Committee of Experts on the Transport of Dangerous Goods and on the Globally Harmonized System of Classification and Labelling of Chemicals

Sub-Committee of Experts on the Globally Harmonized System of Classification and Labelling of Chemicals **21 October 2011**

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Updating of the Globally Harmonized System of Classification and Labelling of Chemicals (GHS): Health hazards

Editorial revision of chapters 3.2 and 3.3: Status report

Transmitted by the expert from Germany on behalf of the informal correspondence group on the editorial revision of Chapters 3.2 and 3.3

1. The mandate of the informal correspondence group is an editorial revision of chapters 3.2 and 3.3. The purpose of this paper is to inform the sub-committee on the current state of work.

2. Annex I and II to this information document contain the draft revised chapters 3.2 and 3.3, including all the proposals already agreed by the group. Some further issues will be discussed in December 2011. The correspondence group intends to submit this work as a formal document to the 23rd session (June 2012).

Annex I

Draft revised chapter 3.2

"CHAPTER 3.2

SKIN CORROSION/IRRITATION

3.2.1 Definitions and general considerations

3.2.1.1 *Skin corrosion* is 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[1]. 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 should be considered to evaluate questionable lesions.

Skin irritation is the production of reversible damage to the skin following the application of a test substance for up to 4 hours[1].

3.2.1.2 In a tiered approach, emphasis should be placed upon existing human data, followed by existing animal data, followed by in vitro data and then other sources of information. Classification results directly when the data satisfy the criteria. In case the criteria cannot be directly applied, classification of a substance or a mixture is made on the basis of the total weight of evidence (see 1.3.2.4.9). This means that all available information bearing on the determination of skin corrosion/irritation is considered together, including the results of appropriate validated *in vitro* tests, relevant animal data, and human data such as epidemiological and clinical studies and well-documented case reports and observations.

3.2.2 Classification criteria for substances

3.2.2.1 Substance classification based on standard animal test data

3.2.2.1.1 *Skin corrosion*

3.2.2.1.1.1 Corrosive substances shall be classified in Category 1 where sub-categorization is not required by a competent authority or where data are not sufficient for sub-categorization. A corrosive substance is a test material 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 should be considered to discern questionable lesions.

3.2.2.1.1.2 For those authorities wanting more than one designation for corrosivity, up to three sub-categories are provided within the corrosive category (Category 1, see Table 3.2.1): sub-category 1A, where responses are noted following up to 3 minutes exposure and up to 1 hour observation; sub-category 1B, where responses are described following exposure between 3 minutes and 1 hour and observations up to 14 days; and sub-category 1C, where responses occur after exposures between 1 hour and 4 hours and observations up to 14 days.

[1] *This is a working definition for the purpose of this document.*

Table 3.2.1: Skin corrosion category and sub-categories [a]

Category 1: Corrosive	**Corrosive sub-categories**	**Corrosive in ≥ 1 animal**	
		Exposure	**Observation**
corrosive	1A	≤ 3 min	≤ 1 h
	1B	> 3 min ≤ 1 h	≤ 14 days
	1C	> 1 h ≤ 4 h	≤ 14 days

[a] *The use of human data is discussed in 3.2.2.2.1, in the Chapter 1.1 (para.* 1.1.2.5(c)), *and in Chapter 1.3 (para. 1.3.2.4.7).*

3.2.2.1.2 ***Skin irritation***

3.2.2.1.2.1 A single *irritant category (Category 2)* is provided that:

(a) recognizes that some test materials may lead to effects which persist throughout the length of the test; and

(b) acknowledges that animal responses in a test may be quite variable.

An additional *mild irritant category (Category 3)* is available for those authorities that want to have more than one skin irritant category.

3.2.2.1.2.2 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 should be considered to be an irritant.

3.2.2.1.2.3 Animal irritant responses within a test can be quite variable, as they are with corrosion. A separate irritant criterion accommodates cases when there is a significant irritant response but less than the mean score criterion for a positive test. For example, a test material might be designated as an irritant if at least 1 of 3 tested animals shows a very elevated mean score throughout the study, including lesions persisting at the end of an observation period of normally 14 days. Other responses could also fulfil this criterion. However, it should be ascertained that the responses are the result of chemical exposure. Addition of this criterion increases the sensitivity of the classification system.

3.2.2.1.2.4 A single irritant category (Category 2) is presented in the table using the results of animal testing. Authorities (e.g. pesticides) also have available a less severe mild irritant category (Category 3). Several criteria distinguish the two categories (Table 3.2.2). They mainly differ in the severity of skin reactions. The major criterion for the irritant category is that at least 2 tested animals have a mean score of ≥ 2.3 ≤ 4.0. For the mild irritant category, the mean score cut-off values are ≥ 1.5 < 2.3 for at least 2 tested animals. Test materials in the irritant category would be excluded from being placed in the mild irritant category.

Table 3.2.2 Skin irritation categories [a]

Categories	Criteria
Irritant (Category 2) (applies to all authorities)	(1) Mean value of ≥ 2.3 ≤ 4.0 for erythema/eschar or for oedema in at least 2 of 3 tested animals from gradings at 24, 48 and 72 hours after patch removal or, if reactions are delayed, from grades on 3 consecutive days after the onset of skin reactions; or (2) Inflammation that persists to the end of the observation period normally 14 days in at least 2 animals, particularly taking into account alopecia (limited area), hyperkeratosis, hyperplasia, and scaling; or (3) In some cases where there is pronounced variability of response among animals, with very definite positive effects related to chemical exposure in a single animal but less than the criteria above.
Mild irritant (Category 3) (applies to only some authorities)	Mean value of ≥ 1.5 < 2.3 for erythema/eschar or for oedema from gradings in at least 2 of 3 tested animals from grades at 24, 48 and 72 hours or, if reactions are delayed, from grades on 3 consecutive days after the onset of skin reactions (when not included in the irritant category above).

[a] *The use of human data is discussed in 3.2.2.2.1, in the Chapter 1.1 (para.* 1.1.2.5(c)), *and in the Chapter 1.3 (paragraph 1.3.2.4.7).*

3.2.2.2 Substance classification in a tiered approach

3.2.2.2.1 Existing human and animal data including information from single or repeated exposure should be the first line of analysis, as they give information directly relevant to effects on the skin. It also stands to reason that if a substance is highly toxic by the dermal route, a skin corrosion/irritation study may not be practicable since the amount of test substance to be applied would considerably exceed the toxic dose and, consequently, would result in the death of the animals. When observations are made of skin corrosion/irritation in acute toxicity studies and are observed up through the limit dose, these data may be used for classification provided that the dilutions used and species tested are equivalent. Solid substances (powders) may become corrosive or irritant when moistened or in contact with moist skin or mucous membranes. In vitro alternatives that have been validated and accepted should be used to make classification decisions. Likewise, pH extremes like ≤ 2 and ≥ 11.5 may indicate skin effects, especially when associated with significant buffering capacity. Generally, such substances are expected to produce significant effects on the skin. In the absence of any other information, a substance is considered corrosive (Skin Category 1) if it has a pH ≤ 2 or a pH $\geq$ 11.5. 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 needs to be carried out to confirm this, preferably by use of an appropriate validated in vitro test. In some cases enough information may be available from structurally related compounds to make classification decisions.

3.2.2.2.2 A *tiered approach* to the evaluation of initial information should be considered, where applicable (Figure 3.2.1), recognizing that not all elements may be relevant.

3.2.2.2.3 The proposed tiered approach provides guidance on how to organize existing information on a substance and to make a weight-of-evidence decision about hazard assessment and hazard classification (ideally without conducting new animal tests).

3.2.2.2.4 Although information might be gained from the evaluation of single parameters within a tier (see 3.2.2.2.2), consideration should be given to the totality of existing information and making an overall weight of evidence determination. This is especially true when there is conflict in information available on some parameters.

Figure 3.2.1: Tiered evaluation of skin corrosion and irritation potential					
Step	**Parameter**		**Finding**		**Conclusion**
1a:	Existing human or animal data [a] ↓ Not corrosive or no data ↓	→	Skin corrosive	→	Classify as a s**kin corrosive** [b]
1b:	Existing human or animal data [a] ↓ Not an irritant or no data ↓	→	Skin irritant	→	Classify as a s**kin irritant** [b]
1c:	Existing human or animal data [a] ↓ No/Insufficient data ↓	→	Not a skin corrosive or skin irritant	→	**Not classified**
2:	Other, existing skin data in animals [c] ↓ No/Insufficient data ↓	→	Yes	→	May be deemed to be a **skin corrosive** or a s**kin irritant** [b]
3:	*Existing ex vivo*/*in vitro* data [d] ↓ No/Insufficient data/ Negative response ↓	→ ↘	Positive: Skin corrosive Positive: Skin irritant	→ →	Classify as a **skin corrosive** [b] Classify as a **skin irritant** [b]
4:	pH-Based assessment (with consideration of buffering capacity of the chemical) [e] ↓ Not a pH extreme, No pH data or extreme pH with data showing low/no buffering capacity ↓	→	pH $\leq$ 2 or $\geq$11.5 with high acid/alkaline reserve or no data for buffering capacity	→	Classify as a **skin corrosive**
5:	Validated Structure/Activity Relationship (SAR) models ↓ No/Insufficient data ↓	→ ↘	Skin corrosive Skin irritant	→ →	May be deemed to be a s**kin corrosive** [b] May be deemed to be a **skin irritant** [b]
6:	Consideration of the total weight of evidence [f] ↓ No concern based on consideration of the sum of available data ↓	→ ↘	Skin corrosive Skin irritant	→ →	Deemed to be a **skin corrosive** [b] Deemed to be a **skin irritant** [b]
7:	**Not classified**				

[a] *Evidence of existing human or animal data could be derived from single or repeated exposure(s) in occupational, consumer, transportation, or emergency response scenarios; from ethically-conducted human clinical studies; or from purposely-generated data from animal studies conducted according to validated and internationally accepted test methods.*

[b] *Classify in the appropriate harmonized category.*

[c] *All pre-existing animal data should be carefully reviewed to determine if sufficient skin corrosion/irritation evidence is available through other, similar information. In evaluating acute dermal toxicity information the reporting of dermal lesions may be incomplete, testing and observations may be made on a species other than the rabbit, and species may differ in sensitivity in their responses.*

[d] *Evidence from studies using validated protocols with isolated human/animal tissues or other, non-tissue-based, though validated, protocols should be assessed. Examples of internationally accepted, validated test methods for skin corrosion include OECD TG 430 (Transcutaneous Electrical Resistance Test (TER)), 431 (Human Skin Model Test), and 435 (Membrane Barrier Test Method). An example of a a validated internationally accepted in vitro test method for skin irritation is OECD TG 439 (Reconstructed Human Epidermis Test Method).*

[e] *Measurement of pH alone may be adequate, but assessment of acid or alkali reserve (buffering capacity) would be preferable. Presently, there is no validated and internationally accepted method for assessing this parameter.*

[f] *All information that is available on a chemical should be considered and an overall determination made on the total weight of evidence. This is especially true when there is conflict in information available on some parameters. Professional Judgment should be exercised prior to making such a determination. Negative results from applicable validated skin irritation in-vitro tests are considered in the total weight of evidence evaluation.*

3.2.3 Classification criteria for mixtures

3.2.3.1 *Classification of mixtures when data are available for the complete mixture*

3.2.3.1.1 The mixture will be classified using the criteria for substances, and taking into account the tiered strategy to evaluate data for this hazard class.

3.2.3.1.2 Unlike other hazard classes, there are alternative tests available for skin corrosivity 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 to help ensure an accurate classification, as well as avoid unnecessary animal testing. In the absence of any other information, a mixture is considered corrosive (Skin Category 1) if it has a pH ≤ 2 or a pH ≥ 11.5. 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 needs to be carried out to confirm this, preferably by use of an appropriate validated *in vitro* test.

3.2.3.2 Classification of mixtures when data are not available for the complete mixture: bridging principles

3.2.3.2.1 Where the mixture itself has not been tested to determine its skin corrosion/irritation, but there are sufficient data on both the individual ingredients and similar tested mixtures to adequately characterize the hazards of the mixture, these data will be used in accordance with the following agreed bridging principles. This ensures that the classification process uses the available data to the greatest extent possible in characterizing the hazards of the mixture without the necessity for additional testing in animals.

3.2.3.2.2 *Dilution*

If a tested mixture is diluted with a diluent which has an equivalent or lower corrosivity/irritancy classification than the least corrosive/irritant original ingredient and which is not expected to affect the corrosivity/irritancy of other ingredients, then the new diluted mixture may be classified as equivalent to the original tested mixture. Alternatively, the method explained in 3.2.3.3 could be applied.

3.2.3.2.3 *Batching*

The skin corrosion/irritation potential of a tested production batch of a mixture can be assumed to be substantially equivalent to that of another untested production batch of the same commercial product when produced by or under the control of the same manufacturer, unless there is reason to believe there is significant variation such that the toxicity of the untested batch has changed. If the latter occurs, a new classification is necessary.

3.2.3.2.4 *Concentration of mixtures of the highest corrosion/ irritation category*

If a tested mixture classified in the highest sub-category for corrosion is concentrated, the more concentrated untested mixture should be classified in the highest corrosion sub-category without additional testing. If a tested mixture classified in the highest category for skin irritation is concentrated and does not contain corrosive ingredients, the more concentrated untested mixture should be classified in the highest irritation category without additional testing.

3.2.3.2.5 *Interpolation within one toxicity category*

For three mixtures (A, B and C) with identical ingredients, where mixtures A and B have been tested and are in the same skin corrosion/irritation toxicity category, and where untested mixture C has the same toxicologically active ingredients as mixtures A and B but has concentrations of toxicologically active ingredients intermediate to the concentrations in mixtures A and B, then mixture C is assumed to be in the same skin corrosion/irritation category as A and B.

3.2.3.2.6 *Substantially similar mixtures*

Given the following:

(a) Two mixtures: (i) A +B;
(ii) C + B;

(b) The concentration of ingredient B is essentially the same in both mixtures;

(c) The concentration of ingredient A in mixture (i) equals that of ingredient C in mixture (ii);

(d) Data on skin corrosion/irritation for A and C are available and substantially equivalent, i.e. they are in the same hazard category and are not expected to affect the toxicity of B.

If mixture (i) or (ii) is already classified based on test data, then the other mixture can be classified in the same hazard category.

3.2.3.2.7 *Aerosols*

An aerosol form of a mixture may be classified in the same hazard category as the tested non-aerosolized form of mixture provided that the added propellant does not affect the irritation or corrosive properties of the mixture upon spraying.

3.2.3.3 ***Classification of mixtures when data are available for all ingredients or only for some ingredients of the mixture***

3.2.3.3.1 In order to make use of all available data for purposes of classifying the skin corrosion/irritation hazards of mixtures, the following assumption has been made and is applied where appropriate in the tiered approach:

The "relevant ingredients" of a mixture are those which are present in concentrations ≥ 1% (w/w for solids, liquids, dusts, mists and vapours and v/v for gases), unless there is a presumption (e.g. in the case of corrosive ingredients) that an ingredient present at a concentration < 1% can still be relevant for classifying the mixture for skin corrosion/irritation.

3.2.3.3.2 In general, the approach to classification of mixtures as irritant or corrosive to skin when data are available on the ingredients, but not on the mixture as a whole, is based on the theory of additivity, such that each corrosive or irritant ingredient 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 ingredients when they are present at a concentration below the 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 ingredients exceeds a cut-off value/concentration limit.

3.2.3.3.3 Table 3.2.3 below provides the cut-off value/concentration limits to be used to determine if the mixture is considered to be an irritant or a corrosive to the skin.

3.2.3.3.4 Particular care must be taken when classifying certain types of chemicals such as acids and bases, inorganic salts, aldehydes, phenols, and surfactants. The approach explained in 3.2.3.3.1 and 3.2.3.3.2 might not work given that many of such substances are corrosive or irritant at concentrations < 1%. For mixtures containing strong acids or bases the pH should be used as classification criteria (see 3.2.3.1.2) since pH will be a better indicator of corrosion than the concentration limits of Table 3.2.3. A mixture containing corrosive or irritant ingredients that cannot be classified based on the additivity approach shown in Table 3.2.3, due to chemical characteristics that make this approach unworkable, should be classified as skin Category 1 if it contains ≥ 1% of a corrosive ingredient and as skin Category 2/3 when it contains ≥ 3% of an irritant ingredient. Classification of mixtures with ingredients for which the approach in Table 3.2.3 does not apply is summarized in Table 3.2.4 below.

3.2.3.3.5 On occasion, reliable data may show that the skin corrosion/irritation of an ingredient will not be evident when present at a level above the generic concentration cut-off values mentioned in Tables 3.2.3 and 3.2.4. In these cases the mixture could be classified according to those data (see also *Classification of hazardous substances and mixtures – Use of cut-off values/Concentration limits* (1.3.3.2)). On occasion, when it is expected that the skin corrosion/irritation of an ingredient will not be evident when present at a level above the generic concentration cut-off values mentioned in Tables 3.2.3 and 3.2.4, testing of the mixture may be considered. In those cases the tiered weight of evidence strategy should be applied as described in 3.2.3 and illustrated in Figure 3.2.1.

3.2.3.3.6 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 should be classified accordingly (see also *Classification of hazardous substances and mixtures – Use of cut-off values/Concentration limits* (1.3.3.2)).

Table 3.2.3: Concentration of ingredients of a mixture classified as skin Category 1, 2 or 3 that would trigger classification of the mixture as hazardous to skin (Category 1, 2 or 3)

Sum of ingredients classified as:	Concentration triggering classification of a mixture as:		
	Skin corrosive	Skin irritant	
	Category 1 (see note below)	Category 2	Category 3
Skin Category 1	≥ 5%	≥ 1% but < 5%	
Skin Category 2		≥ 10%	≥ 1% but < 10%
Skin Category 3			≥ 10%
(10 × Skin Category 1) + Skin Category 2		≥ 10%	≥ 1% but < 10%
(10 × Skin Category 1) + Skin Category 2 + Skin Category 3			≥ 10%

NOTE: *In case of use of the sub-categories of skin Category 1 (corrosive) , the sum of all ingredients of a mixture classified as skin Category 1A, 1B or 1C respectively, should each be ≥5% in order to classify the mixture as either skin Category 1A, 1B or 1C. In case the sum of the skin Category 1A ingredients is < 5% but the sum of skin Category ingredients 1A+1B is ≥5%, the mixture should be classified as skin Category 1B. Similarly, in case the sum of skin Category 1A + 1B is <5% but the sum of Category 1A + 1B + 1C is ≥ 5% the mixture would be classified as Category 1C. In case at least one relevant ingredient in a mixture is classified as Cat. 1 without sub-categorisation, the mixture should be classified as Cat.1 without sub-categorisation.*

Table 3.2.4: **Concentration of ingredients of a mixture for which the additivity approach does not apply, that would trigger classification of the mixture as hazardous 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 (Category 1) ingredients for which additivity does not apply	≥ 1%	Category 1
Other irritant (Category 2/3) ingredients for which additivity does not apply, including acids and bases	≥ 3%	Category 2

3.2.4 Hazard communication

General and specific considerations concerning labelling requirements are provided in *Hazard communication: Labelling* (Chapter 1.4). Annex 2 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority. The table below presents specific label elements for substances and mixtures that are classified as irritating or corrosive to the skin based on the criteria set forth in this chapter.

Table 3.2.5: Label elements for skin corrosion/irritation

	Category 1			Category 2	Category 3
	1 A	**1 B**	**1 C**		
Symbol	Corrosion	Corrosion	Corrosion	Exclamation mark	*No symbol*
Signal word	Danger	Danger	Danger	Warning	Warning
Hazard statement	Causes severe skin burns and eye damage	Causes severe skin burns and eye damage	Causes severe skin burns and eye damage	Causes skin irritation	Causes mild skin irritation

3.2.5 Decision logic

The decision logic which follows is not part of the harmonized classification system but is provided here as additional guidance. It is strongly recommended that the person responsible for classification study the criteria before and during use of the decision logic.

3.2.5.1 ***Decision logic 3.2.1 for skin corrosion/irritation***

[To be drafted]

3.2.5.2 ***Decision logic 3.2.2 for skin corrosion/irritation***

[To be drafted]”

Annex II

Draft revised chapter 3.3

"CHAPTER 3.3

SERIOUS EYE DAMAGE/EYE IRRITATION

3.3.1 Definitions and general considerations

3.3.1.1 *Serious eye damage* is 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[2].

Eye irritation is 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[1].

3.3.1.2 In a tiered approach, emphasis should be placed upon existing human data, followed by existing animal data, followed by in vitro data and then other sources of information. Classification results directly when the data satisfy the criteria. In case the criteria cannot be directly applied, classification of a substance or a mixture is made on the basis of the total weight of evidence (see 1.3.2.4.9). This means that all available information bearing on the determination of serious eye damage/eye irritation is considered together, including the results of appropriate validated *in vitro* tests, relevant animal data, and human data such as epidemiological and clinical studies and well-documented case reports and observations.

3.3.2 Classification criteria for substances

3.3.2.1 Substance classification based on standard animal test data

3.3.2.1.1 ***Irreversible effects on the eye/serious damage to eyes (Category 1)***

A single harmonized hazard category is adopted for substances that have the potential to seriously damage the eyes. This hazard category - Category 1 (irreversible effects on the eye) - includes the criteria listed below. These observations include animals with grade 4 cornea lesions and other severe reactions (e.g. destruction of cornea) observed at any time during the test, as well as persistent corneal opacity, discoloration of the cornea by a dye substance, adhesion, pannus, and interference with the function of the iris or other effects that impair sight. In this context, persistent lesions are considered those which are not fully reversible within an observation period of normally 21 days. Hazard classification: Category 1 also contains substances fulfilling the criteria of corneal opacity ≥ 3 or iritis > 1.5 detected in a Draize eye test with rabbits, because severe lesions like these usually do not reverse within a 21 days observation period.

[2] *This is a working definition for the purpose of this document.*

Table 3.3.1: Irreversible eye effects category [a]

Serious eye damage Category 1 (irreversible effects on the eye) applies to a substance that produces:
(a) in at least one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days; and/or
(b) in at least 2 of 3 tested animals, a positive response of: (i) corneal opacity ≥ 3; and/or (ii) iritis > 1.5; calculated as the mean scores following grading at 24, 48 and 72 hours after instillation of the test material.

[a] *The use of human data is discussed in 3.3.2.2.1, in the Chapter 1.1 (para.* 1.1.2.5(c)) *and in the Chapter 1.3 (para. 1.3.2.4.7).*

3.3.2.1.2 ***Reversible effects on the eye (Category 2)***

A single category is adopted for substances that have the potential to induce reversible eye irritation. This single hazard category provides the option to identify within the category a sub-category for substances inducing eye irritant effects reversing within an observation time of 7 days.

Those authorities desiring one single category for classification of "eye irritation" may use the overall harmonized Category 2 (irritating to eyes); others may want to distinguish between Category 2A (irritating to eyes) and Category 2B (mildly irritating to eyes).

Table 3.3.2: Reversible eye effects categories[a]

Eye irritant Category 2A (irritating to eyes) applies to a substance that produces:
(a) in at least 2 of 3 tested animals a positive response of: (i) corneal opacity ≥ 1; and/or (ii) iritis ≥ 1; and/or (iii) conjunctival redness ≥ 2; and/or (iv) conjunctival oedema (chemosis) ≥ 2 calculated as the mean scores following grading at 24, 48 and 72 hours after instillation of the test material, and which fully reverses within an observation period of normally 21 days.
Within this category an eye irritant is considered **mildly irritating to eyes (Category 2B)** when the effects listed above are fully reversible within 7 days of observation.

[a] *The use of human data is discussed in 3.3.2.2.1, in the Chapter 1.1 (para.* 1.1.2.5(c)), *and in the Chapter 1.3 (para. 1.3.2.4.7).*

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

3.3.2.2 Substance classification in a tiered approach

3.3.2.2.1 Existing human and animal data should be the first line of analysis, as they give information directly relevant to effects on the eye. 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. *In vitro* alternatives that have been validated and accepted should be used to make classification decisions. Likewise, pH extremes like ≤ 2 and ≥ 11.5, may indicate serious eye damage, especially when associated with significant buffering capacity. Generally, such substances are expected to produce significant effects on the eyes. In the absence of any other

information, a substance is considered to cause serious eye damage (Category 1) if it has a pH ≤ 2 or ≥ 11.5. If consideration of alkali/acid reserve suggests the substance or 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. In some cases enough information may be available from structurally related compounds to make classification decisions.

3.3.2.2.2 A tiered approach to the evaluation of initial information should be considered where applicable, recognizing that not all elements may be relevant.

3.3.2.2.3 The proposed tiered approach provides guidance on how to organize existing information and to make a weight-of-evidence decision about hazard assessment and hazard classification (ideally without conducting new animal tests). Animal testing with corrosive substances should be avoided whenever possible.

3.3.2.2.4 Although information might be gained from the evaluation of single parameters consideration should be given to the totality of existing information and making an overall weight of evidence determination. This is especially true when there is conflict in information available on some parameters.

Figure 3.3.1: Tiered evaluation of serious eye damage/eye irritation potential (see also Figure 3.2.1)

Step	**Parameter**		**Finding**		**Conclusion**
1a:	Existing human or animal data, Eye [a] ↓ No/Insufficient data or unknown ↓	→ ↘	Serious eye damage Eye irritant	→	Classify as causing **Serious eye damage** [b] Classify as an **eye irritant** [b]
1b:	Existing human or animal data, skin corrosion ↓ No/Insufficient data or unknown ↓	→	Skin corrosive	→	Deemed to cause **serious eye damage** [b]
1c:	Existing human or animal data, Eye [a] ↓ No/Insufficient data ↓	→	Existing data that show that substance does not cause serious eye damage or eye irritation	→	**Not classified**
2:	Other, existing skin corrosion/eye data in animals [c] ↓ No/Insufficient data ↓	→	Yes; existing data that show that substance may cause serious eye damage or eye irritation	→	May be deemed to cause **Serious eye damage** or to be an **eye irritant** [b]
3:	*Existing ex vivo* / *in vitro* eye data [d] ↓ No/Insufficient data / Negative response ↓	→ ↘	Positive: serious eye damage Positive: eye irritant	→ →	Classify as causing **serious eye damage** [b] Classify as an **eye irritant** [b]

Figure 3.3.1: Tiered evaluation of serious eye damage/eye irritation potential (see also Figure 3.2.1)

Step	Parameter		Finding		Conclusion
4:	pH-Based assessment (with consideration of buffering capacity of the chemical) [e] ↓ Not a pH extreme, No pH data, or extreme pH with data showing low/no buffering capacity ↓	→	pH ≤ 2 or ≥11.5 with high acid/alkaline reserve or no data for buffering capacity	→	Classify as causing **serious eye damage**
5:	Validated Structure/Activity Relationship (SAR) models ↓ No/Insufficient data ↓	↗ → ↘	Severe damage to eyes Eye irritant Skin corrosive	→ → →	May be deemed to cause **serious eye damage** [b] May be deemed to be an **eye irritant** [b] May be deemed to cause **serious eye damage** [b]
6:	Consideration of the total weight of evidence [f] ↓ No concern based on consideration of the sum of available data ↓	→ ↘	Serious eye damage Eye irritant	→ →	Deemed to cause **serious eye damage** [b] Deemed to be an **eye irritant** [b]
7:	**Not classified**				

[a] *Evidence of existing human or animal data could be derived from single or repeated exposure(s) in occupational, consumer, transportation, or emergency response scenarios; from ethically-conducted human clinical studies; or from purposely-generated data from animal studies conducted according to validated and internationally accepted test methods. At present, there are no internationally accepted test methods for human eye irritation testing.*

[b] *Classify in the appropriate harmonized category.*

[c] *Pre-existing animal data should be carefully reviewed to determine if sufficient serious eye damage/eye irritation evidence is available through other, similar information.*

[d] *Evidence from studies using validated protocols with isolated human/animal tissues or other, non-tissue-based, through validated, protocols should be assessed. Examples of internationally accepted, validated test methods for identifying eye corrosives and severe irritants (i.e., Serious Eye Damage) include OECD TG 437 (Bovine Corneal Opacity and Permeability (BCOP)) and 438 (Isolated Chicken Eye). Presently there are no validated and internationally accepted in vitro test methods for identifying eye irritation. A positive test result from a validated in vitro test on skin corrosion would lead to the conclusion to classify as causing serious eye damage.*

[e] *Measurement of pH alone may be adequate, but assessment of acid/alkaline reserve (buffering capacity) would be preferable. Presently, there is no validated and internationally accepted method for assessing this parameter.*

[f] *All information that is available on a chemical should be considered and an overall determination made on the total weight of evidence. This is especially true when there is conflict in information available on some*

parameters. The weight of evidence including information on skin irritation could lead to classification of eye irritation:

Existing human or animal experience, Skin irritation ➔ Skin irritant ➔ May be deemed to be eye irritant

It is recognized that not all skin irritants are eye irritants as well. Professional judgment should be exercised prior to making such a determination. Negative results from applicable validated in-vitro tests are considered in the total weight of evidence evaluation.

3.3.3 Classification criteria for mixtures

3.3.3.1 *Classification of mixtures when data are available for the complete mixture*

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.

3.3.3.1.2 Unlike other hazard classes, there are alternative tests available for skin corrosivity of certain types of chemicals 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 manufacturers 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. In the absence of any other information, a mixture is considered to cause serious eye damage (Eye Category 1) if it has a pH ≤ 2 or ≥ 11.5. If consideration of alkali/acid reserve suggests the substance or 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.

3.3.3.2 *Classification of mixtures when data are not available for the complete mixture: bridging principles*

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 eye irritation, but there are sufficient data on both the individual ingredients and similar tested mixtures to adequately characterize the hazards of the mixture, these data will be used in accordance with the following agreed bridging principles. This ensures that the classification process uses the available data to the greatest extent possible in characterizing the hazards of the mixture without the necessity for additional testing in animals.

3.3.3.2.2 *Dilution*

If a tested mixture is diluted with a diluent which has an equivalent or lower classification for serious eye damage/eye irritation classification than the least damaging/irritant original ingredient and which is not expected to affect the corrosivity/irritancy of other ingredients, then the new diluted mixture may be classified as equivalent to the original tested mixture. Alternatively, the method explained in 3.3.3.3 could be applied.

3.3.3.2.3 *Batching*

The serious eye damage/eye irritation potential of a tested production batch of a mixture can be assumed to be substantially equivalent to that of another untested production batch of the same commercial product when produced by or under the control of the same manufacturer, unless there is reason to believe there is significant variation such that the toxicity of the untested batch has changed. If the latter occurs, a new classification is necessary.

3.3.3.2.4 *Concentration of mixtures of the highest serious eye damage/eye irritation category*

If a tested mixture classified in the highest category for serious eye damage is concentrated, the more concentrated untested mixture should be classified in the highest serious eye damage category without additional testing. If a tested mixture classified in the highest sub-category for eye irritation is concentrated and does not contain

serious eye damage ingredients, the more concentrated untested mixture should be classified in the highest eye irritation category without additional testing.

3.3.3.2.5 *Interpolation within one toxicity category*

For three mixtures (A, B and C) with identical ingredients, where mixtures A and B have been tested and are in the same serious eye damage/eye irritation toxicity category, and where untested mixture C has the same toxicologically active ingredients as mixtures A and B but has concentrations of toxicologically active ingredients intermediate to the concentrations in mixtures A and B, then mixture C is assumed to be in the same serious eye damage/eye irritation category as A and B.

3.3.3.2.6 *Substantially similar mixtures*

Given the following:

(a) Two mixtures: (i) A +B
(ii) C + B;

(b) The concentration of ingredient B is essentially the same in both mixtures;

(c) The concentration of ingredient A in mixture (i) equals that of ingredient C in mixture (ii);

(d) Data on serious eye damage/eye irritation for A and C are available and substantially equivalent, i.e. they are in the same hazard category and are not expected to affect the toxicity of B.

If mixture (i) or (ii) is already classified by testing, the other mixture can be assigned in the same hazard category.

3.3.3.2.7 *Aerosols*

An aerosol form of a mixture may be classified in the same hazard category as the tested non-aerosolized form of mixture provided that the added propellant does not affect the irritation or corrosive properties of the mixture upon spraying[3].

3.3.3.3 *Classification of mixtures when data are available for all ingredients or only for some ingredients of the mixture*

3.3.3.3.1 In order to make use of all available data for purposes of classifying the serious eye damage/eye irritation properties of the mixtures, the following assumption has been made and is applied where appropriate in the tiered approach:

The "relevant ingredients" of a mixture are those which are present in concentrations ≥ 1% (w/w for solids, liquids, dusts, mists and vapours and v/v for gases), unless there is a presumption (e.g. in the case of corrosive ingredients) that an ingredient present at a concentration < 1% can still be relevant for classifying the mixture for eye irritation/serious eye damage.

3.3.3.3.2 In general, the approach to classification of mixtures as seriously damaging to the eye or eye irritant when data are available on the ingredients, but not on the mixture as a whole, is based on the theory of additivity, such that each corrosive or irritant ingredient contributes to the overall irritant or corrosive properties of the mixture in

[3] *Bridging principles apply for the intrinsic hazard classification of aerosols, however, the need to evaluate the potential for "mechanical" eye damage from the physical force of the spray is recognized.*

proportion to its potency and concentration. A weighting factor of 10 is used for corrosive ingredients when they are present at a concentration below the 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 seriously damaging to the eye or eye irritant when the sum of the concentrations of such ingredients exceeds a threshold cut-off value/concentration limit.

3.3.3.3.3 Table 3.3.3 provides the cut-off value/concentration limits to be used to determine if the mixture should be classified as seriously damaging to the eye or an eye irritant.

3.3.3.3.4 Particular care must be taken when classifying certain types of chemicals such as acids and bases, inorganic salts, aldehydes, phenols, and surfactants. The approach explained in 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 %. For mixtures containing strong acids or bases the pH should be used as classification criteria (see 3.3.3.1) since pH will be a better indicator of serious eye damage than the concentration limits of Table 3.3.3. A mixture containing corrosive or irritant ingredients that cannot be classified based on the additivity approach applied in Table 3.3.3 due to chemical characteristics that make this approach unworkable, should be classified as Eye Category 1 if it contains ≥ 1% of a corrosive ingredient and as Eye 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 summarized 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 cut-off values/concentration limits mentioned in Tables 3.3.3 and 3.3.4. In these cases the mixture could be classified according to those data (see also 1.3.3.2 *"Use of cut-off values/Concentration limits"*). On occasion, when it is expected that the skin corrosion/irritation or the reversible/irreversible eye effects of an ingredient will not be evident when present at a level above the generic concentration/cut-off levels mentioned in Tables 3.3.3 and 3.3.4, testing of the mixture may be considered. In those cases, the tiered weight of evidence strategy should be applied as referred to in section 3.3.3, Figure 3.3.1 and explained in detail in this chapter.

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 should be classified accordingly (see also 1.3.3.2 *"Use of cut-off values/concentration limits"*).

Table 3.3.3: Concentration of ingredients of a mixture classified as skin Category 1 and/or eye Category 1 or 2 that would trigger classification of the mixtures as hazardous to 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 2A**
Skin Category 1 + Eye Category 1[a]	≥ 3%	≥ 1% but < 3%
Eye Category 2		≥ 10%[b]
10 × (Skin Category 1 + Eye Category 1)[a] + Eye Category 2		≥ 10%

[a] *If an ingredient is classified as both Skin Category 1 and Eye Category 1 its concentration is considered only once in the calculation.*

[b] *A mixture may be classified as eye Cat. 2B in case all relevant ingredients are classified as eye Cat. 2B.*

Table 3.3.4: Concentration of ingredients of a mixture for which the additivity approach does not apply, that would 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 (Category 1) ingredients for which additivity does not apply	≥ 1%	Category 1
Other eye irritant (Category 2) ingredients for which additivity does not apply, including acids and bases	≥ 3%	Category 2

3.3.4 Hazard communication

General and specific considerations concerning labelling requirements are provided in *Hazard communication: Labelling* (Chapter 1.4). Annex 2 contains summary tables about classification and labelling. Annex 3 contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority.

Table 3.3.5: Label elements for serious eye damage/eye irritation[a]

	Category 1	Category 2A	Category 2B
Symbol	Corrosion	Exclamation mark	*No symbol*
Signal word	Danger	Warning	Warning
Hazard statement	Causes serious eye damage	Causes serious eye irritation	Causes eye irritation

[a] *In case a chemical is classified as skin Cat.1, labelling for serious eye damage/eye irritation may be omitted as this information is already included in the hazard statement for skin Cat. 1 (Causes severe skin burns and eye damage) (see 1.4.10.5.3.3).*

3.3.5 Decision logic

The decision logic which follows is not part of the harmonized classification system but is provided here as additional guidance. It is strongly recommended that the person responsible for classification study the criteria before and during use of the decision logic.

3.3.5.1 *Decision logic 3.3.1 for serious eye damage/eye irritation*

[To be drafted]

3.3.5.2 *Decision logic 3.3.2 for serious eye damage/eye irritation*

[To be drafted]"