

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

Health hazards

Proposal for the editorial revision of Chapter 3.3

**Submitted by the expert from Germany on behalf of the informal
correspondence group on the editorial revision of chapters 3.2 and 3.3**

Introduction

This document contains the full version of Chapter 3.3, as amended in accordance with the the proposed list of amendments in document ST/SG/AC.10/C.4/2012/12, which were agreed by the informal correspondence group.

The text of Chapter 3.3 showing the amendments in visible mode (“track-changes”) is circulated as informal document INF.4.

“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 application¹.

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 application¹.

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 1.3, para. 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 irritation), as follows:

- (a) Category 1 (serious eye damage/irreversible effects on the eye):
Substances that have the potential to seriously damage the eyes (see Table 3.3.1);
- (b) Category 2 (serious eye irritation/reversible effects on the eye):
substances that have the potential to induce reversible eye irritation (see Table 3.3.2);

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).

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

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

as Category 1 also contains substances fulfilling the criteria of corneal opacity ≥ 3 or iritis > 1.5 observed in at least 2 of 3 tested animals, because severe lesions like these usually do not reverse within a 21-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, and in chapters 1.1 (para. 1.1.2.5 (c)) and 1.3 (para. 1.3.2.4.7).

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

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

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

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 for further categorization. In case of further categorization, Category 2A is equivalent to Category 2.

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: (a) corneal opacity ≥ 1 ; and/or (b) iritis ≥ 1 ; and/or (c) conjunctival redness ≥ 2 ; and/or (d) conjunctival oedema (chemosis) ≥ 2 calculated as the mean scores following grading at 24, 48 and 72 hours after instillation of the test material, and which fully reverses within an observation period of normally 21 days.
Category 2B	Within Category 2A 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 addressed in 3.3.2.2, and in chapters 1.1 (para. 1.1.2.5 (c)) and 1.3 (para. 1.3.2.4.7).

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

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

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 within a tier (see 3.3.2.1.1), 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 3.3.1: Tiered evaluation for serious eye damage/eye irritation
(see also Figure 3.2.1)**

Step	Parameter	Finding	Conclusion
1a:	Existing human or animal serious eye damage/eye irritation data ^a ↓ Negative data/Insufficient data/No data ↓	→ Serious eye damage → Eye irritant	→ Classify as causing serious eye damage → Classify as eye irritant ^b
1b:	Existing human or animal data, skin corrosion ↓ Negative data /Insufficient data/No data ↓	→ Skin corrosion	→ Deemed to cause serious eye damage
1c:	Existing human or animal serious eye damage/eye irritation data ^a ↓ No/Insufficient data ↓	→ Existing data showing that substance does not cause serious eye damage or eye irritation	→ Not classified
2:	Other, existing skin/eye data in animals ^c ↓ No/Insufficient data ↓	→ Yes; other 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 ^b
3:	Existing <i>ex vivo/in vitro</i> eye data ^d ↓ No/Insufficient data/Negative response ↓	→ Positive: serious eye damage → Positive: eye irritant	→ Classify as causing serious eye damage → Classify as eye irritant ^b
4:	pH-based assessment (with consideration of acid/alkaline reserve of the chemical) ^e ↓ Not pH extreme, no pH data or extreme pH with data showing low/no acid/alkaline reserve ↓	→ pH ≤ 2 or ≥ 11.5 with high acid/alkaline reserve or no data for acid/alkaline reserve	→ Classify as causing serious eye damage

Figure 3.3.1: Tiered evaluation for serious eye damage/eye irritation (see also Figure 3.2.1)			
Step	Parameter	Finding	Conclusion
5:	Validated Structure Activity Relationship (SAR) methods ↓ No/Insufficient data ↓	→ Severe damage to eyes →	Deemed to cause serious eye damage
		→ Eye irritant →	Deemed to be eye irritant ^b
		→ Skin corrosive →	Deemed to cause serious eye damage
6:	Consideration of the total weight of evidence ^f ↓	→ Serious eye damage →	Deemed to cause serious eye damage
		→ Eye irritant →	Deemed to be eye irritant ^b
7:	Not classified		

^a 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 from accident or poison centre databases can provide evidence for classification absence of incidents is not itself evidence for no classification as exposures are generally unknown or uncertain;

^b Classify in the appropriate category as applicable;

^c Existing animal data should be carefully reviewed to determine if sufficient serious eye damage/eye irritation evidence is available through other, similar information. It is recognized that not all skin irritants are eye irritants. Expert judgment should be exercised prior to making such a determination;

^d 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;

^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 substance should be considered and an overall determination made on the total weight of evidence. This is especially true when there is conflict in information available on some parameters. The weight of evidence including information on skin irritation may lead to classification for eye irritation. Negative results from applicable validated in vitro tests are considered in the total weight of evidence evaluation.

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 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.

- (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 spraying².

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 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 3.3.3.1.2) since pH will 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.

² *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.*

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 to the skin or seriously damaging to the eye/eye irritating at a concentration of < 1% (corrosive to the skin or seriously damaging to the eye) 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	
	Serious eye damage	Eye irritation
	Category 1	Category 2/2A
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 Category 2B when all relevant ingredients are classified as eye Category 2B.

Table 3.3.4: Concentration of ingredients of a mixture when 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.

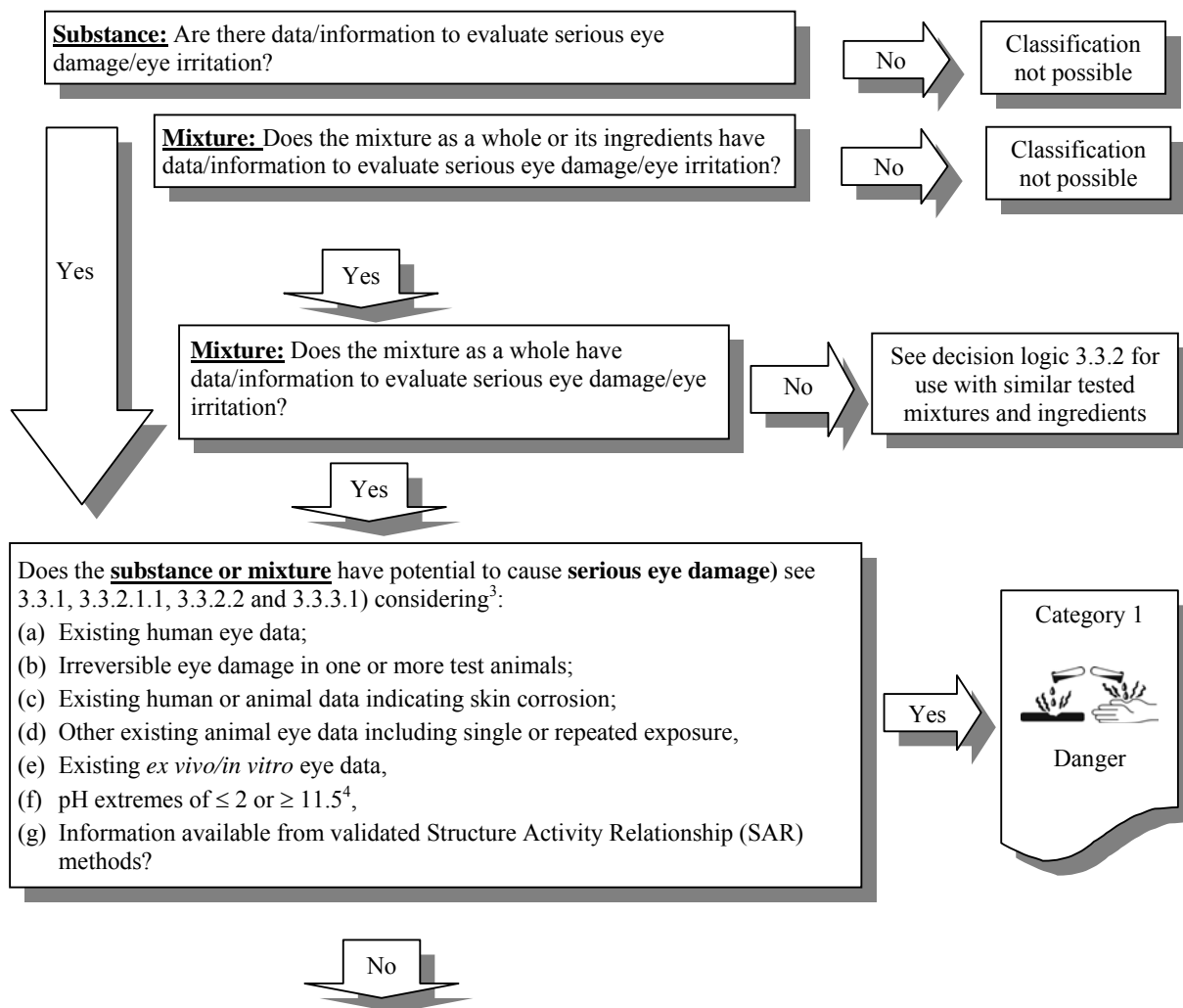
Table 3.3.5: Label elements for serious eye damage/eye irritation ^a

	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 1.4, para. 1.4.10.5.3.3).

3.3.5 Decision logic

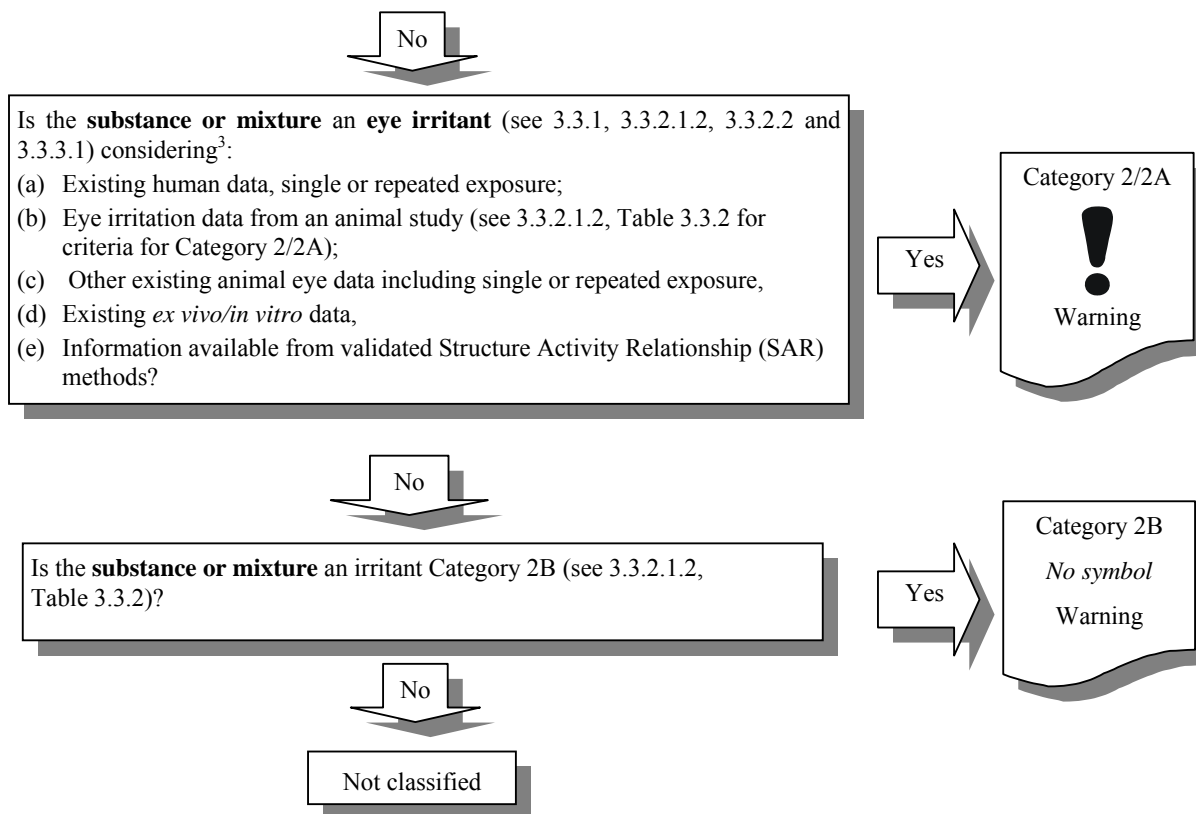
The decision logic which follows is not part of the harmonized classification system but is provided here as additional guidance. It is strongly recommended that the person responsible for classification study the criteria before and during use of the decision logic.

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

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³ Taking into account consideration of the total weight of evidence as needed.

⁴ Not applicable if consideration of pH and acid/alkaline reserve indicates the substance or mixture may not cause serious eye damage and confirmed by other data, preferably by data from an appropriate validated *in vitro* test.

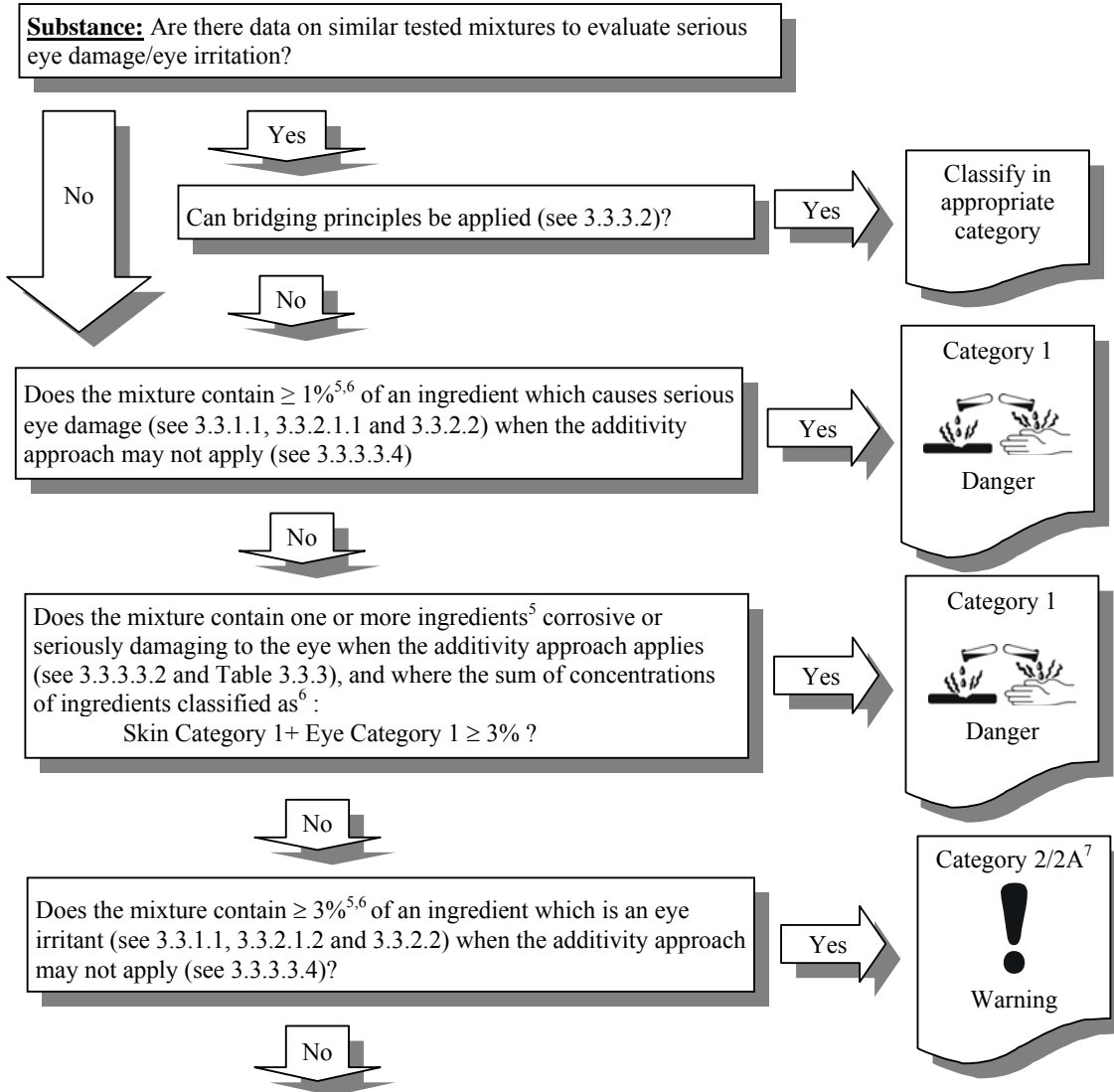


³ Taking into account consideration of the total weight of evidence as needed.

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 ingredients

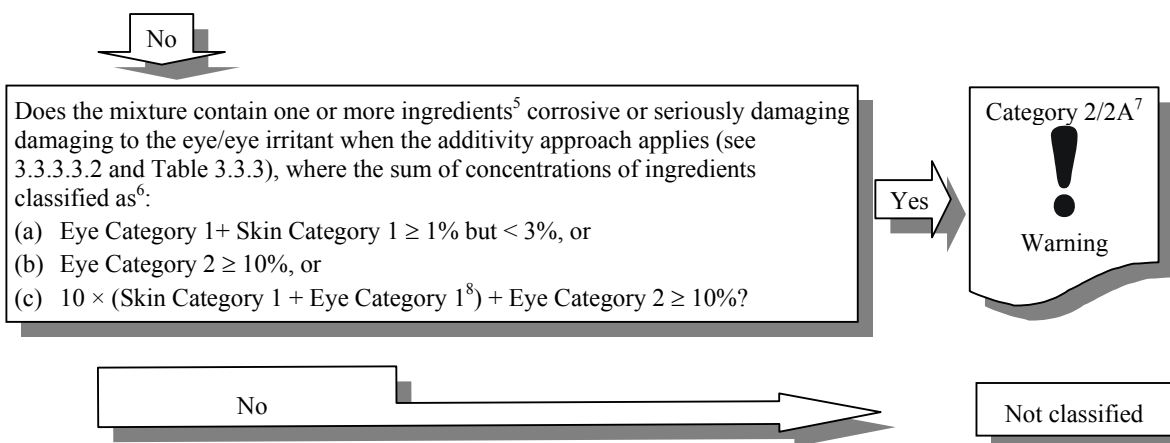


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⁵ Where relevant $< 1\%$, see 3.3.3.3.1.

⁶ For specific concentration limits, see 3.3.3.3.5 and 3.3.3.3.6. See also Chapter 1.3, para. 1.3.3.2 for "Use of cut-off values/concentration limits".

⁷ A mixture may be classified as eye Category 2B in case all relevant ingredients are classified as eye Category 2B.



⁵ Where relevant < 1%, see 3.3.3.3.1.

⁶ For specific concentration limits, see 3.3.3.3.6. See also Chapter 1.3, para. 1.3.3.2 for "Use of cut-off values/concentration limits".

⁷ A mixture may be classified as eye Category 2B in case all relevant ingredients are classified as eye Category 2B.

⁸ If an ingredient is classified as both skin Category 1 and eye Category 1 its concentration is considered only once in the calculation.

3.3.5.3 *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 criteria do 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) at least in 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)

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) at least in 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) at least in 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.
-