for classification for developmental toxicity
 22 should be used to determine the potency for developmental toxicity only. The same applies to
 23 effects on sexual function and fertility. This means that for substances fulfilling the criteria
 24 for classification for both developmental effects and effects on sexual function and fertility,
 25 two ED₁₀ values are derived which may differ and lead eventually to different SCLs. For
 26 both developmental effects and effects on sexual function and fertility, the lowest ED₁₀ for
 27 the effect(s) that fulfil the criteria for classification in the different studies, is then used as the
 28 ED₁₀ that determines the potency of that substance. Where there are doubts as to whether a
 29 specific effect fulfils the classification criteria, ED₁₀ values for different effects could be
 30 taken forward to the next step, when modifying factors are considered, to determine the
 31 impact.

32 The calculation of the ED₁₀ by linear interpolation requires a different approach depending on
 33 whether the effect is measured as an incidence (quantal data, non-parametric data), a
 34 magnitude (continuous data, parametric data) or both.
3.7.2.5.3.2 Quantal or non-
35 parametric data

36 For effects that are measured as changes in incidence, such as an increase in the number of
 37 malformations or resorptions, the ED₁₀ is defined as the dose level at which 10% of the test
 38 population above the incidence in the concurrent control shows the effect. There may be
 39 occasions where the historical control data have to be taken into account (for example when
 40 the concurrent control data are atypical and close to the extremes of the historical data). In
 41 the example in Table 3.7.2.5.1, the ED₁₀ is 90 mg/kg bw/day because at this dose level 12% -
 42 2% (control) = 10% of the test population shows the effect above the incidence in the control
 43 group.

44 Table 3.7.2.5.1 Example of the calculation of the ED₁₀

Dose	0	10	30	90
------	---	----	----	----

	mg/kg	mg/kg	mg/kg	mg/kg
Malformations	2%	3%	7%	12%

1 For some effects the results of the calculation of the ED₁₀ based on the incidence in pups may
 2 be different from that based on the incidence in litters. Scientific evidence may indicate
 3 which parameter is more appropriate, but in the absence of such information it is not possible
 4 to estimate which ED₁₀ is more appropriate for a specific effect. In such cases, both the
 5 incidence in offspring and the incidence in litters should be calculated, and the lower ED₁₀
 6 value should be used.

7 3.7.2.5.3.3 Continuous or parametric data

8 For effects that are measured as changes in magnitude such as mean pup weight or testis
 9 weight, the ED₁₀ is defined as the dose at which a change of 10% compared to the control
 10 group is observed. In the example in Table 3.7.2.5.2, the ED₁₀ is 19.3 mg/kg bw/day because
 11 at this dose level the mean foetal bodyweight is calculated to be 90% of the control value. A
 12 10% reduction of the control value of 6.2 g gives 5.58 g. Interpolation between 10 and 30
 13 mg/kg bw/day to a dose level which would be expected to result in a foetal bodyweight of
 14 5.58 g gives a value of 19.3 mg/kg bw/day.

15 Calculations: $(30 - 10) / (6 - 5.1) = 22.2$; $6.0 - 5.58 = 0.42$; $0.42 \times 22.2 = 9.3$; $10 + 9.3 = 19.3$
 16 mg/kg bw/day.

17 Table 3.7.2.5.2 Example on the calculation of the ED₁₀

dose	0 mg/kg	10 mg/kg	30 mg/kg	90 mg/kg
Mean foetal bodyweight (g)	6.2	6.0	5.1	4.5
		NOAEL	LOAEL	

18 3.7.2.5.3.4 Data combining incidence and magnitude

19 Some effects such as histopathological changes in the testis are a combination of effects on
 20 incidence and magnitude (grading of the effect by a pathologist). However, calculation of an
 21 ED₁₀ taking both the incidence and the magnitude into account is not possible or at least more
 22 complex. The ED₁₀ should therefore be based on the incidence of the effect below or above a
 23 certain magnitude. The magnitude of the effects that will be selected as a starting point has to
 24 be chosen carefully. Normally the particular effect size would be the lowest relevant for the
 25 respective classification. The ED₁₀ is then determined as the dose level at which the
 26 incidence, of effects with a magnitude above that of the starting point, is 10% above the
 27 incidence in the control group. In practice this means that the grading system is converted
 28 into a simplified system where only percentages of animals in each dose group with an effect
 29 with a magnitude above the starting point are regarded as positive. However, it is recognised
 30 that this approach uses only a part of the actual data and is imprecise, and it may be
 31 appropriate that other effects also be considered in determining the ED₁₀.

32 Table 3.7.2.5.3 Example on the calculation of the ED₁₀ for testicular effects (N=10)

	Dose (mg/kg)	Testicular degeneration (n)				
		none	slight	moderate	marked	severe
	0	4	5	1	0	0

	10	5	5	0	0	0
NOAEL	30	5	4	1	0	0
LOAEL	90	0	0	4	2	4

1 For the example in Table 3.7.2.5.3, the effects observed in the 10 mg/kg and 30 mg/kg dose
2 groups have to be considered as equivalent to the effects of the control group so the NOAEL
3 is 30 mg/kg. The magnitude of the testicular effect in the control group and the 10 and 30
4 mg/kg bw/day groups is slight or less. Because of the incidence observed in these three
5 groups, the level of damage estimated as the starting point magnitude is ‘slight’. The ED₁₀ is
6 then defined as a 10% increase of moderate effects or more above the control. In this example
7 the incidences for moderate testicular degeneration or more are 10%, 0%, 10% and 100% at
8 respectively 0, 10, 30 and 90 mg/kg bw/day. The ED₁₀ is then defined as the dose level with
9 20% (control plus 10%) of moderate testicular effects. The ED₁₀ would be 36.6 mg/kg
10 bw/day based on interpolation between 30 and 90 mg/kg bw/day to a dose with 20% animals
11 with moderate testicular degeneration or higher.

12 3.7.2.5.3.5 Specific data types

13 Non-oral studies

14 In most cases only oral studies will be available and used for determination of the potency.
15 However, if the classification is based on the effects seen in non-oral studies or only non-oral
16 studies are available, then these data should also be used to determine the potency. This
17 requires route-to-route extrapolation of the external dermal or inhalatory dose to a
18 corresponding oral dose. This should be done as described in the ECHA guidance on
19 information requirements and chemical safety assessment in REACH (IR/CSA, section R.8).

20 Extrapolation from dermal exposure to oral exposure should only be done when there are
21 sufficient kinetic data on dermal availability because assuming a high dermal availability is
22 not a worst case assumption. In cases where such data are not available a direct comparison
23 of the dermal dose with the oral potency ranges could be performed in exceptional cases.
24 However, such comparison should not result in moving the substance to a lower potency
25 group (higher ED₁₀) – only moving the substance to a higher potency group (lower ED₁₀)
26 should be considered.

27 Extrapolation from inhalatory exposure to oral exposure can only be done when there are
28 sufficient kinetic data on inhaled availability because assuming a high inhaled availability is
29 not a worst case assumption. If no inhalatory information on availability is available then it
30 should be assumed that the inhalation and oral availability are comparable. However, such
31 comparison should not result in moving the substance to a lower potency group (higher ED₁₀)
32 – only moving the substance to a higher potency group (lower ED₁₀) should be considered.

33 Human data

34 The use of human data for ED₁₀ calculation has several drawbacks including limited data on
35 exposure, limited data on the size of the exposed population and limited information on
36 whether the exposure included the window of sensitivity. For all these reasons, it is difficult
37 to determine an ED₁₀ based on human data. Therefore, and because in most instances animal
38 data are also available for determining an ED₁₀, these data are evaluated together on a case by
39 case basis. Guidance on the use of human data for the derivation of DNELs and DMELs has
40 been developed by ECHA and is available at the ECHA website, see
41 http://guidance.echa.europa.eu/guidance4_en.htm

1 **3.7.2.5.4 Provisional evaluation of the potency classification**

2 A preliminary potency evaluation applying the ED₁₀ value is made at this stage.

3 ED₁₀ values can be used to place substances classified as a reproductive toxicant into selected
4 ranges that define potency groups. In this way, it is possible to identify reproductive toxicants
5 of high, medium and low potency. For the purpose of determining the preliminary potency
6 group, the boundaries in Table 3.7.2.5.4 are used.

7 Table 3.7.2.5.4 Boundaries of the potency groups.

Potency group	Boundaries
High potency group	ED ₁₀ value ≤ 4 mg/kg bw/day
Medium potency group	4 mg/kg bw/day < ED ₁₀ value < 400 mg/kg bw/day
Low potency group	ED ₁₀ value ≥ 400 mg/kg bw/day.

8 **3.7.2.5.5 Modifying factors**

9 Modifying factors are a means to account for case-specific data situations which indicate that
10 the potency group for a substance as obtained by the preliminary assessment, should be
11 changed. While most modifying factors would result in a higher potency group than the
12 preliminary one, also the opposite could occur: If substance-specific knowledge is available
13 (such as e.g. toxicokinetic information on a higher bioavailability in test animals vs. humans),
14 also a lower potency class might be assigned.

15 While some modifying factors should always be taken into account, other modifying factors
16 could be more relevant when the potency is close to the boundary between two groups (see
17 Table 3.7.2.5.4 above).

18 Some modifying factors are of a more qualitative nature. When applied, they will simply
19 point to a potency group different from the one resulting from the preliminary assessment.
20 Other modifying factors might be quantifiable, at least on a semi-quantitative scale. In such
21 cases, a potency group higher (or lower) than the preliminary one should be chosen if the
22 estimated size of the modifying factor exceeds the distance of the preliminary ED₁₀ to the
23 border of the relevant (higher or lower) adjacent potency group.

24 Furthermore, for some substances more than one modifying factor will apply. It will then take
25 expert judgement to decide on how to reasonably combine all of these individual factors into
26 one overall modifying factor. In exceptional cases, such a combination of individual factors
27 might even result in a change of two potency classes (e.g. assignment of the high potency
28 class, where the preliminary assessment had resulted in the low potency class).

29 In this context, it should be noted that several of the modifying factors may be interrelated.
30 Moreover, some factors may have already been taken into account in deciding on the
31 classification as a reproductive toxicant. Where such considerations have been made, care
32 should be taken not to use that information again when determining the potency. For
33 example, when the effects determining the ED₁₀ were observed at dose levels also causing
34 maternal toxicity, this should already have been taken into consideration during the
35 classification and should not be used again to set a higher SCL.

36 **3.7.2.5.5.1 Type of effect / severity**

37 The type of effect(s) resulting in the same classification as reproductive toxicant differs
38 between substances. Some effects could be considered as more severe than others, however,

1 ranking different effects based on their severity is controversial and difficult to establish
2 criteria. Further, the effects of a developmental toxicant can differ between dose levels from
3 variations via malformations to death of the foetuses. The adverse effects on fertility and
4 sexual function of a substance can differ between dose levels from small changes in testes
5 histopathology through effects on fertility to an irreversible and complete absence of fertility.
6 As the difference between the dose levels is often smaller than the proposed potency groups
7 (factor 10-100) this will make no difference in most cases. Also classification is in most cases
8 based on severe effects like malformations or death of the foetuses for developmental
9 toxicants and effects on fertility or histopathological changes of the reproductive organs for
10 fertility toxicants. For most classified substances such severe effects were already observed at
11 the lowest dose with reproductive effects [(Muller et al, 2012)]. Therefore, differentiation
12 between types of effect is considered to have limited added value. Exceptions can be dealt
13 with on a case by case basis.

14 For example, if the ED₁₀ results in a preliminary conclusion for the medium potency group
15 but is close to the border for the high potency group and the ED₁₀ is based on a severe effect
16 like malformations or irreversible effects on sexual function and fertility then using the
17 higher potency group (lower ED₁₀) for that substance should be considered. To determine
18 what is “close to the border” is to compare the distance to the next category border with the
19 significance of modifying factors.

20 **3.7.2.5.5.2 Data availability**

21 There are several aspects to this modifying factor, some of which are:

- 22 • limited data availability where certain test protocols are lacking and therefore certain
23 parameters have not been evaluated,
- 24 • limited data availability where the spectrum of evaluated parameters is sufficient, but
25 only studies with limited duration are available, and
- 26 • limited data availability where only a LOAEL, but no NOAEL could be identified.

27 Where only limited data are available, such as a screening study (OECD 421 and 422), a 28-
28 day repeated dose toxicity study or non-OECD studies which do not exclude the presence of
29 reproductive effects at lower dose levels, the calculated ED₁₀ should not be used to set a SCL
30 above the GCL.

31 Furthermore it should be considered to assign a modifying factor accounting for the
32 limitations in the database in a similar approach to the one used in deriving DNELs under
33 REACH. Guidance regarding the potential size of such a factor can be obtained from
34 ECHA’s Guidance on IR/CSA R.8 (‘Characterisation of dose [concentration]-response for
35 human health’). Section R.8.4.3.2 of that guidance gives recommendations on how to set
36 factors for extrapolating to longer study durations as well as for compensation of the lack of a
37 NOAEL or of the generally poor quality of a database.

38 If there are only limited data which result in an ED₁₀ in the medium potency group which is
39 close to the border for the high potency group, then using the higher potency group should be
40 considered. For example an ED₁₀ of 8 mg/kg bw/day might have been estimated based on a
41 LOAEL for malformations in the absence of a NOAEL, This ED₁₀ is only higher by a factor
42 of 2 (i.e 2 times the border of the high potency group of 4 mg/kg bw/d : see. Table 3.7.2.5.4
43 above), however, the IR/CSA guidance R.8 recommends a factor of 3 to 10 for extrapolation
44 from a LOAEL to a NOAEL. Thus, there is uncertainty, if the ED₁₀ based on the LOAEL

1 alone was sufficiently conservative, and assigning the high potency group should be
2 considered until additional data at lower dose levels are available.

3 **3.7.2.5.5.3 Dose-response relationship**

4 The ED₁₀ will in most cases probably be in the same range as the NOAEL and LOAEL.
5 However, in cases of a shallow dose effect relationship curve, the LOAEL may sometimes be
6 clearly below the ED₁₀. In such situations, if a substance would fall into a lower potency
7 group based on the ED₁₀ but into a higher potency group based on the LOAEL then the
8 higher potency group should be used for that substance.

9 **3.7.2.5.5.4 Mode or mechanism of action**

10 It is assumed that effects observed in animal studies are relevant to humans. Where it is
11 known that the mode or mechanism of action is not relevant for humans or is of doubtful
12 relevance to humans, this should have been taken into account in the classification and should
13 not be used again as a modifying factor for potency. However, quantitative differences in
14 toxicodynamics can be taken into account when not already taken into account in the
15 classification. In cases where mechanistic information shows a lower sensitivity in humans
16 than in experimental animals, this may move substances which are close to the potency
17 boundaries to a lower potency group. In cases where mechanistic information indicates a
18 higher sensitivity in humans than in experimental animals, this may move substances near the
19 potency boundaries to a higher potency group. In general, more conclusive evidence is
20 required when moving a substance to a lower potency group than to a higher potency group.

21 **3.7.2.5.5.5 Toxicokinetics**

22 The toxicokinetics of a substance can differ between the tested animal species and humans.
23 Where a difference is known this should be taken into account when determining the potency
24 group of a substance. This should be based on a comprehensive knowledge of all involved
25 toxicokinetic factors and not only on a single parameter. Also differences in kinetics between
26 pregnant and non-pregnant animals and transport to the foetus should be taken into account.
27 Quantification of this modifying factor has to be performed case by case, based on the
28 available data. This modifying factor can work in both directions, as e.g. bioavailability in
29 humans might be known to be lower or higher than in the animal species tested.. In general,
30 more conclusive evidence is required when moving a substance to a lower potency group
31 than to a higher potency group.

32 **3.7.2.5.5.6 Bio-accumulation of substances**

33 The study design of, for example, developmental studies is aimed at exposure only during
34 development. For substances which bio-accumulate, the actual exposure in the time window
35 of sensitivity for some developmental effects may therefore be much lower than when
36 exposure at the same external dose level would have started long before the sensitivity
37 window. Furthermore, human exposure may occur for a long period before the sensitive
38 window. This should be taken into account when determining the potency group. For
39 substances for which no experimental data are available with respect to their potential for
40 accumulation, section R.7.12 of ECHA's IR/CSA Guidance R.7c ('Endpoint specific
41 guidance') provides some hints on how to make an informed estimate about a respective
42 concern.

43 "Suspected" bio-accumulating substances should be considered to be moved into the next
44 higher potency group (lower ED₁₀) unless:

- the relevant studies used for the ED₁₀ were performed in a way that internal doses could have been expected to have reached a steady state during a sufficiently long part of the study time, and in particular with developmental studies during critical time windows of development, or
- the increase in the internal dose caused by the accumulation versus that following a single administration, is smaller than the distance between the ED₁₀ and the border to the next higher potency group.

For example, if a substance preliminarily assigned to the medium potency group is known or suspected to be bio-accumulative and the ED₁₀ for development has been obtained from a pre-natal developmental study in rats without any significant pre-treatment of the dams before mating, assignment to the high potency category should be considered. Conversely, if reliable toxicokinetic data demonstrate that steady state plasma levels after prolonged repeated administration do not exceed those after single exposure by more than a factor of 2, while the preliminary ED₁₀ is 20 mg/kg bw/d (i.e. factor 5 from the border to the high potency category) changing the potency class might not appear necessary.

3.7.2.5.6 Assigning specific concentration limits (SCLs)

Based upon the preliminary potency evaluation using only the ED₁₀ and applying the modifying factors, a substance can be placed in the final potency group using the table below. The GCL or SCL of that substance can then be found in the same table.

Table 3.7.2.5.5 SCLs for substances in each potency group and classification category

	Category 1		Category 2	
	Dose	SCL	Dose	SCL
Group 1 high potency	ED ₁₀ below 4 mg/kg bw/day	0.03% (factors of 10 lower for extremely potent substances ^B)	ED ₁₀ below 4 mg/kg bw/day	0.3% (factors of 10 lower for extremely potent substances)
Group 2 medium potency	ED ₁₀ ≥ 4 mg/kg bw/day, and ≤ 400 mg/kg bw/day	0.3% (GCL)	ED ₁₀ ≥ 4 mg/kg bw/day, and ≤ 400 mg/kg bw/day	3% (GCL)
Group 3 low potency	ED ₁₀ above 400 mg/kg bw/day	3%	ED ₁₀ above 400 mg/kg bw/day	3-10% ^A

^A The limit of 10% may be considered in certain cases, such as for substances with a ED₁₀ value above 1000 mg/kg bw/day and a NOAEL below 1000 mg/kg bw/day.

^B For substances with an ED₁₀ more than 10 fold below 4 mg/kg bw/day, meaning an ED₁₀ below 0.4 mg/kg bw/day, a 10-fold lower SCL should be used. For even more potent substance the SCL should be lowered with a factor of 10 for every factor of 10 the ED₁₀ is below 4 mg/kg bw/day.

3.7.2.5.6.1 Assigning two SCLs to a substance

A substance toxic to reproduction is classified in one category for both effects on development and on sexual function and fertility. Within each category effects on development and on sexual function & fertility are considered separately. The potency and

1 resulting concentration limits have to be determined separately for the two main types of
2 reproductive toxic effects. In case the potency and resulting specific concentration limits are
3 different for sexual function/fertility and development for a substance, the substance needs to
4 be assigned one SCL for developmental toxicity and another SCL for effects on sexual
5 function and fertility. These concentration limits will in all cases trigger different
6 specifications of the hazard statements for the two main types of effects, to be applied to
7 mixtures containing the substance (see also 3.7.4.1, Annex I, CLP)

1 **3.7.6 Examples**

2 **3.7.6.1 Examples of the determination of SCLs**

3 Four examples are given below:

4 **3.7.6.1.1 Example 1**

5 **1. Identification**

Substance Name:	XXXXXX
------------------------	--------

6 **2. EU CLP classification**

Repro	1B
H	360D

7 **3. ED₁₀ in animals**

8 **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.

9 **Remarks on the study used for the determination of the ED₁₀**

Species, strain, sex:	Female Wistar rat
Study type:	OECD 414
Route of administration:	Oral gavage
Effect descriptor for LOAEL:	Post-implantation loss, anasarca, cleft palate
Mode of action:	Not known
Genotoxicity classification:	None
Potential to accumulate:	No data. not known

10 **Determination of the ED₁₀ value**

Control resorption rate (= postimplantation loss) is 7.9%. ED₁₀ 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 ED₁₀ of 89.8 mg/kg bw/d.

Calculation:

$(180 - 60) / (43 - 9.6) = 3.593$ mg/kg per % (steepness). Going from 9.6% to 17.9% requires addition of 8.3%. This equals $8.3\% * 3.593$ mg/kg per % = 29.8 plus 60 as the starting point = 89.8 mg/kg bw/day.

The ED₁₀ for other relevant effects was above 89.8 mg/kg bw/day.

1 **Preliminary potency group**

medium

2 **4. Elements that may modify the preliminary potency evaluation**

3 **4.1. Dose-response relationship**

Not relevant as ED₁₀ not borderline.

4 **4.2. Type of effect / severity**

Not relevant as ED₁₀ not borderline.

5 **4.3. Data availability**

Not relevant. Only one valid study available.

6 **4.4. Mode of action**

No data.

7 **4.5. Toxicokinetics**

No data.

8 **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).

9 **5. Allocation of potency group and SCL**

medium potency, GCL

10 **6. References**

Confidential

11

1 **3.7.6.1.2 Example 2 (developmental part only)**

2 **1. Identification**

Substance Name :	XXXXXX
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3 **2. EU CLP classification**

Repro	1B
H	360 FD

4 **3. ED₁₀ in animals**

5 **Brief summary**

Study used for the determination of the ED ₁₀ : Pregnant females received daily gavage doses of 0, 25, 50, 100 or 175 mg/kg during the gestation period (GD 6-19).					
LOAEL effect	0 mg/k g	25 mg/k g	50 mg/k g	100 mg/k g	175 mg/k g
Skeletal malformations	2/22 (9 %)	2/17 (12 %)	5/15 (33 %)	10/1 9 (53 %)	6/12 (50 %)
Clear maternal toxicity was evident only at the highest dose level.					

6 **Remarks on the study used for the determination of the ED₁₀**

Species, strain, sex:	Rabbit, New Zealand White, female
Study type:	Developmental 6-19
Route of administration:	Gavage
Effect descriptor for LOAEL:	Skeletal malformations (axial skeleton, ribs)
Mode of action:	Substance is metabolised to a substance which causes the developmental effect
Genotoxicity classification:	None
Potential to accumulate:	Unknown

1 **Determination of the ED₁₀ value**

ED₁₀ was determined as 33 mg/kg.

Control skeletal malformations is 9%. ED₁₀ rate would be 19%. Interpolation between NOAEL (classification) (12% at 25 mg/kg) and LOAEL (classification) (33% at 50 mg/kg) leads to an ED₁₀ of 33.3 mg/kg bw/day.

Calculation:

$(50 - 25) / (33 - 12) = 1.19 \text{ mg/kg per \% (steepness)}$. Going from 12% to 19% requires addition of 7%. This equals $7\% * 1.19 \text{ mg/kg per \%} = 8.3$ plus 25 as the starting point = 33.3 mg/kg bw/day.

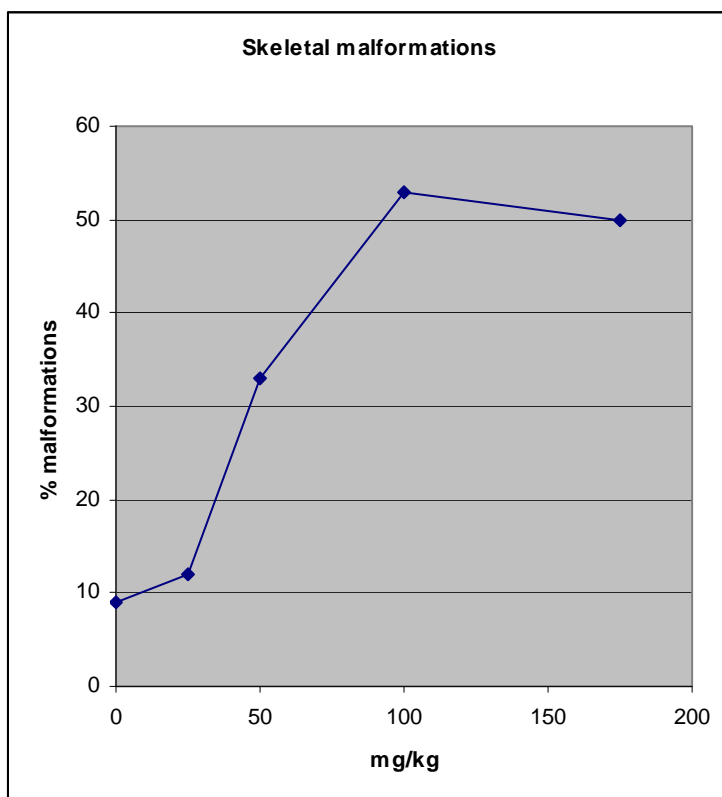
2 **Preliminary potency group**

Medium potency group.

3 **4. Elements that may modify the preliminary potency evaluation:**

4 **4.1 Dose-response relationship**

The effect on which the classification is based is the occurrence of malformations. As the lowest ED₁₀ was the ED₁₀ for skeletal malformations, this ED₁₀ was chosen as the basis for the SCL. The dose effect relationship is clear. The ED₁₀ (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.



1 **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.

2 **4.3 Data availability**

Not relevant. Different studies are available showing a developmental effect on different species (rat, mouse, rabbit).

3 **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 **4.5 Toxicokinetics**

Human and rat liver microsomal preparations (mixtures) 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.

5 **4.6 Bio-accumulation**

Unknown

6 **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 ED₁₀ (33 mg/kg) is based on a severe effect like malformations, it is justified to move the substance to the highest potency group.

7 **6. References**

Confidential

8

1 **3.7.6.1.3 Example 3 (limited to developmental toxicity)**

2 **1. Identification**

Substance Name :	XXXXXX
------------------	--------

3 **2. EU CLP classification**

Repro	1B
H	360 fD

4 **3. ED₁₀ in animals**

5 **Brief summary**

6 Several studies in rats were available for the evaluation of the developmental effect of
 7 this substance. These included 2-generation studies, developmental toxicity studies, and
 8 studies with exposure in sensitive periods during gestation. The most relevant study for
 9 the evaluation of potency was considered to be a two-generation study performed
 10 according to the revised OECD Test Guideline 416. In this study the substance was
 11 administered in the diet. Developmental toxicity was evident as reduced absolute and
 12 adjusted AGD in F1 and F2 offspring as well as and reduced foetal and testicular
 13 weight in offspring. The NOAEL was 50 mg/kg bw/day based on reduced AGD from
 14 250 mg/kg bw/day. These effects were reported in the absence of marked maternal
 15 toxicity. Effects on the reproductive organs were also reported in male offspring in the
 developmental toxicity studies at higher doses.

15 **Remarks on the study used for the determination of the ED₁₀**

Species, strain, sex:	CD(Sprague-Dawley) rats male and female:
Study type:	2-generation according to OECD 416
Route of administration:	Oral in feed
Effect descriptor for LOAEL:	Overall: reduced anogenital distance Classification: increase in areolae in males
Mode of action:	Antiandrogenic effect, mechanism relevant for humans
Genotoxicity classification:	Not classified for germ cell mutagenicity
Potential to accumulate:	No

1 **Determination of the ED₁₀ value**

Calculation of the ED ₁₀ value: 416 mg/kg bw/day	
Dose (mg/kg bw/day)	% male F1 with areola
0	2.63
50	0.0
250 (NOAEL)	0.76
750 (LOAEL)	32.3

The ED₁₀ 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 (ED₁₀) is expected at 250 + 10 * 16.67 = 416 mg/kg bw/day.

2 **Preliminary potency group**

Low potency

3 **4. Elements that may modify the preliminary potency evaluation**

4 **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)).

5 **4.2 Type of effect / severity**

<p>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.</p> <p>Maternal toxicity: organ weight changes, and histopathological lesions in the liver graded as minimal in females at 750 mg/kg bw/day.</p> <p>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.</p> <p>NOAEL for maternal toxicity: 250 mg/kg bw/day.</p>
--

6 **4.3 Data availability**

A two-generation study is considered relevant for the assessment of development toxicity.

7 **4.3 Mode of action**

The mechanism (antiandrogen activity) is considered relevant for humans.
--

1 **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.

2 **4.6 Bio-accumulation**

Low to medium bioaccumulation

3 **5. Allocation of potency group and SCL**

The ED₁₀ 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.

4 **6. References**

Confidential.

5

1 **3.7.6.1.4 Example 4**

2 **1 Identification**

Substance Name :	XXXXXX
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3 **2 EU CLP classification**

Repro	2
H	361f

4 **3 ED₁₀ in animals**

5 **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.

6 **Remarks on the study used for the determination of the ED₁₀**

Species, strain, sex:	Rats, CD(SD)BR males
Study type:	90 days, 5 days per week, 120 day observation period
Route of administration:	gavage
Effect descriptor for LOAEL:	testicular atrophy
Mode of action:	A metabolite is assumed to be causing the testicular effects. A direct effect of this metabolite on the Sertoli cells is postulated.
Genotoxicity classification:	none
Potential to accumulate:	unknown

7 **Determination of the ED₁₀ value**

A ED₁₀ 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

8 **Preliminary potency group**

Low potency group

9 **4 Elements that may modify the preliminary potency evaluation**

10 **4.1 Dose-response relationship**

There is no data available on the dose response relationship.

1 **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.

2 **4.3 Data availability**

There is only limited data available at one exposure level. This is insufficient for determining an ED₁₀. 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.

3 **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 **4.5 Toxicokinetics**

Unknown

5 **4.6 Bio-accumulation**

Unknown

6 **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.

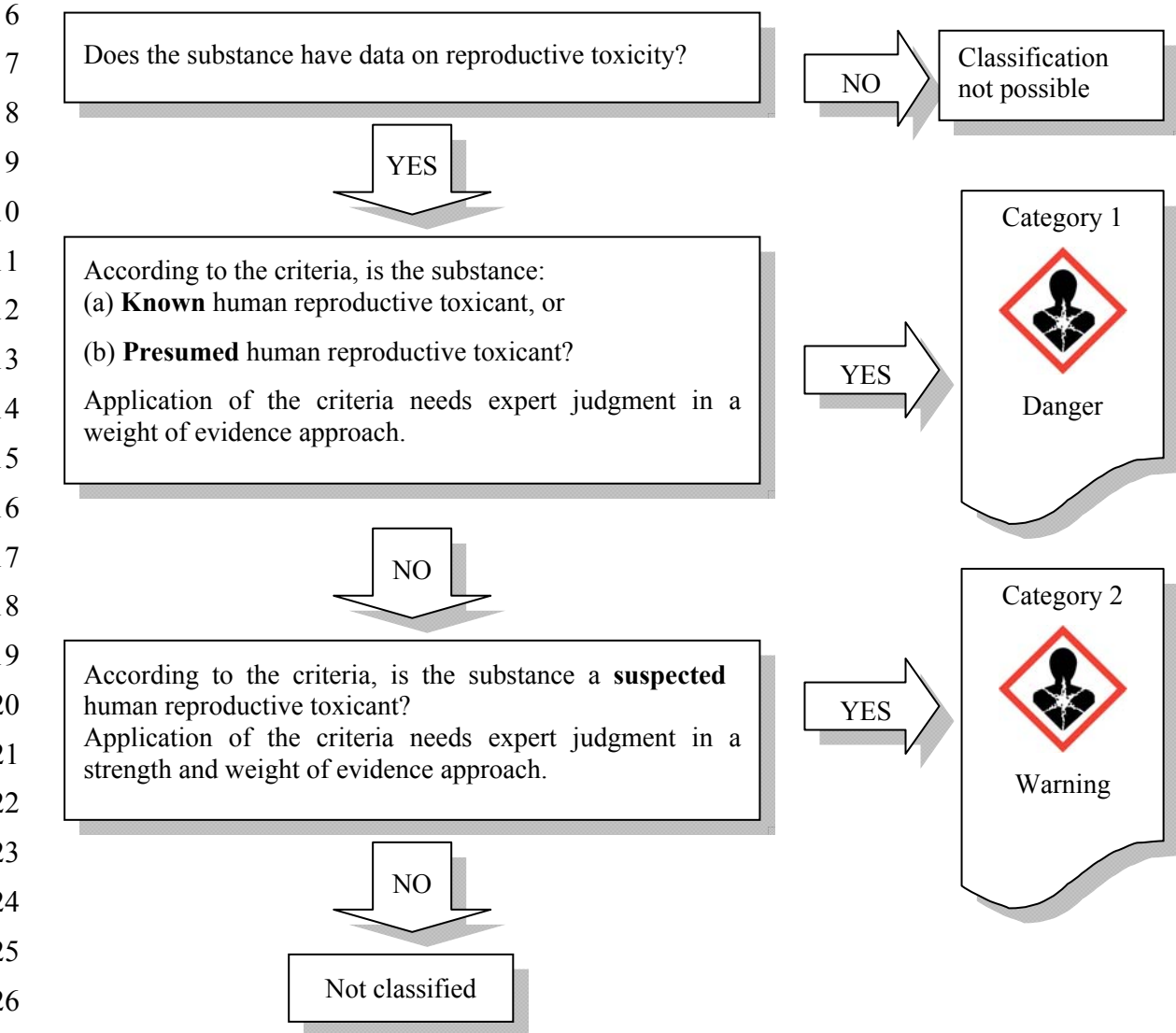
7 **6 References**

Confidential

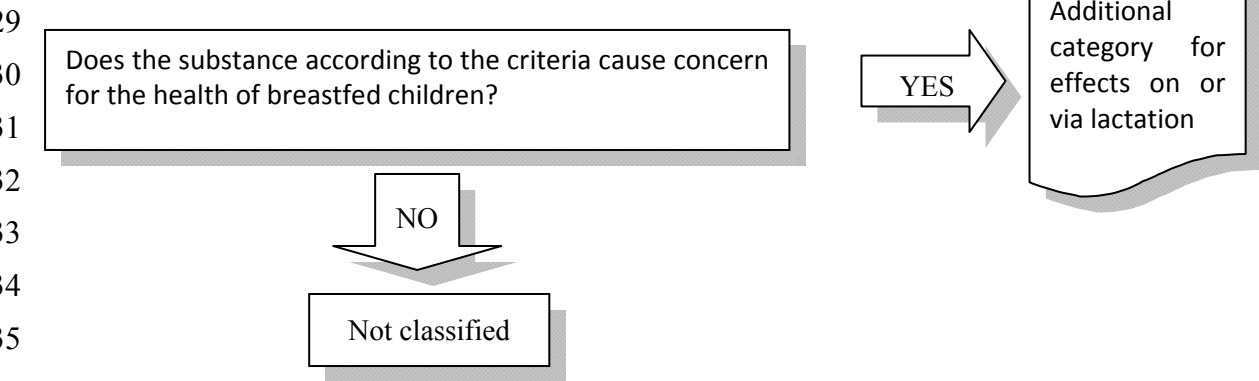
1 **3.7.2.6 Decision logic**

2 The decision logic which follows is provided here as additional guidance. It is strongly
 3 recommended that the person responsible for classification study the criteria before and
 4 during use of the decision logic.

5 Classification of substances for fertility or developmental effects:



28 Classification of substances for effects via lactation:



1 **3.7.3 Classification of mixtures for reproductive toxicity**

2 **3.7.3.1 Classification criteria**

3 Reproductive toxicity classification of mixtures is based on the presence of an ingredient
 4 classified for reproductive toxicity (see CLP Article 6(3) and Annex I, section 3.7.3). Only in
 5 case there is data available for the mixture itself which demonstrate effects not retrieved from
 6 the ingredients, this data might be used for classification. If such data is not available for the
 7 mixture itself, data on a similar mixture can be used in accordance to the bridging principle
 8 (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				
Ingredient classified as:	Generic concentration limits triggering classification of a mixture as:			
	Category 1A reproductive toxicant	Category 1B reproductive toxicant	Category 2 reproductive toxicant	Additional category for effects on or via lactation
Category 1A reproductive toxicant	≥ 0,3 % [Note 1]			
Category 1B reproductive toxicant		≥ 0,3 % [Note 1]		
Category 2 reproductive toxicant			≥ 3,0 % [Note 1]	
Additional category for effects on or via lactation				≥ 0,3 % [Note 1]
<i>Note</i>				
The concentration limits in the table above apply to solids and liquids (w/w units) as well as gases (v/v units).				
<i>Note 1</i>				
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.				

9 **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.

1 **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.

2 **3.7.3.1.3 When data are not available for the complete mixture: bridging principles**

3

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.

4

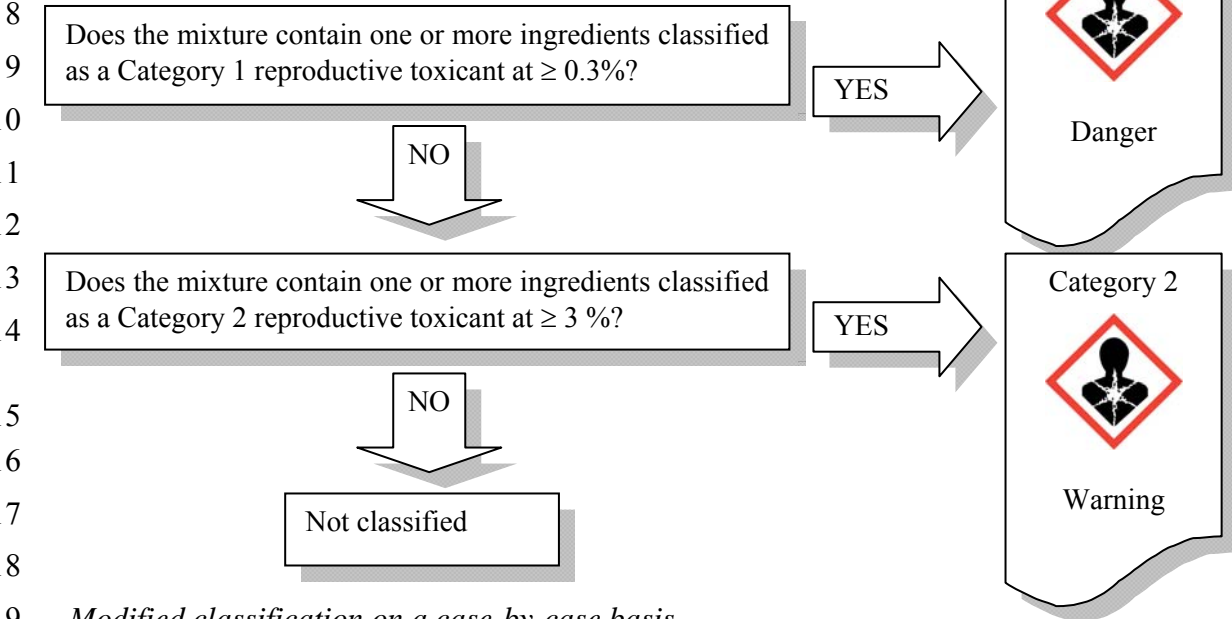
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2 **3.7.3.2 Decision logic**

3 The decision logic which follows is provided here as additional guidance. It is strongly
 4 recommended that the person responsible for classification study the criteria before and
 5 during use of the decision logic.

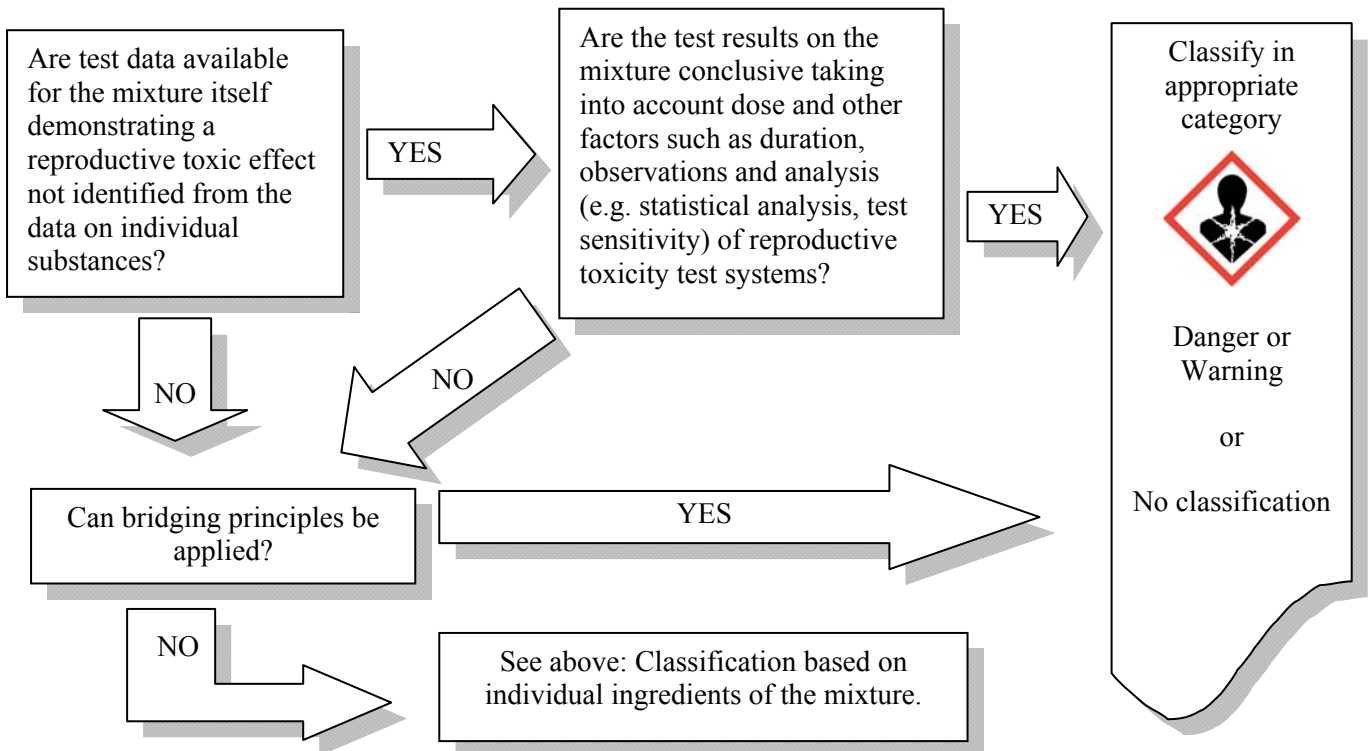
6 Classification of mixtures for fertility or developmental effects:

7 Classification based on individual ingredients of the mixture



19 *Modified classification on a case-by-case basis*

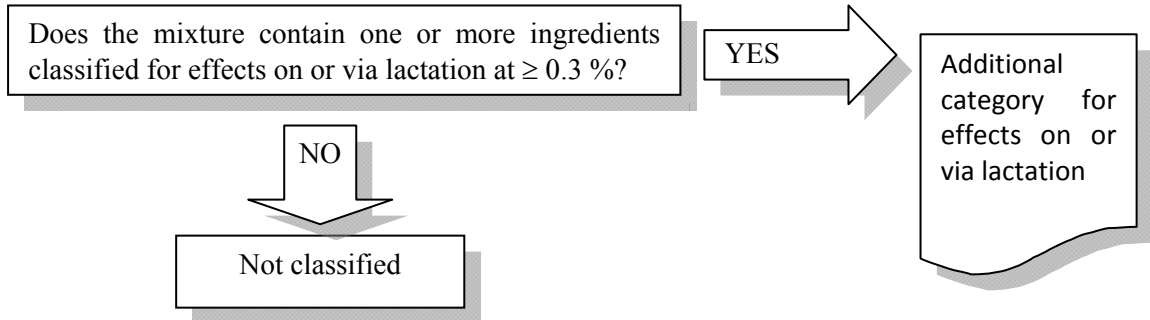
20 Test data on mixtures may be used for classification when demonstrating effects that have not been
 21 established from the evaluation based on the individual ingredients (CLP Annex I, 3.7.3.1.1, see also
 22 CLP Article 6(3)).



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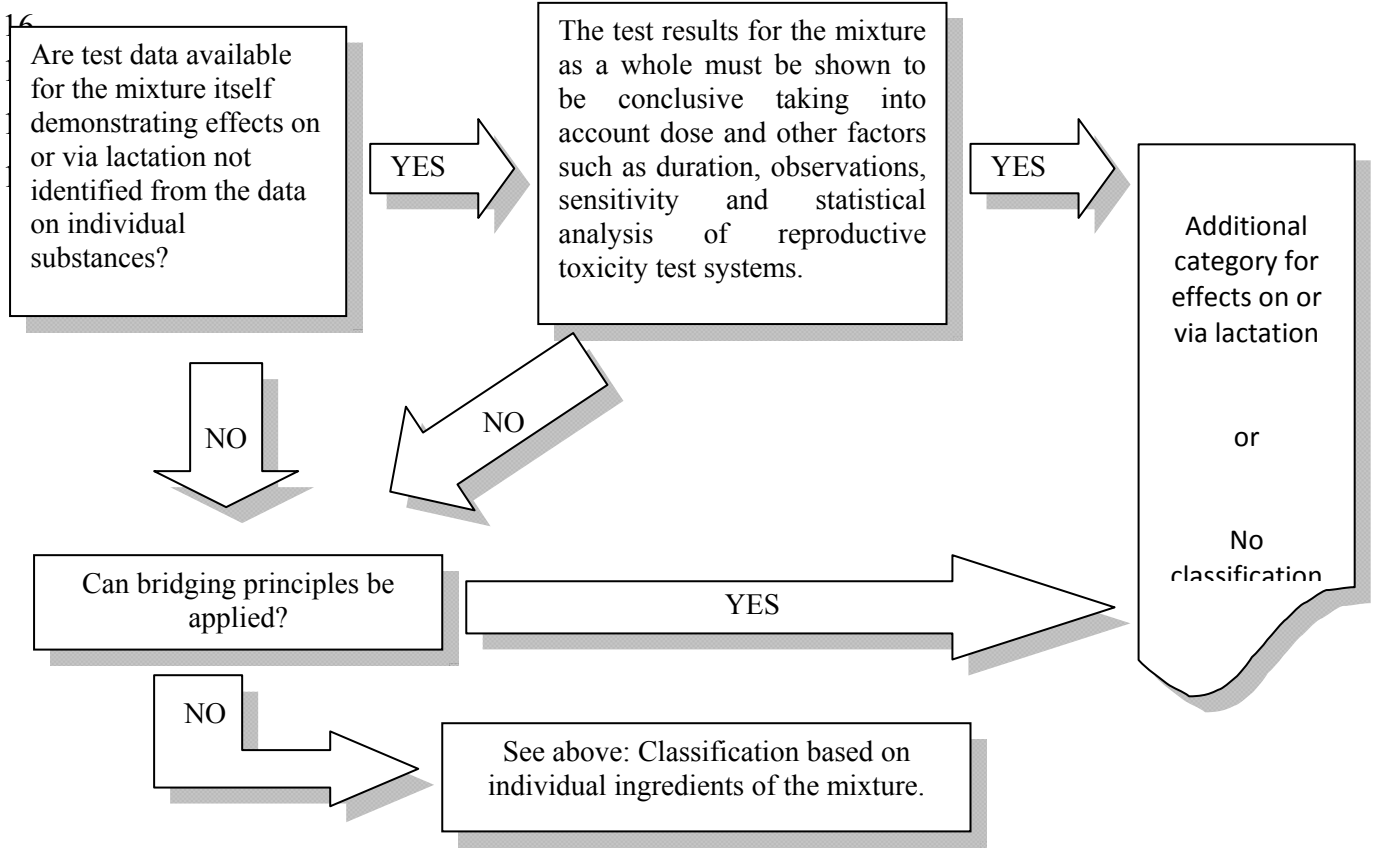
Classification of mixtures for effects via lactation:

Classification based on individual ingredients of the mixture



Modified classification on a case-by-case basis

Test data on mixtures may be used for classification when demonstrating effects that have not been established from the evaluation based on the individual ingredients (CLP Annex I, 3.7.3.1.1, see also CLP Article 6(3)).



1



2 **3.7.4 Hazard communication in form of labelling for reproductive toxicity**

3 **3.7.4.1 Pictograms, signal words, hazard statements and precautionary statements**

Annex I: 3.7.4.1. Label elements shall be used for substances or mixtures meeting the criteria for classification in this hazard class in accordance with Table 3.7.3.

Table 3.7.3

Label elements for reproductive toxicity

Classification	Category 1A or Category 1B	Category 2	Additional category for effects on or via lactation
GHS Pictograms			No pictogram
Signal Word	Danger	Warning	No signal word
Hazard Statement	H360: May damage fertility or the unborn child (state specific effect if known)(state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	H361: Suspected of damaging fertility or the unborn child (state specific effect if known) (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	H362: May cause harm to breast-fed children.
Precautionary Statement Prevention	P201 P202 P281	P201 P202 P281	P201 P260 P263 P264 P270
Precautionary Statement Response	P308 + P313	P308 + P313	P308 + P313
Precautionary Statement Storage	P405	P405	

4 As shown in CLP Annex I, Table 3.7.3, a substance classified as reproductive toxicant in
 5 Category 1A or 1B shall be assigned the hazard statements H360 and a substance classified in
 6 Category 2 shall be assigned H361. Each of these two hazard statements includes the
 7 mentioning of the adverse effects on sexual function and fertility or adverse effects on
 8 development of the offspring.

9 Depending on the data available, the hazard statement H360 or H361 shall e.g. be assigned a
 10 reproductive toxic substance: in the case the criteria for Category 1A/1B or 2 are fulfilled, for
 11 *either* sexual function or fertility *or* developmental toxicity and when the other reproductive
 12 effect cannot be excluded.

1 In case reliable and adequate data are available on reproductive toxicity, (so that it is possible
 2 to ascribe one category for the fertility effects and one category for developmental toxic
 3 effects); it is possible to specify the hazard in the hazard statement. The resulting different
 4 variants of H360 and H361 are shown in the table below, which also provides some examples
 5 when they should be assigned a substance.

6 **Table 3.7.4.1:** Hazard statements for reproductive toxicity: H360 and H361, and their
 7 specifications

H360	<p>“May damage fertility or the unborn child”</p> <p><i>Examples:</i></p> <p>1) a substance classified in Repr Cat 1A/B because of adverse effects on fertility and for which developmental toxic effects cannot be excluded</p> <p>2) a substance classified in Repr Cat 1 A/B but the effects cannot be specified with respect to fertility or developmental toxicity</p>
H361	<p>“Suspected of damaging fertility or the unborn child”</p> <p><i>Example:</i></p> <p>1) a substance classified in Repr. Cat 2 on the basis of effects on developmental toxicity and for which fertility effects cannot be excluded</p> <p>2) a substance classified in Repr. Cat 2 but the effects cannot be specified with respect to fertility or developmental toxicity</p>
H360F	<p>“May damage fertility.”</p> <p><i>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</i></p>
H360D	<p>“May damage the unborn child.”</p> <p><i>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</i></p>
H361f	<p>“Suspected of damaging fertility”.</p> <p><i>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</i></p>
H361d	<p>Suspected of damaging the unborn child.</p> <p><i>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</i></p>
H360FD	<p>May damage fertility. May damage the unborn child.</p> <p><i>Example: a substance classified in Repr Cat 1A/B on the basis of fertility effects and developmental toxicity.</i></p>
H361fd	<p>Suspected of damaging fertility. Suspected of damaging the unborn child.</p> <p><i>Example: a substance classified in Repr Cat 2 on the basis of fertility effects and developmental toxicity.</i></p>
H360Fd	<p>May damage fertility. Suspected of damaging the unborn child.</p> <p><i>Example: a substance classified in Repr Cat 1A/B on the basis of fertility effects and in</i></p>

	<i>Repr Cat 2 on the basis of developmental toxicity.</i>
H360Df	May damage the unborn child. Suspected of damaging fertility. <i>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.</i>

1 According to CLP Annex I, section 3.7.4.1, the hazard statements shall be amended by
 2 specifying the route of exposure if it is conclusively proven that no other routes of exposure
 3 will lead to an adverse effect on sexual function or fertility or development of the offspring.
 4 When conclusively proven, it is meant that valid *in vivo* test data need to be available for all
 5 three exposure routes clearly indicating that only one exposure route has caused positive
 6 results i.e. adverse effects on the reproduction. Moreover, such a finding should be
 7 considered plausible with respect to the mechanism or mode of action. It is estimated that
 8 such a situation would rarely occur. Thus, amendment of the hazard statement with the route
 9 of exposure generally does not have to be considered.

10 **3.7.4.2 Additional labelling provisions**

11 There are no additional labelling provisions for reproductive toxic substances and mixtures in
 12 CLP, however there are provisions laid out in Annex XVII to REACH. The packaging of
 13 substances harmonised classified for reproductive toxicity category 1A or category 1B, and
 14 mixtures containing such substances, "must be marked visibly, legibly and indelibly as
 15 follows: 'Restricted to professional users'." (REACH, Annex XVII, point 30).

16 **3.7.5 Re-classification of substances and mixtures classified for reproductive** 17 **toxicity according to DSD and DPD**

18 **3.7.5.1 Is direct "translation" of classification and labelling possible?**

19 Generally yes. In case there is no re-evaluation of the data, the hazard statement specifying
 20 both 'damage to fertility' and 'damage to the unborn child' should be assigned. It is possible to
 21 omit the hazard statement specifying fertility or developmental effects; in case there are
 22 clearly negative results (see [section 3.7.4.1](#)).

23 However, in some very rare situations, a reproductive toxicant classified with Repr. Cat. 3;
 24 R62 may need classification with Repr. Cat. 1B H360 under CLP. According to Annex VI to
 25 DSD, for the classification of a substance into Category 2 for impaired fertility, there should
 26 normally be clear evidence in one animal species, with supporting evidence on mechanism of
 27 action or site of action, or chemical relationship to other known anti-fertility agents or other
 28 information from humans which would lead to the conclusion that effects would be likely to
 29 be seen in humans. According to CLP, such supporting evidence is not needed.

30 Classification for effects on or via lactation according to CLP is directly equivalent to
 31 assignment of R64 according to DSD as the criteria are essentially the same. Therefore, direct
 32 translation of R64 to H362 is possible.

1 **3.8 SPECIFIC TARGET ORGAN TOXICITY – SINGLE EXPOSURE (STOT-**
2 **SE)**

3 **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).

4 There are two hazard classes for single exposure toxicity: “Acute toxicity” and “STOT-SE”.
5 These are independent of each other and both may be assigned to a substance or a mixture if
6 the respective criteria are met. Acute toxicity refers to lethality and STOT-SE to non lethal
7 effects. However, care should be taken not to assign both classes for the same toxic effect,
8 essentially giving a “double classification”, even where the criteria for both classes are
9 fulfilled. In such a case the most appropriate class should be assigned.

10 Acute toxicity classification is generally assigned on the basis of evident lethality (e.g.an
11 LD₅₀/LC₅₀ value) or where the potential to cause lethality can be concluded from evident
12 toxicity (e.g. from fixed dose procedure). STOT-SE should be considered where there is clear
13 evidence of toxicity to a specific organ especially when it is observed in the absence of
14 lethality.

15 Furthermore, specific toxic effects covered by other hazard classes are not included in STOT-
16 SE. STOT-SE should only be assigned where the observed toxicity is not covered more
17 appropriately by another hazard class. For example, specific effects caused after a single
18 exposure like corrosion of skin or effects on the reproductive organs should be used for
19 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.

20 The hazard class STOT-SE has 3 categories, with Categories 1 and 2 being distinct from
21 Category 3 in terms of the toxicity they cover and the criteria. Categories 1 and 2 for non
22 lethal “significant and/or severe toxic effects” are the basis for classification with the
23 category reflecting the dose level required to cause the effect. Category 3 covers “transient
24 effects” occurring after single exposure, specifically respiratory tract irritation (RTI) and
25 narcotic effects (NE). The relationship between Categories 1/2 vs. Category 3 is discussed in
26 **section 3.8.2.4** of this document.

27

28

1 3.8.2 Classification of substances for STOT-SE

2 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.

3 CLP does not require testing of substances or mixtures for classification purposes. The
4 assessment is based on the respective criteria together with available adequate and robust test
5 data/information. Generally, information relevant to STOT-SE can be obtained from human
6 experience or acute toxicity studies in animals.

7 3.8.2.1.1 Identification of human data

8 Relevant information with respect to toxicity after single exposure may be available from
9 case reports, epidemiological studies, medical surveillance and reporting schemes and
10 national poisons centres.

11 Data on sensory irritation of the airways may be available from volunteer studies including
12 objective measurements of RTI such as electrophysiological responses, data from
13 lateralization threshold testing, biomarkers of inflammation in nasal or bronchoalveolar
14 lavage fluids (IR/CSA, section 7.2.3.2). For more details see IR/CSA, section 7.4.3.2 and
15 R.7.2.

16 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.

17

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, ...

18 Non-testing data

19 *Physicochemical data*

20 Physicochemical properties, such as pH, physical form, solubility, vapour pressure, particle
21 size, can be important parameters in evaluating toxicity studies and in determining the most
22 appropriate classification especially with respect to inhalation where physical form and
23 particle size can have a significant impact on toxicity.

24 *(Q)SAR models, Read across*

25 “Non-testing” data (i.e. data not obtained from experimental methods) can be provided by the
26 use of techniques such as grouping/category formation, Quantitative and qualitative Structure
27 Activity Relationship (Q)SAR models and expert systems, which generally relate physico-
28 chemical properties and chemical structure to toxicity. The use of these methods is described
29 in more detail in Section 2.3.2 and IR/CSA, section R.7.4.4.1.

1 The potential use of (Q)SAR models for predicting effects relevant to STOT-SE Categories
2 1/2 is currently quite limited and may only be applicable in specific cases. However, they
3 may be somewhat more useful for STOT-SE Category 3 where there are some well
4 established relationships between physicochemical properties or chemical structure and
5 effects such as narcosis and respiratory tract irritation. For instance substances such as
6 aldehydes, unsaturated carbonic esters and reactive inorganic compounds are generally found
7 to be respiratory tract irritants.

8 In addition, there are systems which can predict the metabolism of substances. These can be
9 useful in providing information on the potential for the substance to be metabolised to
10 substances with known toxicity. An example is certain esters, which after enzymatic cleavage
11 to carbonic acids and alcohols in the nasal region, cause respiratory irritation.

12 For more details see IR/CSA, section 7.4.3.1.

13 Testing data

14 *Animal data*

15 The standard tests on acute toxicity are listed in IR/CSA, section R.7.4.3.1.

16 For **Category 1 and 2**, in general terms, most studies involving single exposure via any
17 relevant route of exposure, such as acute toxicity studies, can be used for classification
18 purposes. Older acute toxicity studies which tended to only measure lethality as an
19 observational endpoint (e.g. to determine LD₅₀/LC₅₀) will generally not provide useful
20 information for STOT-SE. However, newer acute toxicity test protocols, such as the fixed-
21 dose and up-down procedures, have a wider range of observations on signs of toxicity and
22 therefore may provide information relevant for STOT-SE. Other standard studies, e.g.
23 neurotoxicity tests, or ad-hoc studies designed to investigate acute toxicity, can also provide
24 valuable information for STOT-SE.

25 Care must be taken not to classify for STOT-SE for effects which are not yet lethal at a
26 certain dose, but would lead to lethality within the numeric classification criteria. In other
27 words, if lethality would occur at relevant doses then a classification for acute toxicity would
28 take precedence and STOT-SE would not be assigned.

29 Although classification in **Category 3** is primarily based on human data, if available, animal
30 data can be included in the evaluation. These animal data on RTI and NE will generally come
31 from standard acute inhalation studies, although it is possible that narcosis could be observed
32 in studies using other routes. Standard acute toxicity tests are often more useful for Category
33 3 than for STOT-SE Categories 1/2 because overt findings of narcosis and RTI are more
34 often reported in clinical observations.

35 The Alarie test gives specific information on the potential for sensory irritation. Further,
36 information on this test and its limitations can be found in IR/CSA, Section R.7.2.

37 Furthermore the Inhalation Hazard Test (Annex to OECD TG 403) might give information on
38 the potential for RTI of volatile substances. Though the focus of STOT-SE is on effects
39 caused by single exposure, data from studies with repeated exposure might give additional
40 valuable information, especially with respect to the underlying mode of action of RTI.

41 In vitro data

42 Since there are currently no *in vitro* tests that have been officially adopted by the EU or
43 OECD for assessment of acute toxicity, there are also no useful test systems for STOT-SE
44 (see IR/CSA, section R.7.4.3.1). Any available studies should be assessed using expert
45 judgement.

1

2 **3.8.2.2 Classification criteria for Categories 1 and 2**

Annex I: 3.8.2.1.1. Substances are classified for immediate or delayed effects separately, by the use of expert judgement (see 1.1.1) on the basis of the weight of all evidence available, including the use of recommended guidance values (see 3.8.2.1.9). Substances are then placed in Category 1 or 2, depending upon the nature and severity of the effect(s) observed (Table 3.8.1).

Table 3.8.1

Categories for specific target organ toxicity-single exposure

Categories	Criteria
Category 1	<p>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</p> <p>Substances are classified in Category 1 for specific target organ toxicity (single exposure) on the basis of:</p> <p>(a) reliable and good quality evidence from human cases or epidemiological studies; or</p> <p>(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.</p>
Category 2	<p>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</p> <p>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.</p> <p>In exceptional cases, human evidence can also be used to place a substance in Category 2 (see 3.8.2.1.6).</p>

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).

3 STOT-SE Category 1 and 2 is assigned on the basis of findings of “significant” or “severe”
 4 toxicity. In this context “significant” means changes which clearly indicate functional
 5 disturbance or morphological changes which are toxicologically relevant. “Severe” effects
 6 are generally more profound or serious than “significant” effects and are of a considerably
 7 adverse nature with significant impact on health. Both factors have to be evaluated by weight
 8 of evidence and expert judgement.

1 **3.8.2.2.1 Guidance values**

Annex 1: 3.8.2.1.9.1 In order to help reach a decision about whether a substance shall be classified or not, and to what degree it shall be classified (Category 1 or Category 2), dose/concentration 'guidance values' are provided for consideration of the dose/concentration which has been shown to produce significant health effects.

2

Annex 1: 3.8.2.1.9.3. The guidance value (C) ranges for single-dose exposure which has produced a significant non-lethal toxic effect are those applicable to acute toxicity testing, as indicated in Table 3.8.2.

Table 3.8.2

Guidance value ranges for single-dose exposures ^a

			Guidance value ranges for:*	
Route of exposure	Units	Category 1	Category 2	Category 3
Oral (rat)	mg/kg body weight	$C \leq 300$	$2000 \geq C > 300$	Guidance values do not apply ^b
Dermal (rat or rabbit)	mg/kg body weight	$C \leq 1000$	$2000 \geq C > 1000$	
Inhalation (rat) gas	ppmV/4h	$C \leq 2500$	$20000 \geq C > 2500$	
Inhalation (rat) vapour	mg/l/4h	$C \leq 10$	$20 \geq C > 10$	
Inhalation (rat) dust/mist/fume	mg/l/4h	$C \leq 1.0$	$5,0 \geq C > 1,0$	

Note

(a) The guidance values and ranges mentioned in Table 3.8.2 above are intended only for guidance purposes, i.e. to be used as part of the weight of evidence approach, and to assist with decision about classification. They are not intended as strict demarcation values.

(b) Guidance values are not provided for Category 3 substances since this classification is primarily based on human data. Animal data, if available, shall be included in the weight of evidence evaluation.

3 * Note: There is a misprint in Annex I, Table 3.8.2; the heading 'Guidance value ranges for:' should also belong
4 to the column 'Category 1'.

5 Where significant or severe toxicity has been observed in animal studies, the dose/exposure
6 level causing these effects is compared to the guidance values provided to determine if
7 classification in Category 1 or 2 is most appropriate.

8 In cases of inhalation studies with exposure times different to 4 hours an extrapolation can be
9 performed similar to the one described in the [section 3.1](#) for acute toxicity.

10 **3.8.2.3 Classification criteria for Category 3: Transient target organ effects**

11 Currently, the criteria for classification in category 3 only cover the transient effects of
12 "respiratory tract irritation" and "narcotic effects".

13

14

Annex I: Table 3.8.1 (continued)	
Categories for specific target organ toxicity-single exposure	
Categories	Criteria
Category 3	<p>Transient target organ effects</p> <p>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</p>

1

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.

2 It is clearly indicated in the CLP that there are currently no validated animal tests that deal
 3 specifically with RTI, but that animal studies can be used as a part of weight of evidence
 4 evaluation (3.8.2.2.1.2(d)). However when there are no data in human and animal data
 5 suggesting RTI effects, expert judgement is needed to estimate the severity of the effects
 6 observed in animals, the conditions of the test, the physical-chemical properties of the
 7 substance and whether those considerations alone might be sufficient for a classification in
 8 Category 3 for RTI.

9 The generic term RTI covers two different effects: “sensory irritation” and “local cytotoxic
 10 effects”. Classification in STOT-SE Category 3 for respiratory tract irritation is generally
 11 limited to local cytotoxic effects.

- 1 Sensory irritation refers to the local and central reflex interaction of a substance with the
2 autonomic nerve receptors, which are widely distributed in the mucosal tissues of the eyes
3 and upper respiratory tract. It helps to minimize exposure by decreasing the respiration-time-
4 volume and inducing the exposed to leave the areas of irritant concentrations, if possible.
5 Sensory irritation-related effects are fully reversible given that its biological function is to
6 serve as a warning against substances that could damage the airways.
- 7 Local cytotoxic irritant effects induce tissue changes at the site of contact which can be
8 detected by clinico-pathological or pathological methods. Such effects may induce long
9 lasting functional impairment of the respiratory system.
- 10 The basic mechanisms underlying morphological changes comprise cytotoxicity and
11 induction of inflammation. Based on the quality and severity of morphological changes, the
12 function of the respiratory system will be impaired, which may lead to the development of
13 consequential systemic effects, i.e. there might be consequences on distal organs by a
14 diminution of the oxygen supply. As the functional impairment is seldom evaluated by
15 experimental inhalation studies in animals, data on functional changes will mainly be
16 available from experience in humans.
- 17 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.

18 **3.8.2.4 Evaluation of hazard information on STOT-SE for substances**

19 **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.

20

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.

21

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.

1 Human data are potentially very valuable for determining an appropriate classification as they
2 provide direct evidence on the effects of a substance in humans. However, the evaluation of
3 human data is often made difficult by various limitations frequently found with the types of
4 studies and data highlighted in section 3.8.2.4.1 of this document. These include uncertainties
5 relating to exposure assessment (i.e. unreliable information on the amount of a substance the
6 subjects were exposed to or ingested) and confounding exposures to other substances. As a
7 result it should be acknowledged that human data often do not provide sufficiently robust
8 evidence on their own to support classification but may contribute to a weight of evidence
9 assessment with other available information such as animal studies.

10 Categories 1 and 2

11 In general, where reliable and robust human data are available showing that the substance
12 causes significant target organ toxicity these take precedence over other data, and directly
13 support classification in Category 1. Available animal data may support this conclusion but
14 do not detract from it (e.g. if the same effect is not observed in animals).

15 In exceptional cases, where target organ toxicity is observed in humans but the data reported
16 are not sufficiently convincing to support Category 1 because of the lack of details in the
17 observations or in the exposure conditions, and/or with regard to the nature and the severity
18 of the effects observed, then classification in Category 2 could be justified (CLP Annex I,
19 3.8.2.1.6). In this case, any animal data must also be consistent with Category 2 and not
20 support Category 1 (see below). In this case, if the animal data support Category 1, they will
21 take precedence over the human data. This is because the reliability of the human data in this
22 case is probably lower than the reliability of data from standard well conducted animal
23 studies and should accordingly have less weight in the assessment.

24 When using human data, there is no consideration of the human dose/exposure level that
25 caused those effects.

26 Category 3

27 *Respiratory Tract Irritation*

28 Human evidence for RTI often comes from occupational case reports where exposure is
29 associated with signs of RTI. Such reports should be interpreted carefully using expert
30 judgement to ensure that they provide reliable information. For instance, there should be a
31 clear relationship between exposure and the development of signs of RTI, with RTI appearing
32 relatively soon after the start of exposure. A solid substance which causes RTI due to
33 physical/mechanical irritation when inhaled as a dust should not be classified. For more
34 details on RTI, see R7a.7.2.1, and example n° 3 for sulfur dioxide.

35 *Narcotic Effects*

36 Narcotic effects may range from slight dizziness to deep unconsciousness and may be caused
37 by several mechanisms:

- 1 – pharmaceutical drugs (designed effect; often receptor-mediated; effective dose usually
2 low; patient under professional observation; limited importance for industrial chemicals
3 and their safety assessment.)
- 4 – unspecific effects of many organic industrial chemicals on CNS-membranes at high dose
5 levels (often solvent vapours, ≥ 6000 ppm in respired air volume). Such effects can be
6 expected at high exposure levels due to otherwise low toxicity.
- 7 – organic chemicals with similarities to and interference with CNS-transmitters; often
8 metabolic transformation necessary; certain solvents, e.g. butandiol, butyrolactone,
9 methoxyethanol; medium levels of effective dose. Children may be considerably more
10 susceptible than adults.
- 11 – chemicals with high specific CNS toxicity; narcotic effects usually close to near-lethal
12 doses (example: H₂S).

13 Narcotic effects are usually readily reversible on cessation of exposure with no permanent
14 damage or changes.

15 Human evidence relating to narcosis should be evaluated carefully. Often the reporting of
16 clinical signs is relatively subjective and reports of effects such as severe headache and
17 dizziness should be interpreted carefully to judge if they provide robust evidence of narcosis.
18 Where relevant human data do not mirror realistic exposure conditions, for instance in case
19 reports from accidental over-exposure situations, supportive information may be needed to
20 corroborate the observed effects. A single case report from accidental or deliberate exposure
21 (i.e. abuse) is unlikely to provide sufficiently robust evidence to support classification
22 without other evidence. For more details on evaluation of available human information see
23 also [section 3.1.2.3.1](#) and IR/CSA, section R.7.4 (especially R.7.4.4.2). Example n° 4 for
24 toluene illustrates the procedure.

25 **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.

26

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.

27

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.

28 The type of evidence mentioned in CLP Annex I, sections 3.8.2.1.7 and 3.8.2.1.8 to support
29 or not to support classification (e.g. clinical biochemistry, changes in organ weights with no
30 evidence of organ dysfunction) is rarely obtained from animal tests designed to measure
31 acute lethality/toxicity (see [section 3.8.2.1.2](#)).

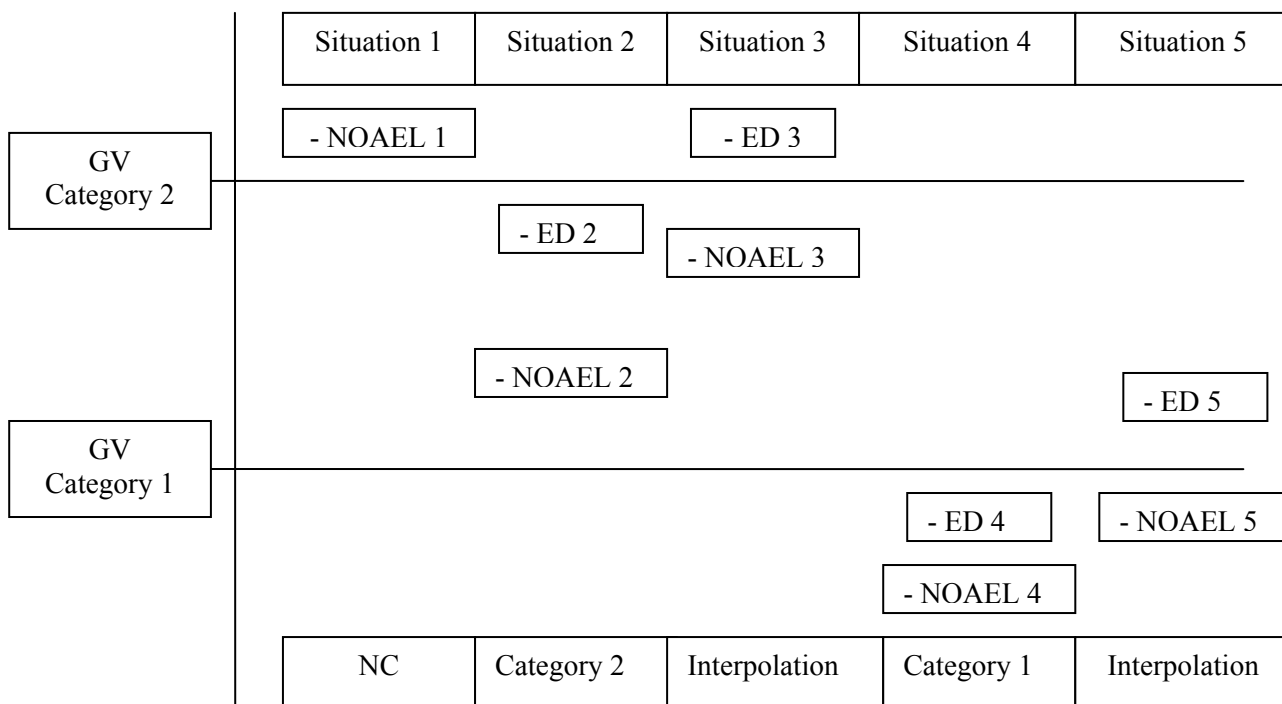
32 Categories 1 and 2

1 Generic guidance on data evaluation is presented in IR/CSA, Section R.7.4 and R.7.4.4.2. All
 2 available animal data which are of acceptable quality should be used in a weight of evidence
 3 approach based on a comparison with the classification criteria described above. The
 4 assessment should be done for each route of exposure.

5 For each study the effects seen in each sex at or around the guidance values (GV) for
 6 Category 1 and Category 2 should be compared with the effects warranting classification in
 7 Category 1 and 2. In general findings in the most sensitive sex would be used to determine
 8 the classification. If the NOAEL from the study is above the GV, the results of that study do
 9 not indicate classification for that category (situations 1 and 2 in Figure 1). If the NOAEL is
 10 below the GV then the effective dose (ED) level, the lowest dose inducing significant/severe
 11 target organ toxicity as defined in section 3.8.2.2.1 should be determined based on the criteria
 12 described above. If the ED is below the GV then this study indicates that classification is
 13 warranted (situations 2 and 4 in Figure 1).

14 In a case where the ED is above a GV but the NOAEL is below the GV (situations 3 and 5)
 15 then interpolation between the ED and the NOAEL is required to determine whether the
 16 effects expected at or below the GV would warrant classification .

17 **Figure 3.8.2.4.2 Comparison between the NOAEL and the ED versus the guidance values**



18
 19 Where a number of studies are available these should be assessed using a weight of evidence
 20 approach to determine the most appropriate classification. Where the findings from individual
 21 studies would lead to a different classification then the studies should be assessed in terms of
 22 their quality, species and strain used, nature of the tested substance (including the impurity
 23 profile and physical form) etc to choose the most appropriate study to support classification.
 24 In general, the study giving the most severe classification will be used unless there are good
 25 reasons that it is not the most appropriate. If the effects observed in animals are not
 26 considered relevant for humans then these should not be used to support classification.
 27 Similarly, if there is robust evidence that humans differ in sensitivity or susceptibility to the
 28 effect observed in the study then this should be taken into account, possibly leading to an

1 increase or decrease in the classification assigned. The final classification based on non
2 human data will be the most severe classification of the three exposure routes.

3 Category 3

4 There are no similar guidance values for category 3. Therefore, if the study shows clear
5 evidence for narcotic effects or respiratory tract irritation at any dose level then this could
6 support classification with category 3.

7 In evaluating inhalation studies a differentiation of respiratory tract effects and systemic
8 effects should always be attempted. In addition, the region in the respiratory tract and the
9 qualitative nature of observed effects is pivotal. Often, the lesions observed are representing
10 stages of a reaction pattern leading to severe and irreversible functional and structural
11 alterations. Therefore reversibility of effects is a significant discriminator. For further details
12 see also **section 3.8.2.3**.

13 **3.8.2.4.3 Evaluation of non-testing and *in vitro* data**

14 Non-testing and *in vitro* data can contribute to the weight of evidence supporting a
15 classification. As described in Annex XI of REACH approaches such as (Q)SAR, grouping
16 and read-across can provide information on the hazardous properties of substances in place of
17 testing and can be used for classification purposes. Also see R7.4.4.1.

18 **3.8.2.4.4 Conversions**

19 The guidance values are given in mg/kg bodyweight. Where the doses in a study are given in
20 different units they will need to be converted as appropriate. For instance the dosages in
21 feeding and drinking water studies are often expressed in ppm, mg test substance/ kg (feed)
22 or mg (test substance)/l (drinking water).

23 The conversion from mg/l to ppm assuming an ambient pressure of 1 at 101.3 kPa and 25°C
24 is $\text{ppm} = 0.0245 \text{ mg/l} \times 1/\text{MW}$.

25 **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.

26 The available information should be considered using expert judgement and a weight of
27 evidence assessment, as described in CLP Annex I, 1.1.1 and Module 1.

28 Valid human data generally take precedence over animal and other non-test data. If there are
29 human data indicating no classification but there are also non-human data indicating
30 classification then the classification is based on the non-human data unless it is shown that
31 the human data cover the exposure range of the non-human data or that the non-human data

1 are not relevant for humans. If the human and non-human data both indicate no classification
2 then classification is not required.

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

4 **3.8.2.5 Decision on classification of substances**

5 Decision on classification for STOT-SE is based on the results of weight of evidence
6 approach described in [section 2.3](#).

7 STOT-SE and acute toxicity are independent of each other and both may be assigned to a
8 substance if the respective criteria are met. However, care should be taken not to assign each
9 class for the same effect, in other words a double classification for the same effect has to be
10 avoided. STOT-SE will be considered where there is clear evidence for a specific organ
11 toxicity especially in absence of lethality, see examples no 1 and no 3 (methanol and
12 tricresylphosphate).

13 If no classification has been warranted for acute toxicity despite significant toxic effect, the
14 substance should be considered for classification as STOT-SE.

15 Normally, the assignment of STOT-SE Category 1 or 2 is independent to the assignment of
16 Category 3. Therefore, a substance may be classified in both Category 1/2 and Category 3 if
17 the respective criteria are met, for instance, in the case of a neurotoxic substance that also
18 causes transient narcotic effects. If category 1/2 is assigned on the basis of effects in the
19 respiratory tract then Category 3 should not be assigned as this would provide no additional
20 information.

21 Classification as acutely toxic and/or corrosive is considered to cover and communicate the
22 specific toxicological effect(s) adequately. An additional classification as specific target
23 organ toxicant (single exposure, category 1 or 2) is not indicated if the severe toxicological
24 effect is the consequence of the local (i.e. corrosive) mode of action.

25 It is a reasonable assumption that corrosive substances may also cause respiratory tract
26 irritation when inhaled at exposure concentrations below those causing frank respiratory tract
27 corrosion. If there is evidence from animal studies or from human experience to support this
28 then Category 3 may be appropriate. In general, a classification for corrosivity is considered
29 to implicitly cover the potential to cause RTI and so the additional Category 3 is considered
30 to be superfluous, although it can be assigned at the discretion of the classifier. The Category
31 3 classification would occur only when more severe effects in the respiratory system are not
32 observed.

33 Category 3 effects should be confined to changes, whether functional or morphological,
34 occurring in the upper respiratory tract (nasal passages, pharynx and larynx). Localized
35 irritation with associated adaptive responses (e.g., inflammation, epithelial metaplasia, goblet
36 cell hyperplasia, proliferative effects) may occur and are consistent with Category 3
37 responses. Injury of the olfactory epithelium should be distinguished in terms of irritation-
38 related (non-specific) and metabolic/ non-irritant (specific).

39 **3.8.2.6 Setting of specific concentration limits for STOT-SE**

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

Specific concentration limits shall be set by the manufacturer, importer or downstream user where

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

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

1
2 Specific concentration limits (SCLs) for STOT-SE may be set by the supplier in some
3 situations according to Article 10 of CLP. For STOT-SE, this may only be done for
4 substances inducing STOT-SE Category 1 at a dose level or concentration clearly (more than
5 one magnitude) below the guidance values according to Table 3.8.2, e.g. below 30 mg/kg
6 bodyweight from the oral single exposure study. This will be mainly based on data in
7 experimental animals but can also be based on human data if reliable exposure data are
8 available. The SCL for classification of a mixture in Category 1 (SCL Cat. 1) based on
9 substances classified in Category 1 can be determined using the following formula:

$$10 \quad SCL_{Cat.1} = \frac{ED}{GV1} \times 100\% \quad \text{Equation 3.8.2.6(a)}$$

11 In this formula the ED is the dose inducing significant specific target organ toxicity and GV1
12 is the guidance value for Category 1 according to Table 3.8.2 of Annex I. The resulting SCL
13 is rounded down to the nearest “preferred value”³ (1, 2 or 5).

14 Example for a substance in SCL Category 1:

$$15 \quad = \frac{0.7 \text{ mg / kgbw}}{300 \text{ mg / kgbw}} \times 100\% = 0.22\% \rightarrow 0.2\%$$

16
17 Though classification of a mixture in Category 1 is not triggered if a Category 1 constituent is
18 present in lower concentrations than the established SCL, a classification in Category 2
19 should be considered.

20 The SCL for classification of a mixture in Category 2 (SCL Cat. 2) based on substances
21 classified in Category 1 can be determined using the following formula:

$$22 \quad SCL_{Cat.2} = \frac{ED}{GV2} \times 100\% \quad \text{Equation 3.8.2.6(b)}$$

23 In this formula the ED is the dose inducing specific target organ toxicity and GV2 is the
24 upper guidance value for Category 2 according to Table 3.8.2 of Annex I. The resulting SCL
25 is rounded down to the nearest preferred values (1, 2 or 5). However, if the calculated SCL
26 Category 2 mixture is above 1%, which is the GCL, then this should be corrected to 1%.

³ This is the “preferred value approach” as used in EU and are values to be established preferentially as the numerical values 1, 2 or 5 or multiples by powers of ten.

1 Example for a substance in SCL Category 2:

$$2 \quad = \frac{0.7 \text{ mg/kgbw}}{2000 \text{ mg/kgbw}} \times 100\% \quad = 0.035 \text{ --> } 0.02\% \text{ (rounded down)}$$

3

4 For example, a substance inducing specific target organ toxicity at 0.7 mg/kg bw/day in an
5 acute oral study would require a SCL for Category 1 mixture of 0.2% and for Category 2
6 mixture of 0.02%.

7 It is not appropriate to determine SCLs for substances classified in Category 2 since
8 ingredients with a higher potency (i.e. lower effect doses than the lower guidance values of
9 Category 2) will be classified in Category 1; substances with higher effect doses than the
10 upper guidance value of Category 2 will generally not be classified.

11 Classification in STOT-SE Category 3 for RTI and narcotic effects does not take into account
12 potency and consequently does not have any guidance values. A pragmatic default GCL of
13 20% is suggested, although a lower or higher SCL may be used where it can be justified.
14 Therefore, an SCL can be determined on a case-by-case basis for substances classified as
15 STOT-SE Category 3 and expert judgement shall be exercised.

16 Specific concentration limits for each of the hazard classes skin and eye irritation, and STOT-
17 SE Category 3 for respiratory tract irritation need to be addressed separately, while
18 unjustified read-across of SCLs from one hazard category to another is not acceptable.

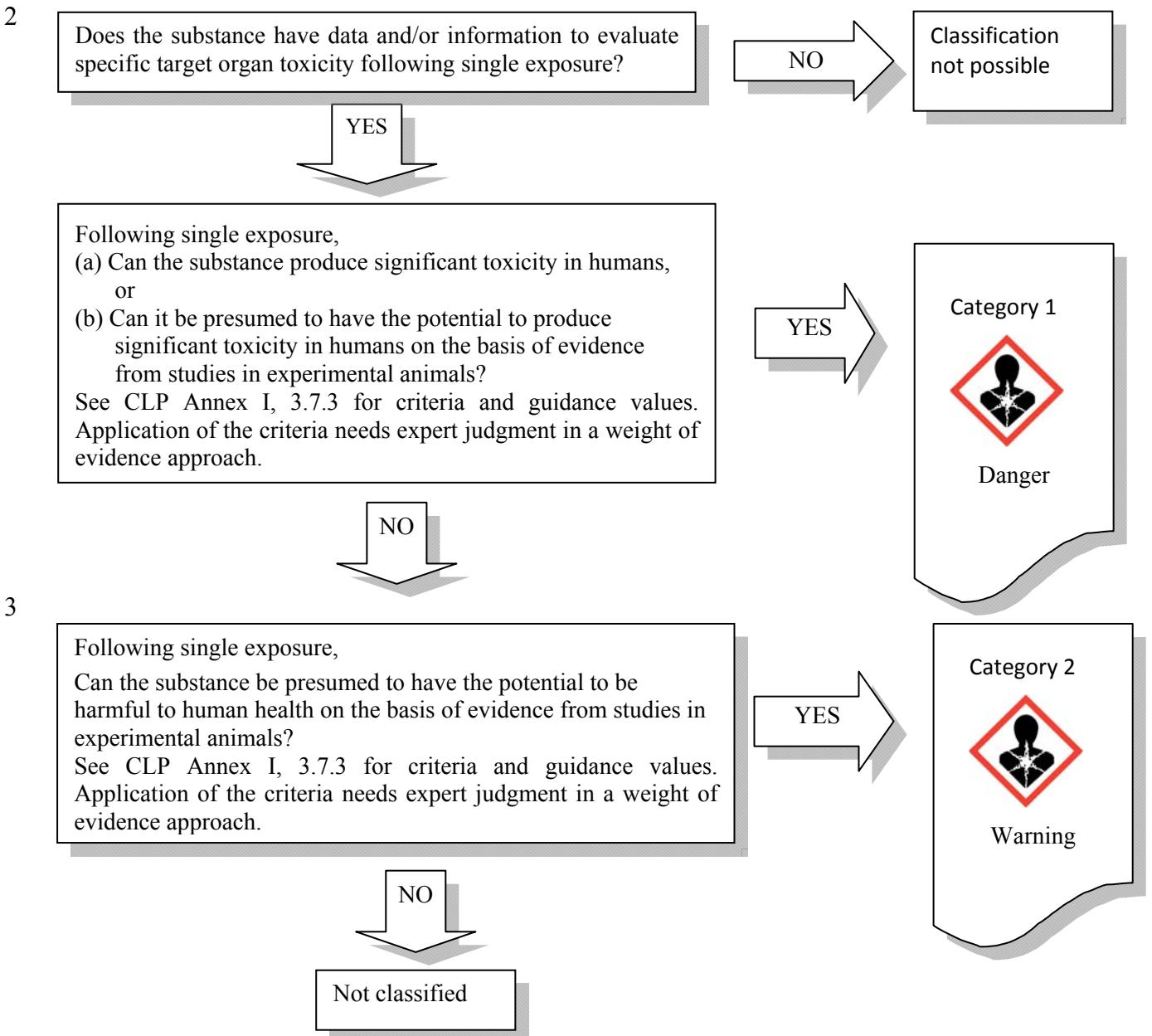
19 For narcotic effects, the factors to be taken into consideration in order to set lower or higher
20 SCLs are the effective dose/concentration, and for liquids in addition the volatility (saturated
21 vapour concentration) of the substance.

22 **3.8.2.7 Decision logic**

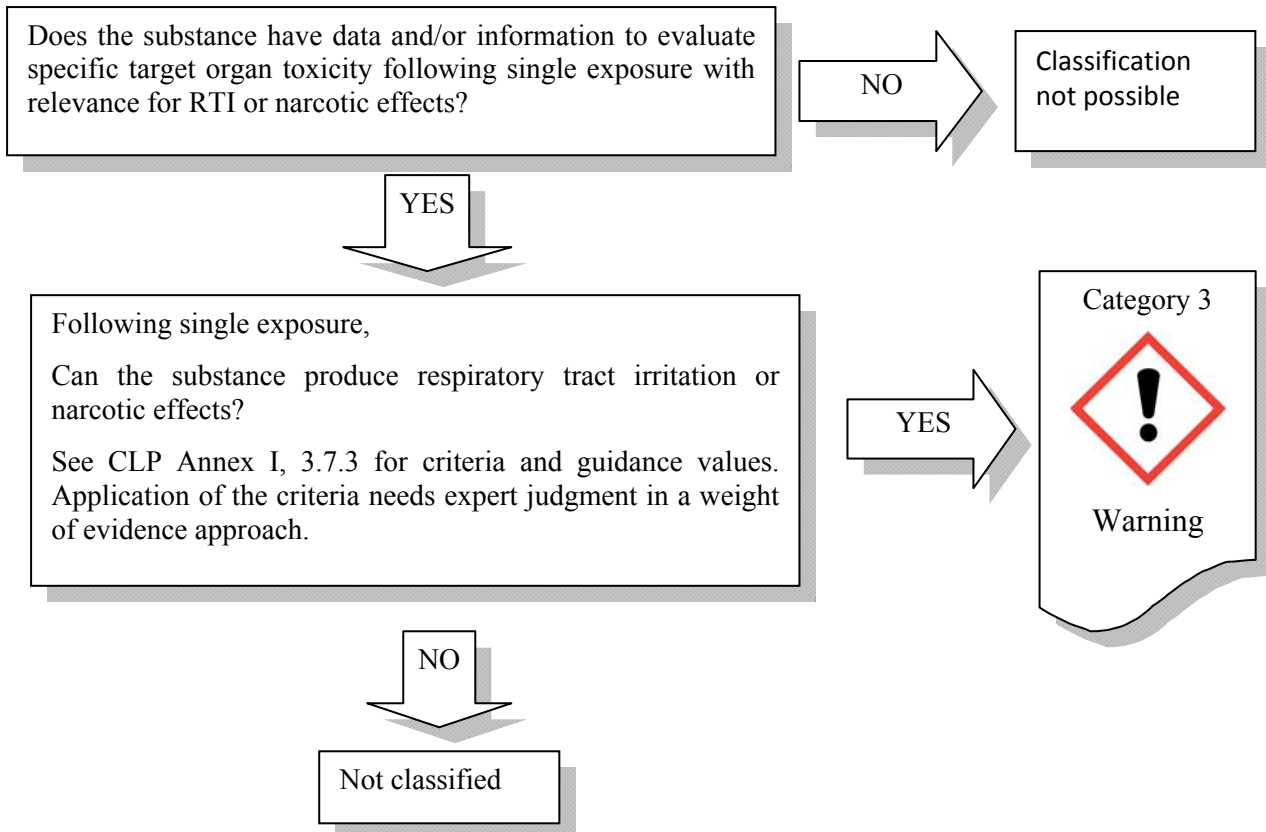
23 The decision logic is provided as additional guidance. It is strongly recommended that the
24 person responsible for classification study the criteria for classification before and during use
25 of the decision logic.

26 This decision logic deviates slightly from the original UNGHS in separating the connection
27 between category 2 and category 3, since, different from the procedure in other hazard
28 classes, they have to be regarded as independent.

1 Classification in Category 1 and Category 2



1 Classification in Category 3



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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

1 approach explained above (see section 3.8.2.3). More information on classification of
2 mixtures into category 3 is provided below (section 3.8.3.3)

3 **3.8.3.2.4 Components of a mixture that should be taken into account for the purpose**
4 **of classification**

5 Components with a concentration equal to or greater than the generic concentration limits
6 (1% for category 1 components and 10% for category 2, see Table 3.8.3) or with a Specific
7 Concentration Limit (see section 3.8.2.6) will be taken into account for classification
8 purposes. For Category 3, the GCL is 20%. Specific concentration limits have preference
9 over the generic ones.

10 **3.8.3.3 Generic concentration limits for substances triggering classification of**
11 **mixtures for STOT-SE**

12 The STOT-SE hazard class does not foresee summation of category 1 or 2 substances in the
13 classification process of a mixture. Furthermore, as category 1 and 2 depict different hazards
14 than category 3 the assessment must be done independently from each other.

Annex 1: Table 3.8.3		
Generic concentration limits of ingredients of a mixture classified as a specific target organ toxicant that trigger classification of the mixture as Category 1 or 2		
Ingredient classified as:	Generic concentration limits triggering classification of the mixture as :	
	Category 1	Category 2
Category 1 Specific Target Organ Toxicant	Concentration \geq 10%	1.0% \leq concentration < 10%
Category 2 Specific Target Organ Toxicant		Concentration \geq 10% [(Note 1)]
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.		
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.		

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Categories 1 and 2

Each single classified component in a concentration range given in Table 3.8.3 triggers the classification of the mixture, i.e. additivity of the concentrations of the components is not applicable.

Category 3

When a mixture contains a number of substances classified with Category 3 and present at a concentration below the GCL (i.e. 20%), an additive approach to determine the classification of the mixture as a whole may be appropriate. In the additive approach the concentrations of the individual substances with the same hazard (i.e. RTI or narcotic effects) are totalled separately. If each individual total is greater than the GCL then the mixture should be classified as Category 3 for that hazard. A mixture may be classified either as STOT SE 3 (RTI) or STOT SE 3 (narcotic effects) or both.

Example

The following example shows whether or not additivity should be considered for Specific Target Organ Toxicity – Single Exposure (STOT-SE) Category 3 transient effects.

Ingredient information:

Ingredient	Wt%	Classification
Ingredient 1	0.5	-
Ingredient 2	3.5	Category 3 – Respiratory Tract Irritation
Ingredient 3	15	Category 3 - Narcotic effects
Ingredient 4	15	Category 3 - Narcotic effects
Ingredient 5	66	-

Answer:

Mixture is Category 3 – Narcotic effects

$\sum\%$ Category 3 – Narcotic effects = 15% + 15% = 30% which is > 20%, therefore classify as Category 3 – Narcotic Effects

$\sum\%$ Category 3 – Respiratory Irritation = 3.5%, which is < 20%, not classified for Respiratory Irritation

Rationale:

- (a) Classification via application of substance criteria is not possible since test data was not provided for the mixture (paragraph 3.8.3.2);
- (b) Classification via the application of bridging principles is not possible since data on a similar mixture was not provided (paragraph 3.8.3.3.1);
- (c) Application of paragraph 3.8.3.4.5 is used for classification. Expert judgement is necessary when applying this paragraph. Paragraph 3.8.3.4.5 notes that a cut-off value/concentration limit of 20% has been suggested, but that the cut-off value/concentration limit at which effects occur may be higher or less depending on

1 the Category 3 ingredient(s). In this case, the classifiers judged that 30% is
2 sufficient to classify.

3 SCLs

4 In the case where a specific concentration limit has been established for one or more
5 ingredients these SCLs have precedence over the generic concentration limit.

6 **3.8.3.4 Decision logic for mixtures**

7 A mixture should be classified either in category 1 or in category 2, according to the criteria
8 described above. The corresponding hazard statement (H370 for category 1 or H371 for
9 category 2) should be used without specifying the target organs, except if the classification of
10 the mixture is based on data available for the complete mixture, in which case the target
11 organs may be given. In the same way, the route of exposure should not be specified, except
12 if data are available for the complete mixture and it is conclusively demonstrated that no
13 other routes of exposure cause the hazard.

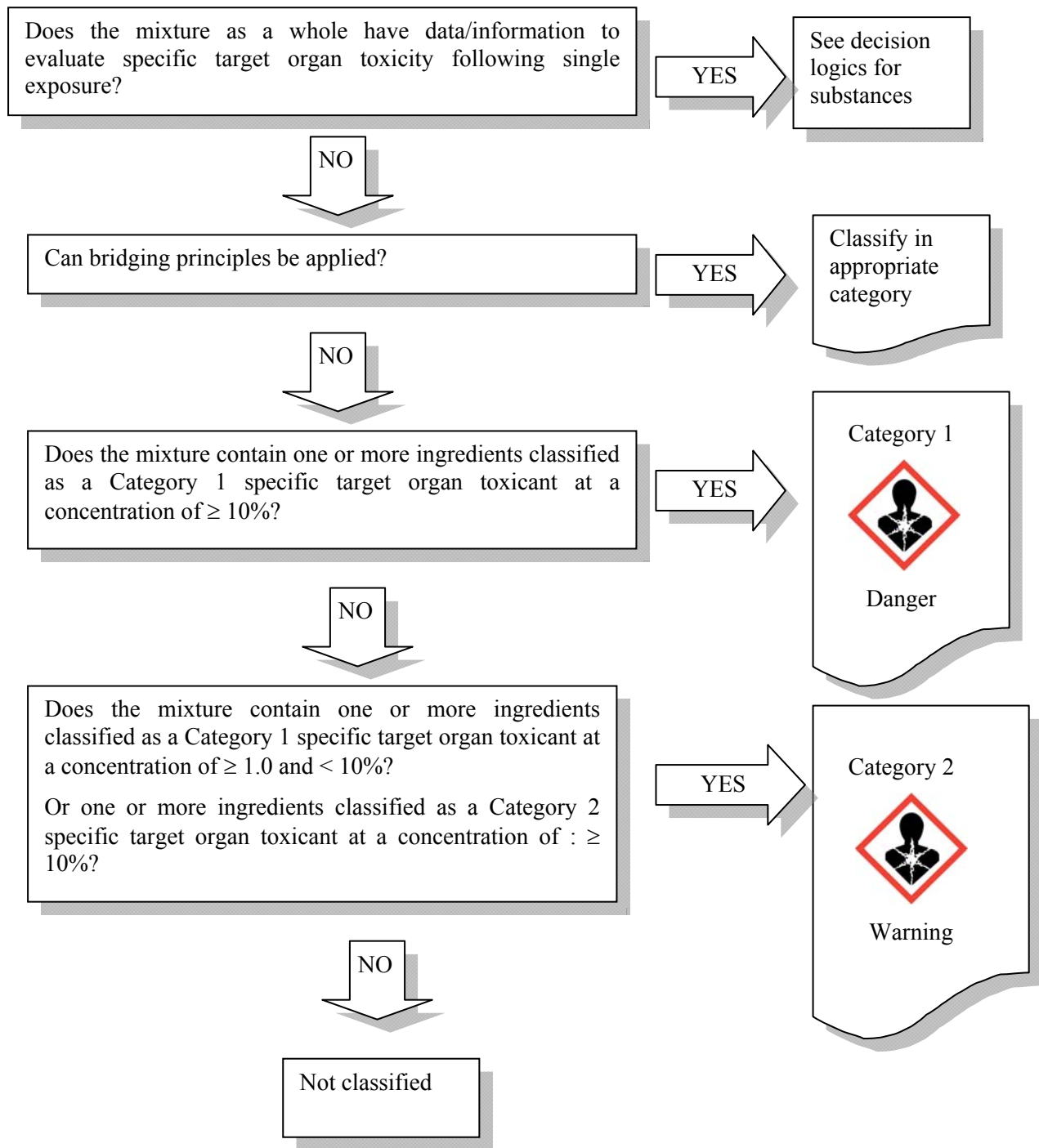
14 If the criteria are fulfilled to classify also the mixture in category 3 for respiratory irritation or
15 narcotic effects, only the corresponding hazard statement (H335 and/or H336) will be added
16 in hazard communication.

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

20 This decision logic deviates slightly from the original UNGHS in separating the connection
21 between category 2 and category 3, since different from the procedure in other hazard classes
22 they have to be regarded as independent.

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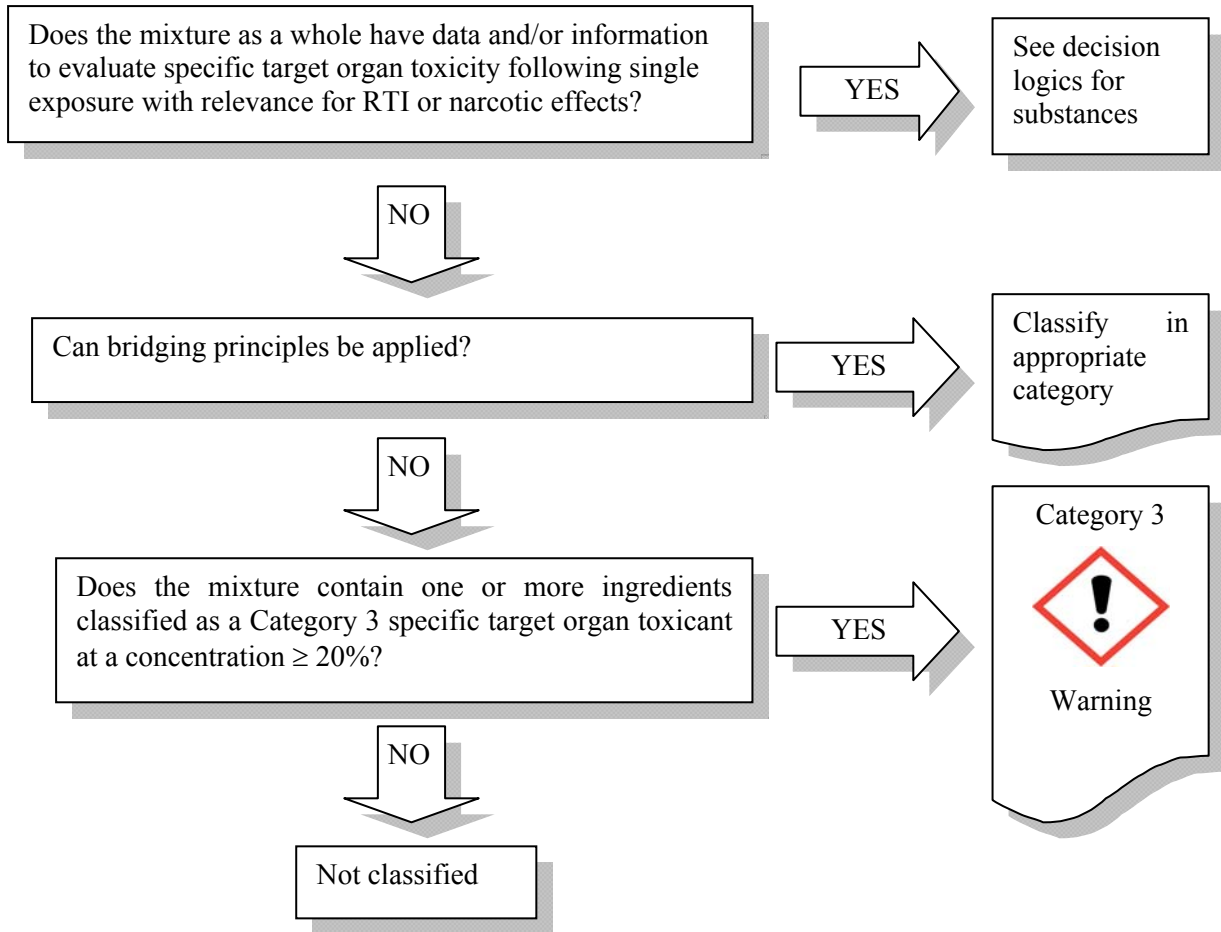
Classification in Category 1 or 2



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1 Classification in Category 3

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2 **3.8.4 Hazard communication in form of labelling for STOT-SE**3 **3.8.4.1 Pictograms, signal words, hazard statements and precautionary statements**

Annex I: 3.8.4.1. Label elements shall be used in accordance with Table 3.8.4., for substances or mixtures meeting the criteria for classification in this hazard class.

Table 3.8.4

Label elements for specific target organ toxicity after single exposure

Classification	Category 1	Category 2	Category 3
GHS Pictograms			
Signal word	Danger	Warning	Warning
Hazard statement	H370: Causes damage to organs (or state all organs affected, if known) (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	H371: May cause damage to organs (or state all organs affected, if known) (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	H335: May cause respiratory irritation; or H336: May cause drowsiness and dizziness
Precautionary statement Prevention	P260 P264 P270	P260 P264 P270	P261 P271
Precautionary Statement Response	P307 + P311 P321	P309 + P311	P304 + P340 P312
Precautionary Statement Storage	P405	P405	P403 + P233 P405
Precautionary Statement Disposal	P501	P501	P501

4 The hazard statement should include the primary target organ(s) of toxicity. Organs in which
5 secondary effects were observed should not be included. The route of exposure should not be
6 specified, except if it is conclusively demonstrated that no other routes of exposure cause the
7 hazard. When a mixture is classified for STOT-SE on basis of test data, the hazard statement
8 will specify the target organs, in the same way as for a substance. If a mixture is classified on
9 basis of the ingredients, the hazard statement (H370 for category 1 or H371 for category 2)
10 may be used without specifying the target organs, as appropriate.

11 In the same way, the route of exposure should not be specified, except if data are available
12 for the complete mixture and if it is conclusively demonstrated that no other routes of
13 exposure cause the hazard. It is recommended to include no more than three primary target

1 organs for practical reasons and because the classification is for specific target organ toxicity.
2 If more target organs are effected it is recommended that the overall systemic damage should
3 be reflected by using the phrase “damage to organs”.

4 **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.

5 According to CLP Annex I, section 3.8.2.1.10.4 the saturated vapour concentration shall be
6 considered as an additional element for providing specific health and safety protection. Thus
7 if a classified substance is highly volatile a supplementary precautionary advice (e.g.
8 “Special/additional care should be taken due to the high saturated vapour pressure”) might be
9 given in order to emphasize the hazard in case it is not already covered by the general
10 **Precuati**onary statements. (As a rule substances for which the ratio of the effect
11 concentration at ≤ 4 h to the SVC at 20° C is $\leq 1/10$).

12 Diluted corrosive substances (may) exhibit an irritation potential with respect to the
13 respiratory tract if they have a sufficient saturated vapour concentration. Expert judgement is
14 needed for a decision with respect to a classification in STOT-SE Category 3. In these cases a
15 switch from one hazard class (skin corrosion/irritation) to another (STOT-SE) would be
16 justified.

17 **3.8.5 Re-classification of substances and mixtures classified for STOT-SE** 18 **according to DSD and DPD**

19 Classification with STOT-SE 1 and 2 according to CLP is comparable to the classification
20 with R39/X and R68/X according to DSD. Classification with R39 – 41 has been used
21 occasionally for substances inducing mortality in eye irritation studies. This classification
22 should not be translated to STOT SE but will result in additional labelling with EUH070.
23 Classification with STOT-SE 3 according to CLP is comparable to the classification with
24 R37 and R67 according to DSD.

25 **3.8.5.1 Is direct “translation” of Classification and Labelling possible for STOT-SE** 26 **substances?**

27 Direct translation of substances or mixtures classified with R39/X is possible but the category
28 may change. All substances or mixtures classified with R39/24, R39/25, R39/27, R38/28
29 and/or vapours and dusts/mists/fumes classified with R39/26 or R39/23 shall be classified as
30 STOT SE 1 because less adverse effects and higher guidance values are required for
31 classification according to CLP compared to DSD. Setting of SCLs may be considered for
32 substances showing STOT SE at levels clearly below the guidance values (see **section**
33 **3.8.2.6**).

34 All substances or mixtures classified with R68/22, R68/21 and/or R68/20 (for vapours) shall
35 be classified at least as STOT SE 2. However, due to the higher guidance values, the
36 requirement for less severe effects, and because STOT SE in humans always leads to
37 classification in category 1, this is a minimal classification and may not adequately convey
38 the seriousness of the toxicity. Therefore, classification in category 1 should be considered.
39 Dusts/mists/fumes classified with R68/20 can be directly translated into STOT SE 2 because
40 the guidance values are the same. Gasses classified with R68/20 should be re-evaluated
41 because of the change from guidance values in mg/L into ppm.

1 If translation results in a classification in STOT SE 1 for one route and in STOT SE 2 for
2 another route only classification in Category 1 is required (for both routes).

3 Classification as STOT SE is not route specific as it was for classification with R39/X and
4 R68/X. The route specificity of STOT SE is included in the hazard statement and includes
5 route-to-route extrapolation by default unless conclusively shown otherwise. Therefore, the
6 route specific data on STOT SE should be re-evaluated. A re-evaluation is also necessary
7 because the primary target organs for STOT SE should be stated in the hazard statement.

8 All substances or mixtures classified with R67 shall be classified as STOT SE Category 3
9 H336.

10 All substances or mixtures classified with R37 shall be classified as STOT SE Category 3
11 H335. Also additional labelling with EUH071 (Corrosive to the respiratory tract) shall be
12 considered.

13 **3.8.5.2 Re-evaluation of the STOT-SE data**

14 Gasses classified with R39/23 or R39/26 should be re-evaluated because of the change from
15 guidance values in mg/L into ppm.

16 Substances or mixtures not classified for STOT-SE, should be considered for re-evaluation
17 because less adverse effects and higher guidance values are required for classification
18 according to CLP compared to DSD. Also, effects in humans are now considered for
19 classification without restrictions to the exposure level.

20 **3.8.6 Examples of classification for STOT-SE**

21 **3.8.6.1 Examples of substances fulfilling the criteria for classification**

22 **3.8.6.1.1 Example 1: Methanol**

Application	Use of adequate and reliable human data, where animal data are not appropriate. Independent classification for STOT-SE and Acute toxicity due to different effects		
	Test Data	Classification	Rationale
Available information	<p><i>Animal data:</i></p> <p>LD₅₀ rat > 5,000 (mg/kg)</p> <p>No specific target organ toxicity (impairment of seeing ability) observed in rats, even in high doses.</p>	Classification not possible	The rat is known to be insensitive to the toxicity of methanol and is thus not considered to be a good model for human effects (different effect/mode of action)
	<p><i>Human experience:</i></p> <p>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)</p>	STOT-SE Category 1	The classification criteria for Category 1 are fulfilled: clear human evidence of a specific target organ toxicity effect which is not covered by Acute toxicity.
Remarks	<p>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.</p> <p>Labelling:</p> <p>Pictogram GHS 08; Signal word: Danger; Hazard statement: H370 Causes damage to the eye.</p>		

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3.8.6.1.2 Example 2: Tricresyl phosphate

Application	Use of valid human evidence supported by animal data		
	Test Data	Classification	Rationale
Available information	<p>Human experience: There are well documented case reports about severe neurotoxic effects</p> <p>Animal experiments: Severe neurotoxic effects (Paralysis) were observed after single exposure of doses < 200 mg/kg</p> <p>LD₅₀ rat oral 3000 - 3900 mg/kg</p>	STOT-SE Category 1	The classification criteria are clearly fulfilled based on human experience as well as on results of animal studies
Remarks	<p>Labelling:</p> <p>Pictogram GHS 08; Signal word: Danger; Hazard Statement: H370 Causes damage to the central nervous system.</p>		

1 **3.8.6.1.3 Example 3: Sulfur dioxide**

Application	Use of valid human evidence		
	Test Data	Classification	Rationale
Available information	<p>Human experience: Broad, well documented human experience on irritating effect to respiratory system.</p>	STOT-SE Category 3	The classification criteria for Category 3 (Respiratory Tract Irritation) are fulfilled based on well documented experience in humans
Remarks	<p>Labelling:</p> <p>Pictogram GHS 07; Signal word: Warning; Hazard statement: H335 May cause respiratory irritation</p>		

2 **3.8.6.1.4 Example 4: Toluene**

Application			
	Test Data	Classification	Rationale
Available information	<p>Animal data: In valid animal experiments narcotic effects (transient effect on nervous system) at ≥ 8 mg/l were observed.</p>	STOT-SE Category 3	The classification criteria for Category 3 (Narcotic Effects) are fulfilled based on well documented results in animal experiments
Remarks	<p>Labelling:</p> <p>Pictogram GHS 07; Signal word: Warning; Hazard statement: H336 May cause drowsiness and dizziness</p>		

3 **3.8.6.2 Examples of substances not fulfilling the criteria for classification**

4 **3.8.6.2.1 Example 5: ABC**

Application	SE in case same effect leading to Acute toxicity classification		
	Test Data	Classification	Rationale
Available information	<p>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</p>	No classification in STOT- SE	Though a specific organ is damaged, the substance will be classified in Acute Toxicity (Category 4), since lethality was observed which was due to the liver impairment. It is assumed that the LD ₅₀ =ATE is ≤ 2,000 mg/kg. There should be no double classification for the same effect/mechanism causing lethality by impairment of a specific organ, thus no classification for STOT-SE

1 **3.8.6.2.2 Example 6: N,N-Dimethylaniline**

Application	No classification for STOT-SE in case same effect leading to Acute toxicity classification		
	Test Data	Classification	Rationale
Available information	<p>Animal data: Acute oral toxicity: LD₅₀ values > 1,120-1,300 oral rat and 1,690 mg/kg bw dermal rabbit; ca. 50 mg/kg are lethal in cats due to high Met HB formation ; no specific target organ toxicity (blood toxicity) observed in rats.</p>	No classification in STOT-SE	The criteria for STOT-SE classification are not fulfilled despite a clear specific target organ effect in humans and in a relevant animal species. The substance is classified in Category 3 Acute Toxicity since the Met HB formation is causative for the lethality in humans and in animals (cats) in low doses.
	<p>Human experience: Broad human experience from many case reports about lethal intoxications caused by methemoglobinemia following oral/dermal/inhalation exposure to aromatic amines</p>	No classification in STOT-SE	
Remarks	The standard animal species for single exposure (acute) tests, the rat, is not sensitive, i.e. no appropriate species for this specific effect.		

2 **3.9 SPECIFIC TARGET ORGAN TOXICITY – REPEATED EXPOSURE**
3 **(STOT-RE)**

4 **4 PART 4: ENVIRONMENTAL HAZARDS**

1 **ANNEXES**

2 **I ANNEX I: AQUATIC TOXICITY**

3 **II ANNEX II: RAPID DEGRADATION**

4 **III ANNEX III: BIOACCUMULATION**

5 **IV ANNEX IV: METALS AND INORGANIC METAL COMPOUNDS**

6 **V ANNEX V: COLLECTION OF INTERNET LINKS FOR THE USERS OF**
7 **THE GUIDANCE**

8

9

NOTE TO RAC and Forum on the New Annex

10 Members are asked to consider if the new Annex is required as an annex, or should
11 the relevant text be included in the main body of the guidance document?

12 This “new Annex” was initially proposed as a “Background paper” for providing
13 explanation of how the guidance document is written with the intention to publish it
14 as a stand alone document. However, it is not possible to publish such a document
15 separately (in the ECHA procedures), so it is included as a new Annex, but will it
16 have served its purpose once the full consultation is completed, and can be deleted?

17 The recommendation from the PEG consultation is to keep the Annex, as presented in
18 the draft revised guidance document.

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

23

24 1 Executive summary

25 Regulation (EC) No 1272/2008 on the classification, labelling and packaging of substances
26 and mixtures (CLP Regulation or CLP) contains rules including criteria for the classification
27 of substances and mixtures. While the classification of substances for human health hazards
28 is based on specific criteria for each hazard class, the classification of mixtures is mainly
29 based on the concentration and the classification of the substances contained in the mixture.
30 CLP includes generic concentration limits (GCLs) which are specific for a hazard class and
31 category and which indicate a threshold above which the presence of a substance in a mixture
32 leads to classification of the mixture. However, under certain conditions specific
33 concentration limits (SCLs) must or may be used. As the Regulation itself does not provide
34 any further guidance on when and how to set SCLs, guidance has been developed for certain

1 hazard classes (see the respective chapters on setting SCLs in Part 3 of the Guidance on the
2 Application of the CLP Criteria).

3 This Annex provides a background to the method for the determination of SCLs for
4 substances classified as reproductive toxicants as outlined in the guidance in Part 3.

5 The potency, expressed as the dose for the induction of reproductive effects was identified as
6 the best determinant for setting SCLs. The ED₁₀ for effects warranting classification was
7 selected as the most appropriate parameter for estimating the potency. The ED₁₀ is the dose
8 level which induces reproductive effects in 10% of the animals above the control group or a
9 change of 10% in the effect compared to the control group. Based on the ED₁₀ the substance
10 is placed in a potency group. However, modifying factors can alter the potency group,
11 especially when the potency estimate is close to the boundary between two groups.

12 The distribution of the potency of a large number of substances classified in Annex VI to
13 CLP as developmental toxicants and/or substances affecting sexual function and fertility was
14 determined by means of establishing two databases. In line with other methods for setting
15 SCLs for other hazard classes, it is proposed to define three potency groups. The boundaries
16 for the potency groups were determined in line with the provisions outlined in Article 10(1)
17 of CLP, the results of the database analyses and policy considerations. Most substances are
18 foreseen to fall into the medium potency group which is linked to the GCL. For substances in
19 the high and low potency group, the SCLs included in the table below are proposed.

20

	Category 1		Category 2	
	Dose	SCL	Dose	SCL
High potency group	ED ₁₀ below 4 mg/kg bw/day	0.03% (factors of 10 lower for extremely potent substances ^B)	ED ₁₀ below 4 mg/kg bw/day	0.3% (factors of 10 lower for extremely potent substances)
Medium potency group	ED ₁₀ ≥ 4 mg/kg bw/day, and ≤ 400 mg/kg bw/day	0.3% (GCL)	ED ₁₀ ≥ 4 mg/kg bw/day, and ≤ 400 mg/kg bw/day	3% (GCL)
Low potency group	ED ₁₀ above 400 mg/kg bw/day	3%	ED ₁₀ above 400 mg/kg bw/day	3-10% ^A

21 ^AThe limit of 10% may be considered in certain cases, such as for substances with a ED₁₀ value above 1000
22 mg/kg bw/day and a NOAEL below 1000 mg/kg bw/day

23 ^B For substances with an ED₁₀ more than 10 fold below 4 mg/kg bw/day, meaning an ED₁₀ below 0.4 mg/kg
24 bw/day, a 10-fold lower SCL should be used. For even more potent substance the SCL should be lowered with a
25 factor of 10 for every factor of 10 the ED₁₀ is below 4 mg/kg bw/day.

26

1 2 Introduction

2 2.1 General description of the classification system for reprotoxic substances and
3 mixtures

4 Regulation (EC) No 1272/2008 (CLP) contains rules for the classification of substances and
5 mixtures. In chapter 3.7 of Annex I to this Regulation, criteria are given for the classification
6 of substances as reprotoxicants in one of the following categories:

7 Category 1: Known or presumed human reproductive toxicant

8 Substances are classified in Category 1 for reproductive toxicity when they are
9 known to have produced an adverse effect on sexual function and fertility, or
10 on development in humans or when there is evidence from animal studies,
11 possibly supplemented with other information, to provide a strong
12 presumption that the substance has the capacity to interfere with reproduction
13 in humans. The classification of a substance is further distinguished on the
14 basis of whether the evidence for classification is primarily from human data
15 (Category 1A) or from animal data (Category 1B).

16

17 Category 1A: Known human reproductive toxicant

18 The classification of a substance in Category 1A is largely based on evidence
19 from humans.

20 Category 1B: Presumed human reproductive toxicant

21 The classification of a substance in Category 1B is largely based on data from
22 animal studies. Such data must provide clear evidence of an adverse effect on
23 sexual function and fertility or on development in the absence of other toxic
24 effects, or if occurring together with other toxic effects the adverse effect on
25 reproduction is considered not to be a secondary non-specific consequence of
26 other toxic effects. However, when there is mechanistic information that raises
27 doubt about the relevance of the effect for humans, classification in Category 2
28 may be more appropriate.

29 Category 2: Suspected human reproductive toxicant

30 Substances are classified in Category 2 for reproductive toxicity when there is
31 some evidence from humans or experimental animals, possibly supplemented
32 with other information, of an adverse effect on sexual function and fertility, or
33 on development, and where the evidence is not sufficiently convincing to
34 place the substance in Category 1. If deficiencies in the study make the quality
35 of evidence less convincing, Category 2 could be the more appropriate
36 classification. Such effects shall have been observed in the absence of other
37 toxic effects, or if occurring together with other toxic effects the adverse effect
38 on reproduction is considered not to be a secondary non-specific consequence
39 of the other toxic effects.

40 Effects on or via lactation are also part of the hazard class reproductive toxicity.
41 Classification for these effects is independent of the classification in the classes 1A, 1B or 2
42 as described above. Development of a method for the determination of SCLs for substances

1 with effects on or via lactation is outside the scope of this document. Therefore, these effects
2 and this classification are not further considered in this document.

3 The classification of mixtures containing substances classified for reproductive toxicity and
4 of substances containing impurities, additives or constituents classified for reproductive
5 toxicity is based on the concentration of the reproductive toxic component(s). Table 3.7.2 of
6 Annex I to CLP contains GCLs above which classification for reproductive toxicity is
7 required. The GCL is 0.3% for reprotoxicants Category 1A and 1B and 3.0% for Category 2.
8 However, a GCL for all substances may not be protective for high potency substances and
9 may be overprotective for substances with a low potency. Therefore, SCLs may be needed for
10 such substances.

11 According to CLP Article 10, SCLs shall be set where adequate and reliable scientific
12 information shows that the hazard of a substance is evident at a level below the GCL. This
13 results in SCLs below the GCLs. SCLs above the GCLs may be set in exceptional
14 circumstances where adequate, reliable and conclusive scientific information shows that a
15 hazard of a substance is not evident at a concentration above the GCL. Normally, substances
16 that fulfil the criteria for reproductive toxicity are subject to a harmonised classification and
17 labelling and included in Annex VI to CLP. In such cases, SCLs are set via the procedure for
18 harmonisation of classification and labelling of substances in line with CLP Article 37. When
19 there is no such harmonised entry in Annex VI to CLP, a manufacturer, importer or
20 downstream user must self-classify reproductive toxic substances and must set lower or may
21 set higher SCLs than the GCLs if justified according to CLP Article 10(1). He may also
22 provide a proposal for a harmonised classification (CLP Article 37(2)), including an SCL
23 where appropriate.

24 2.2 Description of the process for the development of a method to set SCLs for
25 reproductive toxic substances

26 There are no hazard specific criteria for the setting of SCLs in CLP . According to CLP
27 Article 10 (7), the European Chemicals Agency (ECHA) is required to provide further
28 guidance on the setting of SCLs. A working group was established to develop such guidance
29 for the hazard class reproductive toxicity, with the exception of the effects on or via lactation.

30 The work on the proposal for guidance on the determination of SCLs for reproductive
31 toxicants was initiated by an EU working group of the TC C&L (Technical Committee on
32 Classification and Labelling of Dangerous Substances), continued under the REACH
33 Implementation Project (RIP) 3.6 and subsequently under the auspices of ECHA.

34 To get an impression of the possible parameters for potency and their distribution, two
35 databases were compiled, containing several parameters for a large number of substances
36 classified for developmental toxicity and impaired fertility. Based on the compiled data
37 choices were made for the most appropriate parameter, the boundaries of the potency groups
38 and the associated SCLs.

39 In the course of the guidance development, three documents have been produced. The first
40 document is the actual guidance chapter included in the Guidance on the Application of the
41 CLP Criteria. The second document is this annexed background document, describing the
42 process and considerations and providing the rationale for the proposed guidance. The third
43 document is a publication of the databases of parameters for developmental toxicants and

1 substances with an effect on sexual function or fertility and the analyses of the databases
2 [(Muller et al., 2012)]

3 Chapter 2 of this document describes potency parameters and contains a number of
4 theoretical considerations on the determination of the most appropriate parameter and the
5 SCLs. A description of the databases and the analyses is also provided in this chapter.
6 Chapter 4 is dedicated to the non-modifying factors. Chapter 5 describes and justifies the
7 potency boundaries and corresponding SCLs.

8 2.3 Considering potency in setting specific concentration limits for various health hazards

9 The criteria for classification for reproductive toxicity are based on the strength of scientific
10 evidence that the substance can cause reproductive toxicity. In general, no specific
11 considerations are given to the potency of the substance to induce reproductive toxicity.

12 On the other hand, classification for several other health hazard classes is based on potency.
13 Substances with different potency are classified in different categories within the hazard
14 class. The classification of mixtures for that hazard class is then based on the concentration of
15 the substance in the mixture and the hazard category or the potency (for acute toxicity) of the
16 substance.

17 For acute toxicity, the potency is based on the acute toxicity estimate (ATE). The ATE is the
18 dose level which induces 50% mortality in a acute toxicity study (LD₅₀ or LC₅₀) or the
19 estimated LD₅₀ or LC₅₀ using fixed dose procedure or the acute toxic class method. This
20 value is used to classify a substance into one of several categories. For mixtures, the ATE
21 value is used to estimate the potency of a mixture by calculation. The estimated potency is
22 then used to classify the mixture into a hazard category.

23 For specific target organ toxicity (STOT) after single and repeated exposure, the potency is
24 defined as the dose at which the substance shows significant toxic effects in a study. Based
25 on the potency, a substance is either classified for STOT into one of two hazard categories or
26 not classified. The classification of a mixture containing a substance classified for STOT
27 depends on the percentage of the substance in the mixture and the hazard category of the
28 substance. A minimal percentage is included in the criteria. SCLs have to be determined for
29 substances with a very high potency.

30 Classification for carcinogenicity is, as for reproductive toxicity, based on the strength of
31 scientific evidence and again no specific consideration is given to the potency. The
32 classification of mixtures containing a carcinogenic substance is based on the GCL unless a
33 SCL has been allocated for that substance as provided in Annex VI to CLP. SCLs for
34 carcinogenic substances are determined based on the potency for carcinogenic effects based
35 on the T25. The T25 is defined as the daily dose (in mg/kg bw) inducing a tumour incidence
36 of 25% upon lifetime exposure after correction for the spontaneous incidence. This is mainly
37 based on animal studies. Substances are divided into 3 groups based on the T25. High
38 potency substances have a $T25 \leq 1\text{mg/kg bw/day}$, medium potency substances have a T25
39 between 1 -100 mg/kg bw/day, and $T25 > 100\text{ mg/kg bw/day}$ for low potency substances.
40 Besides the T25, other elements were included that modify the potency evaluation
41 (Commission Working Group, date unknown). This method has been included in the
42 Guidance on the Application of the CLP Criteria.

1 The use of potency for the classification into different categories for several other hazard
2 classes and the use of the potency to set SCLs for carcinogenic substances, justifies the use of
3 potency as a first approach also for setting SCLs for reproductive toxic substances. As no
4 definition of potency for reproductive toxicants was available, the following definition is
5 used as a working definition:

6 *Reproductive toxicity potency is defined as the dose which induces reproductive toxic effects*
7 *with a specific type, incidence and magnitude, considering the study design in terms of*
8 *species and strain, exposure route, exposure duration, exposure window in the life cycle, and*
9 *possible concomitant parental toxicity.*

10 According to this definition ‘Potency’ is primarily based on applied *dose* and can be modified
11 by consideration of ‘severity’. Within this definition the dose is defined as the amount of
12 substance to which the animals or humans that showed the effect (meaning type, incidence
13 and magnitude) were exposed on an mg/kg bw/day basis. The incidence is the proportion of
14 animals or humans that showed the effect. The type of effect describes which property of an
15 organ or system of the animal or human is affected and the magnitude describes the level of
16 change compared to the control. Together, the incidence, type and magnitude describe the
17 ‘severity’ of the effect, meaning how adverse the effect or combination of effects is. With
18 specific incidence, type and magnitude (together specific severity) a comparable level of
19 severity is indicated for different effects.

20 The working definition above allows potency to be defined at different levels of specific
21 severity, for example at the ED₁₀ and the LOAEL (Lowest Observed Adverse Effect Level),
22 and for different type of effects. Therefore, several possible estimates for potency were
23 investigated.

24 2.4 Parameters for potency for reproductive toxicity

25 A consistent database to derive potency estimates for reproductive toxicity was lacking.
26 Therefore, data on substances classified for effects on reproduction were collected and
27 analysed. This was done separately for substances with an effect on development and
28 substances with an effect on sexual function and fertility because the types of effects clearly
29 differ between these two main types of reproductive effects. Therefore, this chapter falls into
30 two parts, namely one for parameters for potency of substances with developmental effects
31 (chapter 2.3.1) and one for parameters for potency of substances with effects on sexual
32 function and fertility (chapter 2.3.2). As potency is primarily based on the dose in mg/kg
33 bw/day at which different adverse effects are observed, a number of parameters/dose
34 descriptors (e.g. NOAEL⁴, LOAEL⁵, ED₁₀ etc.) exist for each type of adverse effect. The
35 collected data included the NOAEL, LOAEL and ED₁₀ (effective dose with a 10% incidence
36 or effect level above the background) as parameters for the effect on reproduction of each
37 substance. They were further divided into effects fulfilling the criteria for classification
38 (named “LOAEL (classification)” for example) and any effects on reproduction (named
39 “NOAEL (overall)” for example). Together, this sub-division results in 6 different potency
40 parameters, see Table 1. Other data, e.g. a mutagenicity classification of a substance, the type
41 of effect at the LOAEL and species used in the test, were also collected. These parameters
42 were analysed and the results tabulated and plotted graphically. The results are published by

⁴ NOAEL means No Observed Adverse Effect Level

⁵ LOAEL means Lowest Observed Adverse Effect Level

1 Muller et al., 2012. As the data for these two main types of reproductive toxicity were
2 analysed separately, the results are provided separately.

3 2.4.1 Potency parameters for developmental toxicants (Muller et al, 2012)

4 Data for one or more of the parameters for development were available for 99 substances
5 classified for developmental toxicity when the work on this guidance development started.
6 For almost all substances a LOAEL is available but a NOAEL and ED₁₀ were sometimes
7 missing. The absence of a NOAEL is mostly caused by the absence of a dose level without an
8 effect in the study or database of a substance. The absence of an ED₁₀ value is mainly caused
9 by the absence of a NOAEL and in most of those cases an ED₁₀ could only be derived by a
10 benchmark dose (BMD) approach to avoid interpolation between the LOAEL and the vehicle
11 control. Another cause for the absence of ED₁₀ values is the limited reporting of effect levels
12 in the consulted study summaries or study reports.

13 The difference in the average value between the highest and lowest of the 6 parameters for
14 potency is a factor of 4 or less. This is very small compared to the difference in potency
15 between substances for each parameter of up to 1,000,000 fold (Table 1). The potency
16 difference is more pronounced for a NOAEL or LOAEL compared to an ED₁₀ mainly
17 because for most potent substances only a NOAEL and/or a LOAEL was available but not an
18 ED₁₀. The available data indicate that there is a close relation between the NOAEL, LOAEL
19 and ED₁₀ for most substances. The average LOAEL is between a factor of 2 and 3 above the
20 average NOAEL. The fact that it is not closer to the factor of 3 to 4 that is normally used
21 between dose levels is probably due to the absence of a NOAEL for a number of substances.
22 The average ED₁₀ (classification), is slightly higher than the average LOAEL (classification).
23 The difference is more pronounced for the “overall” values, namely approximately a factor of
24 2. These findings are caused by both the dose spacing in the studies and the limited
25 discriminative power of the NOAEL approach.

26 Table 1. Average values (assuming log/normal distribution) (in mg/kg bw/day) and potency
27 differences for parameters for all developmental toxicants of the database (Muller et al, 2012)

Parameter	N	Average	Standard deviation	Lowest value	Highest value	Potency difference
NOAEL (overall)	68	12	10	0.002	684	342000
LOAEL (overall)	98	25	13	0.002	2281	1140500
ED ₁₀ (overall)	59	43	6	0.3	785	2617
NOAEL (classification)	76	18	11	0.002	1100	550000
LOAEL (classification)	97	40	13	0.002	2281	1140500
ED ₁₀ (classification)	63	48	6	0.3	933	3110

28
29 A part of the differences in average values and potency between the different parameters in
30 Table 1 is probably caused by the difference in the number of substances for which a
31 particular variable is present. When only substances are used for which all 6 parameters were
32 present, this reduces the database to 44 substances (Table 2). A part of the difference between
33 the parameters in potency difference can be explained by the unusual dose levels (NOAEL

1 0.026 mg/kg bw/day and LOAEL 0.26 mg/kg bw/day) used in the study for the substance that
2 had the lowest values for all parameters (cadmium oxide).

3 Table 2. Average values (assuming log/normal distribution) (in mg/kg bw/day) and potency
4 differences for parameters for developmental toxicants (N=44) with all 6 parameters (Muller
5 et al, 2012)

Parameter	Average	Standard deviation	Lowest value	Highest value	Potency difference
NOAEL (overall)	19	7	0.026	684	26308
LOAEL (overall)	58	7	0.260	2281	8773
ED ₁₀ (overall)	44	5	0.300	570	1900
NOAEL (classification)	25	7	0.026	684	26308
LOAEL (classification)	71	6	0.260	2281	8773
ED ₁₀ (classification)	49	6	0.300	933	3110

6
7 Comparing Tables 1 and 2 indicates no major changes in average, standard deviation and
8 highest value for each parameter. However, the lowest value changes for several parameters.
9 The resulting potency difference becomes much more comparable between the parameters.
10 This indicates that the difference between the parameters in potency difference in Table 1 is
11 mainly due to the absence of an ED₁₀ for some very potent substances.

12 2.4.2 Potency parameters for substances with an adverse effect on sexual function and 13 fertility (Muller et al, 2012)

14 Data for one or more of the potency parameters were available for 93 substances classified
15 for adverse effects on sexual function and fertility (hereafter called fertility toxicants) when
16 the work with the guidance development started. For all substances, an LOAEL was available
17 but a NOAEL and an ED₁₀ were sometimes missing. The absence of a NOAEL is mostly
18 caused by the absence of a dose level without an effect in the study or database of a
19 substance. The absence of an ED₁₀ value is mainly caused by the absence of a NOAEL and in
20 most of those cases an ED₁₀ could only be derived by a Benchmark Dose (BMD) approach to
21 avoid interpolation between the LOAEL and the vehicle control. Another cause for the
22 absence of an ED₁₀ values is the limited reporting of effect levels in the consulted study
23 summaries or study reports.

24 The difference in the average values between the highest and lowest of the 6 parameters for
25 potency is less than a factor of 4. This is small compared to the difference in potency between
26 substances for each parameter of up to 30,000 (Table 3). The difference in potency within the
27 parameters is more pronounced for the NOAEL values than for the values of LOAEL and
28 ED₁₀, which is mainly due to one substance with a NOAEL of 0.032 mg/kg bw/day but an
29 LOAEL of 10 mg/kg bw/day. The available data indicate that there is a close relation
30 between the NOAEL, LOAEL and ED₁₀ for most substances. The average LOAEL is
31 between a factor 2 and 3 above the average NOAEL. The fact that it is not closer to the factor
32 of 3 to 4 that is normally used between dose levels is probably due to the absence of an
33 NOAEL for a number of substances. The average ED₁₀ is between the average NOAEL and
34 LOAEL.

1 Table 3. Average values (assuming log/normal distribution) (in mg/kg bw/day) and potency
2 differences for parameters for all fertility toxicants of the database

Parameter	N	Average	Standard deviation	Lowest value	Highest value	Potency difference
NOAEL (overall)	68	20	7	0.032	635	19844
LOAEL (overall)	93	54	7	0.25	2060	8240
ED ₁₀ (overall)	37	31	5	0.6	1065	1775
NOAEL (classification)	70	24	7	0.032	940	29375
LOAEL (classification)	93	62	7	0.33	2060	6242
ED ₁₀ (classification)	37	33	6	0.6	1065	1775

3
4 A part of the differences in the average values and in potency between the different
5 parameters in Table 3 is probably caused by the difference in the number of substances for
6 which a particular parameter is present. When only substances are used for which all 6
7 parameters were present, this reduces the database to 34 substances (Table 4).

8 Table 4. Average values (assuming log/normal distribution) (in mg/kg bw/day) and potency
9 differences for parameters for fertility toxicants (N=34) with all 6 parameters

Parameter	Average	Standard deviation	Lowest value	Highest value	Potency difference
NOAEL (overall)	19	6	0.3	250	833
LOAEL (overall)	72	6	0.7	1000	1429
ED ₁₀ (overall)	35	5	1.3	1065	819
NOAEL(classification)	24	6	0.3	940	3133
LOAEL(classification)	89	6	0.7	1580	2257
ED ₁₀ (classification)	39	5	1.3	1065	819

10
11 Comparing Tables 3 and 4 indicates no major changes in average, standard deviation and
12 highest value for each parameter. However, the lowest value changes for some parameters.
13 The resulting potency difference becomes much more comparable between the parameters.
14 This indicates that part of the differences between the parameters in potency difference in
15 Table 3 is due to the absence of an ED₁₀ for some very potent substances.

16 2.4.3 Conclusions on the most appropriate parameter for potency

17 As LOAELs are available for almost all substances, this could be considered the most useful
18 informed parameter on which to base potency. However, in the absence of a NOAEL, a
19 LOAEL is not a suitable parameter for potency because there is no indication to what extent
20 the real LOAEL could be lower than the LOAEL observed. The lower number of substances

1 for which an ED₁₀ is available is probably due to the limitations of the available study
2 summaries for several substances. Use of the ED₁₀ requires access to a detailed summary of
3 the study or the study report itself which was not available for several substances in the
4 database.

5 However, this guidance will be applied by both industry and Member State Competent
6 Authorities when preparing proposals for harmonised classification and labelling, and by
7 industry in case of self-classification of a reproductive toxic substance for which there is no
8 entry in Annex VI to CLP.

9 Companies have access to their own studies. It is expected that by the completion of the
10 REACH registration deadlines, more detailed information including ED₁₀ will be available
11 for more substances than in this database used to develop this guidance.

12 Member States will have access to the study summaries in the registrations. The full studies
13 could be requested by ECHA or by a Member State Competent Authority, according to CLP
14 Article 49(3).

15 It should be noted that in the absence of a NOAEL, an ED₁₀ cannot be determined by
16 interpolation, in case the size of the effect at the LOAEL is more than 10%. However, an
17 ED₁₀ can be estimated using bench mark dose (BMD) software when sufficient data are
18 available. A NOAEL and LOAEL cannot be estimated using the BMD approach. In addition,
19 a fixed level of effect of e.g. 10% (ED₁₀) is considered to be more representative for the
20 potency and facilitates comparisons of relative potency between substances to a greater
21 extent, than a LOAEL which is a chosen dose level.

22 For most other hazard classes, the SCLs are based on effect levels. For carcinogenicity the
23 T25 is used, and for skin sensitisation the EC₃ value or the dose level with a certain level of
24 responders is used. Therefore, the LOAEL or ED₁₀ is considered a more appropriate
25 parameter for determination of an SCL than the NOAEL.

26 For substances where there is a difference in the LOAEL overall (lowest dose with any effect
27 on reproduction) versus the LOAEL classification (lowest dose with an effect on
28 reproduction fulfilling the classification criteria), this is in most cases due to non-significant
29 increases in lethalties or malformations or decreases in foetal body weight at the LOAEL
30 overall versus significant increases in lethalties or malformations at the LOAEL
31 classification. The difference between significant and non-significant effects will disappear if
32 the ED₁₀ is used as parameter for potency.

33 The difference in parameters between “overall” and “classification” was sometimes due to
34 limited effects that normally do not warrant classification such as a small increase in
35 variations at the LOAEL and to more severe effects warranting classification at a higher dose
36 level. To have a more consistent parameter for potency, it was preferred to use the parameters
37 for effects warranting classification.

38 Overall, the use of the ED₁₀ for effects warranting classification is proposed as the most
39 appropriate estimate for the potency. The advantage of this parameter is that it is a dose level
40 with a specified level of effects of at least a certain severity. This is in line with most
41 classification criteria and with other methods for the determination of SCLs.

1 Furthermore, not all aspects included in the working definition of reproductive potency are
2 fully taken into account in the ED₁₀. Therefore, certain additional parameters should be
3 considered which can change the potency group as determined by using the ED₁₀, resulting in
4 the setting of lower or higher concentration limits. See chapter 4 for such modifying factors.

5 3 Modifying factors

6 Several possible elements of reproductive toxicity were considered as elements which should
7 also be taken into account when determining the potency group for reproductive toxicity of a
8 substance (modifying factors). Modifying factors may change the potency group for a
9 substance. While some modifying factors should always be taken into account, other
10 modifying factors could be more relevant when the potency is close to the boundary between
11 two groups (see Table 8 above). It should be noted that several of the elements may be
12 interrelated.

13 Some factors may have already been taken into account in deciding on the classification as a
14 reproductive toxicant. Where such considerations have been made, care should be taken not
15 to use that information again when determining the potency. For example, when the effects
16 determining the ED₁₀ were observed at dose levels also causing maternal toxicity, this should
17 already have been taken into consideration during the classification and should not be used
18 again to set a higher SCL. Factors considered not to be used as modifying factors are
19 included in section 4.7 of this Annex. The following factors are used as modifying factors:

- 20 • Type of effect / severity
- 21 • Data availability
- 22 • Dose-response relationship
- 23 • Mode or mechanism of action
- 24 • Toxicokinetics
- 25 • Bio-accumulation of substances

26
27 The justification of the use of these modifying factors is provided in the guidance (see section
28 3.7.2.5.5)

29 30 4 Non-modifying factors

31 A wide range of parameters were considered as possible modifying factors for the
32 determination of reproductive potency. Parameters selected as modifying factors are included
33 above. Parameters or factors considered but not included as modifying factors are listed
34 below:

35 4.1 Species and strains

36 The species used to determine the ED₁₀ could be considered as a modifying factor if it is
37 shown that a certain species is generally more sensitive to reproductive toxicants, meaning
38 showing effects at a lower exposure level, and this can be considered relevant to humans.
39 However, comparison of the different parameters between the two most used species for
40 developmental effects, rats and rabbits, did not indicate a difference in average NOAEL,
41 LOAEL or ED₁₀ in this analysis. Furthermore, almost all studies that were determinative for
42 the classification for fertility were studies in rats. Therefore, species is not regarded as a
43 modifying factor. The most sensitive species for each substance has to be used to determine
44 the potency parameter unless there is clear evidence that the observed effects are not relevant

1 to humans or when there is good evidence for a difference in sensitivity between humans and
2 the test species. This also applies to different strains.

3 4. 2 Systemic or maternal toxicity

4 Adverse effects on fertility and sexual function may be caused as a secondary effect of
5 systemic toxicity to other organs. Developmental effects may be caused as a secondary effect
6 of maternal toxicity. However, this should have already been taken into account for
7 classifying a substance in a specific category. Therefore, this should not also be used for
8 modifying the concentration limit.

9 4. 3 Mutagenicity

10 Analyses of the databases [(Muller et al., 2012)] indicate that substances classified both for
11 reproductive toxicity and mutagenicity have a higher potency (lower ED₁₀) than substances
12 classified for reproductive toxicity only. However, as this higher potency is already included
13 in the lower ED₁₀, there is no need to use mutagenicity as a modifying factor.

14 4.4 Volatility

15 Volatility is a physical property related to exposure rather than to the intrinsic hazardous
16 potency of a substance. However, the exposure level to a substance in a mixture is not only
17 influenced by the concentration but also by the volatility of the substance. The higher the
18 volatility of a substance the higher the inhalation exposure may be when handling such a
19 substance in a mixture. Inhalation exposure to vapours are not covered by the experimental
20 oral testing limit of 1000 mg/kg bw/day as the exposure at workplaces can be more than one
21 order of magnitude above the extrapolated exposure level covered by the limit dose
22 (Schneider et al., 2007). This is probably the reason why no limit dose for classification is
23 included in the classification criteria (see appendix I, 3.7.2.5.4). Therefore, volatility could be
24 considered as a modifying factor.

25 However this argument is not specific for reproductive toxicity and should then apply to all
26 relevant hazard classes. In methods for setting SCLs for other hazard classes such as
27 carcinogenicity, the volatility is not used as a modifying factor, although it is suggested to be
28 a factor to take into consideration when setting SCLs for narcotic effects (STOT-SE 3).
29 Further, volatility is not specifically mentioned in the criteria for classification for any other
30 hazard class other than STOT-SE and -RE (3.8.2.1.10.4 and 3.9.2.10.4) for which the
31 guidance recommends a specific precautionary statement on the label for highly volatile
32 substances.

33 However for some hazard classes, volatility is taken into account in the classification of
34 substances and mixtures by using different numeric criteria (acute toxicity, table 3.1.1) or
35 guidance values (STOT-SE table 3.8.2 and STOT-RE, table 3.9.2 and 3.9.3) for vapours than
36 for dusts and mists. For STOT-SE and STOT-RE, the method for setting SCLs is directly
37 depending on these guidance values.

38 It was decided not to include volatility as a modifying factor because it is a physical property
39 that depends also on other factors (e.g. temperature and composition of the mixture) and is
40 therefore more related to exposure rather than to the intrinsic hazardous potency of the
41 substance.

42

43 5 Potency groups and specific concentration limits

44 5.1 Justification of the proposed potency boundaries and specific concentration limits

1 In the following some general considerations on potency groups are first provided, followed
2 by justifications for the approach taken and for the suggested boundaries of the potency
3 groups and the corresponding concentration limits.

4 5.1.1 General considerations on potency groups

5 5.1.1.1 Legal requirements

6 According to the second subparagraph of CLP Article 10(1)

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

11 According to the third subparagraph of CLP Article 10(1)

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

17 5.1.1.2 Scientific results of the database analysis

18 The databases with ED₁₀ values for substances (Category 1 and 2) with an effect on
19 development and with an effect on sexual function and fertility were compared to determine
20 whether there is a difference in potency between Category 1 and Category 2 substances
21 [(Muller et al, 2012)]. The results should be carefully interpreted because of the limitations of
22 the database: the database is based on a limited number of substances and the available data
23 per substance is reduced to a single number (ED₁₀) and some modifying factors. Reducing the
24 data in the database would have included removal of differences in effects and doubts
25 between Category 1 and Category 2. In any case, the comparisons indicate that the average
26 potency of substances with an effect on development and with an effect on sexual function
27 and fertility are comparable and that also the average potencies of Category 1 and 2
28 substances are comparable and certainly do not differ by a factor of 10.

29 5.1.1.3 Policy related considerations and proposed method

30 Data derived from an insensitive test method could in some cases not be regarded as
31 adequate, reliable and conclusive evidence, as mentioned in Article 10 (1) (3rd para). For
32 example, a screening assay which only uses a limited number of animals and studied
33 endpoints, cannot be used to set higher SCLs (but can be used to set lower SCLs). Also a
34 study resulting in an LOAEL without an NOAEL cannot be used to set higher SCLs.

35 Determination of the boundaries of the potency groups (see Table 8) and the SCL or GCL for
36 each group is a policy related issue. CLP Article 10, the criteria in Annex I to CLP and the
37 available data do not give a clear direction. Therefore, a simple system was developed.
38 Furthermore, the approach taken is similar to the one developed for other hazard classes such
39 as skin sensitization and carcinogenicity, which should be an appropriate justification for the
40 current method.

41 Determination of the potency for reproductive toxicity will in most cases be based on limited
42 data from one or a few studies. It was recognised that an exact SCL for each substance that

1 also differs for each substance would indicate a precision that is not realistic or scientifically
2 justified. Also, Janer (2007) has shown that the variation in the NOAELs of 2-generation
3 studies for one substance is considerable. Therefore, it is proposed to divide the substances
4 into large potency groups with associated SCLs as it is done for other hazard classes. Three
5 potency groups are proposed. As shown in Table 10 below, substances with the lowest
6 potency (highest ED₁₀) fall in a group with an SCL above the GCL. Most substances should
7 fall in the group with the GCL. Only substances with a very high potency (low ED₁₀) should
8 fall in the group with a SCL below the GCL. It is proposed to include approximately 70 –
9 80% in the GCL potency group and 5 to 15% in the low and high potency groups. Further, as
10 the average potency of developmental toxicants and substances affecting sexual function and
11 fertility are comparable, it is proposed to use the same boundaries for both types of effect.
12 Also, the database shows there is no difference in potency between substances in Category 1
13 and Category 2. Therefore it is proposed to use the same boundaries for Category 1 and 2
14 substances.

15 5.1.1.4. Other methods considered

16 Several other options for a method for determining SCLs were discussed including a method
17 that was used by the TC C&L in a limited number of cases in the past. This method is based
18 on the limit dose of 1000 mg/kg bw/day, as described in the test guideline OECD 414 and
19 416.

20 The concentration limit expressed as a % in mixtures is derived by dividing the NOAEL by
21 the limit dose followed by multiplication by 100 (see ECBI/47/02 Add.7). This method
22 would result in an individual SCL for each substance. This would indicate a precision that
23 cannot be expected from standard reproduction studies. Also this would result in an SCL for
24 most substances and in a GCL for only some substances. Therefore, this method was not
25 considered. Potency groups are used in the proposed method because this does not give the
26 impression of a high precision and allow the placing of many substances in the medium
27 potency group with the connected GCL.

28 5.1.2 Justification of the boundaries between the three potency groups.

29 The estimated percentages of already classified substances in each group for both Category 1
30 and 2 substances with an effect on development or an adverse effect on fertility and sexual
31 function are provided in the tables below. They are based on the distribution of potencies of
32 known developmental toxicants and of known fertility toxicants [(Muller et al., 2012)].
33 Several possible values of the boundaries between the three groups are tested. The
34 estimations are based on counting the number of substances above or below a number of
35 possible boundaries and applying some of the modifying factors such as the presence of a
36 NOAEL and considering also the saturated vapour concentration for substances in the low
37 potency group. However, the saturated vapour concentration, reflecting volatility, is not
38 proposed as a modifying factor in the guidance.

39 Taking into account all modifying factors for all substances would imply a full assessment of
40 the potency for all substances. This was not possible within the available resources. As most
41 modifying factors result in a shift from the low potency group into the medium potency group
42 and from the medium potency group into the high potency group, it is likely that the
43 percentages in the low potency group may decrease and the percentages in the high potency
44 group may increase. (Thus, the effect of volatility on the frequencies in Table 9 should be
45 marginal.)

1 Based on the ED₁₀ distribution a rough estimate was made by the Working group of the
 2 optimal boundaries using a range of a factor of 100 for the medium potency group. Then the
 3 number of substances falling into several combinations of boundaries was estimated.

4 Table 9. Percentages of substances in the three potency groups using the ED₁₀ and some of
 5 the modifying factors for different boundaries of the potency groups and considering the
 6 saturated vapour concentration of low potency substances.

			Boundaries of the high and low potency groups					
			<2 mg/kg	<3 mg/kg	<4 mg/kg	<5 mg/kg	<6 mg/kg	<7 mg/kg
Type of effect	Classification	Potency group	>200 mg/kg	>300 mg/kg	>400 mg/kg	>500 mg/kg	>600 mg/kg	>700 mg/kg
Development	Cat 1A/1B H360D	High potency	12,1	13,8	17,2	20,7	20,7	20,7
		Medium potency	75,9	77,6	79,3	77,6	79,3	79,3
		Low potency	12,1	8,6	3,4	1,7	0,0	0,0
		% with SCL	24,1	22,4	20,7	22,4	20,7	20,7
	Cat 2 H361d	High potency	10,3	13,8	13,8	17,2	17,2	20,7
		Medium potency	72,4	72,4	79,3	75,9	82,8	79,3
		Low potency	17,2	13,8	6,9	6,9	0,0	0,0
		% with SCL	27,6	27,6	20,7	24,1	17,2	20,7
Fertility	Cat 1A/1B H360F	High potency	3,4	3,4	3,4	6,9	10,3	13,8
		Medium potency	89,7	93,1	96,6	93,1	89,7	86,2
		Low potency	6,9	3,4	0,0	0,0	0,0	0,0
		% with SCL	10,3	6,9	3,4	6,9	10,3	13,8
	Cat 2 H361f	High potency	6,3	9,4	10,9	15,6	15,6	17,2
		Medium potency	71,9	76,6	81,3	78,1	79,7	79,7
		Low potency	21,9	14,1	7,8	6,3	4,7	3,1
		% with SCL	28,1	23,4	18,8	21,9	20,3	20,3
All		avg high potency	8.0	10.1	11.3	15.1	16.0	18.1
		avg high potency	77.5	79.9	84.1	81.2	82.9	81.1
		avg high potency	14.5	10.0	4.5	3.7	1.2	0.8
		avg % with SCL	22,5	20,1	15,9	18,8	17,1	18,9

7
 8 As shown in Table 9 boundaries of 4 to 400 mg/kg bw/day would result in the maximum
 9 number of substances being included in the medium potency range for most types of effects
 10 and classifications and for both type of effects and classifications combined. For
 11 developmental effects Category 1 and 2 the percentage of substances in the medium potency
 12 group is within the target of ca. 70-80%. For effects on sexual function and fertility Category
 13 2 this is almost the case. Only for Category 1 is this not the case. The percentage of
 14 substances in the medium potency group could be reduced by reducing the factor of 100
 15 between the boundaries. However, because of the large difference in potency of the
 16 substances classified for reproductive toxicity of up to a million, this was not considered
 17 necessary. The percentage of substances in the high potency group is higher than the

1 percentage in the lower potency group for the boundaries of 4 to 400 mg/kg bw/day.
 2 However, the percentage of substances in the high potency group was above 15% for
 3 substances classified for an effect on development in Category 1.

4 Following the PEG consultation, it was agreed that volatility was not considered a modifying
 5 factor and thus, the ED₁₀ distribution changes as shown in table 10. Borders of 4 to 400
 6 mg/kg bw/day would result in the maximum number of substances being included in the
 7 medium potency range for most type of effects and classifications and for both type of effects
 8 and classifications combined. However, the same value also applies to some of the other
 9 borders. For developmental effects Category 1 and 2 the percentage of substances in the
 10 medium potency group is within the target of ca. 70-80%. For effects on sexual function and
 11 fertility Category 2 this is not the case. The percentage of substances in the medium potency
 12 group could be reduced by reducing the factor of 100 between the borders. However, because
 13 of the large difference in potency of the substances classified for reproductive toxicity of up
 14 to a million, this was not considered necessary. The percentage of substances in the high
 15 potency group is approximately the same as the percentage in the lower potency group for the
 16 borders of 4 to 400 mg/kg bw/day.

17 Table 10. Percentages of substances in the three potency groups using the ED₁₀ and some of
 18 the modifying factors but not volatility for different borders of the potency groups and
 19 considering the saturated vapour concentration of low potency substances.

			Borders of the high and low potency groups					
			≤2 mg/kg	≤3 mg/kg	≤4 mg/kg	≤5 mg/kg	≤6 mg/kg	≤7 mg/kg
Type of effect	Classification	Potency group	≥200 mg/kg	≥300 mg/kg	≥400 mg/kg	≥500 mg/kg	≥600 mg/kg	≥700 mg/kg
Development	Cat 1A/1B H360D	High potency	12.1	13.8	17.2	20.7	20.7	20.7
		Medium potency	67.2	74.1	77.6	75.9	79.3	79.3
		Low potency	20.7	12.1	5.2	3.4	0	0
		% with SCL	32.8	25.9	22.4	24.1	20.7	20.7
	Cat 2 H361d	High potency	7.3	9.8	9.8	12.2	12.2	14.6
		Medium potency	68.2	65.8	70.7	70.7	75.6	78.1
		Low potency	24.4	24.4	19.5	17.1	12.2	7.3
		% with SCL	31.7	34.2	29.3	29.3	24.4	21.9
Fertility	Cat 1A/1B H360F	High potency	3.4	3.4	3.4	6.9	10.3	13.8
		Medium potency	86.3	89.7	93.2	89.7	86.3	86.2
		Low potency	10.3	6.9	3.4	3.4	3.4	0
		% with SCL	13.7	10.3	6.8	10.3	13.7	13.8
	Cat 2 H361f	High potency	6.3	9.4	10.9	15.6	15.6	17.2
		Medium potency	68.7	73.4	78.2	75.0	76.6	76.5
		Low potency	25.0	17.2	10.9	9.4	7.8	6.3
		% with SCL	31.3	26.6	21.8	25.0	23.4	23.5

All	avg high potency	7.3	9.1	10.3	13.9	14.7	16.6
	avg medium potency	72.6	75.7	79.9	77.8	79.4	80.0
	avg low potency	20.1	15.2	9.8	8.3	5.9	3.4
	avg % with SCL	27.4	24.3	20.1	22.2	20.6	20.0

1

2 On average, combining both effect types and both classification categories, the goal of 70-
3 80% of the substances in the medium potency group and 5 -15% of the substances in the low
4 and high potency group was fulfilled with boundaries of 4 and 400 mg/kg bw/day. However,
5 other combinations of boundaries such as 3 and 300 and 5 to 500 mg/kg bw/day also fulfill
6 these requirements. Using these boundaries would result in a change of potency group for 10
7 to 14 substances (5 – 7%). Further it could be considered to lower the factor of 100 between
8 the borders to increase the number of substances. For example, using boundaries of 5 to 300
9 mg/kg bw/day would result in 13.9% high potency substances, 15.2% low potency substances
10 and 71% substances in the medium potency group. Also, the percentages provided in the
11 tables 9 and 10 are calculated not using every modifying factor. Therefore, it can be stated
12 that the choice of the boundaries is arbitrary. However, based on the available information,
13 the boundaries of 4 to 400 mg/kg bw/day seem to be reasonable.

14 5.1.3 Concentration limits for Category 1 and Category 2 substances

15 The generic concentration limit (GCL) from the respective categories will be used for
16 medium potency substances (group 2). As mentioned earlier the GCL is 0.3% for
17 reproductive toxicants Category 1A and 1B and 3.0% for Category 2.

18 Category 1A and 1B

19 Different concentration limits have to be used for the different potency groups. Substances
20 classified in Category 1 in the low potency group (group 3) can have a SCL above the GCL
21 of 0.3%. We propose to use an SCL of 3% which is tenfold of the GCL. A factor of 10 is
22 used often in CLP as difference in GCL between hazard categories. This factor is also used in
23 the guidance for setting SCLs for carcinogens. For substances in group 1 (high potency), it is
24 proposed to use a SCL of 0.03%. For extremely potent reproductive toxicants with an ED₁₀
25 (classification) of more than 10 fold below the boundary limit of 4 mg/kg bw/day it is
26 proposed to use even lower SCLs. For every factor of 10 below the upper limit the SCL is
27 reduced with a factor of 10.

28 Category 2

29 Substances classified in Category 2 in the low potency group (group 3) can have a SCL above
30 the GCL of 3%. We propose to use an SCL of 3-10% which is one to 3-fold of the GCL. An
31 SCL above 10% was considered too high. The upper SCL of 10% can only be used in
32 exceptional cases (NOAEL below 1000 mg/kg bw/day but ED₁₀ above 1000 mg/kg bw/day).
33 This would account for none of the substances in the database. For high potency substances
34 (group 1), it is proposed to use an SCL of 0.3%. For extremely potent reproductive toxicants
35 with an ED₁₀ (classification) of more than 10-fold below the boundary limit of 4 mg/kg
36 bw/day it is proposed to use even lower SCLs. For every factor of 10 below the upper limit,
37 the SCL is reduced by a factor of 10.

38 The resulting SCLs for each potency group are presented in Table 11.

1 Table 11. SCLs for substances in each potency group and classification category

	Category 1		Category 2	
	Dose	SCL	Dose	SCL
Group 1 high potency	ED ₁₀ (classification) below 4 mg/kg bw/day	0.03% (factors of 10 lower for extremely potent substances ^B)	ED ₁₀ (classification) below 4 mg/kg bw/day	0.3% (factors of 10 lower for extremely potent substances)
Group 2 medium potency	ED ₁₀ ≥ 4 mg/kg bw/day, and ≤ 400 mg/kg bw/day	0.3% (GCL)	ED ₁₀ ≥ 4 mg/kg bw/day, and ≤ 400 mg/kg bw/day	3% (GCL)
Group 3 low potency	ED ₁₀ (classification) above 400 mg/kg bw/day	3%	ED ₁₀ (classification) above 400 mg/kg bw/day	3-10% ^A

2 ^A The limit of 10% may be considered in certain cases, such as for substances with an ED₁₀
3 value above 1000 mg/kg bw/day and a NOAEL below 1000 mg/kg bw/day.

4 ^B For substances with an ED₁₀ more than 10 fold below 4 mg/kg bw/day, meaning an ED₁₀ below 0.4 mg/kg
5 bw/day, a 10-fold lower SCL should be used. For even more potent substance the SCL should be lowered with a
6 factor of 10 for every factor of 10 the ED₁₀ is below 4 mg/kg bw/day.

7 Assigning two SCLs to a substance

8 A reproductive toxic substance is classified in one category for both effects on development
9 and on sexual function and fertility. Within each category effects on development and on
10 sexual function & fertility are considered separately. The potency and resulting concentration
11 limits have to be determined separately for the two main types of reproductive toxic effects.
12 In case the potency and resulting specific concentration limits are different for sexual
13 function/fertility and development for a substance, the substance needs to be assigned one
14 SCL for developmental toxicity and another SCL for effects on sexual function and fertility.
15 These concentration limits will in all cases trigger different specifications of the hazard
16 statements for the two main types of effects, to be applied to mixtures containing the
17 substance (see also 3.7.4.1, Annex I, CLP).

18 5.2 Assigning SCLs

19 The SCL or GCL for each substance can be determined using the final potency group of the
20 substance using Table 9.

21

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