

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**

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Item 2 (b) of the provisional agenda

**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, representing the current state of discussion and also including all the proposals already agreed by the group. Some further issues will be discussed at the 23rd session. The correspondence group intends to submit this work as a formal document to the 24th session (December 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 hours¹. 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 hours¹.

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 some cases, classification of a substance or a mixture is made on the basis of the weight of evidence within a tier. In a total weight of evidence approach 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 (see Chapter 1, 1.3.2.4.9).

3.2.2 Classification criteria for substances

Substances can be allocated to one of the following three categories within this hazard class:

- (a) Skin corrosion

This category may be further divided into up to three sub-categories (1A, 1B and 1C) which can be used by those authorities requiring more than one designation for corrosivity (see table 3.2.1)

- (b) Skin irritation (see table 3.2.2)

- (c) Mild skin irritation (see table 3.2.2)

This category is available for those authorities that want to have more than one skin irritation category.

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

3.2.2.1 *Classification based on standard animal test data*

3.2.2.1.1 *Skin corrosion*

3.2.2.1.1.1 A substance is corrosive to skin when it produces destruction of skin tissue, namely, visible necrosis through the epidermis and into the dermis, in at least one tested animal after exposure for up to 4 hours..

3.2.2.1.1.2 Corrosive substances should be classified in Category 1 where sub-categorization is not required by a competent authority or where data are not sufficient for sub-categorization.

3.2.2.3.1.3 When data are sufficient and where required by a competent authority substances may be classified in one of the three sub-categories 1A, 1B or 1C in accordance with the criteria in table 3.2.1.

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

Table 3.2.1: Skin corrosion category and sub-categories ^a

	Criteria
Category 1	Destruction of skin tissue, namely, visible necrosis through the epidermis and into the dermis, in at least one tested animal after exposure \leq 4 h
Sub-category 1A	Corrosive responses in at least one animal following exposure \leq 3 min during an observation period \leq 1 h
Sub-category 1B	Corrosive responses in at least one animal following exposure $>$ 3 min and \leq 1 h and observations \leq 14 days
Sub-category 1C	Corrosive responses in at least one animal after exposures $>$ 1 h and \leq 4 h and observations \leq 14 days

^a The use of human data is addressed in 3.2.2.2.1, in Chapter 1.1 (paragraph 1.1.2.5(c)), and in Chapter 1.3 (paragraph 1.3.2.4.7).

3.2.2.1.2 *Skin irritation*

3.2.2.1.2.1 An *irritation 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 variable.

An additional *mild irritation category* (Category 3) is available for those authorities that want to have more than one skin irritation 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 two 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 variable, as they are with corrosion. A separate irritant criterion accommodates cases where 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 irritation category (Category 2) is presented in table 3.2.2 using the results of animal testing. Authorities (e.g. for pesticides) also have available a less severe mild irritation 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 irritation category is that at least two of three tested animals have a mean score of ≥ 2.3 and ≤ 4.0 . For the mild irritation category, the mean score cut-off values are ≥ 1.5 and < 2.3 for at least two of three tested animals. Test materials in the irritation category are excluded from the mild irritation category.

Table 3.2.2 Skin irritation categories^{a, b, c}

Categories	Criteria
Irritation (Category 2) (applies to all authorities)	(1) Mean score of ≥ 2.3 and ≤ 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 irritation (Category 3) (applies to only some authorities)	Mean score of ≥ 1.5 and < 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 irritation category above).

^a The use of human data is addressed in 3.2.2.2.1, in Chapter 1.1 (paragraph 1.1.2.5(c)), and in Chapter 1.3 (paragraph 1.3.2.4.7).

^b Grading criteria are understood as described e.g. in OECD Test Guideline 404.

^c Evaluation of a 4, 5 or 6-animal study should follow the criteria given in chapter 3.2.5.3 background guidance.

3.2.2.2 Classification in a tiered approach

3.2.2.2.1 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.

3.2.2.2.2 Existing human and animal data including information from single or repeated exposure should be the first line of evaluation, as they give information directly relevant to effects on the skin.

3.2.2.2.3 Acute dermal toxicity data may be used for classification. 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.

3.2.2.2.4 *In vitro* alternatives that have been validated and accepted should be used to make classification decisions.

3.2.2.2.5 Likewise, pH extremes like ≤ 2 and ≥ 11.5 may indicate skin effects, especially when associated with significant acid/alkaline reserve (buffering capacity). Generally, such substances are expected to produce significant effects on the skin. In the absence of any other information, a substance is considered corrosive (Skin Category 1) if it has a pH ≤ 2 or a pH ≥ 11.5 . However, if consideration of acid/alkaline reserve suggests the substance may not be corrosive despite the low or high pH value, this needs to be confirmed by other data, preferably by data from an appropriate validated *in vitro* test.

3.2.2.2.6 In some cases sufficient information may be available from structurally related substances to make classification decisions.

3.2.2.2.7 The tiered approach provides guidance on how to organize existing information on a substance and to make a weight-of-evidence decision about hazard assessment and hazard classification (ideally without conducting new animal tests). Although information might be gained from the evaluation of single parameters within a tier (see 3.2.2.2.1), 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 for skin corrosion and irritation

<u>Step</u>	<u>Parameter</u>	<u>Finding</u>	<u>Conclusion</u>
1a:	Existing human or animal skin corrosion/irritation data ²	→ Skin Corrosive	→ Classify as a Skin Corrosive ³
	↓		
	Not Corrosive/No data		
	↓		
1b:	Existing human or animal skin corrosion/irritation data ²	→ Skin Irritant	→ Classify as a Skin Irritant ³
	↓		
	Not Irritant/No data		
	↓		
1c:	Existing human or animal skin corrosion/irritation data ²	→ Not a Skin Corrosive or Skin Irritant	→ Not classified
	↓		
	No/Insufficient data		
	↓		
2:	Other, existing skin data in animals ⁴	→ Yes	→ May be deemed to be a Skin Corrosive ³ or a Skin Irritant ³
	↓		

² Evidence of existing human or animal data could be derived from single or repeated exposure(s), for example in occupational, consumer, transport, or emergency response scenarios; or from purposely-generated data from animal studies conducted according to validated and internationally accepted test methods. Although human data such as accident or poison centre databases can provide evidence for classification, absence of incidents is not itself evidence for no classification as exposures are unknown or uncertain.

³ Classify in the appropriate category/sub-category as applicable.

⁴ All pre-existing animal data should be carefully reviewed to determine if sufficient skin corrosion/irritation evidence is available. This may include evidence from acute dermal toxicity testing. In evaluating such data, however, the reviewer should bear in mind that the reporting of dermal lesions may be incomplete, testing and observations may be made on a species other than the rabbit, and species may differ in sensitivity in their responses.

Figure 3.2.1: Tiered evaluation for skin corrosion and irritation

<u>Step</u>	<u>Parameter</u>		<u>Finding</u>		<u>Conclusion</u>
	No/Insufficient data	↓			
3:	Existing <i>ex vivo</i> / <i>in vitro</i> data ⁵	→	Positive: Skin Corrosive	→	Classify as Skin Corrosive ³
	↓	↘	Positive: Skin Irritant	→	Classify as Skin Irritant ³
	No/Insufficient data/Negative response	↓			
4:	pH-Based assessment (with consideration of acid/alkaline reserve of the chemical) ⁶	→	pH ≤ 2 or ≥ 11.5 with high acid/alkaline reserve or no data for acid/alkaline reserve	→	Classify as Skin Corrosive
	↓				
	Not pH extreme, no pH data or extreme pH with data showing low/no acid/alkaline reserve	↓			
5:	Validated Structure/Activity Relationship (SAR) methods	→	Skin Corrosive	→	Deemed to be Skin Corrosive ³
	↓	↘	Skin Irritant	→	Deemed to be Skin Irritant ³
	No/Insufficient data	↓			
6:	Consideration of the total weight of evidence ⁷	→	Skin Corrosive	→	Deemed to be Skin Corrosive ³
	↓	↘	Skin Irritant	→	Deemed to be Skin Irritant ³
7:	Not Classified				

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 should be classified using the criteria for substances, taking into account the tiered approach to evaluate data for this hazard class (as illustrated in Figure 3.2.1)..

⁵ 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 Test Guideline 430 (Transcutaneous Electrical Resistance Test (TER)), 431 (Human Skin Model Test), and 435 (Membrane Barrier Test Method). An example of a validated internationally accepted *in vitro* test method for skin irritation is OECD Test Guideline 439 (Reconstructed Human Epidermis Test Method).

⁶ 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.

⁷ All information that is available should be considered and an overall determination made on the total weight of evidence. This is especially true when there is conflict in information available on some parameters. Professional judgment should be exercised prior to making such a determination. Negative results from applicable validated skin corrosion/irritation *in vitro* tests are considered in the total weight of evidence evaluation.

3.2.3.1.2 Unlike other hazard classes, there are alternative tests available for skin corrosion 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 approach as included in the criteria for classification of substances for skin corrosion and irritation to help ensure an accurate classification, as well as to avoid unnecessary animal testing. In the absence of any other information, a mixture is considered corrosive (Skin Category 1) if it has a $\text{pH} \leq 2$ or a $\text{pH} \geq 11.5$. However, if consideration of acid/alkaline reserve suggests the mixture may not be corrosive despite the low or high pH value, this needs to be confirmed by other data, preferably by data from an appropriate validated *in vitro* test.

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 potential, but there are sufficient data on both the individual ingredients and similar tested mixtures to adequately characterize the hazards of the mixture, these data should 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 skin corrosion/irritation potential 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 skin 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 for skin irritation (Category 2) is concentrated and does not contain skin corrosive ingredients, the more concentrated untested mixture should be classified for skin irritation (Category 2) 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 skin corrosion/irritation potential 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 skin corrosion/irritation 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 $\geq 1\%$ (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 skin 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 a skin irritant or 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 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 may be a better indicator of corrosion than the concentration limits in 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 corrosion Category 1 if it contains $\geq 1\%$ of a corrosive ingredient and as skin irritation Category 2 or Category 3 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 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 limits/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 approach 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 to skin 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: Where the sub-categories of Skin Category 1 (corrosive) are used, 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. Where 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, where the sum of Skin Category 1A + 1B is < 5% but the sum of Category 1A + 1B + 1C is ≥ 5% the mixture should be classified as Category 1C. Where at least one relevant ingredient in a mixture is classified as Category 1 without sub-categorisation, the mixture should be classified as Category 1 without sub-categorisation if the sum of all ingredients is ≥ 5%.

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) ingredient	≥ 1%	Category 1
Other irritant (Category 2/3) ingredient, 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.

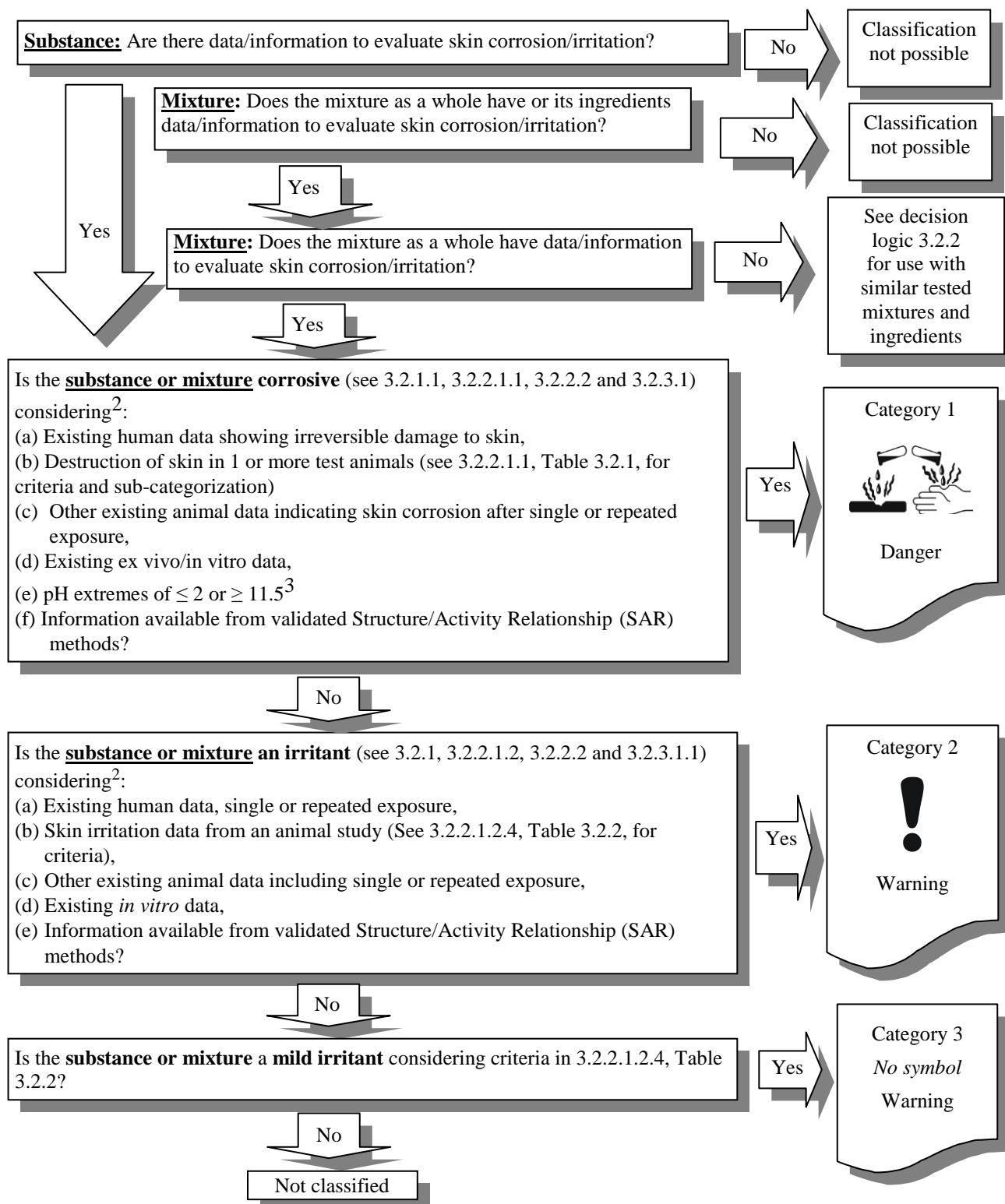
Table 3.2.5: Label elements for skin corrosion/irritation

	Category 1			Category 2	Category 3
	1 A	1 B	1 C		
Symbol	Corrosion	Corrosion	Corrosion	Exclamation mark	<i>No symbol</i>
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*

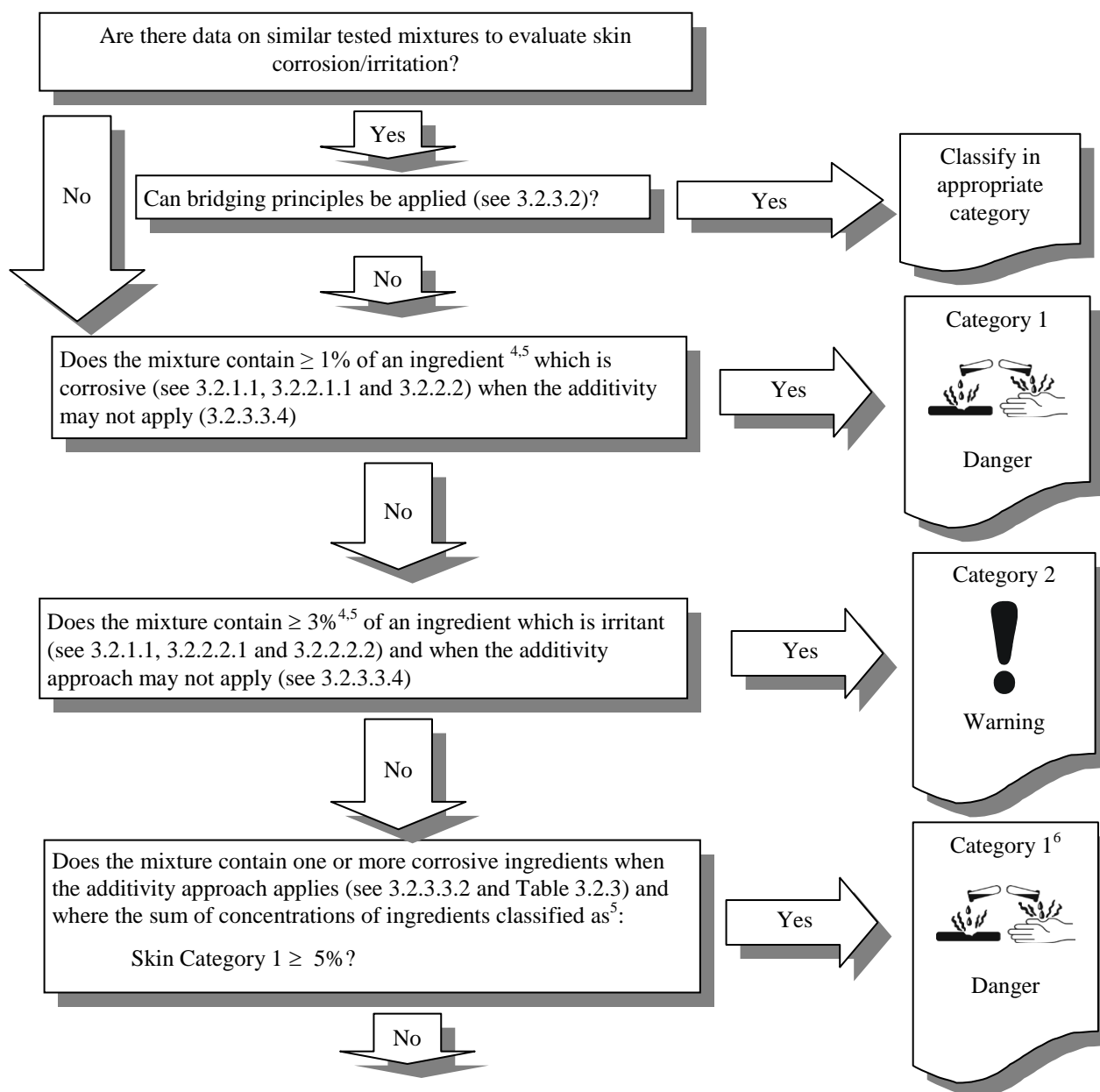


² Taking into account consideration of the total weight of evidence as needed.

³ Not applicable if consideration of pH and acid/alkaline reserve indicates substance or mixture may not be corrosive and confirmed by other data, preferably by data from an appropriate validated *in vitro* test.

3.2.5.2 *Decision logic 3.2.2 for skin corrosion/irritation*

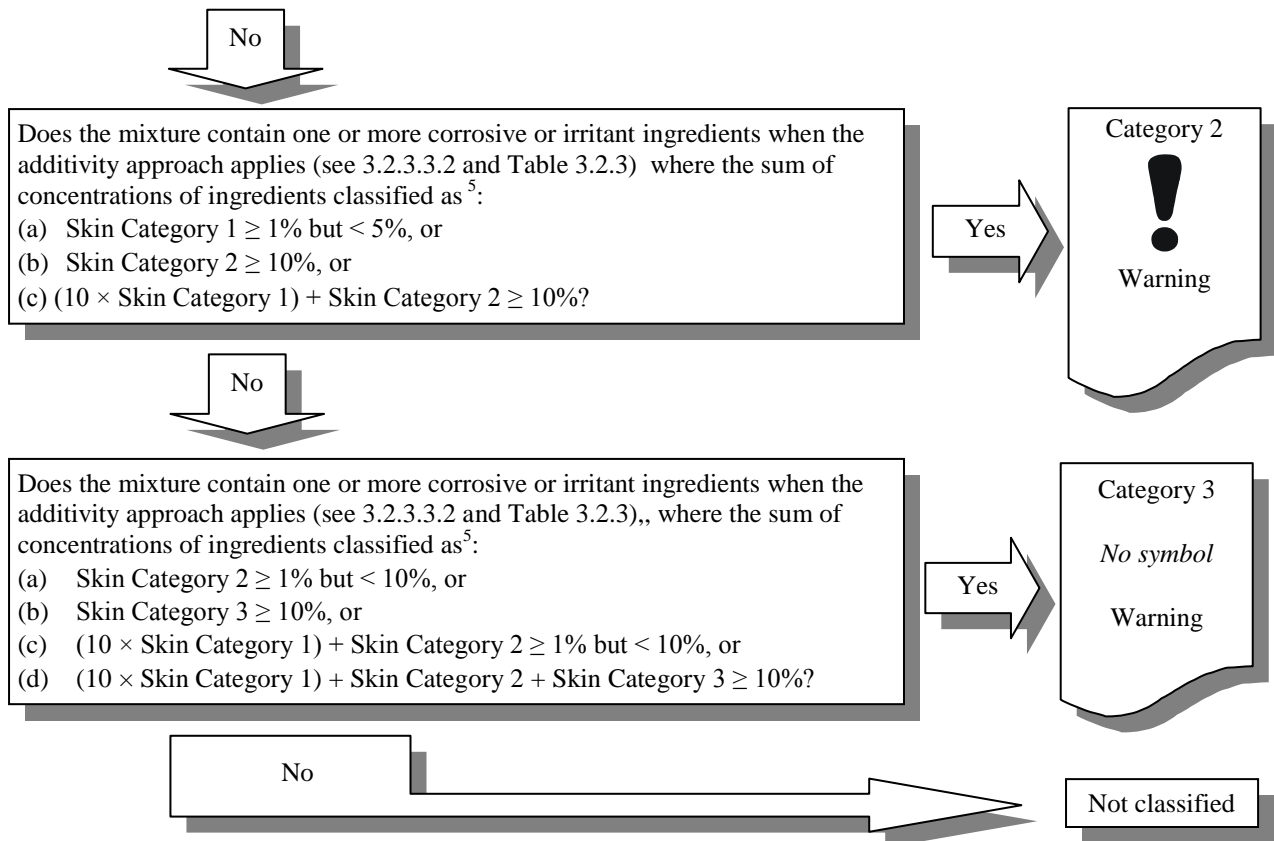
Classification of mixtures on the basis of information/data on similar tested mixtures and/or ingredients



⁴ Or where relevant $< 1\%$, see 3.2.3.3.1.

⁵ For specific concentration limits, see 3.2.3.3.6. See also 1.3.3.2 for "Use of cut-off values/concentration limits".

⁶ See note to Table 3.2.3 for details on use of Category 1 sub-categories.



3.2.5.3 Background guidance

3.2.5.3.1 Classification criteria for the skin and eye hazard classes are detailed in the GHS in terms of a 3-animal test. It has been identified that some older test methods may have used up to 6 animals. However, the GHS does not specify how to classify based on existing data from tests with more than 3 animals. Guidance on how to classify based on existing data from studies with 4 or more animals is given in the following paragraphs.

3.2.5.3.2 Classification criteria based on a 3-animal test are detailed in 3.2.2.1. Evaluation of a 4, 5 or 6-animal study should follow the criteria in the following paragraphs, depending on the number of animals tested. Scoring for erythema/eschar and oedema should be performed at 24, 48 and 72 hours after exposure or, if reactions are delayed, from grades on 3 consecutive days after the onset of skin reactions.

3.2.5.3.3 In the case of a study with 6 animals the following principles apply:

- (a) The substance or mixture is classified as skin corrosion Category 1 if destruction of skin tissue (that is, visible necrosis through the epidermis and into the dermis) occurs in at least one animal after exposure up to 4 hours in duration;
- (b) The substance or mixture is classified as skin irritation Category 2 if at least 4 out of 6 animals show a mean score per animal of $\geq 2.3 \leq 4.0$ for erythema/eschar or for oedema;
- (c) The substance or mixture is classified as skin irritation Category 3 if at least 4 out of 6 animals show a mean score per animal of $\geq 1.5 < 2.3$ for erythema/eschar or for oedema.

3.2.5.3.4 In the case of a study with 5 animals the following principles apply:

- (a) The substance or mixture is classified as skin corrosion Category 1 if destruction of skin tissue (that is, visible necrosis through the epidermis and into the dermis) occurs in at least one animal after exposure up to 4 hours in duration;
- (b) The substance or mixture is classified as skin irritation Category 2 if at least 3 out of 5 animals show a mean score per animal of $\geq 2.3 \leq 4.0$ for erythema/eschar or for oedema;
- (c) The substance or mixture is classified as skin irritation Category 3 if at least 3 out of 5 animals show a mean score per animal of $\geq 1.5 < 2.3$ for erythema/eschar or for oedema.

3.2.5.3.5 In the case of a study with 4 animals the following principles apply:

- (a) The substance or mixture is classified as skin corrosion Category 1 if destruction of skin tissue (that is, visible necrosis through the epidermis and into the dermis) occurs in at least one animal after exposure up to 4 hours in duration;
- (b) The substance or mixture is classified as skin irritation Category 2 if at least 3 out of 4 animals show a mean score per animal of $\geq 2.3 \leq 4.0$ for erythema/eschar or for oedema;
- (c) The substance or mixture is classified as skin irritation Category 3 if at least 3 out of 4 animals show a mean score per animal of $\geq 1.5 < 2.3$ for erythema/eschar or for oedema.

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 application¹³.

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 application¹³.

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 other cases, classification of a substance or a mixture is made on the basis of the weight of evidence within a tier. In a total weight of evidence approach 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 (see Chapter 1, 1.3.2.4.9).

3.3.2 Classification criteria for substances

Substances are allocated to one of the categories within this hazard class, Category 1 (serious eye damage) or Category 2 (eye irritant), as follows:

- (a) Category 1 (irreversible effects on the eye): substances that have the potential to seriously damage the eyes;
- (b) Category 2 (reversible effects on the eye): substances that have the potential to induce reversible eye irritation.

Those authorities desiring one category for classification of “eye irritation” may use the overall Category 2; others may want to distinguish between Category 2A and Category 2B (see table 3.3.2).

¹³ *This is a working definition for the purpose of this document*

3.3.2.1 Classification based on standard animal test data**3.3.2.1.1 Serious eye damage (Category 1)/Irreversible effects on the eye**

A single hazard category (Category 1) is adopted for substances that have the potential to seriously damage the eyes. This hazard category includes as criteria the observations listed in Table 3.3.1. These observations include animals with grade 4 cornea lesions and other severe reactions (e.g. destruction of cornea) observed at any time during the test, as well as persistent corneal opacity, discoloration of the cornea by a dye substance, adhesion, pannus, and interference with the function of the iris or other effects that impair sight. In this context, persistent lesions are considered those which are not fully reversible within an observation period of normally 21 days. Hazard classification as Category 1 also contains substances fulfilling the criteria of corneal opacity ≥ 3 or iritis > 1.5 observed in 2 of 3 tested animals, because severe lesions like these usually do not reverse within a 21 day observation period.

Table 3.3.1: Serious eye damage/irreversible eye effects category ^{a, b, c}

	Criteria
Category 1 serious eye damage/irreversible effects on the eye	<p>A substance that produces:</p> <p>(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</p> <p>(b) in at least 2 of 3 tested animals, a positive response of:</p> <p>(i) corneal opacity ≥ 3; and/or</p> <p>(ii) iritis > 1.5;</p> <p>calculated as the mean scores following grading at 24, 48 and 72 hours after instillation of the test material.</p>

^a The use of human data is addressed in 3.3.2.2.1, in Chapter 1.1 (paragraph 1.1.2.5(c)) and in Chapter 1.3 (paragraph 1.3.2.4.7).

^b Grading criteria are understood as described e.g. in OECD Test Guideline 405.

^c Evaluation of a 4, 5 or 6-animal study should follow the criteria given in chapter 3.3.5.3 background guidance.

3.3.2.1.2 Reversible effects on the eye/eye irritation (Category 2)

3.3.2.1.2.1 Substances that have the potential to induce reversible eye irritation should be classified in Category 2 where further categorization into Category 2A and/or Category 2B is not required by a competent authority or where data are not sufficient. Category 2 is equivalent to Category 2A.

3.3.2.1.2.2 For those authorities wanting more than one designation for reversible eye irritation, Categories 2A and 2B are provided.

- (a) When data are sufficient and where required by a competent authority substances may be classified in Category 2A or 2B in accordance with the criteria in table 3.3.2.
- (b) For substances inducing eye irritant effects reversing within an observation time of normally 21 days, Category 2A applies. For substances inducing eye irritant effects reversing within an observation time of 7 days, Category 2B applies.

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

Table 3.3.2: Reversible eye effects categories^{a, b, c}

	Criteria
Substances that have the potential to induce reversible eye irritation.	
Category 2A	Substances that produce in at least 2 of 3 tested animals a positive response of: <ul style="list-style-type: none"> (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.
Category 2B	Substances that produce in at least 2 of 3 tested animals the effects listed under sub-category 2A when they are fully reversible within 7 days of observation

^a The use of human data is addressed in 3.3.2.2.1, in Chapter 1.1 (paragraph 1.1.2.5(c)), and in Chapter 1.3 (paragraph 1.3.2.4.7).

^b Grading criteria are understood as described e.g. in OECD Test Guideline 405.

^c Evaluation of a 4, 5 or 6-animal study should follow the criteria given in chapter 3.3.5.3 background guidance.

3.3.2.2 Classification in a tiered approach

3.3.2.2.1 A tiered approach to the evaluation of initial information should be considered where applicable (Figure 3.3.1), recognizing that not all elements may be relevant.

3.3.2.2.2 Existing human and animal data should be the first line of evaluation, as they give information directly relevant to effects on the eye. Possible skin corrosion has to be evaluated prior to consideration of any testing for serious eye damage/eye irritation in order to avoid testing for local effects on eyes with skin corrosive substances.

3.3.2.2.3 *In vitro* alternatives that have been validated and accepted should be used to make classification decisions.

3.3.2.2.4 Likewise, pH extremes like ≤ 2 and ≥ 11.5 may indicate serious eye damage, especially when associated with significant acid/alkaline reserve (buffering capacity). Generally, such substances are expected to produce significant effects on the eyes. In the absence of any other information, a substance is considered to cause serious eye damage (Category 1) if it has a pH ≤ 2 or ≥ 11.5 . However, if consideration of acid/alkaline reserve suggests the substance may not cause serious eye damage despite the low or high pH value, this needs to be confirmed by other data, preferably by data from an appropriate validated *in vitro* test.

3.3.2.2.5 In some cases sufficient information may be available from structurally related substances to make classification decisions.

3.3.2.2.6 The 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. 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 for serious eye damage/eye irritation
(see also Figure 3.2.1)

<u>Step</u>	<u>Parameter</u>	<u>Finding</u>	<u>Conclusion</u>
1a:	Existing human or animal serious eye damage/eye irritation data ¹⁴	➔ Serious Eye Damage	➔ Classify as causing Serious Eye Damage
	↓ No/Insufficient data/No data	➔ Eye Irritant	➔ Classify as Eye Irritant ¹⁵
1b:	Existing human or animal data, Skin Corrosion	➔ Skin Corrosion	➔ Deemed to cause Serious Eye Damage
	↓ No/Insufficient data/No data		
1c:	Existing human or animal serious eye damage/eye irritation data ²	➔ Existing data showing that substance does not cause Serious Eye Damage or Eye Irritation	➔ Not classified
	↓ No/Insufficient data		
2:	Other, existing skin corrosion/eye data in animals ¹⁶	➔ Yes; existing data showing that substance may cause Serious Eye Damage or Eye Irritation	➔ May be deemed to cause Serious Eye Damage or to be an Eye Irritant ¹⁵
	↓ No/Insufficient data		
3:	Existing <i>ex vivo</i> / <i>in vitro</i> eye data ¹⁷	➔ Positive: Serious Eye Damage	➔ Classify as causing Serious Eye Damage
	↓	➔ Positive: Eye Irritant	➔ Classify as Eye Irritant ¹⁵

¹⁴ Evidence of existing human or animal data could be derived from single or repeated exposure(s), for example in occupational, consumer, transportation, or emergency response scenarios; or from purposely-generated data from animal studies conducted according to validated and internationally accepted test methods. Although human data such as accident or poison centre databases can provide evidence for classification, absence of incidents is not itself evidence for no classification as exposures are unknown or uncertain.

¹⁵ Classify in the appropriate category as applicable.

¹⁶ Pre-existing animal data should be carefully reviewed to determine if sufficient serious eye damage/eye irritation evidence is available through other, similar information.

¹⁷ Evidence from studies using validated protocols with isolated human/animal tissues or other non-tissue-based, 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(ICE)). 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.

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

<u>Step</u>	<u>Parameter</u>	<u>Finding</u>	<u>Conclusion</u>
	No/Insufficient data/Negative response ↓		
4:	pH-based assessment (with consideration of acid/alkaline reserve of the chemical) ¹⁸ ↓	→ pH ≤ 2 or ≥ 11.5 with high acid/alkaline reserve or no data for acid/alkaline reserve	→ Classify as causing Serious Eye Damage
	Not a pH extreme, no pH data, or extreme pH with data showing low/no acid/alkaline reserve ↓		
5:	Validated Structure/Activity Relationship (SAR) methods ↓	↗ Severe damage to eyes → Eye Irritant ↘ Skin Corrosive	→ Deemed to cause Serious Eye Damage → Deemed to be Eye Irritant ¹⁵ → Deemed to cause Serious Eye Damage
	No/Insufficient data ↓		
6:	Consideration of the total weight of evidence ¹⁹ ↓	→ Serious Eye Damage ↘ Eye Irritant	→ Deemed to cause Serious Eye Damage → Deemed to be Eye Irritant ¹⁵
7:	Not Classified		

¹⁸ 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.

¹⁹ All information that is available on a substance should be considered and an overall determination made on the total weight of evidence. This is especially true when there is conflict in information available on some parameters. The weight of evidence including information on skin irritation may lead to classification for eye irritation:
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 should be classified using the criteria for substances, and taking into account the tiered approach to evaluate data for this hazard class (as illustrated in Figure 3.3.1).

3.3.3.1.2 Unlike other hazard classes, there are alternative tests available for serious eye damage for 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 classifiers are encouraged to use a tiered weight of evidence approach as included in the criteria for classification of substances for skin corrosion and serious eye damage/eye irritation to help ensure an accurate classification, as well as to 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 . However, if consideration of acid/alkaline reserve suggests the mixture may not cause serious eye damage despite the low or high pH value, this needs to be confirmed by other data, preferably by data from 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 should 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 damage/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 serious eye damage/eye irritation potential 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 for serious eye damage (Category 1) is concentrated, the more concentrated untested mixture should be classified for serious eye damage (Category 1) without additional testing. If a tested mixture classified in the highest category for eye irritation (Category 2A) is concentrated and does not contain serious eye damage ingredients, the more concentrated untested mixture should be classified in the highest eye irritation category (Category 2A) 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 serious eye damage/eye irritation potential 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 serious eye damage/eye irritation properties of the mixture upon spraying²⁰.

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

3.3.3.3.2 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 serious eye damaging/eye irritant ingredient contributes to the overall serious eye damage/eye irritation properties of the mixture in proportion to its potency and concentration. A weighting factor of 10 is used for corrosive and serious eye damaging 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

²⁰ 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.

serious eye damaging/eye 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 such substances are seriously damaging to the eye/eye irritating at concentrations < 1 %. For mixtures containing strong acids or bases the pH should be used as classification criterion (see 3.3.3.1) since pH may be a better indicator of serious eye damage (subject to consideration of acid/alkali reserve) than the concentration limits in Table 3.3.3. A mixture containing corrosive or serious eye damaging/eye irritating 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 $\geq 1\%$ of a corrosive or serious eye damaging ingredient and as Eye Category 2 when it contains $\geq 3\%$ of an eye 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 irreversible/reversible 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 irreversible/reversible 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 approach 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 seriously damaging to the eye/eye irritating at a concentration of < 1% (corrosive) or < 3% (eye 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 mixture 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 2/2A
Skin Category 1 + Eye Category 1 ^a	$\geq 3\%$	$\geq 1\%$ but < 3%
Eye Category 2		$\geq 10\%$ ^b
$10 \times (\text{Skin Category 1} + \text{Eye Category 1})^a + \text{Eye Category 2}$		$\geq 10\%$

^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 Category 2B when all relevant ingredients are classified as eye Category 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 (Eye Category 1) ingredient	≥ 1%	Category 1
Other eye irritant (Eye Category 2) ingredient, 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

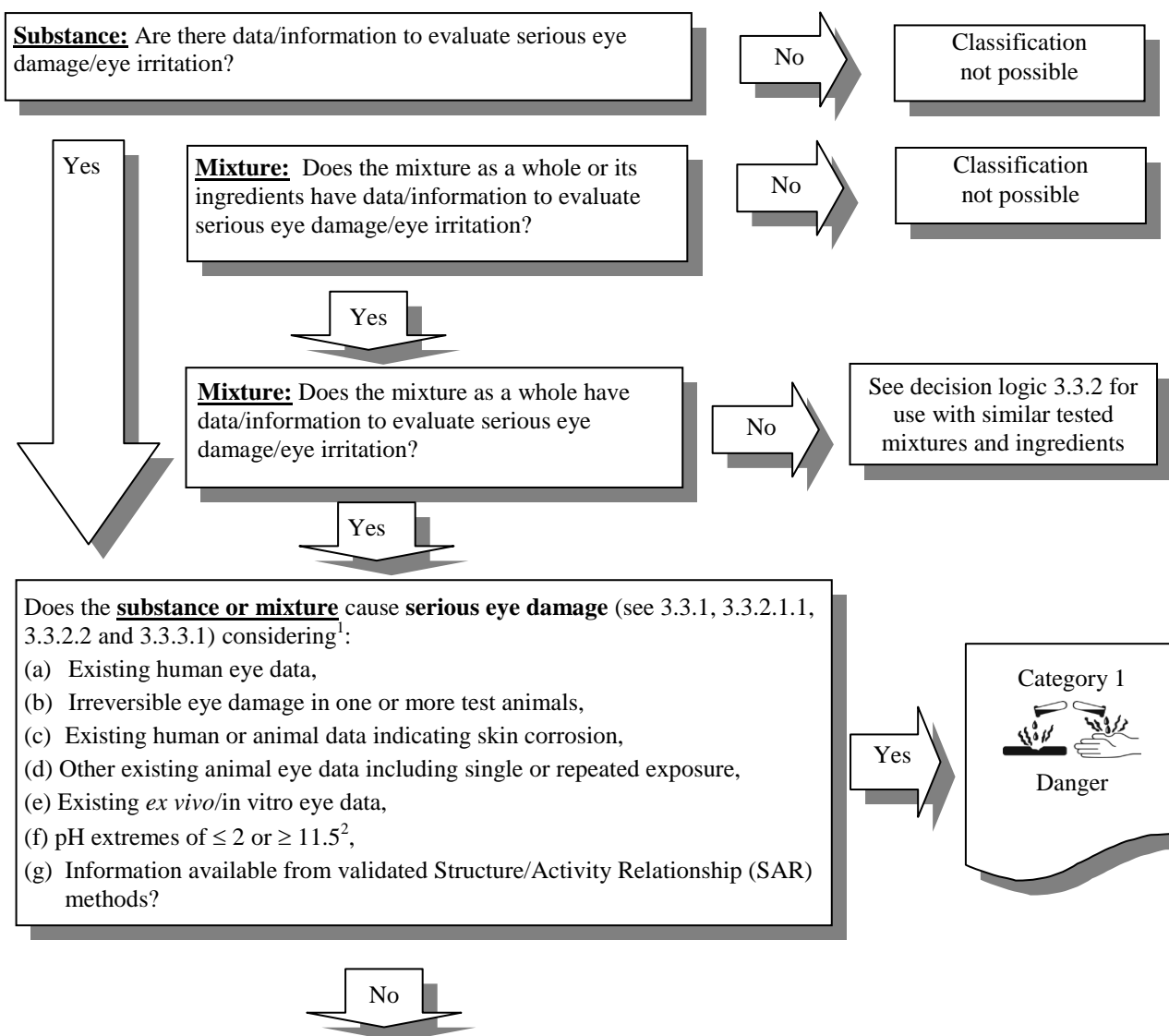
	Category 1	Category 2/2A	Category 2B
Symbol	Corrosion	Exclamation mark	<i>No symbol</i>
Signal word	Danger	Warning	Warning
Hazard statement	Causes serious eye damage	Causes serious eye irritation	Causes eye irritation

^a Where a chemical is classified as Skin Category 1, labelling for serious eye damage/eye irritation may be omitted as this information is already included in the hazard statement for Skin Category 1 (Causes severe skin burns and eye damage) (see Chapter 1, 1.4.10.5.3.3).

3.3.5 Decision logic

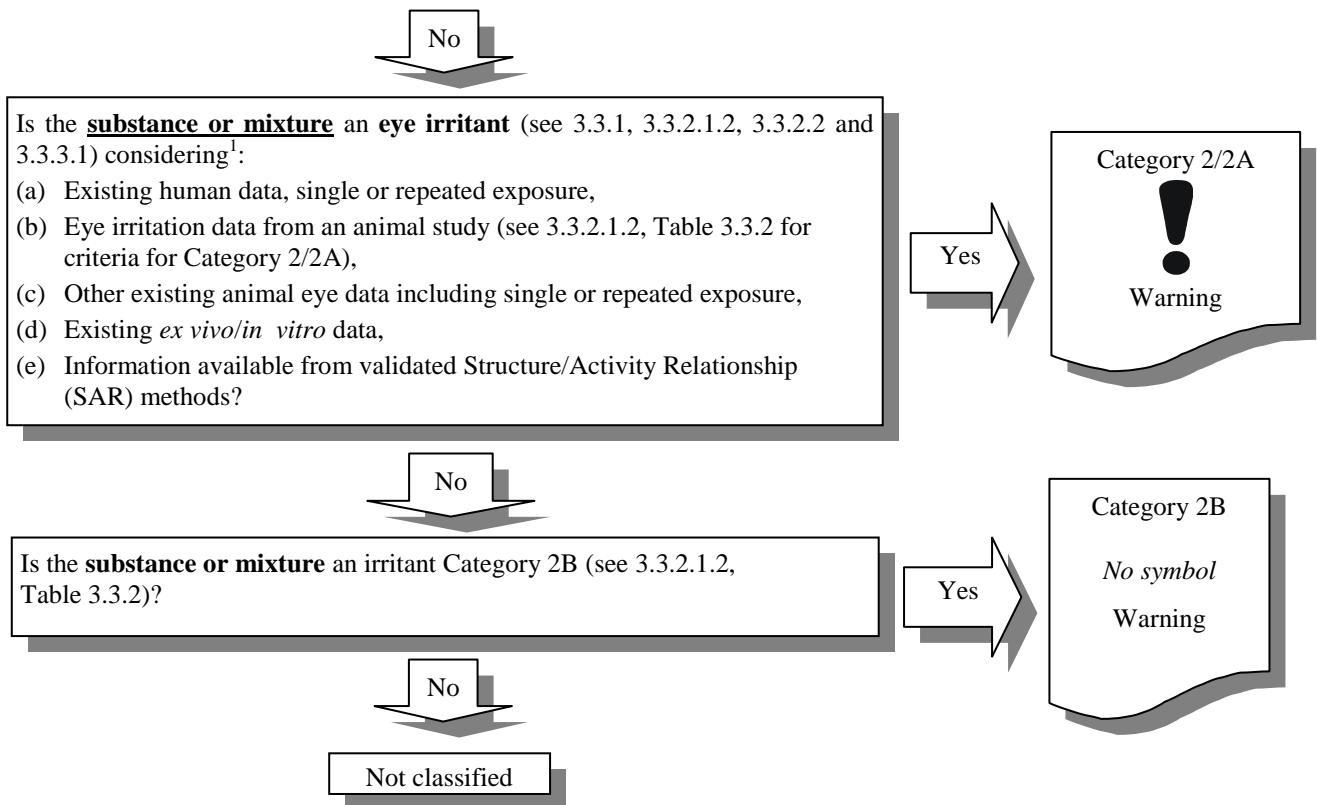
The decision logic which follows is not part of the harmonized classification system but is provided here as additional guidance. It is strongly recommended that the person responsible for classification study the criteria before and during use of the decision logic.

3.3.5.1 Decision logic 3.3.1 for serious eye damage/eye irritation



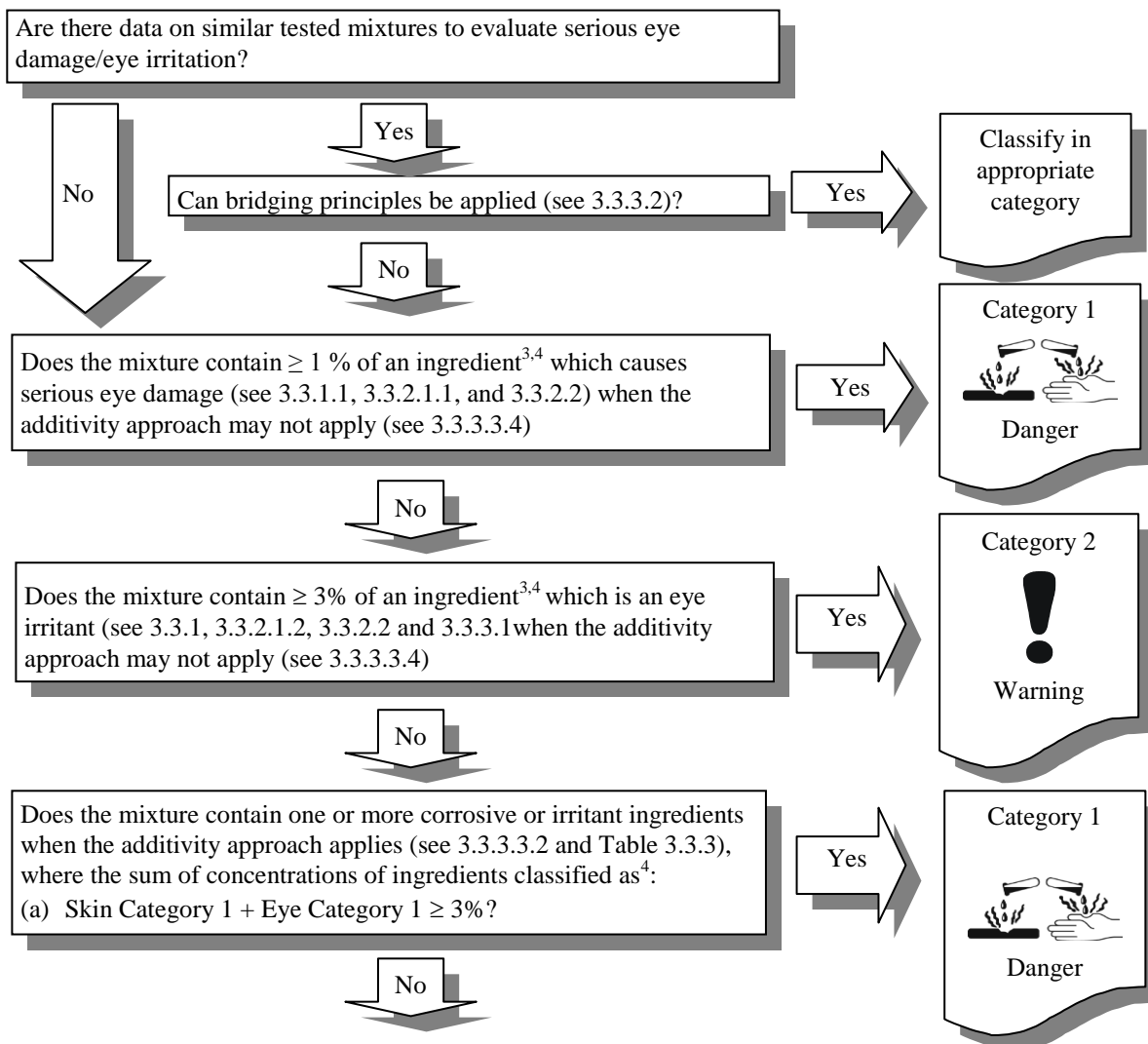
¹ Taking into account consideration of the total weight of evidence as needed.

² Not applicable if consideration of pH and acid/alkaline reserve indicates substance or mixture may not cause serious eye damage and confirmed by other data, preferably by data from an appropriate validated in vitro test.



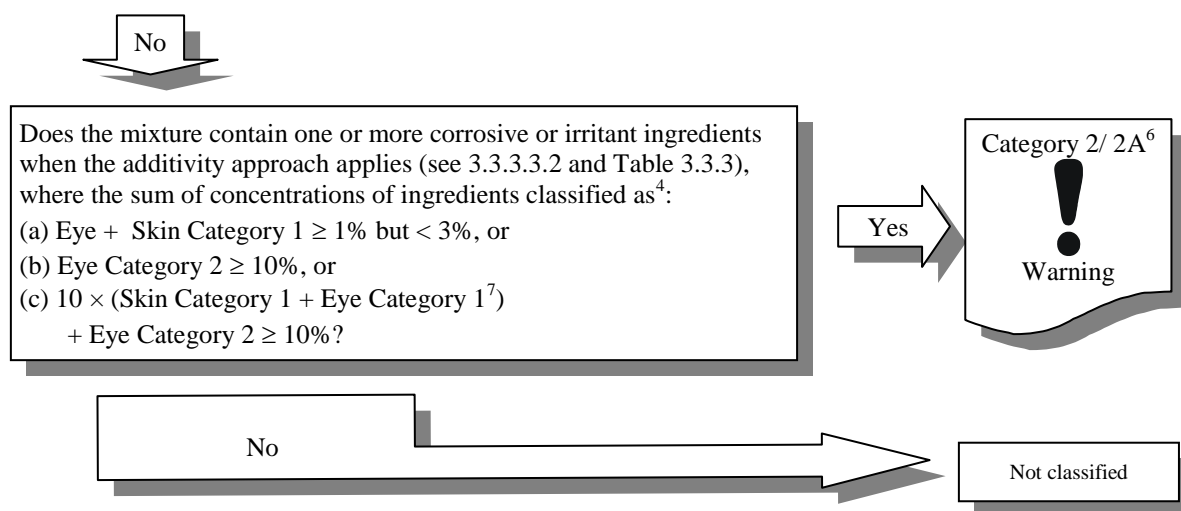
3.3.5.2 Decision logic 3.3.2 for serious eye damage/eye irritation

Classification of mixtures on the basis of information/data on similar tested mixtures and/or ingredients



³ Or where relevant < 1 %, see 3.3.3.3.1.

⁴ For specific concentration limits, see 3.3.3.3.6. See also 1.3.3.2 for “Use of cut-off values/concentration limits”.



3.3.5.3 Background guidance

3.3.5.3.1 Classification criteria for the skin and eye hazard classes are detailed in the GHS in terms of a 3-animal test. It has been identified that some older test methods may have used up to 6 animals. However, the GHS does not specify how to classify based on existing data from tests with more than 3 animals. Guidance on how to classify based on existing data from studies with 4 or more animals is given in the following paragraphs.

3.3.5.3.2 Classification criteria based on a 3-animal test are detailed in 3.3.2.1. Evaluation of a 4, 5 or 6 animal study should follow the criteria in the following paragraphs, depending on the number of animals tested. Scoring should be done at 24, 48 and 72 hours after instillation of the test material.

3.3.5.3.3 In the case of a study with 6 animals the following principles apply:

- (a) The substance or mixture is classified as serious eye damage Category 1 if:
 - (i) in at least one animal effects on the cornea, iris or conjunctiva are not expected to reverse or have not fully reversed within an observation period of normally 21 days; and/or
 - (ii) at least 4 out of 6 animals show a mean score per animal of ≥ 3 for corneal opacity and/or > 1.5 for iritis.
- (b) The substance or mixture is classified as eye irritation Category 2/2A if at least 4 out of 6 animals show a mean score per animal of:
 - (i) ≥ 1 for corneal opacity and/or
 - (ii) ≥ 1 for iritis and/or
 - (iii) ≥ 2 for conjunctival redness and/or
 - (iv) ≥ 2 for conjunctival oedema (chemosis)

⁶ A mixture may be classified as eye Cat. 2B in case all relevant ingredients are classified as eye Cat. 2B.

⁷ If an ingredient is classified as both Skin Category 1 and Eye Category 1 its concentration is considered only once in the calculation.

and which fully reverses within an observation period of normally 21 days.

- (c) The substance or mixture is classified as irritating to eyes (Category 2B) if the effects listed in sub-paragraph (b) above are fully reversible within 7 days of observation.

3.3.5.3.4

In the case of a study with 5 animals the following principles apply:

- (a) The substance or mixture is classified as serious eye damage Category 1 if:
- (i) in at least one animal effects on the cornea, iris or conjunctiva are not expected to reverse or have not fully reversed within an observation period of normally 21 days; and/or
 - (ii) at least 3 out of 5 animals show a mean score per animal of ≥ 3 for corneal opacity and/or > 1.5 for iritis.
- (b) The substance or mixture is classified as eye irritation Category 2/2A if at least 3 out of 5 animals show a mean score per animal of:
- (i) ≥ 1 for corneal opacity and/or
 - (ii) ≥ 1 for iritis and/or
 - (iii) ≥ 2 for conjunctival redness and/or
 - (iv) ≥ 2 for conjunctival oedema (chemosis)

and which fully reverses within an observation period of normally 21 days.

- (c) The substance or mixture is classified as irritating to eyes (Category 2B) if the effects listed in sub-paragraph (b) above are fully reversible within 7 days of observation.

3.3.5.3.5

In the case of a study with 4 animals the following principles apply:

- (a) The substance or mixture is classified as serious eye damage Category 1 if:
- (i) in at least one animal effects on the cornea, iris or conjunctiva are not expected to reverse or have not fully reversed within an observation period of normally 21 days; and/or
 - (ii) at least 3 out of 4 animals show a mean score per animal of ≥ 3 for corneal opacity and/or > 1.5 for iritis.
- (b) Classification as eye irritation Category 2/2A if at least 3 out of 4 animals show a mean score per animal of:
- (i) ≥ 1 for corneal opacity and/or
 - (ii) ≥ 1 for iritis and/or
 - (iii) ≥ 2 for conjunctival redness and/or
 - (iv) ≥ 2 for conjunctival oedema (chemosis)

and which fully reverses within an observation period of normally 21 days.

- (c) The substance or mixture is classified as irritating to eyes (Category 2B) if the effects listed in sub-paragraph (b) above are fully reversible within 7 days of observation.