



**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****Twenty-fourth session**

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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****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 3.3¹****Introduction**

1. The mandate of the informal correspondence group was to undertake an editorial revision of chapters 3.2 and 3.3. The work started in the biennium 2009–2010 and has now been completed.
2. As regards item (e)(iii) of its mandate², the informal correspondence group did not identify any particular criteria which would need alignment/adjustment with respect to the internal consistency of chapters 3.2 and 3.3.
3. This document contains the proposed list of amendments to Chapter 3.3 which were considered necessary and were agreed by the informal correspondence group. The full text of Chapter 3.3 including the amendments listed in this document in track-changes mode is circulated as informal document INF.4. The full version of Chapter 3.2, as amended, is circulated as informal document INF.4/Add.1.

¹ In accordance with the programme of work of the Sub-Committee for 2011-2012 approved by the Committee at its fifth session (refer to ST/SG/AC.10/C.3/76, para. 116 and ST/SG/AC.10/38, para. 16).

² Refer to document ST/SG/AC.10/C.4/10, Annex II, item 1 (e).

4. The Sub-Committee is invited to consider the amendments listed hereafter for adoption.

Proposal

5. Amend Chapter 3.3 as follows:

3.3.1 Amend the heading to read “Definitions and general considerations”.

Insert paragraph number “3.3.1.1” before the definition of “Serious eye damage”.

3.3.1.2 Insert a new paragraph to read as follows:

“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 Replace paragraphs 3.3.2.1, 3.3.2.2, 3.3.2.6, 3.3.2.7 and figure 3.3.1 with the following:

“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 Insert a new sub-heading to read as follows: “3.3.2.1 Classification based on standard animal test data”.

3.3.2.1.1 Former 3.3.2.8 becomes new 3.3.2.1.1 with the following amendments:

- Amend the heading to read as follows: “Serious eye damage (Category 1)/Irreversible effects on the eye”
- In the first sentence, delete “harmonized” and insert “(Category 1)” before “is adopted”
- In the second sentence, delete “- Category 1 (irreversible effects on the eye) -” and replace “includes the criteria listed below” with “includes as criteria the observations listed in Table 3.3.1”.

- In the last sentence, replace “Hazard classification: Category 1” with “Hazard classification as Category 1” and “detected in a Draize eye test with rabbits” with “observed in at least 2 of 3 tested animals,”.

Table 3.3.1 Replace the table and its related note with the following:

"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	A substance that produces: <ul style="list-style-type: none"> (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: <ul style="list-style-type: none"> (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 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 The heading of former 3.3.2.9 becomes new 3.3.2.1.2 with the following amendments:

- Insert “Eye irritation (Category 2)” before “Reversible”
- Delete “(Category 2)” at the end.

3.3.2.1.2.1 and 3.3.2.1.2.2 Insert the following two new paragraphs:

“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 Former sentence under Table 3.3.2 “For those substances where...in determining the classification” becomes new paragraph 3.3.2.1.2.3.

Table 3.3.2 Replace with the following:

	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 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 Insert a new sub-heading to read as follows: “3.3.2.2 Classification in a tiered approach”

3.3.2.2.1 The first sentence of former 3.3.2.6 becomes new paragraph 3.3.2.2.1 with the following amendments:

- Insert “(Figure 3.3.1)” after “applicable”
- Replace “that all elements may not be relevant in certain cases.” with “that not all elements may be relevant.”

3.3.2.2.2 The second and sixth sentences of former 3.3.2.4 (“Accumulated human...effects on the eye” and “Possible skin...corrosive substances”) become new paragraph 3.3.2.2.2 with the following amendments:

- In the first sentence, replace “Accumulated” with “Existing”, “experience” with “data”, “analysis as it gives” with “evaluation as they give”.
- In the second sentence, insert “any testing for” after “consideration of”.

3.3.2.2.3 The seventh sentence of former 3.3.2.4 (“*In vitro* alternatives...decisions”) becomes new paragraph 3.3.2.2.3 with the following amendment: replace “may” with “should”.

3.3.2.2.4 The fourth and fifth sentences of former 3.3.2.4 (“Likewise, pH... effects on the eyes”) become new paragraph 3.3.2.2.4 with the following amendments:

- In the first sentence, replace “produce” with “indicate” and amend the end to read: “significant acid/alkaline reserve (buffering capacity)”.
- Amend the beginning of the second sentence to read: “Generally such substances”
- Add the following new sentences at the end of the second sentence:

“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 The third sentence of former 3.3.2.4 (“In some cases...hazard decisions”) becomes new 3.3.2.5 with the following amendments:

Replace “enough” with “sufficient”, “compounds” with “substances” and “hazard” with “classification”.

3.3.2.2.6 Former 3.3.2.7 becomes new 3.3.2.2.6 with the following amendments:

- Amend the beginning to read “The tiered approach provides guidance” and delete “on a test material”.
- Insert the last sentence of former 3.3.2.5 (“Animal testing...whenever possible”) as the new second sentence.
- Insert the second and third sentences of former 3.3.2.4 (“Although information...but not all parameters”) as the last sentences of the new paragraph, with the following amendments:
 - Replace “(e.g. caustic alkalis with extreme pH should be considered as local corrosives), there is merit in considering” with “(see 3.3.2.1.1) consideration should be given to”.
 - Insert “conflict in” before “information” and delete “but not all”.

Figure 3.3.1 Replace the figure and its related notes with the following:

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

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

Step	Parameter	Finding	Conclusion
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
5:	Validated Structure Activity Relationship (SAR) methods ↓ No/Insufficient data ↓	→ Severe damage to eyes → Eye irritant → Skin corrosive	→ Deemed to cause serious eye damage → Deemed to be eye irritant ^b → Deemed to cause serious eye damage
6:	Consideration of the total weight of evidence ^f ↓	→ Serious eye damage → Eye irritant	→ Deemed to cause serious eye damage → 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”.

- 3.3.3.1 Renumber the two paragraphs currently under 3.3.3.1 as 3.3.3.1.1 and 3.3.3.1.2.
- 3.3.3.1.1 Replace “will” with “should” and amend the end to read: “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 Delete the first sentence (“Unlike...to perform”).
- In the second sentence, replace: “manufacturers” with “classifiers”; “strategy” with “approach” and “as well as avoid” with “as well as to avoid”.
- Amend the beginning of the third sentence, to read as follows: “In the absence of any other information, a mixture is considered...”
- Amend the last sentence to read as follows: “
- “However, if consideration of alkali/acid 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 data from an appropriate validated *in vitro* test.”
- 3.3.3.2.1 In the first sentence, insert “eye” before “irritation”.
- 3.3.3.2.2 Replace “irritancy” with “eye irritation” and “corrosivity” with “damage”.
- 3.3.3.2.3 Replace “irritation/serious eye damage” with “serious eye damage/eye irritation” and “toxicity” with “serious eye damage/eye irritation potential”.
- 3.3.3.2.4 In the heading, insert “eye” before “irritation”
- In the first sentence:
- replace “in the highest category for serious eye damage” with “for serious eye damage (Category 1)”.
 - replace “in the highest serious eye damage Category 1” with “for serious eye damage (Category 1)”.

In the second sentence:

- replace “in the highest sub-category for skin/eye irritation” with “for eye irritation (Category 2 or 2A)”
- replace “in the highest irritation category” with “in the same category (Category 2 or 2A)”.

3.3.3.2.5 In the heading and in the paragraph, replace “toxicity” with “hazard” (twice)
In the paragraph, replace “irritation/serious eye damage” with “serious eye damage/eye irritation” (twice).

3.3.3.2.6 In (d), replace “irritation/serious eye damage” with “serious eye damage/eye irritation” and “toxicity” with “serious eye damage/eye irritation potential”

3.3.3.2.7 Replace “form of the mixture” with “form of mixture” and “irritation or corrosive properties” with “serious eye damage/eye irritation properties”.

3.3.3.3.1 Replace “eye irritation/serious eye damaging properties” with “serious eye damage/eye irritation properties” and “eye irritation/serious eye damage” with “serious eye damage/eye irritation”.

3.3.3.3.2 In the first sentence:

- Delete “eye irritant or” and insert “or eye irritant” before “when data”
- Replace “each corrosive or irritant ingredient” with “each corrosive or serious eye damaging/eye irritant ingredient”
- Replace “overall irritant or corrosive properties” with “overall serious eye damage/eye irritation properties”

In the second sentence:

- Insert “and serious eye damaging” before “ingredients”
- Replace “mixture as an irritant” with “mixture as serious eye damaging/eye irritant”

3.3.3.3.3 Amend the end of the paragraph to read: “classified as seriously damaging to the eye or an eye irritant”

3.3.3.3.4 In the second sentence, replace “many of such substances are corrosive or irritant” with “many such substances are seriously damaging to the eye/eye irritating”.

In the third sentence:

- replace “criteria (see 3.3.3.1)” with “criterion (see 3.3.3.1.2)”;
- insert “(subject to consideration of acid/alkali reserve)” after “eye damage”
- replace “of Table 3.3.3” with “in Table 3.3.3”.

In the fourth sentence:

- replace “corrosive or irritant ingredients” with “corrosive or serious eye damaging/eye irritating ingredients”
- replace “≥ 1% of a corrosive ingredient” with “≥ 1% of a corrosive or serious eye damaging ingredient”

- replace “ $\geq 3\%$ of an irritant ingredient” with “ $\geq 3\%$ of an eye irritant ingredient”
- 3.3.3.3.5 Replace (twice) “reversible/irreversible eye effects” with “irreversible/reversible eye effects” and “strategy” with “approach”.
- 3.3.3.3.6 Replace:
- “may be corrosive or irritant” with “may be corrosive to the skin or seriously damaging to the eye/eye irritating”;
 - “(corrosive)” with “(corrosive to the skin or seriously damaging to the eye)”;
 - “(irritant)” with “(eye irritant)”.

Table 3.3.3 Replace with the following:

“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	$\geq 3\%$	$\geq 1\%$ but $< 3\%$
Eye Category 2		$\geq 10\%$ ^b
$10 \times$ (Skin Category 1 + Eye Category 1) ^a + 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 In the title replace “for which the additivity” with “when the additivity”.

In the third and fourth rows under “Ingredient”, insert “Eye” before “Category” and replace “ingredients for which additivity do not apply” with “ingredient”

In the fourth row, replace “Other irritant” with “Other eye irritant”

Table 3.3.5 Insert a reference to a new note “a” in the heading, as follows:

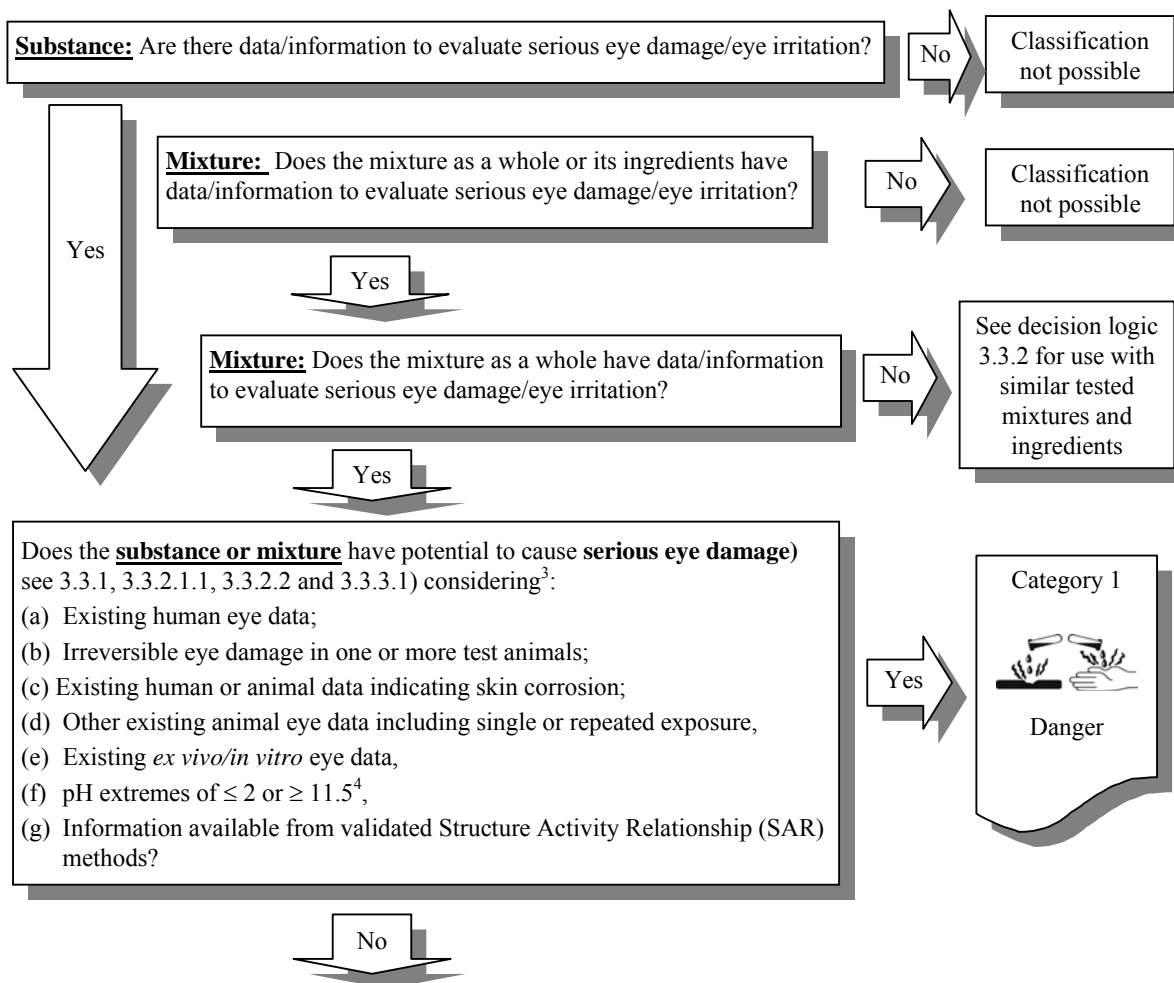
“Label elements for serious eye damage/irritation^{9b}”

Insert the following note “a” under the table

^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).”

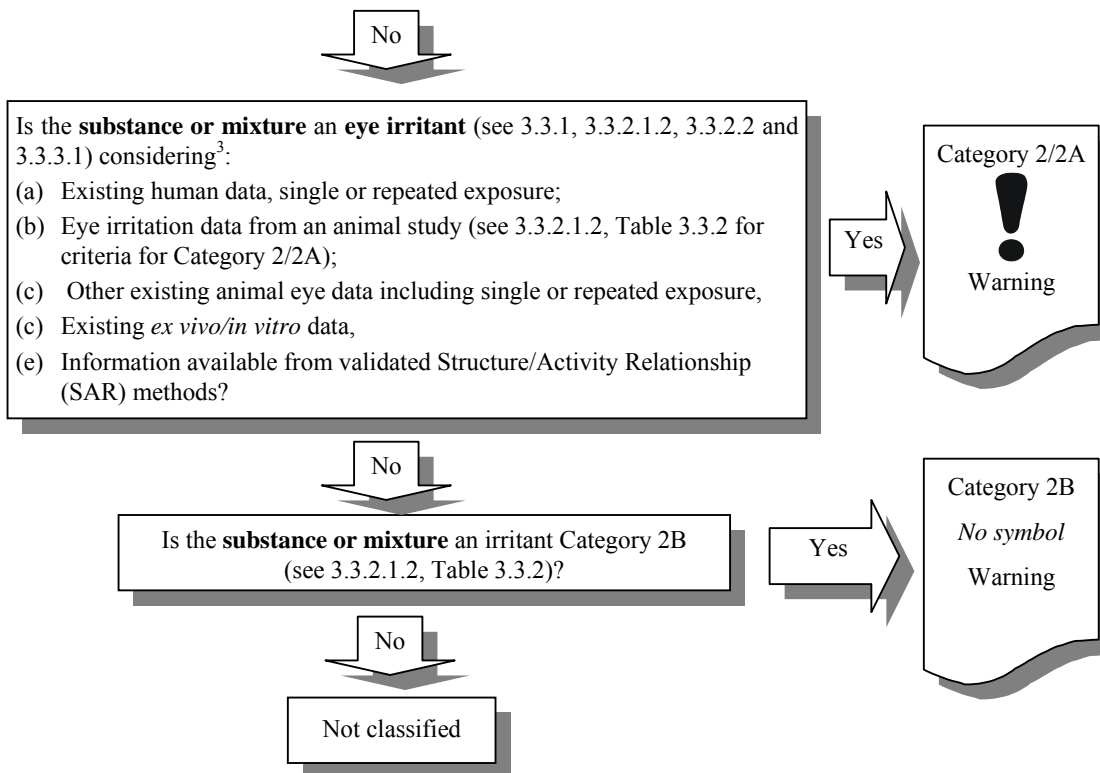
3.3.5.1 Replace decision logic 3.3.1 and its related footnotes with the following:

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



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.”

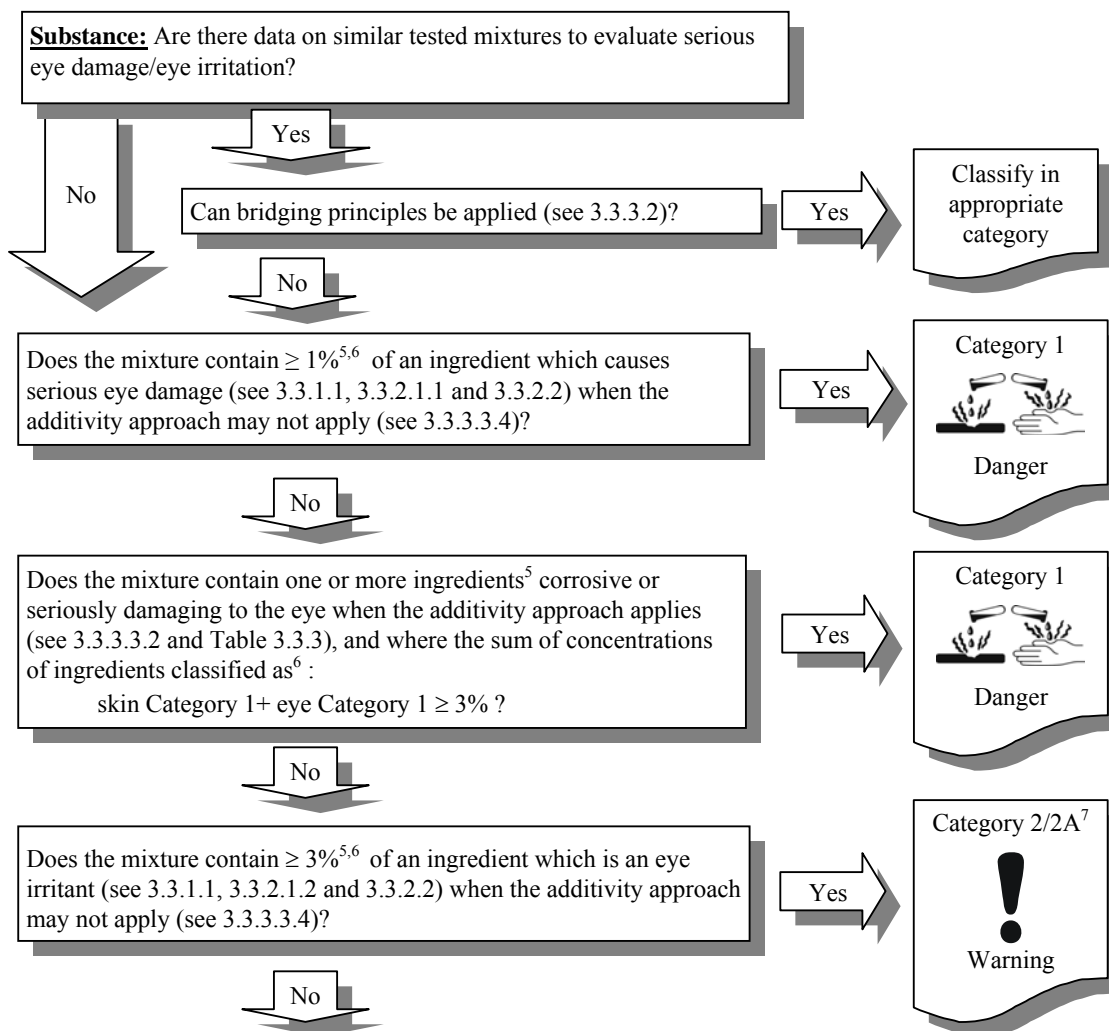


³ Taking into account consideration of the total weight of evidence as needed.”

3.3.5.2 Replace decision logic 3.3.2 with the following:

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

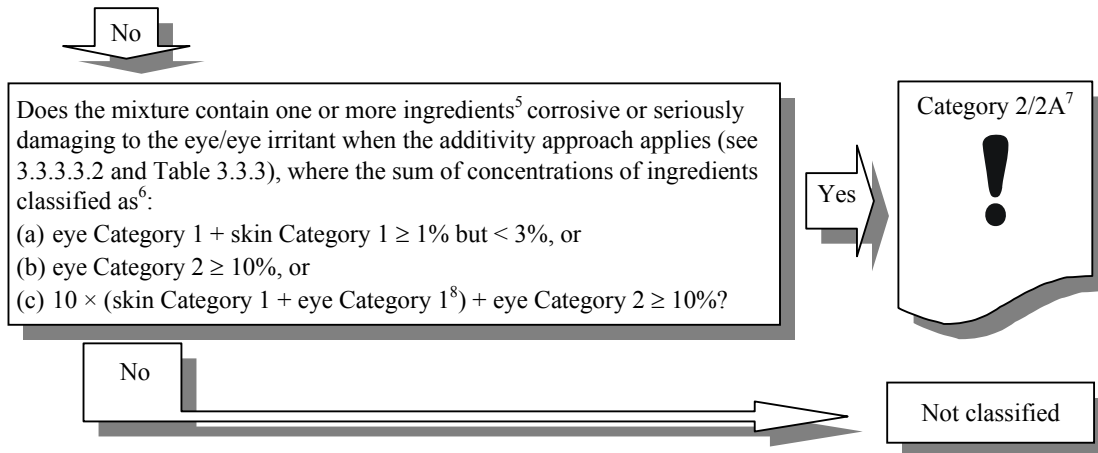
Classification of mixtures on the basis of information/data on similar tested mixtures and ingredients



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 3.3.3.3.5 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."

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 Insert a new sub-section to read as follows:

“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 \geq 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.
-