**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**
                                                        **17 September 2012**

**Twenty-fourth session**
Geneva, 12 – 14 December 2012
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 (track-changes)

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

This document contains the text of Chapter 3.3 as amended in accordance with the proposed list of amendments in document ST/SG/AC.10/C.4/2012/12, as agreed by the informal correspondence group. Amendments are shown in visible mode ("track-changes").

The full text of Chapter 3.3 as amended (i.e. with all the suggested changes accepted) is circulated as INF.4/Add.1.

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**"CHAPTER 3.3**

**SERIOUS EYE DAMAGE /EYE IRRITATION**

**3.3.1        Definitions and general considerations**

3.3.1.1        *Serious eye damage* is the production of tissue damage in the eye, or serious physical decay of vision, following application of a test substance to the anterior surface of the eye, which is not fully reversible within 21 days of application[1] .

*Eye irritation* is the production of changes in the eye following the application of test substance to the anterior surface of the eye, which are fully reversible within 21 days of application[1].

3.3.1.2        In a tiered approach, emphasis should be placed upon existing human data, followed by existing animal data, followed by *in vitro* data and then other sources of information. Classification results directly when the data satisfy the criteria. In 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.~~2.8~~2.1.1        ~~Irreversible effects on the eye/s~~Serious *eye* damage ~~to eyes~~ (Category 1)/*Irreversible effects on the eye***

A single ~~harmonized~~ hazard category (Category 1) is adopted for substances that have the potential to seriously damage the eyes. This hazard category  ~~Category 1 (irreversible effects on the eye)~~  includes as criteria the ~~criteria~~ observations listed ~~below~~ 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

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

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 classification̶ as Category 1 also contains substances fulfilling the criteria of corneal opacity ≥ 3 or iritis > 1.5 ~~detected in a Draize eye test with rabbits~~observed in at least 2 of 3 tested animals, because severe lesions like these usually do not reverse within a 21-̶days observation period.

**Table 3.3.1:  Serious eye damage/Irreversible eye effects categor~~ies~~y[a,b,c]**

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

~~An eye irritant Category 1 (irreversible effects on the eye) is a test material that produces:~~

~~(a)   at least in one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days; and/or~~

~~(b)   at least in 2 of 3 tested animals, a positive response of:~~

~~(i)   corneal opacity ≥ 3; and/or~~

~~(ii)  iritis > 1.5;~~

~~calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material.~~

[a]    *The use of human data is ~~discussed~~ addressed in 3.3.2.2 and in c~~C~~hapters 1.1~~,~~ (para.~~graph~~ 1.1.2.5 (c)) ("Purpose, scope and application"~~and~~ ~~in~~ ~~Chapter~~ 1.3~~,~~ (para.~~graph~~ 1.3.2.4.7). ("Classification of hazardous substances and mixtures").*

[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.~~9~~1.2      *Eye irritation (Category 2)/~~Reversible effects on the eye~~ ~~(Category 2)~~***

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

3.3.2.1.2.2        For ~~T~~those authorities ~~desiring~~ 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. ~~f~~For substances inducing eye irritant effects reversing within an observation time of 7 days, Category 2B applies.

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

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 ~~in~~ 2 of 3 tested animals a positive response of:<br>(~~i~~a)    corneal opacity $\geq$ 1; and/or<br>(~~ii~~b)    iritis $\geq$ 1; and/or<br>(~~iii~~c)    conjunctival redness $\geq$ 2; and/or<br>(~~iv~~d)    conjunctival oedema (chemosis) $\geq$ 2<br>calculated as the mean scores following grading at 24, 48 and 72 hours after ~~installation~~ instillation of the test material, and  which fully reverses within an  observation period of normally 21 days. |
| **Category 2B** | Within ~~this category~~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.*

~~**An eye irritant Category 2A (irritating to eyes)** is a test material that produces:~~

~~(a)   at least in 2 of 3 tested animals a positive response of:~~

~~(i)   corneal opacity $\geq$ 1; and/or~~

~~(ii)  iritis $\geq$ 1; and/or~~

~~(iii) conjunctival redness $\geq$ 2; and/or~~

~~(iv) conjunctival oedema (chemosis) $\geq$ 2~~

~~calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material, and  which fully reverses within an  observation period of normally 21 days.~~

~~Within this category an eye irritant is considered **mildly irritating to eyes (Category 2B)** when the effects listed above are fully reversible within 7 days of observation.~~

**3.3.2.2**         ***Classification in a tiered approach***

3.3.2.2.1~~3.3.2.6~~  A tiered approach to the evaluation of initial information should be considered where applicable (Figure 3.3.1), recognizing that not all elements may ~~not~~ be relevant ~~in certain cases.  The tiered approach explained in~~

~~Figure 3.3.1 was developed with contributions from (inter)national centres and committees for the testing and validation of alternatives to animal testing during a workshop in Solna, Sweden[2].~~

3.3.2.2.2 ~~Accumulated~~ Existing human and animal ~~experience~~ data should be the first line of ~~analysis~~evaluation, as ~~it~~ they ~~gives~~ 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 ~~may~~ should be used to make classification decisions.

3.3.2.2.4 Likewise, pH extremes like $\leq 2$ and $\geq 11.5$, may ~~produce~~ indicate serious eye damage, especially when associated with significant acid/alkaline reserve (buffering capacity). Generally, ~~S~~such ~~agents~~ 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 $\leq 2$ or $\geq 11.5$. 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 ~~enough~~ sufficient information may be available from structurally related ~~compounds~~ substances to make ~~hazard~~ classification decisions.

~~3.3.2.1 A tiered testing and evaluation scheme is presented that combines pre-existing information on serious ocular tissue damage and on eye irritation (including data relating to historical human or animal experience) as well as considerations on structure-activity relationships (SAR) and the output of validated *in vitro* tests in order to avoid unnecessary animal testing.~~

~~3.3.2.2 The proposals for classification of eye irritation and serious damage to the eye include elements that are harmonized and will be used by all authorities as well as optional sub-categories that will be applied by only some authorities (e.g. authorities classifying pesticides).~~

~~The harmonized system includes guidance on the data elements that must be evaluated before animal testing for eye damaging effects is undertaken. It also includes hazard categories for local lesions on the eyes.~~

~~3.3.2.3 Before there is any *in vivo* testing for serious eye damage/eye irritation, all existing information on a test material should be reviewed. Preliminary decisions can often be made from existing data as to whether an agent causes serious (i.e. irreversible) damage to the eyes. If a test material can be classified, no testing is required. A highly recommended way of evaluating existing information on agents or of approaching new uninvestigated substances, is to utilize a tiered testing strategy for serious eye damage and eye irritation.~~

~~3.3.2.4 Several factors should be considered in determining the serious eye damage or irritation potential of substances before testing is undertaken. Accumulated human and animal experience should be the first line of analysis, as it gives information directly relevant to effects on the eye. In some cases enough information may be available from structurally related compounds to make hazard decisions. Likewise, pH extremes like $\leq 2$ and $\geq 11.5$, may produce serious eye damage, especially when associated with significant buffering capacity. Such agents are expected to produce significant effects on the eyes. Possible skin corrosion has to be evaluated prior to consideration of serious eye damage/eye irritation in order to avoid testing for local effects on eyes with skin corrosive substances. *In vitro* alternatives that have been validated and accepted may be used to make classification decisions.~~

~~3.3.2.7~~ 3.3.2.2.6 ~~Where data needed for such a testing strategy cannot be required, the~~ The ~~proposed~~ tiered ~~testing~~ approach provides ~~good~~ guidance on how to organize existing information ~~on a test material~~ and to make a weight-of-evidence decision about hazard assessment and hazard classification (ideally without conducting new animal tests).

~~3.3.2.5        All the above information that is available on a substance should be used in determining the need for *in vivo* eye irritation testing~~. 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) ~~(e.g. caustic alkalis with extreme pH should be considered as local corrosives), there is merit in considering~~ 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 ~~but not all~~ parameters. ~~Generally, primary emphasis should be placed upon expert judgement, considering human experience with the substance, followed by the outcome of skin irritation testing and of well validated alternative methods. Animal testing with corrosive substances should be avoided whenever possible.~~
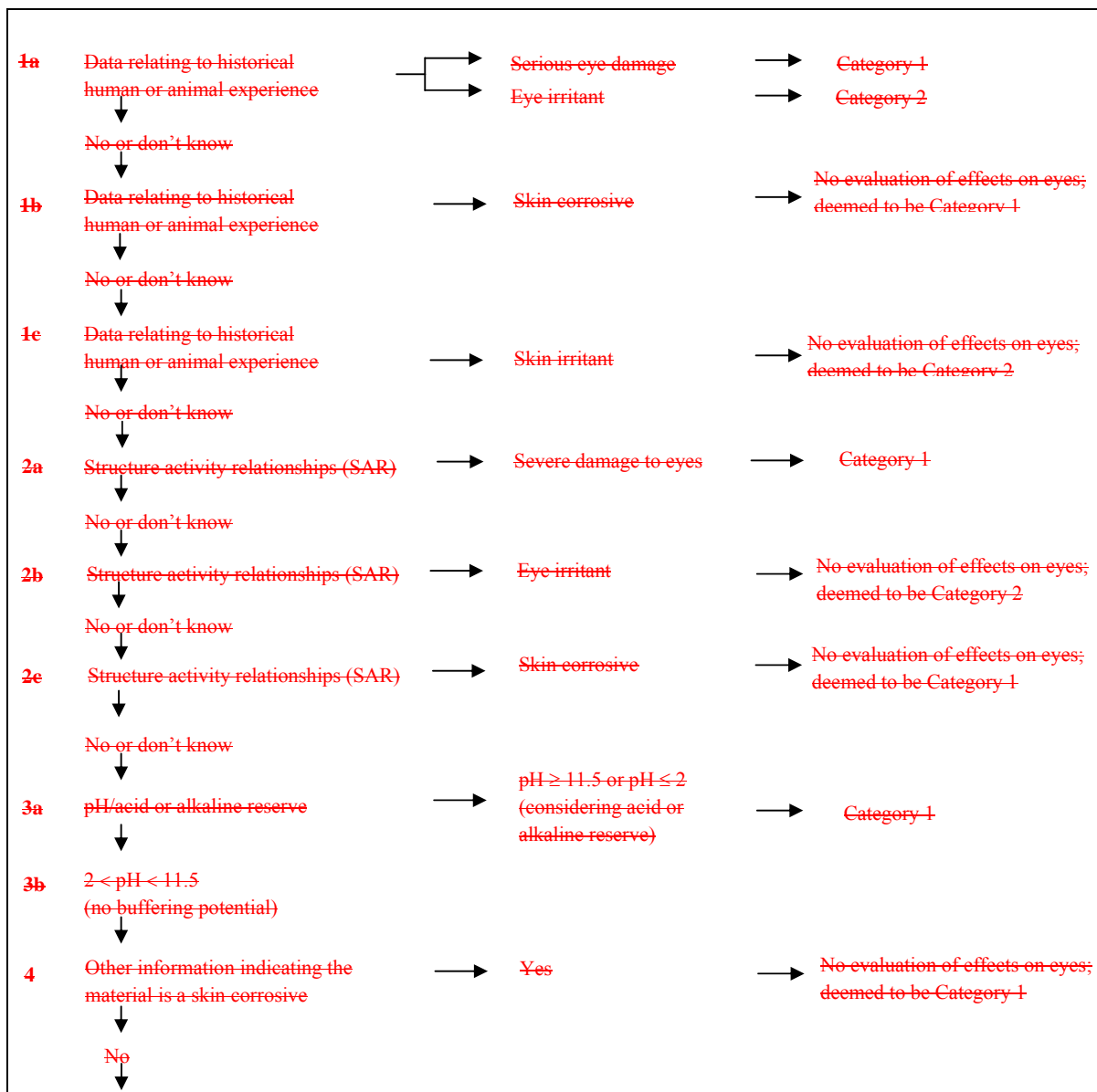
~~3.3.2.6        A tiered approach to the evaluation of initial information should be considered where applicable, recognizing that all elements may not be relevant in certain cases.  The tiered approach explained in Figure 3.3.1 was developed with contributions from (inter)national centres and committees for the testing and validation of alternatives to animal testing during a workshop in Solna, Sweden[3].~~

~~3.3.2.7        Where data needed for such a testing strategy cannot be required, the proposed tiered testing approach provides good guidance on how to organize existing information on a test material and to make a weight-of-evidence decision about hazard assessment and hazard classification (ideally without conducting new animal tests).~~

~~**Figure 3.3.1:  Testing and evaluation strategy for serious eye damage and eye irritation**~~
~~**(see also: "Testing and evaluation strategy for skin irritation/corrosion" Figure 3.2.1)**~~

| ~~Step~~ | ~~Parameter~~ | ~~Findings~~ | ~~Conclusions~~ |
|---|---|---|---|

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~~[3]   OECD (1996). Final Report of the OECD Workshop on Harmonization of Validation and Acceptance Criteria for Alternative Toxicological Test Methods.~~

**1a** — Data relating to historical human or animal experience → Serious eye damage → Category 1

Eye irritant → Category 2

No or don't know

**1b** — Data relating to historical human or animal experience → Skin corrosive → No evaluation of effects on eyes; deemed to be Category 1

No or don't know

**1c** — Data relating to historical human or animal experience → Skin irritant → No evaluation of effects on eyes; deemed to be Category 2

No or don't know

**2a** — Structure activity relationships (SAR) → Severe damage to eyes → Category 1

No or don't know

**2b** — Structure activity relationships (SAR) → Eye irritant → No evaluation of effects on eyes; deemed to be Category 2

No or don't know

**2c** — Structure activity relationships (SAR) → Skin corrosive → No evaluation of effects on eyes; deemed to be Category 1

No or don't know

**3a** — pH/acid or alkaline reserve → pH ≥ 11.5 or pH ≤ 2 (considering acid or alkaline reserve) → Category 1

**3b** — 2 < pH < 11.5 (no buffering potential)

**4** — Other information indicating the material is a skin corrosive → Yes → No evaluation of effects on eyes; deemed to be Category 1

No

*(Cont'd on next page)*

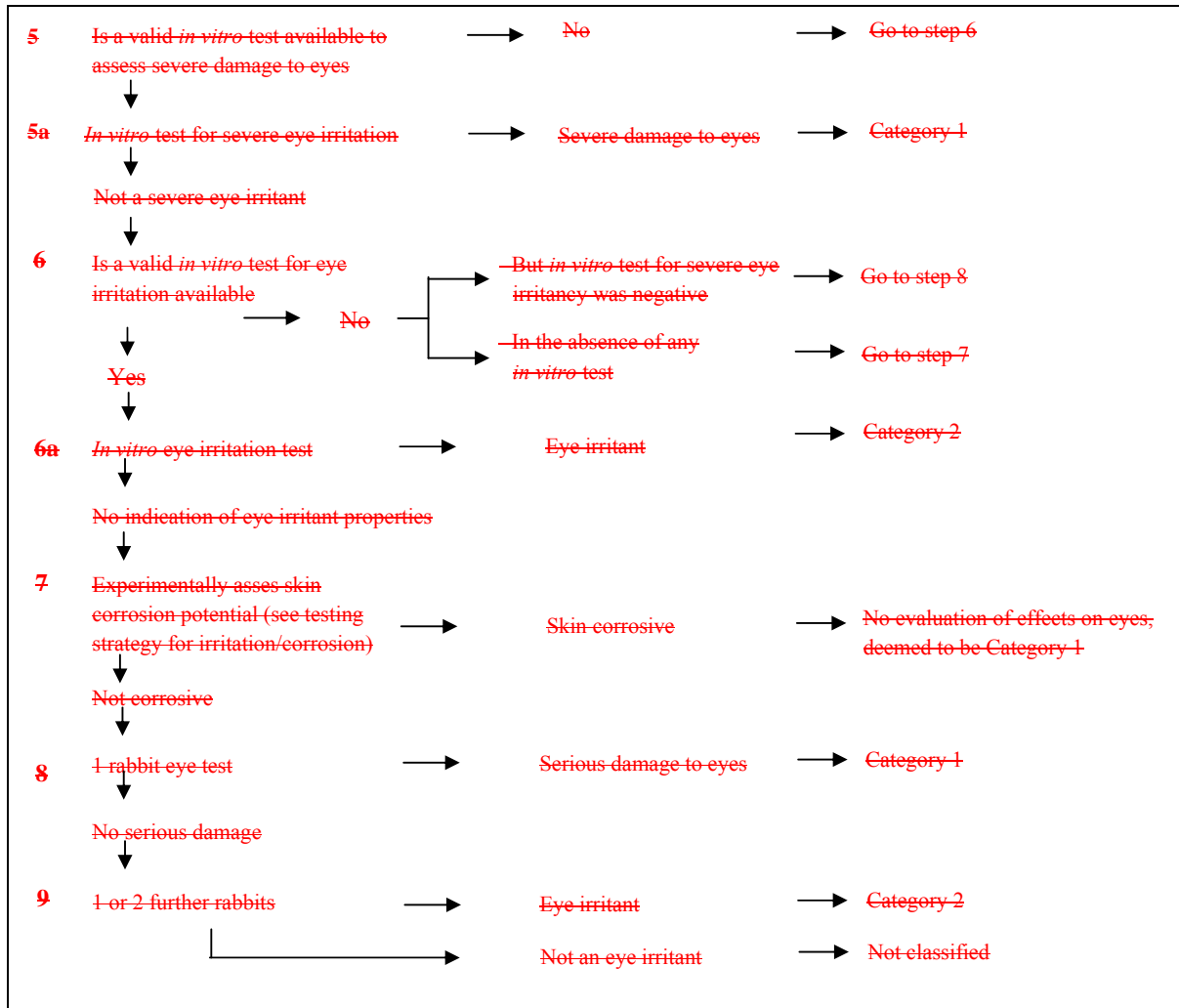**Figure 3.3.1: Testing and evaluation strategy for serious eye damage and eye irritation (see also: "Testing and evaluation strategy for skin irritation/corrosion" Figure 3.2.1)**

| Step | Parameter | Findings | Conclusions |
|------|-----------|----------|-------------|

**5** ~~Is a valid *in vitro* test available to assess severe damage to eyes~~ → ~~No~~ → ~~Go to step 6~~

**5a** ~~*In vitro* test for severe eye irritation~~ → ~~Severe damage to eyes~~ → ~~Category 1~~

~~Not a severe eye irritant~~

**6** ~~Is a valid *in vitro* test for eye irritation available~~ → ~~No~~ → ~~But *in vitro* test for severe eye irritancy was negative~~ → ~~Go to step 8~~

~~In the absence of any *in vitro* test~~ → ~~Go to step 7~~

~~Yes~~

**6a** ~~*In vitro* eye irritation test~~ → ~~Eye irritant~~ → ~~Category 2~~

~~No indication of eye irritant properties~~

**7** ~~Experimentally asses skin corrosion potential (see testing strategy for irritation/corrosion)~~ → ~~Skin corrosive~~ → ~~No evaluation of effects on eyes, deemed to be Category 1~~

~~Not corrosive~~

**8** ~~1 rabbit eye test~~ → ~~Serious damage to eyes~~ → ~~Category 1~~

~~No serious damage~~

**9** ~~1 or 2 further rabbits~~ → ~~Eye irritant~~ → ~~Category 2~~

~~Not an eye irritant~~ → ~~Not classified~~

8

**Figure 3.3.1:** ~~Testing and~~Tiered evaluation ~~strategy~~ for serious eye damage/~~and~~ eye irritation
(see also~~: "Testing and evaluation strategy for skin irritation/corrosion"~~ Figure 3.2.1)

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

**5:** Validated Structure Activity
Relationship (SAR) methods → Eye irritant → Deemed to be **eye irritant** [b]

↓ ↘ Skin corrosive → Deemed to cause **serious eye damage**

No/Insufficient data
↓

**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**


*NOTES to Figure 3.3.1:*

*Step 1a/b:* *Data relating to historical human or animal experience: pre-existing information on eye irritation and skin corrosion are shown separately because evaluation of skin corrosion has to be considered if there is no information on local effects on eyes. Analysis of pre-existing experience with the substance may identify serious eye damage, corrosion and irritation potential for both skin and eye effects:*

    *(i)* *Step 1a - reliable determination of eye irritancy basing on human or animal experience - depends on expert judgement: in most cases human experience is based on accidental events and thus, the local effects detected after an accident have to be compared with classification criteria created for evaluation of animal test data;*

    *(ii)* *Step 1b - evaluation of data on skin corrosivity - skin corrosive substances should not be instilled into the eyes of animals; such substances should be considered as leading to serious damage to the eyes as well (Category 1).*

*Step 2a/b/c:* *SAR (Structure Activity Relationships) for eye irritation and skin corrosion are shown separately but in reality would probably be done in parallel. This stage should be completed using validated and accepted SAR approaches. The SAR analysis may identify serious eye damage, corrosion and irritation potential for both skin and eye effects:*

    *(i)* *Step 2a - reliable determination of eye irritancy only by theoretical evaluations - in most cases it will only be appropriate for substances that are homologous to agents with very well known properties;*

    *(ii)* *Step 2c - theoretical evaluation of skin corrosivity - skin corrosive substances should not be instilled into the eyes of animals; such substances should be considered as leading to serious damage to the eyes as well (Category 1).*

*Step 3:* *pH extremes like ≤ 2 and ≥ 11.5 may indicate strong local effects, especially in combination with assessment of acid or alkaline reserve, substances exhibiting such physico-chemical properties should be considered as leading to serious damage to eyes (Category 1).*

*Step 4:* *All attainable information should be used, including human experience. But this information should be restricted to that which pre-exists (e.g. the results of a skin $LD_{50}$ test or historical information on skin corrosion).*

*Step 5:* *These must be alternative methods for the assessment of eye irritation/or serious damage to eyes (e.g. irreversible corneal opacity) which have been validated in accordance with internationally agreed principles and criteria (see section 1.3.2 in Chapter 1.3).*

*Step 6:* ~~At present this step seems not to be achievable in the near future. Validated alternative methods for the reliable assessment of (reversible) eye irritation need to be developed.~~

*Step 7:* ~~In the absence of any other relevant information, it is essential to obtain this via an internationally recognized corrosion/irritation test before proceeding to a rabbit eye irritation test. This must be conducted in a staged manner. If possible, this should be achieved using a validated, accepted in vitro skin corrosivity assay. If this is not available, then the assessment should be completed using animal tests (see the skin irritation/corrosion strategy, section 3.2.2).~~

*Step 8:* ~~Staged assessment of eye irritation in vivo. If in a limit test with one rabbit serious damage to eyes is detected no further testing is needed.~~

*Step 9:* ~~Only two animals may be employed for irritation testing (including the one used for evaluation of possible serious effects) if these two animals give concordant clearly irritant or clearly non-irritant responses. In the case of different or borderline responses a third animal is needed. Depending on the result of this three-animal test, classification may be required or not.~~

[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 ~~will~~ should be classified using the criteria for substances, and taking into account the ~~testing and evaluation strategies used to develop~~ tiered approach to evaluate data for th~~is~~ese hazard class~~es~~ (as illustrated in Figure 3.3.1).

3.3.3.1.2 ~~Unlike other hazard classes, there are alternative tests available for skin corrosivity of certain types of chemicals that can give an accurate result for classification purposes, as well as being simple and relatively inexpensive to perform.~~ When considering testing of the mixture, ~~manufacturers~~ classifiers are encouraged to use a tiered weight of evidence ~~strategy~~ approach as included in the criteria for classification of substances for skin corrosion and serious eye damage/~~ and~~ eye irritation to help ensure an accurate classification, as well as to avoid unnecessary animal testing. In

the absence of any other information, ~~A~~a mixture is considered to cause serious eye damage (Eye Category 1) if it has a pH ≤ 2 or ≥ 11.5.  However, ~~I~~if consideration of alkali/acid reserve suggests the ~~substance or~~ mixture may not ~~have the potential to~~ cause serious eye damage despite the low or high pH value, ~~then further testing~~ this needs to be ~~carried out to confirm this~~confirmed by other data, preferably ~~by use of~~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 will be used in accordance with the following agreed bridging principles.  This ensures that the classification process uses the available data to the greatest extent possible in characterizing the hazards of the mixture without the necessity for additional testing in animals.

3.3.3.2.2          *Dilution*

          If a tested mixture is diluted with a diluent which has an equivalent or lower classification for serious eye damage/~~irritancy~~ eye irritation classification than the least ~~damaging~~damaging/~~irritant~~ irritant original ingredient and which is not expected to affect the ~~corrosivity~~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 ~~irritation/~~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~~toxicity~~ of the untested batch has changed.  If the latter occurs, a new classification is necessary.

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

          If a tested mixture classified ~~in the highest category~~ for serious eye damage (Category 1) is concentrated, the more concentrated untested mixture should be classified ~~in the highest~~for serious eye damage (~~e~~Category 1) without additional testing. If a tested mixture classified ~~in the highest sub-category~~ for ~~skin/~~eye irritation (Category 2 or 2A) is concentrated and does not contain serious eye damage ingredients, the more concentrated untested mixture should be classified in the ~~highest irritation~~same category (Category 2 or 2A) without additional testing.

3.3.3.2.5          *Interpolation within one ~~toxicity~~ hazard category*

          For three mixtures (A, B and C) with identical ingredients, where mixtures A and B have been tested and are in the same ~~irritation/~~serious eye damage/eye irritation ~~toxicity~~ hazard 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 ~~irritation/~~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 ~~irritation/~~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 ~~toxicity~~ of B.

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

3.3.3.2.7      *Aerosols*

An aerosol form of a mixture may be classified in the same hazard category as the tested non-aerosolized form of ~~the~~ mixture provided that the added propellant does not affect the serious eye damage/eye irritation ~~or corrosive~~ properties of the mixture upon spraying[2].

**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 ~~eye irritation/~~serious eye ~~damaging~~ damage/eye irritation properties of the mixtures, the following assumption has been made and is applied where appropriate in the tiered approach:

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

3.3.3.3.2      In general, the approach to classification of mixtures as ~~eye irritant or~~ 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 irrita~~nt~~tion ~~or corrosive~~ 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~~an~~ irritant. The mixture is classified as seriously damaging to the eye or eye irritant when the sum of the concentrations of such ingredients exceeds a threshold cut-off value/concentration limit.

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

3.3.3.3.4      Particular care must be taken when classifying certain types of chemicals such as acids and bases, inorganic salts, aldehydes, phenols~~,~~ and surfactants. The approach explained in 3.3.3.3.1 and 3.3.3.3.2 might not work given that many ~~of~~ such substances are ~~corrosive or irritant~~seriously damaging to the eye/eye irritating at concentrations < 1%. For mixtures containing strong acids or bases the pH should be used as classification ~~criteria~~ 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 ~~of~~ in Table 3.3.3. A mixture containing corrosive or serious eye damaging/eye irrita~~nt~~ing ingredients that cannot be classified based on the additivity approach applied in Table 3.3.3 due to chemical characteristics that make this approach unworkable, should be classified as Eye Category 1 if it contains ≥ 1% of a corrosive or serious eye damaging ingredient and as Eye Category 2 when it contains ≥ 3% of an eye irritant ingredient.

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[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.*

Classification of mixtures with ingredients for which the approach in Table 3.3.3 does not apply is summarized in Table 3.3.4.

3.3.3.3.5    On occasion, reliable data may show that the ~~reversible/~~irreversible/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 ~~reversible/~~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 ~~strategy~~ 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 irrita~~nt~~ing 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~~s~~ as hazardous to the eye (Category 1 or 2)**

| Sum of ingredients classified as | Concentration triggering classification of a mixture as | |
|---|---|---|
| | ~~Irreversible~~ Serious eye ~~effects~~ damage | ~~Reversible eye effects~~ Eye irritation |
| | Category 1 | Category 2/2A |
| ~~Eye or S~~skin Category 1 + Eye Category 1 [a] | ≥ 3% | ≥ 1% but < 3% |
| ~~Eye Category 2/2A~~ | | ~~≥ 10%~~ |
| ~~(10 × eye Category 1) + e~~Eye Category 2~~/2A~~ | | ≥ 10% [b] |
| ~~Skin Category 1 + eye Category 1~~ | ~~≥ 3%~~ | ~~≥ 1% but < 3%~~ |
| 10 × (~~skin~~ Skin Category 1 + ~~eye~~ Eye Category 1) [a] + ~~eye~~ Eye Category 2A/2B~~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 ~~for which~~ 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~~s for which additivity does not apply~~ | ≥ 1% | Category 1 |
| Other eye irritant (Eye Category 2) ingredient~~s for which additivity does not apply~~, including acids and bases | ≥ 3% | Category 2 |

## 3.3.4    Hazard communication

General and specific considerations concerning labelling requirements are provided in *Hazard communication: Labelling* (Chapter 1.4). Annex 2 contains summary tables about classification and labelling.  Annex 3

contains examples of precautionary statements and pictograms which can be used where allowed by the competent authority.

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

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

[a] *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**

**Substance:** Are there data/information to evaluate serious eye damage/eye irritation?

→ No → Classification not possible

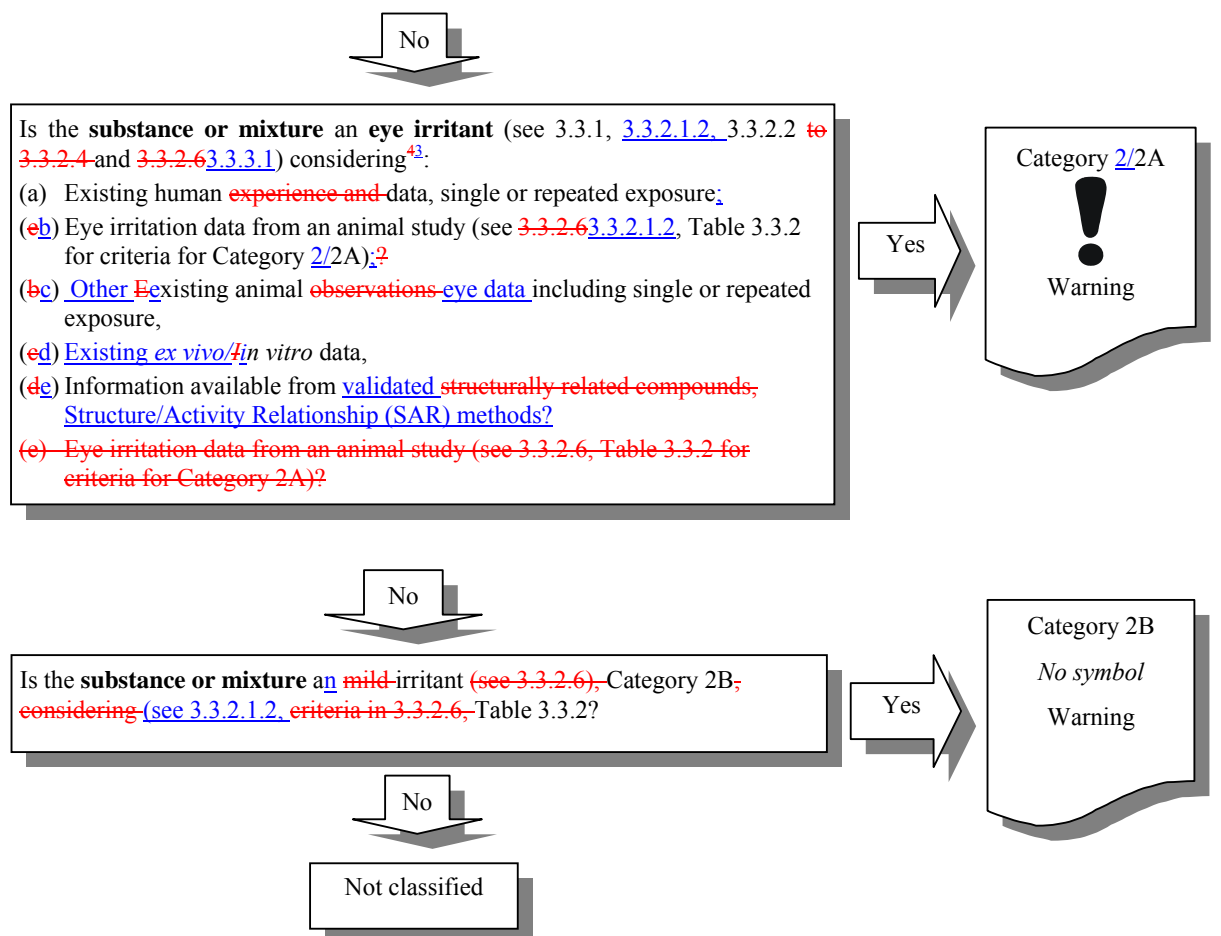**Mixture:** Does the mixture as a whole or its ingredients have data/information to evaluate serious eye damage/eye irritation?

→ No → Classification not possible

Yes

↓ Yes

**Mixture:** Does the mixture as a whole have data/information to evaluate serious eye damage/eye irritation?

→ No → See decision logic 3.3.2 for use with similar tested mixtures and ingredients

↓ Yes

Does the **substance or mixture** have potential to cause ~~irreversible eye damage~~ (**serious eye damage**)~~,~~ see 3.3.1, 3.3.2.1.1, ~~and~~ 3.3.2.2 ~~to~~ and ~~3.3.2.5~~3.3.3.1) considering[4][3]:

(a) Existing human eye ~~experience~~data;~~,~~

(~~f~~b) Irreversible eye damage in one or more test animals~~2~~;

 (c) Existing human or animal data indicating skin corrosion;

(~~b~~d) Other ~~E~~existing animal ~~observations~~ eye data including single or repeated exposure,

(~~c~~e) Existing *ex vivo/I*in vitro eye data,

 (~~e~~f) pH extremes of ≤ 2 or ≥ 11.5[5][4],

(~~d~~g) Information available from ~~structurally related compounds~~validated Structure Activity Relationship (SAR) methods?~~;~~

~~(see 3.3.2.5 and Table 3.3.1 for criteria and sub-categorization)~~

→ Yes → Category 1

Danger

↓ No

*(Cont'd on next page)*

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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 substance or mixture may not cause serious eye damage and confirmed by other data, preferably by data from an appropriate validated in vitro test.*

No

Is the **substance or mixture** an **eye irritant** (see 3.3.1, 3.3.2.1.2, 3.3.2.2 ~~to 3.3.2.4~~ and ~~3.3.2.6~~3.3.3.1) considering[43]:

(a) Existing human ~~experience and~~ data, single or repeated exposure~~;~~
(~~e~~b) Eye irritation data from an animal study (see ~~3.3.2.6~~3.3.2.1.2, Table 3.3.2 for criteria for Category 2/2A)~~;~~~~?~~
(~~b~~c)  Other ~~E~~existing animal ~~observations~~ eye data including single or repeated exposure,
(~~c~~d) Existing *ex vivo/*~~I~~*in vitro* data,
(~~d~~e) Information available from validated ~~structurally related compounds,~~ Structure/Activity Relationship (SAR) methods?
~~(e)  Eye irritation data from an animal study (see 3.3.2.6, Table 3.3.2 for criteria for Category 2A)?~~

Yes →

Category 2/2A

!

Warning

No

Is the **substance or mixture** a~~n~~ ~~mild~~ irritant ~~(see 3.3.2.6),~~ Category 2B~~,~~ ~~considering~~ (see 3.3.2.1.2, ~~criteria in 3.3.2.6,~~ Table 3.3.2?

Yes →

Category 2B

*No symbol*

Warning

No

Not classified

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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*

**Substance:** Are there data on similar tested mixtures to evaluate serious eye damage/eye irritation?

No

Yes

Can bridging principles be applied (see 3.3.3.2)? → Yes → Classify in appropriate category

No
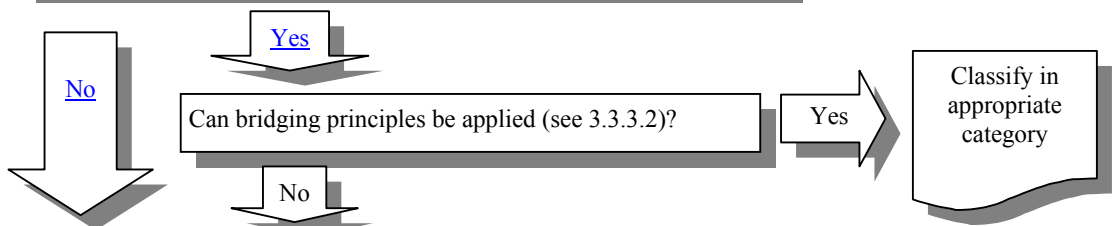
Does the mixture contain ≥ 1%[5,6] of an ingredient [6] which causes ~~irreversible~~ serious eye damage (see 3.3.~~2.4~~1.1, 3.3.2.1.1 and 3.3.2.~~6~~2) ~~and for which~~when the additivity approach may not apply~~, such as~~(see 3.3.3.3.4)~~:~~
~~(a) Acids and bases with extreme pH's ≤ 2 or ≥ 11,5[5], or~~
~~(b) Inorganic salts, or~~
~~(c) Aldehydes, or~~
~~(d) Phenols, or~~
~~(e) Surfactants, or~~
~~(f) Other ingredients?~~

Yes → Category 1 — Danger

No

Does the mixture contain one or more ingredients[5] corrosive or seriously damaging to the eye~~irritant ingredients for which~~when the additivity approach applies (see 3.3.3.3.2 and Table 3.3.3), and where the sum of concentrations of ingredients classified as[7]~~as[6]~~: ~~(a) eye or s~~Skin Category 1+ Eye Category 1~~:~~ ≥ 3% ~~or? (b) skin Category 1 + eye Category 1: ≥ 3%?~~

Yes → Category 1 — Danger

No

Does the mixture contain ≥ 3%[5,6] of an ingredient [7] which is an eye irritant (see 3.3.1.1, 3.3.2.1.2 and 3.3.2.~~4~~2~~and 3.3.2.6~~) ~~and for which~~when the additivity approach may not apply (see 3.3.3.3.4)~~, including acids and bases~~?
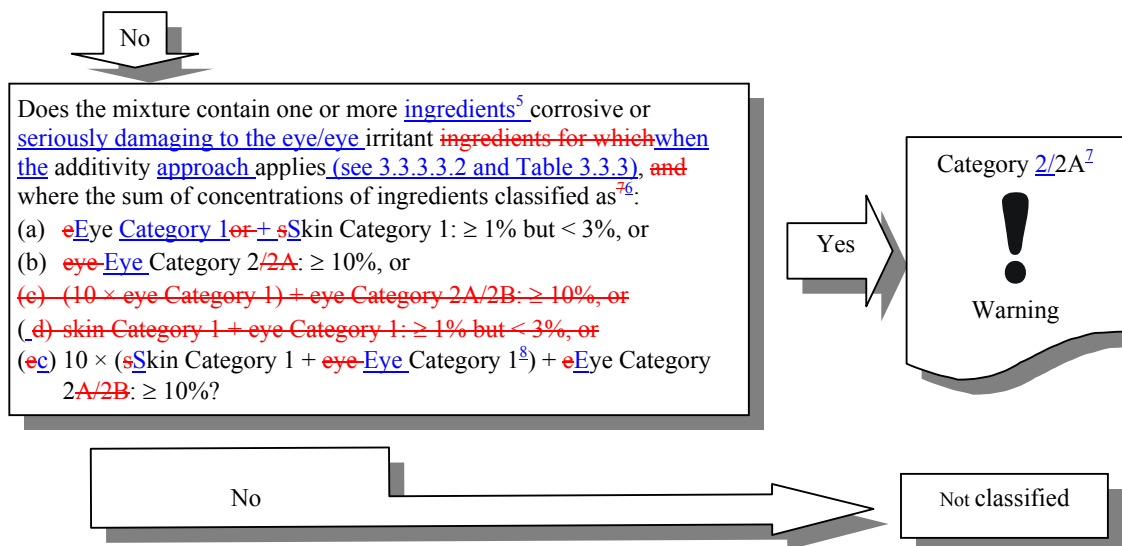
Yes → Category 2[8] — Warning

No

*(Cont'd on next page)*

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[5] ~~Or w~~Where relevant < 1%, see 3.3.3.3.1.

No

Does the mixture contain one or more ingredients[5] corrosive or seriously damaging to the eye/eye irritant ~~ingredients for which~~when the additivity approach applies (see 3.3.3.3.2 and Table 3.3.3), ~~and~~ where the sum of concentrations of ingredients classified as[7][6]:

(a)  ~~e~~Eye Category 1~~or~~ + ~~s~~Skin Category 1: ≥ 1% but < 3%, or

(b)  ~~eye~~ Eye Category 2~~/2A~~: ≥ 10%, or

~~(c)  (10 × eye Category 1) + eye Category 2A/2B: ≥ 10%, or~~

~~( d)  skin Category 1 + eye Category 1: ≥ 1% but < 3%, or~~

(~~e~~c) 10 × (~~s~~Skin Category 1 + ~~eye~~ Eye Category 1[8]) + ~~e~~Eye Category 2~~A/2B~~: ≥ 10%?

Yes →

Category 2/2A[7]

**!**

Warning

No → Not classified

---

**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.

———————