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

Sub-Committee of Experts on the Globally Harmonized System of Classification and Labelling of Chemicals

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Item 2 of the provisional agenda
Recommendations made by the Sub-Committee at its fortieth, forty-first and forty-second sessions

Consolidated list of draft amendments adopted by the Sub-Committee at its fortieth and forty-second session

Note by the secretariat*

This document contains the consolidated list of drafts amendments to the ninth revised edition of the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) (ST/SG/AC.10/30/Rev.9) adopted by the Sub-Committee at its fortieth and forty-second sessions. No amendments to the GHS were adopted at the forty-first session.

* A/75/6 (Sect. 20), par. 20.51.

Chapter 3.1

3.1.2.6.1 Add the following sentence at the end of the existing paragraph:

"Guidance on the conversion of experimental values for times other than a 1-hour exposure is provided in 3.1.5.3."

3.1.5.3 Add a new section 3.1.5.3 to read as follows:

"3.1.5.3 *Guidance*

3.1.5.3.1 The ATE values used for inhalation toxicity classification in Table 3.1.1 are based on a 4-hour experimental exposure in laboratory animals (3.1.2.6.1). Existing inhalation LC_{50} values obtained in studies using exposure times other than 1 hour (3.1.2.6.1) can be adjusted to a 4-hour exposure using the ten Berge equation ($C^n \times t = k$) for gases and vapours and Haber's rule ($C \times t = k$) for dusts and mists, as follows:

Formula for gases and vapours

$$LC_{50}(4\ \text{hours}) = \left(\frac{C^n \times t}{4}\right)^{1/n}$$

where:

C	=	LC_{50} concentration for exposure duration t
n	=	chemical-specific exponent
t	=	exposure duration, in hours, for C

Formula for dusts and mists

$$LC_{50}(4\ \text{hours}) = \frac{C \times t}{4}$$

where:

C	=	LC_{50} concentration for exposure duration t
t	=	exposure duration, in hours, for C

3.1.5.3.2 A default value of 2 is used for n unless additional conclusive information is available to indicate that a different value is more appropriate. The accepted exposure times for conversion are from 30 minutes to 8-hour exposures. A competent authority may decide whether other exposure times are acceptable for conversion. Data from a long-term exposure should not be converted because this hazard class addresses acute toxicity. Guidance on the duration of short-term (i.e., acute) inhalation toxicity exposures can be found in OECD Guidance Document 39 (section 4.1: Outline of the exposure methodology).

Examples: classification using calculated 4-hour LC_{50} values

Example 1: Substance (liquid)

1. For the purpose of this example the substance has an experimental 6-hour vapour LC_{50} = 13.6 mg/l
2. No additional information on n is available so the default value (n = 2) will be used.

Criterion:

$$LC_{50}(4\ \text{hours}) = \left(\frac{C^n \times t}{4}\right)^{1/n}$$

Calculation

$$LC_{50}(4\ \text{hours}) = \left(\frac{C^{n} \times t}{4}\right)^{\frac{1}{n}} = \left(\frac{13.6^{2} \times 6}{4}\right)^{\frac{1}{2}} = \mathbf{16.7}$$

3. Therefore, the substance is classified into Category 4 based on the vapours Category 4 criteria (10.0 < ATE ≤ 20.0) from Table 3.1.1.

Example 2: Substance (solid)

4. For this example, the substance has an experimental 2-hour dust LC_{50} = 0.26 mg/l

Criterion:

$$LC_{50}(4\ \text{hours}) = \frac{C \times t}{4}$$

Calculation

$$LC_{50}(4\ \text{hours}) = \frac{C \times t}{4} = \frac{0.26 \times 2}{4} = 0.13$$

5. Therefore, the substance is classified into Category 2 based on the dusts and mists Category 2 criteria (0.05 < ATE ≤ 0.5) from Table 3.1.1.”.

Chapter 3.2

3.2.1.2 Replace the second sentence with the following:

“Classification should be based on mutually acceptable data generated using methods that are validated according to international procedures. These include both OECD guidelines and equivalent methods (see 1.3.2.4.3).”.

In the last sentence, replace “3.2.2.6” with “3.2.2.7”.

3.2.1.3 In the first sentence, replace “3.2.2.7” with “3.2.2.8”.

In the last sentence, replace “3.2.2.7.3” with “3.2.2.8.3”; “weight of evidence approach” with “weight of evidence assessment” and insert “, 3.2.2.7” after “1.3.2.4.9” in the references between brackets at the end of the paragraph.

3.2.2.1 Add ***“(Tier 1 in Figure 3.2.1)***” at the end of the heading.

3.2.2.2 In the heading: delete “test” and add ***“(Tier 1 in Figure 3.2.1)”*** at the end.

Amend the beginning of the first sentence to read: “OECD Test Guideline 404 is the currently available and internationally accepted animal test method…”.

3.2.2.3 In the heading, add ***“(Tier 2 in Figure 3.2.1)”*** at the end.

3.2.2.3.2 Replace the first sentence (Wherever possible … to be applied”) with the following:

“The classification criteria for the currently available *in vitro/ex vivo* test methods adopted by the OECD in test guidelines 430, 431, 435, and 439 are described in Tables 3.2.6 and 3.2.7 (see 3.2.5.3.4). Other validated *in vitro/ex vivo* test methods accepted by some competent authorities may also be considered. A competent authority may decide which classification criteria, if any, should be applied for other test methods to conclude on classification, including that a substance is not classified for effects on the skin.”.

3.2.2.3.3 (new) Place the two last sentences of current paragraph 3.2.2.3.2 (“*In vitro/ex vivo*…into consideration”) under a new paragraph 3.2.2.3.3 and replace “test method used” with “test method(s) used”.

Renumber current paragraphs 3.2.2.2.3 to 3.2.2.3.3.3 as 3.2.2.3.4 to 3.2.2.3.4.3.

3.2.2.3.4.1 (new, former 3.2.2.3.3.1) Add "(see 3.2.5.3.4)" at the end of the paragraph after "Table 3.2.6".

Renumber current paragraphs 3.2.2.3.4 to 3.2.2.3.4.2 as 3.2.2.3.5 to 3.2.2.3.5.2

3.2.2.3.5.1 (new, former 3.2.2.3.4.1) Add "(see 3.2.5.3.4)" at the end of the paragraph after "Table 3.2.7".

3.2.2.3.5.2 (new, former 3.2.2.3.4.2) Delete the last sentence.

3.2.2.3.6 (new) Insert a new heading to read as follows:

"3.2.2.3.6 *No classification for effect on the skin*"

3.2.2.3.6.1 (new, former 3.2.2.3.4.3) Amend to read as follows:

"3.2.2.3.6.1 Where competent authorities do not adopt Category 3, a negative result in an *in vitro/ex vivo* test method for skin irritation that is validated according to international procedures, e.g. OECD Test Guideline 439, can be used to conclude as not classified for skin irritation. Where competent authorities adopt Category 3, additional information is required to differentiate between Category 3 and no classification.

3.2.2.4 Amend the heading to read as follows:

*"***3.2.2.4 *Classification based on other existing animal skin data (Tier 3 in Figure 3.2.1)***"**

3.2.2.5 Amend to read as follows:

*"***3.2.2.5 *Classification based on extreme pH (pH ≤ 2 or ≥ 11.5) and acid/alkaline reserve (Tier 4 in Figure 3.2.1)***

In general, substances with an extreme pH (pH ≤ 2 or ≥ 11.5) are expected to cause significant skin effects, especially when associated with significant acid/alkaline reserve. A substance with pH ≤ 2 or ≥ 11.5 is therefore considered to cause skin corrosion (Category 1) in this tier if it has a significant acid/alkaline reserve or if no data for acid/alkaline reserve are available. However, if consideration of acid/alkaline reserve suggests the substance may not be corrosive despite the extreme pH value, the result is considered inconclusive within this tier (see Figure 3.2.1). A pH > 2 and < 11.5 is considered inconclusive and cannot be used for classification purposes. Acid/alkaline reserve and pH can be determined by different methods including those described in OECD Test Guideline 122 and Young et al. (1988), acknowledging that there are some differences between these methods (see 3.2.5.3.6). A competent authority may decide which criteria for significant acid/alkaline reserve can be applied."

3.2.2.6 Add ***"(Tier 5 in Figure 3.2.1)"*** at the end of the heading.

3.2.2.6.1 In the last sentence, replace "(structural alerts, SAR); quantitative structure-activity relationships (QSARs); computer experts systems; and" with "(structural alerts, SAR) or quantitative structure-activity relationships (QSARs), computer experts systems, and".

3.2.2.7 (new) Insert a new section 3.2.2.7 to read as follows:

"**3.2.2.7 *Classification based on an overall weight of evidence assessment (Tier 6 in Figure 3.2.1)***

3.2.2.7.1 An overall weight of evidence assessment is indicated where none of the previous tiers resulted in a definitive conclusion on classification.

In some cases, where the classification decision was postponed until the overall weight of evidence, but no further data are available, a classification may still be possible.

3.2.2.7.2 A substance with an extreme pH (pH ≤ 2 or ≥ 11.5) and non-significant acid/alkaline reserve (result considered inconclusive in Tier 4; see 3.2.2.5) and for which no other information is available, should be classified as skin corrosion Category 1 in this tier. If inconclusive information is also available from other tiers but the overall weight of evidence assessment remains inconclusive, the extreme pH (pH ≤ 2 or ≥ 11.5) result should take precedence and the substance should be classified as skin corrosion Category 1 in this tier independently of its acid/alkaline reserve. For mixtures, the approach is different and is detailed in 3.2.3.1.3.".

Renumber current section 3.2.2.7 as 3.3.2.8, and paragraphs 3.2.2.7.1, 3.2.2.7.2 and 3.2.2.7.3 as 3.2.2.8.1, 3.2.2.8.2 and 3.2.2.8.3.

3.2.2.8 (new, former 3.2.2.7) Add "***(Figure 3.2.1)***" at the end of the heading.

3.2.2.8.2 (new, former 3.2.2.7.2) Amend the first sentence to read as follows:

"In the tiered approach (Figure 3.2.1), existing human and standard animal data form the highest tier, followed by *in vitro/ex vivo* data, other existing animal skin data, extreme pH and acid/alkaline reserve, and finally non-test methods.".

In the second sentence, replace "weight of evidence approach" with "weight of evidence assessment".

3.2.2.8.3 (new, former 3.2.2.7.3) Replace (twice) "weight of evidence approach" with "weight of evidence assessment".

In the last sentence, replace "irritation" with "skin irritation" and add "are also available" at the end of the paragraph.

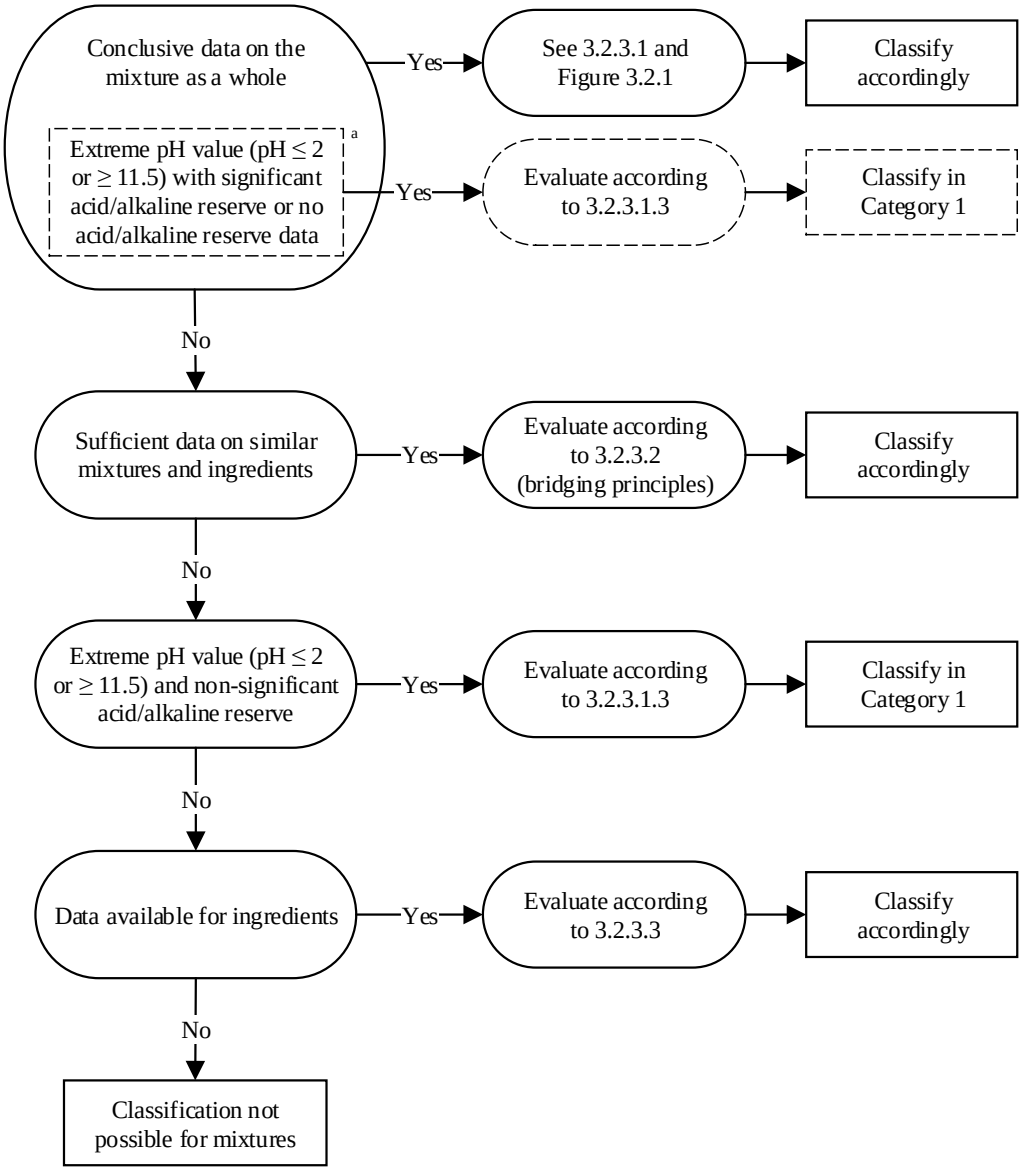
Figure 3.2.1 Amend as follows:

- Text between tier 3 and tier 4 boxes: Replace "*No data or inconclusive*[b]" with "*No data, not classified for skin corrosion/irritation or inconclusive*[b]".
- Text between tier 4 and tier 5 boxes: Replace "*data showing significant acid/alkaline reserve*" with "*data showing non-significant acid/alkaline reserve*".
- Text box for tier 6: replace "(see 3.2.2.7.3)" with "(see 3.2.2.7)" at the end, after "assessment".
- Exit box "Classification not possible": amend the text to read: "Classification not possible for substances[c]".
- In the box on the right-hand side starting with "Assess consistency with lower tiers" replace "3.2.2.7.3" with "3.2.2.8.3".
- In note "a", replace "3.2.2.7" with "3.2.2.8".
- Add a new note "c" to read as follows: "[c] *For mixtures, the flow chart in Figure 3.2.2 should be followed*".

3.2.3 Insert the following new text and figure under the current heading:

"The approach to classification for skin corrosion/irritation is tiered and is dependent upon the amount of information available for the mixture itself and for its ingredients. The flow chart of Figure 3.2.2 below outlines the process to be followed.

Figure 3.2.2: Tiered approach to classification of mixtures for skin corrosion/irritation



[a] *The dashed boxes represent an individual tier within conclusive data on the mixture as whole. However, in contrast to substances, mixtures having an "extreme pH value (pH ≤ 2 or ≥ 11.5) and non-significant acid/alkaline reserve" but no other conclusive data on the mixture as a whole, or no conclusive weight of evidence assessment from all available data on the mixture as whole, are not conclusive within the tiers for conclusive data on the mixture as a whole. Such mixtures should be first evaluated according to the bridging principles before the extreme pH value is considered as conclusive for classification.*".

3.2.3.1.1 In the last sentence, replace "calculation method" with "classification based on ingredients".

3.2.3.1.2 Amend the first sentence to read as follows:

"*In vitro/ex vivo* test methods validated according to international procedures may not have been validated using mixtures; although these methods are considered broadly applicable to mixtures, they can only be used for classification of mixtures when all ingredients of the mixture fall within the applicability domain of the test method(s) used".

3.2.3.1.3 Amend to read as follows:

"A mixture with an extreme pH (pH ≤ 2 or ≥ 11.5) is considered corrosive (Category 1) in Tier 4 if it has a significant acid/alkaline reserve or if no data for acid/alkaline reserve are available. However, if consideration of acid/alkaline reserve suggests the mixture may not be corrosive despite the extreme pH value, the result is considered inconclusive within Tier 4 (see Figure 3.2.1). If the overall weight of evidence assessment remains inconclusive or no data other than pH and acid/alkaline reserve are available, mixtures with an extreme pH (pH ≤ 2 or ≥ 11.5) and non-significant acid/alkaline reserve should be assessed using the bridging principles described in 3.2.3.2. If the bridging principles cannot be applied, mixtures with an extreme pH (pH ≤ 2 or ≥ 11.5) and non-significant acid/alkaline reserve should be classified as skin Category 1 (see Figure 3.2.2). A pH > 2 and < 11.5 is considered inconclusive and cannot be used for classification purposes. Acid/alkaline reserve and pH can be determined by different methods including those described in OECD Test Guideline 122 and Young et al. (1988), acknowledging that there are some differences between these methods (see 3.2.5.3.6). A competent authority may decide which criteria for significant acid/alkaline reserve can be applied."

3.2.3.2.5 Add "category" at the end of the current heading.

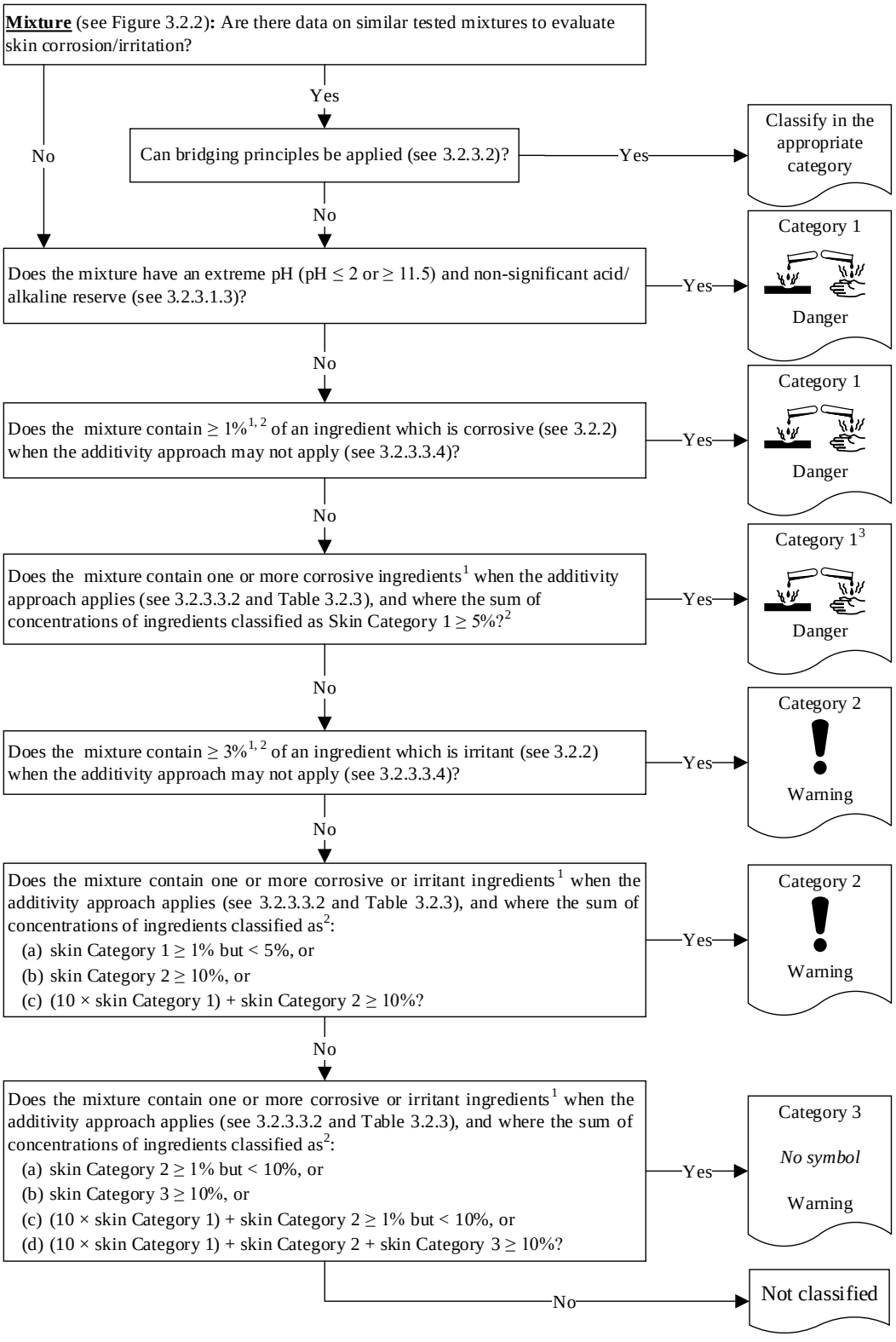
3.2.3.3.4 Amend the middle of the third sentence to read "…the pH should be used as the classification criterion (see 3.2.3.1.3) since extreme pH…".

3.2.5.1 In decision logic 3.2.1, amend the question starting with "Is the **substance or mixture**" to read as follows:

"Is the **substance or mixture corrosive**, an **irritant** or a **mild irritant** (see 3.2.2 and 3.2.3.1) in accordance with the tiered approach (see 3.2.2.8 and Figures 3.2.1 and 3.2.2?".

3.2.5.2 Replace decision logic 3.2.2 with the following:

“



”

In footnote 2, replace “*see 3.2.3.3.6*” with “*see 3.2.3.3.5 and 3.2.3.3.6”.*

3.2.5.3.1 Replace “weight of evidence approach” with “weight of evidence assessment”.

3.2.5.3.4 In the heading, replace “*ex vivo* data” with “*in vitro/ex vivo* data” and in the first sentence replace “or 439” with “and/or 439”.

3.2.5.3.6 Insert the following new paragraphs:

"3.2.5.3.6 *Guidance on the use of pH and acid/alkaline reserve for classification as skin corrosion/irritation*

3.2.5.3.6.1 Methods to determine the pH value such as OECD Test Guideline 122 and the method described by Young et al. (1988) differ in the concentration of the substance or mixture for which the pH is determined and include values of 1%, 10% and 100%. These methods also differ in the way the acid/alkaline reserve is determined, namely up to a pH of 7 for both acids and bases (OECD Test Guideline 122) or up to a pH of 4 for acids and a pH of 10 for bases (Young et al., 1988). Furthermore, there are differences between OECD Test Guideline 122 and Young et al. (1988) in the units used to express the acid/alkaline reserve.

3.2.5.3.6.2 Criteria to identify substances and mixtures requiring classification in Category 1 based on pH and acid/alkaline reserve have been developed for effects on the skin (Young et al., 1988). These criteria were developed using a combination of pH and acid/alkaline reserve values that were determined in a specific way (Young et al., 1988). Therefore, these criteria may not be directly applicable when other test concentrations or methods are used to measure pH and acid/alkaline reserve. Furthermore, the calibration and validation of these criteria was based on a limited dataset for effects on the skin. Thus, the predictive value of the combination of pH and acid/alkaline reserve for classification in Category 1 for effects on the skin is limited, especially for substances and mixtures with an extreme pH but a non-significant acid/alkaline reserve. The criteria developed by Young et al. (1988) for classification in Category 1 may be used as a starting point for determining whether a substance or a mixture has a significant acid/alkaline reserve or a non-significant acid/alkaline reserve. A competent authority may decide which criteria for significant acid/alkaline reserve can be applied.

_____

* *References:*

Young, J.R., M.J. How, A.P. Walker, and W.M. Worth. 1988. Classification as corrosive or irritant to skin of preparations containing acidic or alkaline substances, without testing on animals. Toxicol. In Vitro, 2(1): 19-26. doi: 10.1016/0887-2333(88)90032-x.".

Chapter 3.3

3.3.1.2 Replace with the following:

"3.3.1.2 To classify, all available and relevant information on serious eye damage/eye irritation is collected and its quality in terms of adequacy and reliability is assessed. Classification should be based on mutually acceptable data/results generated using methods and/or defined approaches[1] that are validated according to international procedures. These include both OECD guidelines and equivalent methods/defined approaches (see 1.3.2.4.3). Sections 3.3.2.1 to 3.3.2.8 provide classification criteria for the different types of information that may be available.".

Insert a new footnote 1 to read as follows:

"[1] According to OECD Guidance Document 255 on the reporting of defined approaches to be used within integrated approaches to testing and assessment, a defined approach to testing and assessment consists of a fixed data interpretation procedure (DIP) applied to data generated with a defined set of information sources to derive a result that can either be used on its own,

or together with other information sources within an overall weight of evidence assessment, to satisfy a specific regulatory need.”.

3.3.1.3 and 3.3.1.4 Insert the following two new paragraphs:

“3.3.1.3 A *tiered approach* (see 3.3.2.10) organizes the available information into levels/tiers and provides for decision-making in a structured and sequential manner. Classification results directly when the information consistently satisfies the criteria. However, where the available information gives inconsistent and/or conflicting results within a tier, classification of a substance or a mixture is made on the basis of the weight of evidence within that tier. In some cases when information from different tiers gives inconsistent and/or conflicting results (see 3.3.2.10.3) or where data individually are insufficient to conclude on the classification, an overall weight of evidence assessment is used (see 1.3.2.4.9, 3.3.2.9 and 3.3.5.3.1).

3.3.1.4 Guidance on the interpretation of criteria and references to relevant guidance documents are provided in 3.3.5.3.”.

3.3.2 Delete “(see Table 3.3.1)” in sub-paragraph (a) and “(see Table 3.3.2)” in sub-paragraph (b) and in the last sentence.

3.3.2.1 and 3.3.2.2 (new) Insert the following two new paragraphs:

“**3.3.2.1** ***Classification based on human data (Tier 1 in Figure 3.3.1)***

Existing reliable and good quality human data on serious eye damage/eye irritation should be given high weight where relevant for classification (see 3.3.5.3.2) and should be the first line of evaluation, as this gives information directly relevant to effects on the eye. Existing human data could be derived from single or repeated exposure(s), for example in occupational, consumer, transport or emergency response scenarios and epidemiological and clinical studies in well-documented case reports and observations (see 1.1.2.5 (c), 1.3.2.4.7 and 1.3.2.4.9). 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.

3.3.2.2 ***Classification based on standard animal data (Tier 1 in Figure 3.3.1)***

OECD Test Guideline 405 is the currently available and internationally accepted animal test method for classification as serious eye damage or eye irritant (see Tables 3.3.1 and 3.3.2, respectively) and is the standard animal test. The current version of OECD Test Guideline 405 uses a maximum of 3 animals. Results from animal studies conducted under previous versions of OECD Test Guideline 405 that used more than 3 animals are also considered standard animal tests when interpreted in accordance with 3.3.5.3.3.”.

3.3.2.1.1 to 3.3.2.1.2.3 Current paragraphs 3.3.2.1.1 to 3.3.2.1.2.3 become new paragraphs 3.3.2.2.1 to 3.3.2.2.2.3.

Table 3.3.1 Delete note “a”. Current notes “b” and “c” become “a” and “b” respectively.

In note “b” replace “3.3.5.3” with “3.3.5.3.3”.

3.3.2.2.2.1 (new, former 3.3.2.1.2.1) In the last sentence, replace “chemical” with “substance”.

3.3.2.2.2.2 (new, former 3.3.2.1.2.2) Replace “categories 2A and 2B” with “Category 2A and Category 2B”.

Table 3.3.2 Delete note “a”. Current notes “b” and “c” become “a” and “b” respectively.

In note “b”, replace “3.3.5.3” with “3.3.5.3.3.”.

3.3.2.2 and 3.3.2.2.1 Current paragraphs 3.3.2.2 and 3.3.2.2.1 become new paragraphs 3.3.2.10 and 3.3.2.10.1.

Delete paragraphs 3.3.2.2.2; 3.3.2.2.3, 3.3.2.2.4, 3.3.2.2.5 and 3.3.2.2.6.

3.3.2.3 to 3.3.2.9 Insert the following new paragraphs (and related footnotes 2 and 3):

"3.3.2.3 *Classification based on defined approaches (Tier 2 in Figure 3.3.1)*

Defined approaches consist of a rule-based combination of data obtained from a predefined set of different information sources (e.g. *in vitro* methods, *ex vivo* methods, physico-chemical properties, non-test methods). It is recognized that most single *in vitro*/*ex vivo* methods are not able to replace *in vivo* methods fully for most regulatory endpoints. Thus, defined approaches can be useful strategies of combining data for classifying substances and mixtures. Results obtained with a defined approach validated according to international procedures, such as an OECD defined approach guideline or an equivalent approach, is conclusive for classification for serious eye damage/eye irritation if the criteria of the defined approach are fulfilled (see 3.3.5.3.4)[2]. Data from a defined approach can only be used for classification when the tested substance is within the applicability domain of the defined approach used. Additional limitations described in the published literature should also be taken into consideration.

3.3.2.4 *Classification based on in vitro/ex vivo data (Tier 2 in Figure 3.3.1)*

3.3.2.4.1 The classification criteria for the currently available *in vitro*/*ex vivo* test methods adopted by the OECD in test guidelines 437, 438, 460, 491, 492, 494 and 496 are described in Table 3.3.6 (see 3.3.5.3.5.1). When considered individually, these *in vitro/ex vivo* OECD test guidelines address serious eye damage and/or no classification for eye hazard, but do not address eye irritation. Therefore, data from a single *in vitro/ex vivo* OECD test guideline can only be used to conclude on either classification in Category 1 or no classification and cannot be used to conclude on classification in Category 2. When the result of a single *in vitro*/*ex vivo* method is "no stand-alone prediction can be made" (e.g. see Table 3.3.6), a conclusion cannot be drawn on the basis of that single result and further data are necessary for classification (see 3.3.5.3.4.3 and 3.3.5.3.4.4).

3.3.2.4.2 Other validated *in vitro/ex vivo* test methods accepted by some competent authorities are described in 3.3.5.3.5.2. Some of these *in vitro/ex vivo* test methods may be useful to classify in Category 2. A competent authority may decide which classification criteria, if any, should be applied for these test methods to conclude on classification, including that a substance is not classified for effects on the eye.

3.3.2.4.3 *In vitro/ex vivo* data can only be used for classification when the tested substance is within the applicability domain of the test method(s) used. Additional limitations described in the published literature should also be taken into consideration.

3.3.2.4.4 *Serious eye damage (Category 1)/Irreversible effects on the eye*

3.3.2.4.4.1 Where tests have been undertaken in accordance with OECD test guidelines 437, 438, 460, 491 and/or 496, a substance is classified for serious eye damage in Category 1 based on the criteria in Table 3.3.6 (see 3.3.5.3.5.1).

3.3.2.4.4.2 Although the currently available OECD *in vitro*/*ex vivo* test guidelines and equivalent methods have not been developed to identify substances inducing discolouration of the eye, some comparable effects may be observed in these tests. Therefore, where, after washing, discolouration of the cornea or of the tested cells compared to the control is observed in OECD Test Guideline 437, 438, 492 or 494, or in other equivalent methods,

suggesting a permanent effect, a competent authority may require classification of a substance for serious eye damage in Category 1.

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

3.3.2.4.5.1 A positive result in an *in vitro*/*ex vivo* test method that is validated according to international procedures for identification of substances inducing eye irritation can be used to classify for eye irritation in Category 2/2A[3].

3.3.2.4.5.2 Where competent authorities adopt Category 2A and Category 2B, it is important to note that the currently validated *in vitro/ex vivo* test methods for effects on the eye do not allow discrimination between these two categories. In this situation, if the criteria for classification in Category 2 have been considered fulfilled, and no other relevant information is available, classification in Category 2/2A should be applied.

3.3.2.4.6 *No classification for effects on the eye*

OECD test guidelines 437, 438, 491, 492, 494 and 496 (see Table 3.3.6 in 3.3.5.3.5.1) can be used to conclude that a substance is not classified for effects on the eye.

3.3.2.5 *Classification based on conclusive human data, standard animal data or in vitro/ex vivo data for skin corrosion (Tier 3 in Figure 3.3.1)*

Substances classified as corrosive to skin (skin Category 1) based on conclusive human data, standard animal data or *in vitro*/*ex vivo* data for skin corrosion according to the criteria in Chapter 3.2 are also deemed as inducing serious eye damage (eye Category 1). Skin irritation (skin Category 2), mild skin irritation (skin Category 3) and no classification for skin irritation, as well as human patch data (as described in Chapter 3.2), cannot be used alone to conclude on eye irritation or no classification for effects on the eye, but may be considered in an overall weight of evidence assessment.

3.3.2.6 *Classification based on other existing animal skin or eye data (Tier 4 in Figure 3.3.1)*

Other existing skin or eye data in animals may be used for classification, but there may be limitations regarding the conclusions that can be drawn (see 3.3.5.3.6). Substances classified as corrosive to skin (skin Category 1) based on other existing skin data according to the criteria in Chapter 3.2 are also deemed as inducing serious eye damage (eye Category 1). Other existing skin data leading to classification in skin Category 2, 3 or no classification, cannot be used alone to conclude on eye irritation or no classification for effects on the eye, but may be considered in an overall weight of evidence assessment."

3.3.2.7 *Classification based on extreme pH (pH ≤ 2 or ≥ 11.5) and acid/alkaline reserve (Tier 5 in Figure 3.3.1)*

In general, substances with an extreme pH (pH ≤ 2 or ≥ 11.5) are expected to cause significant eye effects, especially when associated with significant acid/alkaline reserve. A substance with pH ≤ 2 or ≥ 11.5 is therefore considered to cause serious eye damage (Category 1) in this tier if it has a significant acid/alkaline reserve or if no data for acid/alkaline reserve are available. However, if consideration of acid/alkaline reserve suggests the substance may not cause serious eye damage despite the extreme pH value, the result is considered inconclusive within this tier (see Figure 3.3.1). A pH > 2 and < 11.5 is considered inconclusive and cannot be used for classification purposes. Acid/alkaline reserve and pH can be determined by different methods including those described in OECD Test Guideline 122 and Young et al. (1988), acknowledging that there are some differences between these methods (see 3.3.5.3.7). A competent authority may decide which criteria for significant acid/alkaline reserve can be applied.

3.3.2.8 ***Classification based on non-test methods for serious eye damage/eye irritation or for skin corrosion (Tier 6 in Figure 3.3.1)***

3.3.2.8.1 Classification, including the conclusion not classified, can be based on non-test methods, with due consideration of reliability and applicability, on a case-by-case basis. Such methods include computer models predicting qualitative structure-activity relationships (structural alerts, SAR) or quantitative structure-activity relationships (QSARs), computer expert systems, and read-across using analogue and category approaches.

3.3.2.8.2 Read-across using analogue or category approaches requires sufficiently reliable test data on similar substance(s) and justification of the similarity of the tested substance(s) with the substance(s) to be classified. Where adequate justification of the read-across approach is provided, it has in general higher weight than (Q)SARs.

3.3.2.8.3 Classification based on (Q)SARs requires sufficient data and validation of the model. The validity of the computer models and the prediction should be assessed using internationally recognized principles for the validation of (Q)SARs. With respect to reliability, lack of alerts in a SAR or expert system is not sufficient evidence for no classification.

3.3.2.8.4 Conclusive non-test data for skin corrosion may be used for classification for effects on the eye. Thus, substances classified as corrosive to skin (skin Category 1) according to the criteria in Chapter 3.2 are also deemed as inducing serious eye damage (eye Category 1). Skin irritation (skin Category 2), mild skin irritation (skin Category 3) and no classification for skin irritation according to Chapter 3.2 cannot be used alone to conclude eye irritation or no classification for effects on the eye, but may be considered in an overall weight of evidence assessment.

3.3.2.9 ***Classification based on an overall weight of evidence assessment (Tier 7 in Figure 3.3.1)***

3.3.2.9.1 An overall weight of evidence assessment using expert judgement is indicated where none of the previous tiers resulted in a definitive conclusion on classification. In some cases, where the classification decision was postponed until the overall weight of evidence, but no further data are available, a classification may still be possible.

3.3.2.9.2 A substance with an extreme pH (pH ≤ 2 or ≥ 11.5) and non-significant acid/alkaline reserve (result considered inconclusive in Tier 5; see 3.3.2.7) and for which no other information is available, should be classified as serious eye damage Category 1 in this tier. If inconclusive information is also available from other tiers but the overall weight of evidence assessment remains inconclusive, the extreme pH (pH ≤ 2 or ≥ 11.5) result should take precedence and the substance should be classified as serious eye damage Category 1 in this tier independently of its acid/alkaline reserve. For mixtures, the approach is different and is detailed in 3.3.3.1.3.”.

Footnotes Insert the following new footnotes 2 and 3 at the bottom of the page in relation to paragraphs 3.3.2.3 (for footnote 2) and 3.3.2.4.5.1 (for footnote 3):

“[2] *Some defined approaches have been proposed for serious eye damage/eye irritation (Alépée et al., 2019a, b) but no classification criteria have yet been agreed internationally.”.*

“[3] *Although no classification criteria have yet been agreed internationally for some validated and/or accepted in vitro/ex vivo test methods proposed for identifying substances inducing eye irritation, these test methods may still be accepted by some competent authorities (see 3.3.2.4.2). If a defined approach (see 3.3.2.3) is not available or is not adequate for classification, data from these methods may be considered in a weight of evidence assessment within this tier.”.*

3.3.2.10 and 3.3.2.10.1 (new, former 3.3.2.2 and 3.3.2.2.1) Amend to read as follows:

"3.3.2.10 *Classification in a tiered approach (Figure 3.3.1)"*

3.3.2.10.1 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. However, all available and relevant information of sufficient quality needs to be examined for consistency with respect to the resulting classification.".

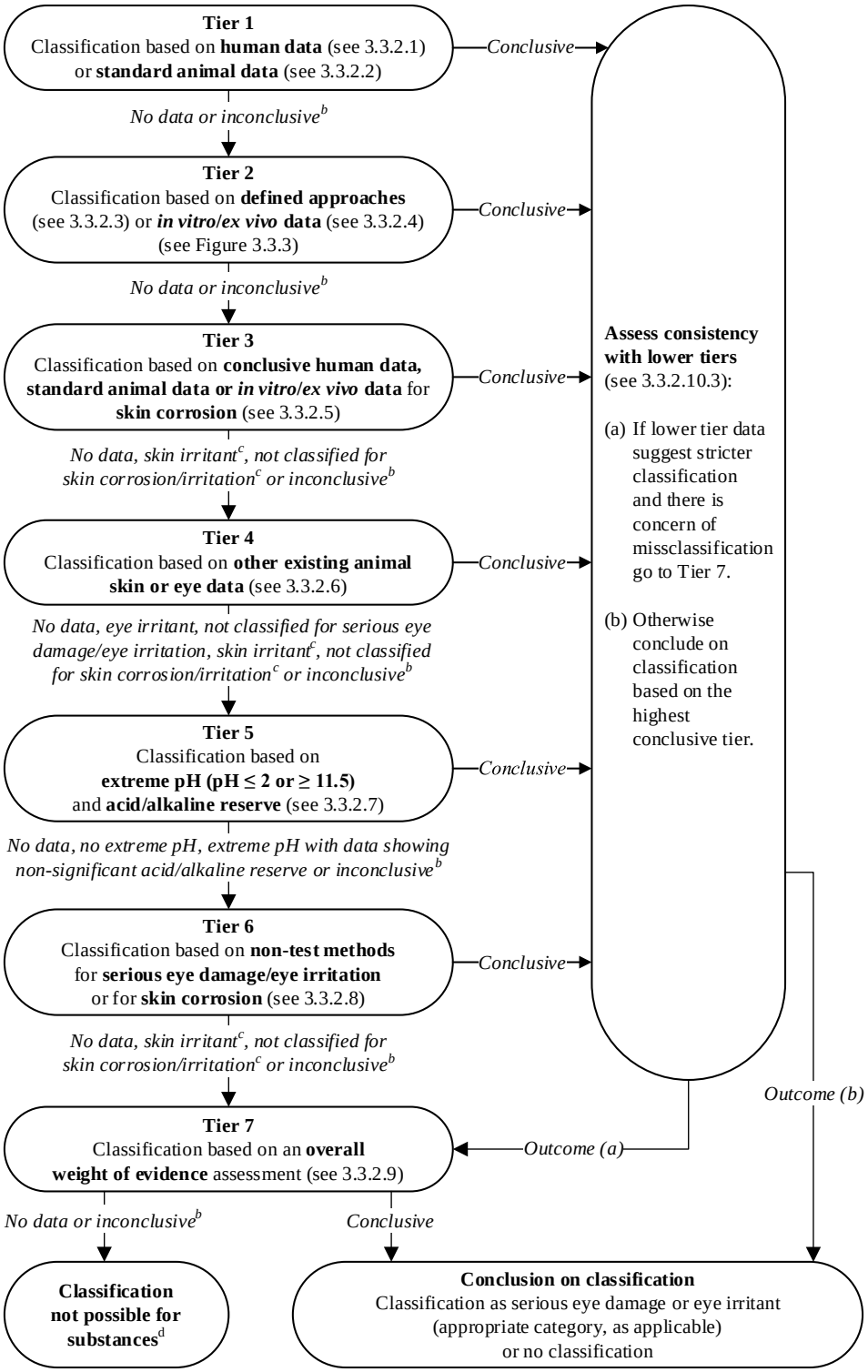
3.3.2.10.2 and 3.3.2.10.3 Insert the following two new paragraphs:

"3.3.2.10.2 In the tiered approach (Figure 3.3.1), existing human and standard animal data for eye effects form the highest tier, followed by defined approaches and *in vitro/ex vivo* data for eye effects, existing human/standard animal/*in vitro*/*ex vivo* data for skin corrosion, other existing animal skin or eye data, extreme pH and acid/alkaline reserve, and finally non-test methods. Where information from data within the same tier is inconsistent and/or conflicting, the conclusion from that tier is determined by a weight of evidence assessment.

3.3.2.10.3 Where information from several tiers is inconsistent and/or conflicting with respect to the resulting classification, information of sufficient quality from a higher tier is generally given a higher weight than information from a lower tier. However, when information from a lower tier would result in a stricter classification than information from a higher tier and there is concern for misclassification, then classification is determined by an overall weight of evidence assessment. For example, having consulted the guidance in 3.3.5.3 as appropriate, classifiers concerned with a negative result for serious eye damage in an *in vitro/ex vivo* study when there is a positive result for serious eye damage in other existing eye data in animals would utilise an overall weight of evidence assessment. The same would apply in the case where there is human data indicating eye irritation but positive results from an *in vitro/ex vivo* test for serious eye damage are also available."

Figure 3.3.1: Replace with the following:

"**Figure 3.3.1: Application of the tiered approach for serious eye damage/eye irritation[a]**"



".

Replace current notes “a”, “b”, “c” and “d” to Figure 3.3.1 with the following:

“[a] *Before applying the approach, the explanatory text in 3.3.2.10 as well as the guidance in 3.3.5.3 should be consulted. Only adequate and reliable data of sufficient quality should be included in applying the tiered approach.*

[b] *Information may be inconclusive for various reasons, e.g.:*

- *The available data may be of insufficient quality, or otherwise insufficient/inadequate for the purpose of classification, e.g. due to quality issues related to experimental design and/or reporting;*
- *The available data may be insufficient to conclude on the classification, e.g. they might be indicative for absence of serious eye damage, but inadequate to demonstrate eye irritation;*
- *Where competent authorities make use of the eye irritation categories 2A and 2B, the available data may not be capable of distinguishing between Category 2A and Category 2B.”*

[c] *It is recognized that not all skin irritants are eye irritants and that not all substances that are non-irritant to skin are non-irritant to the eye (see 3.3.2.5, 3.3.2.6, 3.3.2.8.4 and 3.3.2.9.1).”*

[d] *For mixtures, the flow chart in Figure 3.3.2 should be followed.”.*

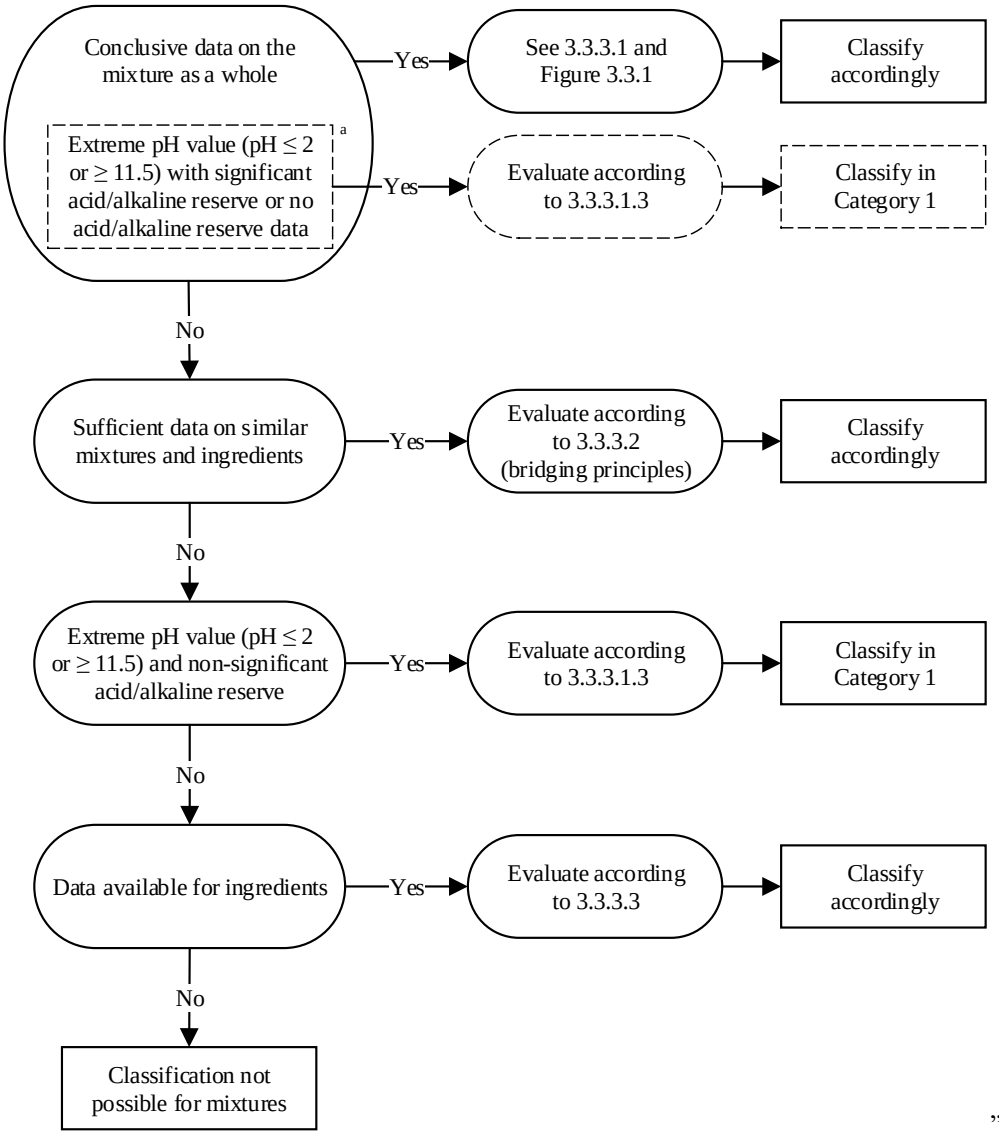
Delete current notes “e” and “f” to Figure 3.3.1.

3.3.3 Amend to read as follows:

“3.3.3 Classification criteria for mixtures

The approach to classification for serious eye damage/eye irritation is tiered and is dependent upon the amount of information available for the mixture itself and for its ingredients. The flow chart of Figure 3.3.2 below outlines the process to be followed.

Figure 3.3.2: Tiered approach to classification of mixtures for serious eye damage/eye irritation



”

[a] *The dashed boxes represent an individual tier within conclusive data on the mixture as whole. However, in contrast to substances, mixtures having an "extreme pH value (pH ⩽ 2 or ⩾ 11.5) and non-significant acid/alkaline reserve" but no other conclusive data on the mixture as a whole, or no conclusive weight of evidence assessment from all available data on the mixture as whole, are not conclusive within the tiers for conclusive data on the mixture as a whole. Such mixtures should be first evaluated according to the bridging principles before the extreme pH value is considered as conclusive for classification.”.*

3.3.3.1.1 and 3.3.3.1.2 Amend to read as follows:

“3.3.3.1.1 In general, the mixture should be classified using the criteria for substances, taking into account the tiered approach to evaluate data for this hazard class (as illustrated in Figure 3.3.1) and 3.3.3.1.2 and 3.3.3.1.3 below. If classification is not possible using the tiered approach, then the approach described in 3.3.3.2 (bridging principles), or, if that is not applicable, 3.3.3.3 (classification based on ingredients) should be followed.

3.3.3.1.2 Defined approaches and/or *in vitro/ex vivo* test methods validated according to international procedures may not have been validated using mixtures; although these approaches/methods are considered broadly applicable to mixtures, they can only be used for classification of mixtures

when all ingredients of the mixture fall within the applicability domain of the defined approach or test method(s) used. Specific limitations regarding applicability domains are described in the respective defined approaches and test methods and should be taken into consideration as well as any further information on such limitations from the published literature. Where there is reason to assume or evidence indicating that the applicability domain of a particular defined approach or test method is limited, data interpretation should be exercised with caution, or the results should be considered not applicable.”.

3.3.3.1.3 Insert a new paragraph to read as follows:

“3.3.3.1.3 A mixture with an extreme pH (pH ≤ 2 or ≥ 11.5) is considered to cause serious eye damage (Category 1) in Tier 5 if it has a significant acid/alkaline reserve or if no data for acid/alkaline reserve are available. However, if consideration of acid/alkaline reserve suggests the mixture may not cause serious eye damage despite the extreme pH value, the result is considered inconclusive within Tier 5 (see Figure 3.3.1). If the overall weight of evidence assessment remains inconclusive or no data other than pH and acid/alkaline reserve are available, mixtures with an extreme pH (pH ≤ 2 or ≥ 11.5) and non-significant acid/alkaline reserve should be assessed using the bridging principles described in 3.3.3.2. If the bridging principles cannot be applied, mixtures with an extreme pH (pH ≤ 2 or ≥ 11.5) and non-significant acid/alkaline reserve should be classified as eye Category 1 (see Figure 3.3.2). A pH > 2 and < 11.5 is considered inconclusive and cannot be used for classification purposes. Acid/alkaline reserve and pH can be determined by different methods including those described in OECD Test Guideline 122 and Young et al. (1988), acknowledging that there are some differences between these methods (see 3.3.5.3.7). A competent authority may decide which criteria for significant acid/alkaline reserve can be applied.”.

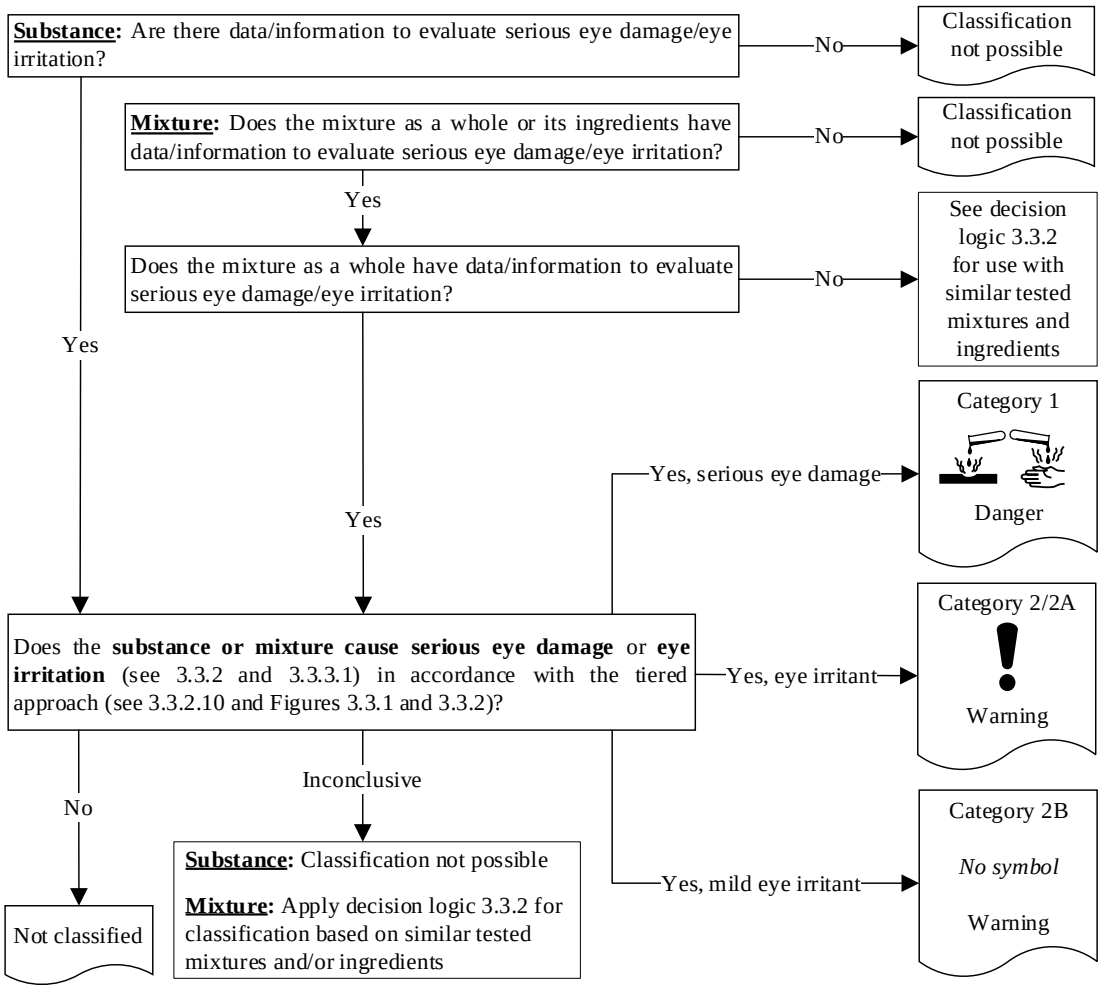
3.3.3.2.7 Replace “aerosolized form of mixture” with “aerosolized form of the mixture”. Renumber footnote 3 as 4.

3.3.3.3.4 In the second sentence, replace “should be used as classification criterion (see 3.3.3.1.2) since pH” with “should be used as the classification criterion (see 3.3.3.1.3) since extreme pH” and delete “(subject to consideration of acid/alkali reserve).

Table 3.3.5, third column Replace “Category 2A” with: “Category 2/2A”.

3.3.5.1 Replace decision logic 3.3.1 with the following:

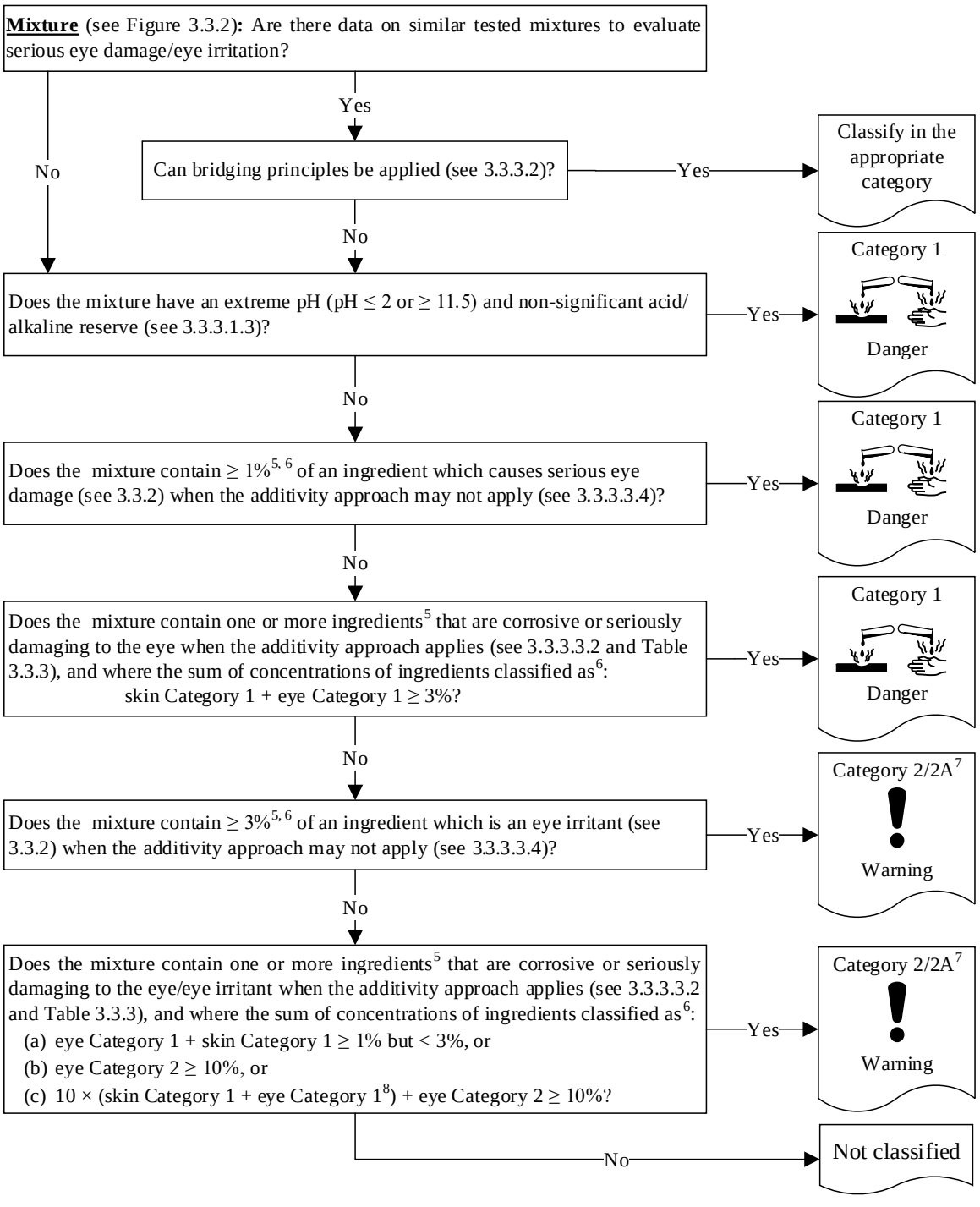
“



”

3.3.5.2 Replace decision logic 3.3.2 with the following:

“



”

Current footnotes “4”, “5”, “6” and “7” become “5”, “6”, “7” and “8”.

3.3.5.3.1 to 3.3.5.3.5 Current paragraphs 3.3.5.3.1 to 3.3.5.3.5 become new paragraphs 3.3.5.3.3.1 to 3.3.5.3.3.5.

3.3.5.3.1 and 3.3.5.3.2 (new) Insert the following two new paragraphs:

“3.3.5.3.1 *Relevant guidance documents*

Helpful information on the strengths and weaknesses of the different test and non-test methods, as well as useful guidance on how to apply a weight of evidence assessment, is provided in OECD Guidance Document

263 on an integrated approach on testing and assessment (IATA) for serious eye damage and eye irritation.

3.3.5.3.2 *Guidance on the use of human data for classification as serious eye damage/eye irritation*

The availability of human data for serious eye damage/eye irritation is limited and the data available may contain some uncertainty. However, where such data exist, they should be considered based on their quality. Human data may be obtained from epidemiological studies, human experience (e.g. consumer experience), poison control centres, national and international home accident surveillance programs, case studies, or worker experience and accidents. Human case studies may have limited predictive value as often the presence of a substance or mixture in the eye will result in pain and quick washing of the eyes. Therefore, the effects observed may underestimate the intrinsic property of the substance or the mixture to affect the eye without washing. Further details on the strengths and limitations of human data for serious eye damage/eye irritation can be found in OECD Guidance Document 263 (section 4.1. Module 1: Existing human data on serious eye damage and eye irritation).".

3.3.5.3.3 Insert the following new heading:

"3.3.5.3.3 *Classification based on standard animal tests with more than 3 animals*"

3.3.5.3.3.2 (new, former 3.3.5.3.2) Replace "3.3.2.1" with "3.3.2.2", "done" with "performed".

3.3.5.3.4 to 3.3.5.3.7.2 Insert the following new sections:

"3.3.5.3.4 *Guidance on the use of defined approaches and/or in vitro/ex vivo data for classification within Tier 2 of Figure 3.3.1*

3.3.5.3.4.1 Defined approaches consist of a predefined set of different information sources (e.g. *in vitro* methods, *ex vivo* methods, physico-chemical properties, non-test methods) which, combined together through a fixed Data Interpretation Procedure (DIP) to convert input data into a prediction (or result), can provide a conclusion on the classification of a substance or mixture. A fixed DIP is defined as any fixed algorithm for interpreting data from one or typically several information sources and is rule-based in the sense that it is based, for example on a formula or an algorithm (e.g. decision criteria, rule or set of rules) that do not involve expert judgment. The output of a DIP generally is a prediction of a biological effect of interest or regulatory endpoint. Since in a defined approach the information sources are prescribed and the set of rules on how to integrate and interpret them is predetermined, the same conclusion will always be reached by different assessors on the same set of data as there is no room for subjective interpretation. In contrast, in a weight of evidence assessment, expert judgment is applied on an ad hoc basis to the available information, which may lead to different conclusions because there are no fixed rules for interpreting the data.

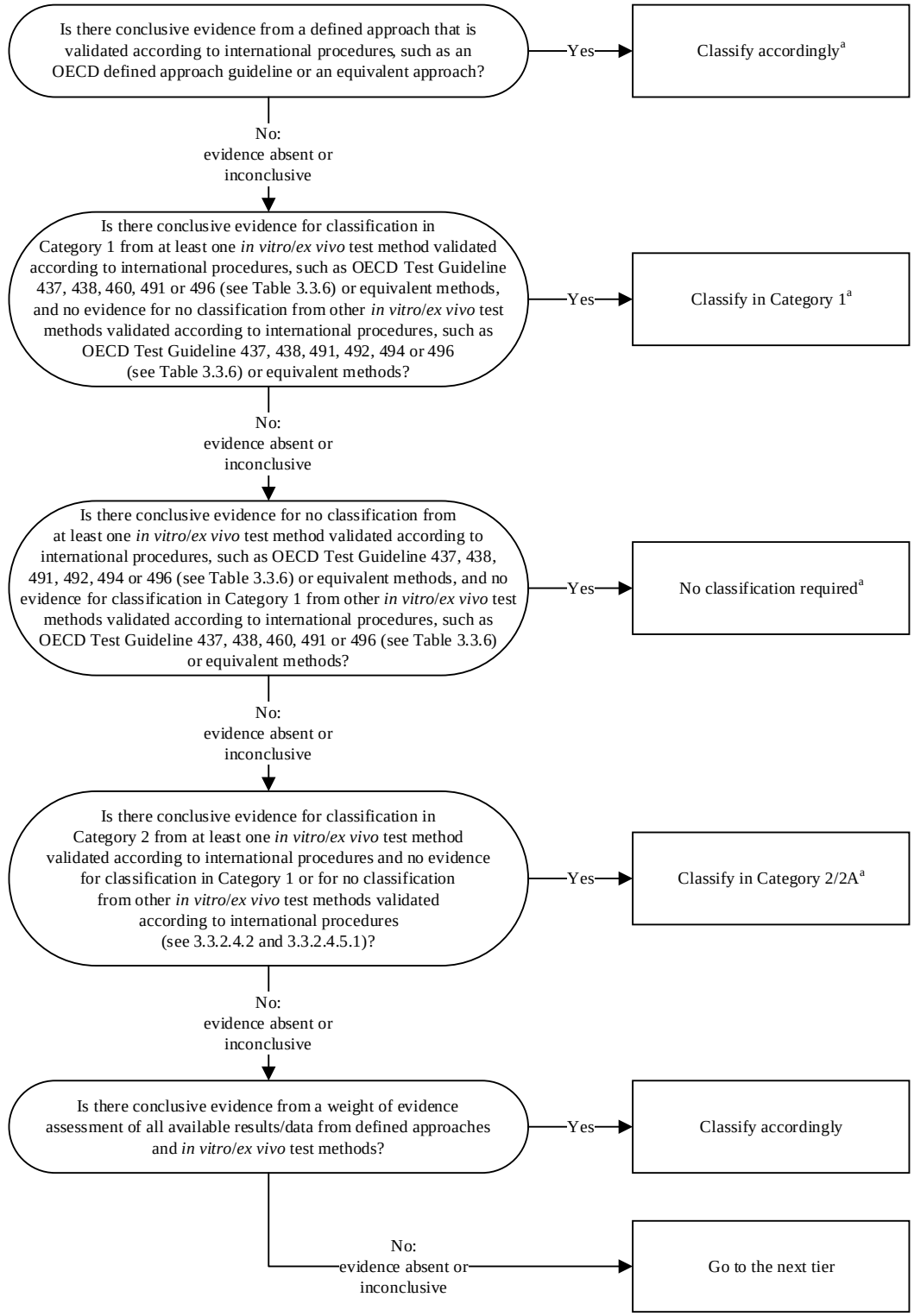
3.3.5.3.4.2 A stepwise approach to the evaluation of information derived from Tier 2 of Figure 3.3.1, i.e. defined approaches and/or *in vitro*/*ex vivo* test methods, should be considered where applicable (Figure 3.3.3), recognizing that not all elements may be relevant. However, all available and relevant information of sufficient quality needs to be examined for consistency with respect to the resulting classification. The outcome of a defined approach containing conclusive animal and/or human data may also eventually be considered during the overall weight of evidence in Tier 7 (see Figure 3.3.1). Where information from several steps is inconsistent and/or conflicting with respect to the resulting classification, information of sufficient quality from a higher step is generally given a higher weight than information from a lower step. However, when information from a lower step would result in a stricter

classification than information from a higher step and there is concern for misclassification, then classification is determined by a within-tier weight of evidence assessment. For example, classifiers concerned with a negative result for serious eye damage in a defined approach when there is a positive result for serious eye damage in an *in vitro*/*ex vivo* method would utilise a within-tier weight of evidence assessment.

3.3.5.3.4.3 Current *in vitro*/*ex vivo* test methods are not able to distinguish between certain *in vivo* effects, such as corneal opacity, iritis, conjunctiva redness or conjunctiva chemosis, but they have shown to correctly predict substances inducing serious eye damage/eye irritation independently of the types of ocular effects observed *in vivo*. Many of the current *in vitro*/*ex vivo* test methods can thus identify substances or mixtures not requiring classification with high sensitivity but with limited specificity when used to distinguish not classified from classified substances or mixtures. This means that it is reasonably certain that a substance or mixture identified as not requiring classification by OECD Test Guideline 437, 438, 491, 492, 494 or 496 (see Table 3.3.6) is indeed not inducing eye effects warranting classification, whereas some substances or mixtures not requiring classification will be over-predicted by these *in vitro*/*ex vivo* test methods when used in isolation. Furthermore, it should be considered that substances inducing serious eye damage are identified by many of these test methods with a high specificity but a limited sensitivity when used to distinguish Category 1 from Category 2 and not classified. This means that it is reasonably certain that a substance or mixture identified as Category 1 by OECD Test Guideline 437, 438, 460, 491 or 496 (see Table 3.3.6) is indeed inducing irreversible eye effects, whereas some substances or mixtures inducing serious eye damage will be under-predicted by these *in vitro*/*ex vivo* test methods when used in isolation. As a consequence, a single *in vitro*/*ex vivo* OECD test guideline method is currently sufficient to conclude on either Category 1 or no classification according to the criteria defined in Table 3.3.6, but not to conclude Category 2. When the result of an *in vitro*/*ex vivo* method is "no stand-alone prediction can be made" (e.g. see Table 3.3.6), a conclusion cannot be drawn on the basis of that single result and further data are necessary for classification. Some *in vitro/ex vivo* test methods validated according to international procedures but not adopted as OECD test guidelines may be accepted by some competent authorities to classify in Category 2 (see 3.3.5.3.5.2). Moreover, combinations of *in vitro*/*ex vivo* methods in tiered approaches or their integration in defined approaches (see 3.3.2.3) may reduce the number of false predictions and show adequate performance for classification purposes.

3.3.5.3.4.4 In the absence of an adequate defined approach (see 3.3.2.3) or of conclusive *in vitro*/*ex vivo* data (see 3.3.2.4.1 and 3.3.2.4.2), a stand-alone prediction is not possible. In such cases, a within-tier weight of evidence assessment of data from more than one method would be needed to classify within Tier 2. If a within-tier weight of evidence assessment is still not conclusive, then data from lower tiers may be required to reach a conclusion (see Figure 3.3.1).

Figure 3.3.3: Classification based on defined approaches and/or *in vitro*/*ex vivo* data within Tier 2 of Figure 3.3.1



[a] *Evidence is considered conclusive if the data fulfil the criteria of the defined approach or of the method and there is no contradicting in vitro/ex vivo information. When information from a lower step would result in a stricter classification than information from a higher step and there is concern for misclassification, then classification is determined by a within-tier weight of evidence assessment.*

3.3.5.3.5 *Classification criteria based on in vitro/ex vivo data*

3.3.5.3.5.1 Where *in vitro/ex vivo* tests have been undertaken in accordance with OECD test guidelines 437, 438, 460, 491, 492, 494 and/or 496, the criteria for classification in Category 1 for serious eye damage/irreversible effects on the eye and for no classification are set out in Table 3.3.6

Table 3.3.6: Criteria for serious eye damage/irreversible effects on the eye and for no classification[a] for *in vitro*/*ex vivo* methods

Category	OECD Test Guideline 437 Bovine Corneal Opacity and Permeability test method	OECD Test Guideline 438 Isolated Chicken Eye test method	OECD Test Guideline 460 Fluorescein Leakage test method	OECD Test Guideline 491 Short Time Exposure test method	OECD Test Guideline 492 Reconstructed human Cornea-like Epithelium (RhCE)-based test methods: Methods 1, 2, 3 and 4 as numbered in Annex II of OECD Test Guideline 492	OECD Test Guideline 494 Vitrigel-Eye Irritancy Test Method	OECD Test Guideline 496 *In vitro* Macromolecular Test Method (test method 1)
	Organotypic *ex vivo* assay using isolated corneas from the eyes of freshly slaughtered cattle. Test chemicals are applied to the epithelial surface of the cornea. Damage by the test chemical is assessed by quantitative measurements of: - Corneal opacity changes measured using a light transmission opacitometer (opacitometer 1) or a laserlight-based opacitometer (LLBO, opacitometer 2) - Permeability (sodium fluorescein dye). Both measurements are used to calculate an *In Vitro* Irritancy Score (IVIS) when using opocitometer 1 or a LLBO Irritancy Score (LIS) when using opacitometer 2. **Criteria based on IVIS or LIS.**	Organotypic *ex vivo* assay based on the short-term maintenance of chicken eyes *in vitro*. Test chemicals are applied to the epithelial surface of the cornea. Damage by the test chemical is assessed by (i) a quantitative measurement of increased corneal thickness (swelling), (ii) a qualitative assessment of corneal opacity, (iii) a qualitative assessment of damage to epithelium based on application of fluorescein to the eye, and (iv) a qualitative evaluation of macroscopic morphological damage to the surface. Histopathology can be used to increase the sensitivity of the method for identifying Category 1 non-extreme pH ($2 < pH < 11.5$) detergents and surfactants. [b] **Criteria based on the scores of corneal swelling, opacity and fluorescein retention, which are used to assign ICE classes (I, II, III or IV) to each endpoint, and on macroscopic and histopathology assessment** [b]	Cytotoxicity and cell-function based *in vitro* assay that is performed on a confluent monolayer of Madin-Darby Canine Kidney (MDCK) CB997 tubular epithelial cells cultured on permeable inserts. The toxic effects of a test chemical are measured after a short exposure time (1 minute) by an increase in permeability of sodium fluorescein through the epithelial monolayer of MDCK cells. The amount of fluorescein leakage that occurs is proportional to the chemical-induced damage to the tight junctions, desmosomal junctions and cell membranes, and is used to estimate the ocular toxicity potential of a test chemical. **Criteria based on mean percent fluorescein leakage following a defined exposure period**	Cytotoxicity-based *in vitro* assay that is performed on a confluent monolayer of Statens Seruminstitut Rabbit Cornea (SIRC) cells. Each test chemical is tested at both 5 % and 0.05 % concentrations. Following five-minute exposure, cell viability is assessed by the enzymatic conversion in viable cells of the vital dye MTT into a blue formazan salt that is quantitatively measured after extraction from cells. **Criteria based on mean percent cell viability following a defined exposure period**	Three-dimensional RhCE tissues are reconstructed from either primary human cells or human immortalised corneal epithelial cells, which have been cultured for several days to form a stratified, highly differentiated squamous epithelium, consisting of at least 3 viable layers of cells and a non-keratinised surface, showing a cornea-like structure morphologically similar to that found in the human cornea. Following exposure and post-treatment incubation (where applicable), tissue viability is assessed by the enzymatic conversion in viable cells of the vital dye MTT into a blue formazan salt that is quantitatively measured after extraction from the tissues. **Criteria based on mean percent tissue viability following defined exposure and post-exposure (where applicable) periods**	*In vitro* assay using human corneal epithelium models fabricated in a collagen vitrigel membrane (CVM) chamber. The eye irritation potential of the test chemical is predicted by analysing time-dependent changes in transepithelial electrical resistance values using the value of three indexes. Resistance values are measured at intervals of 10 seconds for a period of three minutes after exposure to the test chemical preparation. **Criteria based on the 3 measured indexes: time lag, intensity and plateau level of electrical resistance**.	*In vitro* assay consisting of a macromolecular plant-based matrix obtained from jack bean *Canavalis enisformis*. This matrix serves as the target for the test chemical and is composed of a mixture of proteins, glycoproteins, carbohydrates, lipids and low molecular weight components, which form a highly ordered and transparent gel structure upon rehydration. Test chemicals causing ocular damage lead to the disruption and disaggregation of the highly organized macromolecular reagent matrix, and produce turbidity of the macromolecular reagent. Such phenomena is quantified, by measuring changes in light scattering. **Criteria based on a Maximum Qualified Score (MQS) derived from the Optical Density readings at different concentrations, calculated via a software.**

Category	OECD Test Guideline 437 Bovine Corneal Opacity and Permeability test method		OECD Test Guideline 438 Isolated Chicken Eye test method	OECD Test Guideline 460 Fluorescein Leakage test method	OECD Test Guideline 491 Short Time Exposure test method	OECD Test Guideline 492 Reconstructed human Cornea-like Epithelium (RhCE)-based test methods: Methods 1, 2, 3 and 4 as numbered in Annex II of OECD Test Guideline 492				OECD Test Guideline 494 Vitrigel-Eye Irritancy Test Method	OECD Test Guideline 496 *In vitro* Macromolecular Test Method (test method 1)
1	Opacitometer 1 IVIS > 55	Opacitometer 2 LIS > 30 and lux/7 ≤ 145 and OD490 > 2.5, OR LIS > 30 and lux/7 > 145	At least 2 ICE class IV, OR Corneal opacity = 3 at 30 min (in at least 2 eyes), OR Corneal opacity = 4 at any time point (in at least 2 eyes), OR Severe loosening of the epithelium (in at least 1 eye), OR Certain histopathological effects[b]	Chemical concentration causing 20 % of Fluorescein Leakage (FL_{20}) ≤ 100 mg/mL	Viability ≤ 70 % at 5 % and 0.05 %	No stand-alone prediction can be made				No stand-alone prediction can be made	MQS > 30.0
2/2A/2B	No stand-alone prediction can be made.	No stand-alone prediction can be made	No stand-alone prediction can be made	No stand-alone prediction can be made	No stand-alone prediction can be made	No stand-alone prediction can be made				No stand-alone prediction can be made	No stand-alone prediction can be made
Not classified	Opacitometer 1 IVIS ≤ 3	Opacitometer 2 LIS ⩽ 30	ICE class I for all 3 endpoints, OR ICE class I for 2 endpoints and ICE class II for the other endpoint, OR ICE class II for 2 endpoints and ICE class I for the other endpoint	No stand-alone prediction can be made	Viability > 70 % at 5 % and 0.05 %	Test method 1 Liquids and Solids: Viability > 60 %	Test method 2 Liquids: Viability > 60 %; Solids: Viability > 50 %	Test method 3 Liquids and Solids: Viability > 40 %	Test method 4 Liquids: Viability > 35 %; Solids: Viability > 60 %	Time lag > 180 seconds and Intensity < 0.05 %/seconds and Plateau level ≤ 5.0 %	MQS ≤ 12.5

[a] *Grading criteria are understood as described in OECD test guidelines 437, 438, 460, 491, 492, 494 and 496.*

[b] *For criteria, please consult OECD Test Guideline 438*

3.3.5.3.5.2 A non-exhaustive list of other validated *in vitro*/*ex vivo* test methods accepted by some competent authorities but not adopted as OECD test guidelines are listed below. A competent authority may decide which classification criteria, if any, should be applied for these test methods:

- Time to Toxicity (ET_{50}) tests using the Reconstructed human Cornea-like Epithelia (RhCE) described in OECD Test Guideline 492 (Kandarova et al., 2018; Alépée et al., 2020);
- Ex Vivo Eye Irritation Test (EVEIT): an ex vivo assay that uses excised rabbit corneal tissues kept in culture for several days and monitors tissue recovery to model both reversible and non-reversible eye effects. Full-thickness tissue recovery is monitored non-invasively using optical coherence tomography (OCT) (Frentz et al., 2008; Spöler et al., 2007; Spöler et al., 2015);
- Porcine Ocular Cornea Opacity/Reversibility Assay (PorCORA): an ex vivo assay that uses excised porcine corneal tissues kept in culture for up to 21 days and monitors tissue recovery to model both reversible and non-reversible eye effects. The tissues are stained with fluorescent dye and effects on the corneal epithelia are visualised by the retention of fluorescent dye (Piehl et al., 2010; Piehl et al., 2011);
- EyeIRR-IS assay: a genomic approach applied to a RhCE model (Cottrez et al., 2021);
- In vitro Macromolecular Test Method (test method 2), similar to test method 1 described in OECD Test Guideline 496 (Choksi et al., 2020);
- Metabolic activity assay: In vitro assay consisting of measuring changes to metabolic rate in test-material treated L929 cell monolayer (Harbell et al., 1999; EURL ECVAM, 2004a; Hartung et al., 2010; Nash et al., 2014);
- Hen's Egg Test on the Chorio-Allantoic Membrane (HET-CAM): an organotypic assay that uses the vascularised membrane of fertile chicken eggs to assess a test material's potential to cause vascular changes (Spielmann et al., 1993; Balls et al., 1995; Spielmann et al., 1996; Brantom et al., 1997; ICCVAM, 2007; ICCVAM, 2010);
- Chorio-Allantoic Membrane Vascular Assay (CAMVA): an organotypic assay that uses the vascularised membrane of fertile chicken eggs to assess a test material's potential to cause vascular changes (Bagley et al., 1994; Brantom et al., 1997; Bagley et al., 1999; Donahue et al., 2011);
- Neutral Red Release (NRR) assay: In vitro assay that quantitatively measures a substance's ability to induce damage to cell membranes in a monolayer of normal human epidermal keratinocytes (NHEK) (Reader et al. 1989; Reader et al., 1990; Zuang, 2001; EURL ECVAM, 2004b; Settivari et al., 2016); and
- Isolated Rabbit Eye (IRE) test, similar to OECD Test Guideline 438 but using isolated rabbit eyes instead of isolated chicken eyes (Burton et al., 1981; Whittle et al. 1992; Balls et al., 1995; Brantom et al., 1997; ICCVAM, 2007; ICCVAM, 2010).

3.3.5.3.6 *Guidance on the use of other existing skin or eye data in animals for classification as serious eye damage or eye irritation*

3.3.5.3.6.1 The availability of other animal data for serious eye damage/eye irritation may be limited as tests with the eye as the route of exposure are not normally performed. An exception could be historical data from the Low Volume Eye Test (LVET) that might be used in a weight of evidence assessment. The LVET is a modification of the standard OECD Test Guideline 405 test method.

3.3.5.3.6.2 Existing data from the LVET test could be considered for the purpose of classification and labelling but must be carefully evaluated. The differences between the LVET and OECD Test Guideline 405 may result in a classification in a lower category (or no classification) based on LVET data, than if the classification was based on data derived from the standard in vivo test (OECD Test Guideline 405). Thus, positive data from the LVET test could be a trigger for considering classification in Category 1 on its own, but data from this test are not conclusive for a Category 2 classification or no classification (ECHA, 2017). Such data may, however, be used in an overall weight of evidence assessment. It is noted that the applicability domain of the LVET is limited to household detergent and cleaning products and their main ingredients (surfactants) (ESAC, 2009).

3.3.5.3.6.3 Effects on the eyes may be observed in acute or repeated dose inhalation studies with full body exposure. However, normally no scoring according to the Draize criteria is performed and the follow-up period may be shorter than 21 days. Also, the effects on the eyes will likely depend upon the concentration of the substance/mixture and the exposure duration. As there are no criteria for minimal concentration and duration, the absence of effects on the eyes or eye irritation may not be conclusive for the absence of serious eye damage. The presence of irreversible effects on the eye should be considered within a weight of evidence assessment.

3.3.5.3.7 *Guidance on the use of pH and acid/alkaline reserve for classification as serious eye damage*

3.3.5.3.7.1 Methods to determine the pH value such as OECD Test Guideline 122 and the method described by Young et al. (1988) differ in the concentration of the substance or mixture for which the pH is determined and include values of 1%, 10% and 100%. These methods also differ in the way the acid/alkaline reserve is determined, namely up to a pH of 7 for both acids and bases (OECD Test Guideline 122) or up to a pH of 4 for acids and a pH of 10 for bases (Young et al., 1988). Furthermore, there are differences between OECD Test Guideline 122 and Young et al. (1988) in the units used to express the acid/alkaline reserve.

3.3.5.3.7.2 Criteria to identify substances and mixtures requiring classification in Category 1 based on pH and acid/alkaline reserve have been developed for effects on the skin (Young et al., 1988) and the same criteria are applied for effects on the eye. These criteria were developed using a combination of pH and acid/alkaline reserve values that were determined in a specific way (Young et al., 1988). Therefore, these criteria may not be directly applicable when other test concentrations or methods are used to measure pH and acid/alkaline reserve. Furthermore, the calibration and validation of these criteria was based on a limited dataset for effects on the skin. Thus, the predictive value of the combination of pH and acid/alkaline reserve for classification in Category 1 for effects on the eye is limited, especially for substances and mixtures with an extreme pH but a non-significant acid/alkaline reserve. The criteria developed by Young et al. (1988) for classification in Category 1 may be used as a starting point for determining whether a substance or a mixture has a significant acid/alkaline reserve or a non-significant acid/alkaline reserve. A competent authority may decide which criteria for significant acid/alkaline reserve can be applied.

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Annex 3

Section 1

A3.1.2.3 Replace the last sentence with:

"For example, H300 + H310 + H330 indicates that the text to appear on the label is "**Fatal if swallowed, in contact with skin or if inhaled.**"."

A3.1.2.4 Replace the last sentence with the following:

"Also, where a combined hazard statement is permitted for two or more hazard statements (see A3.1.2.5), the competent authority may specify whether the combined hazard statement or the corresponding individual statements should appear on the label or may leave the choice to the manufacturer/supplier."

A3.1.2.5 Insert a new paragraph to read as follows:

"A3.1.2.5 In addition to the combinations found in Table A3.1.2, it is also permitted to combine more than one health hazard statement of equivalent severity if, for example, there is insufficient space on the label. When hazard statements are combined, all hazards must be clearly conveyed and only the repetitive text may be deleted. Statements can be combined by using the word "and", additional punctuation, and changing the case of the initial letter of the word at the beginning of a statement. For example, H317 "May cause an allergic skin reaction" + H340 "May cause genetic defects" + H350 "May cause cancer" may all be combined because they are all for Category 1 health hazards (i.e., health hazard statements of equivalent severity) and have repetitive elements of the hazard statement (i.e., the statements begin with "may cause"). These statements may be combined to "May cause an allergic skin reaction, genetic defects, and cancer." The competent authority may limit the types of combinations permitted to ensure comprehensibility (e.g., limit the number of hazard statements that can be combined)."

Table A3.1.2

- H317, column (3)

  Replace "Sensitization, skin (chapter 3.4)" with "Skin sensitization (chapter 3.4)".

- H334, column (3)

  Replace "Sensitization, respiratory (chapter 3.4)" with "Respiratory sensitization (chapter 3.4)".

- After "H303 + H313 + H333", insert the following new entry:

H315 + H319	Causes skin irritation and serious eye irritation [a]	Skin corrosion/irritation (chapter 3.2) and serious eye damage/eye irritation (chapter 3.3)	2 (skin) + 2/2A (eye)

- For "H315 + H320":

  Under column (2), add a reference to note "[a]"" at the end of the hazard statement, as follows: "Causes skin and eye irritation [a]".

  Under column (4) , replace "2 (skin)/2B (eye)" with "2 (skin) + 2B (eye)".

- Insert the following note "a" under table A3.1.2:

  "[a] *Competent authorities may select the applicable hazard statement(s) depending on the serious eye damage/eye irritation hazard categories implemented in their jurisdiction (2/2A or 2A/2B).".

Section 2

A3.2.5.2.2 Insert the following text after the first sentence:

“Precautionary statements can be combined by using the word “and”, additional punctuation, and changing the case of the initial letter of the word at the beginning of a statement. For example, P302 + P335 + P334 “**IF ON SKIN: Brush off loose particles from skin and immerse in cool water [or wrap in wet bandages].**”

A3.2.2.4 Insert the following new paragraph:

“A3.2.2.4 Where square brackets […] appear around a precautionary statement code, this indicates the precautionary statement is not appropriate in every case and should be used only in certain circumstances. In these cases, conditions for use explaining when the text should be used are given in column (5) of the tables.”.

Table A3.2.2

- P262, column (4): Insert: “3” after: “1, 2”.
- P264 and P270, column (4): For the hazard class acute toxicity (dermal), insert: “3” after: “1, 2”.

Table A3.2.3

For “P302 + P335 + P334”, amend the precautionary statement in column (2) to read as follows: “**IF ON SKIN: Brush off loose particles from skin and immerse in cool water [or wrap in wet bandages].”**

Section 3

- Tables for flammable gases (Chapter 2.2)

  Delete the note under the tables for pyrophoric gases and chemically unstable gases

- Table for pyrophoric solids (chapter 2.10), hazard category 1, column “Response”

  Replace the P302 + P335 + P334 entry with:

  “P302 + P335 + P334
  IF ON SKIN: Brush off loose particles from skin and immerse in cool water or wrap in wet bandages.”

- Table for “Acute toxicity - dermal (Chapter 3.1)”, hazard category 3, column “Prevention”, insert the following entries:

  “P262
  Do not get in eyes, on skin, or on clothing.

  P264
  Wash hands [and ...] thoroughly after handling.
  − text in square brackets to be used when the manufacturer/supplier or competent authority specify other parts of the body to be washed after handling.

  P270
  Do not eat, drink or smoke when using this product.”.

- Tables for “Sensitization – respiratory (Chapter 3.4)

  Amend the heading to read as follows: “RESPIRATORY SENSITIZATION (CHAPTER 3.4)”.

- Table for “Sensitization – skin (Chapter 3.4)”,

  Amend the heading to read as follows: “SKIN SENSITIZATION (CHAPTER 3.4)”.