



**Committee of Experts on the Transport of Dangerous Goods
and on the Globally Harmonized System of Classification
and Labelling of Chemicals****Sub-Committee of Experts on the Globally Harmonized
System of Classification and Labelling of Chemicals****Twenty-fourth session**

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 3.2****Submitted by the expert from Germany on behalf of the informal
correspondence group on the editorial revision of chapters 3.2 and 3.3¹****Introduction**

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

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

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

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

Proposal

5. Amend Chapter 3.2 as follows:

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

Insert paragraph number “3.2.1.1” before the definition of “Skin corrosion”.

- 3.2.1.2 Insert a new paragraph to read as follows:

“3.2.1.2 In a tiered approach, emphasis should be placed upon existing human data, followed by existing animal data, followed by *in vitro* data and then other sources of information. Classification results directly when the data satisfy the criteria. In some cases, classification of a substance or a mixture is made on the basis of the weight of evidence within a tier. In a total weight of evidence approach all available information bearing on the determination of skin corrosion/irritation is considered together, including the results of appropriate validated *in vitro* tests, relevant animal data, and human data such as epidemiological and clinical studies and well-documented case reports and observations (see Chapter 1.3, para. 1.3.2.4.9).”

- 3.2.2 Replace paragraphs 3.2.2.1, 3.2.2.2, 3.2.2.3 and figure 3.2.1 with the following:

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

- (a) Category 1 (skin corrosion)

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

- (b) Category 2 (skin irritation) (see Table 3.2.2)

- (c) Category 3 (mild skin irritation)

This category is available for those authorities (e.g. pesticides) that want to have more than one skin irritation category (see Table 3.2.2).”

- 3.2.2.1 Insert the following new subheading “3.2.2.1 Classification based on standard animal test data”.

- 3.2.2.1.1 Former 3.2.2.4 becomes new 3.2.2.1.1. Amend to read as follows: “Skin corrosion”.

- 3.2.2.1.1.1 Former 3.2.2.4.1 becomes new 3.2.2.1.1.1. Amend to read as follows:

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

- 3.2.2.1.1.2 and 3.2.2.1.1.3 Insert the following new paragraphs:

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

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

- 3.2.2.1.1.4 Former 3.2.2.4.2 becomes new 3.2.2.1.1.4 with the following amendments:
- Replace “one designation for corrosivity” with “one designation for skin corrosion”; and “corrosive category” with “corrosion category”;
 - Insert “corrosive” before “responses” (3 times);
 - Replace (twice) “between 3 minutes and 1 hour” with “greater than 3 minutes and up to 1 hour”.

Table 3.2.1 Replace with the following:

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

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

^{ca} *The use of human data is addressed in 3.2.2.2 and in chapters 1.1 (para. 1.1.2.5(c)), and 1.3 (para. 1.3.2.4.7)."*

- 3.2.2.1.2 Former 3.2.2.5 becomes new 3.2.2.1.2. Amend to read as follows: “Skin irritation”.
- 3.2.2.1.2.1 Insert a new paragraph to read as follows:
- “3.2.2.1.2.1 A substance is irritant to skin when it produces reversible damage to the skin following its application for up to 4 hours.”
- 3.2.2.1.2.2 Former 3.2.2.5.1 becomes new 3.2.2.1.2.2 with the following amendments:
- Amend the introductory sentence to read as follows: “An irritation category (Category 2) is provided that:”
 - Delete (a). Current sub-paragraphs (b) and (c) become (a) and (b) respectively.
 - In new (b) delete “quite”.
 - In the last sentence, replace “irritant” with “irritation” (twice) and insert “(Category 3)” before “is available”.
- 3.2.2.1.2.3 Former 3.2.2.5.2 becomes new 3.2.2.1.2.3.
- 3.2.2.1.2.4 Former 3.2.2.5.3 becomes new 3.2.2.1.2.4 with the following amendment: In the first sentence, delete “quite”.

- 3.2.2.1.2.5 Former 3.2.2.5.4 becomes new 3.2.2.1.2.5 with the following amendments:
- In the first sentence, replace “A single irritant category” with “An irritation category” and “the table” with “Table 3.2.2”.
 - In the second sentence, insert “for” before “pesticides” and replace “irritant” with “irritation”.
 - In the fifth sentence, replace “irritant” with “irritation”; “at least 2 tested” with “at least 2 of 3 tested” and insert “and” after “2.3”.
 - In the sixth sentence, replace “irritant” with “irritation”; “at least 2 tested” with “at least 2 of 3 tested” and insert “and” after “1.5”.
 - Amend the last sentence to read as follows: “Test materials in the irritation category are excluded from the mild irritation category.”.
- Table 3.2.2 In the heading, insert a reference to notes “a”, “b” and “c” as follows: “Skin irritation categories ^{a,b,c}”.
- In the first column, under “Categories”, replace “irritant” with “irritation” (twice).
- In the second column, under “Criteria”:
- First row, paragraph (1): Replace “Mean value of $\geq 2.3 \leq 4.0$ ” with “Mean score of ≥ 2.3 and ≤ 4.0 ”;
 - Second row: Replace “Mean value of $\geq 1.5 < 2.3$ ” with “Mean score of ≥ 1.5 and < 2.3 ”.
- Amend note “a” to read as follows:
- ^a *The use of human data is addressed in 3.2.2.2 and in chapters 1.1 (para.1.1.2.5 (c)) and 1.3 (para.1.3.2.4.7)”.*
- Add the following two new notes “b” and “c” after the table:
- ^b *Grading criteria are understood as described in OECD Test Guideline 404.*
- ^c *Evaluation of a 4, 5 or 6-animal study should follow the criteria given in 3.2.5.3.”.*
- 3.2.2.2 Insert a new sub-heading to read as follows “3.2.2.2 Classification in a tiered approach”.
- 3.2.2.2.1 Former 3.2.2.3 becomes new 3.2.2.2.1. Amend the end of the sentence to read as follows: “recognizing that not all elements may be relevant”.
- 3.2.2.2.2 The third sentence of former 3.2.2.2 (“Existing human experience...effects on the skin”) becomes new 3.2.2.2.2 with the following amendments:
- Replace “Existing human experience and data” with “Existing human and animal data” and “first line of analysis” with “first line of evaluation”;
 - Insert “information” after “including” and delete “and animal observations and data”.
- 3.2.2.2.3 The seventh and eight sentences of former 3.2.2.2 (“It also stands to reason that...and species tested are equivalent”) become new paragraph 3.2.2.2.3 with the following amendments:

- Insert the following sentence as the first sentence of new paragraph 3.2.2.2.3: “Acute dermal toxicity data may be used for classification”;
 - Replace “It also stands to reason that if a substance” with “If a substance”;
 - Replace “skin irritation/corrosion” with “skin corrosion/irritation” (twice);
 - Replace “additional testing would not be needed” with “these data may be used for classification”;
 - Insert the second sentence of former 3.2.2.2 (“Solid substances...mucous membranes”) as the last sentence of new paragraph 3.2.2.2.3.
- 3.2.2.2.4 The last sentence of the first paragraph of former 3.2.2.2 “In vitro alternatives... classification decisions” becomes new paragraph 3.2.2.2.4, with the following amendment: replace “may be used to help make” with “should be used to make”.
- 3.2.2.2.5 The fifth and sixth sentences of former 3.2.2.2 (“Likewise...significant effects on the skin”) become new paragraph 3.2.2.2.5 with the following amendments:
- Replace “especially when buffering capacity is known, although the correlation is not perfect.” with “especially when associated with significant acid/alkaline reserve (buffering capacity).”;
 - Replace “such agents” with “such substances”;
 - Insert the following text as the two last sentences of the new paragraph:
 - “In the absence of any other information, a substance is considered corrosive (Skin Category 1) if it has a $\text{pH} \leq 2$ or a $\text{pH} \geq 11.5$. However, if consideration of acid/alkaline reserve suggests the substance may not be corrosive despite the low or high pH value, this needs to be confirmed by other data, preferably by data from an appropriate validated in vitro test.”.
- 3.2.2.2.6 The fourth sentence of former 3.2.2.2 (“In some cases...decisions”) becomes new paragraph 3.2.2.2.6 with the following amendments: Replace “enough” with “sufficient” and “compounds” with “substances”.
- 3.2.2.2.7 Insert the following new paragraphs:
- “3.2.2.2.7 The tiered approach provides guidance on how to organize existing information on a substance and to make a weight of evidence decision about hazard assessment and hazard classification (ideally without conducting new animal tests). Although information might be gained from the evaluation of single parameters within a tier (see 3.2.2.2.1), consideration should be given to the totality of existing information and making an overall weight of evidence determination. This is especially true when there is conflict in information available on some parameters.”.

Figure 3.2.1 Insert a new figure 3.2.1 and notes, to read as follows:

Figure 3.2.1: Tiered evaluation for skin corrosion and irritation			
Step	Parameter	Finding	Conclusion
1a:	Existing human or animal skin corrosion/irritation data ^a → ↓ Not corrosive/No data ↓	Skin corrosive →	Classify as skin corrosive ^b
1b:	Existing human or animal skin corrosion/irritation data ^a → ↓ Not irritant/No data ↓	Skin irritant →	Classify as skin irritant ^b
1c:	Existing human or animal skin corrosion/irritation data ^a → ↓ No/Insufficient data ↓	Not a skin corrosive or skin irritant →	Not classified
2:	Other, existing skin data in animals ^c → ↓ No/Insufficient data ↓	Yes; other existing data showing that substance may cause skin corrosion or skin irritation →	May be deemed to be a skin corrosive ^b or a skin irritant ^b
3:	Existing <i>ex vivo/in vitro</i> data ^d → ↓ No/Insufficient data/Negative response ↓	Positive: Skin corrosive → Positive: Skin irritant →	Classify as skin corrosive ^b Classify as skin irritant ^b
4:	pH-Based assessment (with consideration of acid/alkaline reserve of the chemical) ^e → ↓ Not pH extreme, no pH data or extreme pH with data showing low/no acid/alkaline reserve ↓	pH ≤ 2 or ≥ 11.5 with high acid/alkaline reserve or no data for acid/alkaline reserve →	Classify as skin corrosive
5:	Validated Structure Activity Relationship (SAR) methods → ↓ No/Insufficient data ↓	Skin corrosive → Skin irritant →	Deemed to be skin corrosive ^b Deemed to be skin irritant ^b
6:	Consideration of the total weight of evidence ^f → ↓	Skin corrosive → Skin irritant →	Deemed to be skin corrosive ^b Deemed to be skin irritant ^b
7:	Not classified		

- ^a Existing human or animal data could be derived from single or repeated exposure(s), for example in occupational, consumer, transport, or emergency response scenarios; or from purposely-generated data from animal studies conducted according to validated and internationally accepted test methods. Although human data 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/sub-category, as applicable;
- ^c All existing animal data should be carefully reviewed to determine if sufficient skin corrosion/irritation evidence is available. In evaluating such data, however, the reviewer should bear in mind that the reporting of dermal lesions may be incomplete, testing and observations may be made on a species other than the rabbit, and species may differ in sensitivity in their responses;
- ^d Evidence from studies using validated protocols with isolated human/animal tissues or other, non-tissue-based, though validated, protocols should be assessed. Examples of internationally accepted, validated test methods for skin corrosion include OECD Test Guideline 430 (Transcutaneous Electrical Resistance Test (TER)), 431 (Human Skin Model Test), and 435 (Membrane Barrier Test Method). An example of a validated internationally accepted *in vitro* test method for skin irritation is OECD Test Guideline 439 (Reconstructed Human Epidermis Test Method);
- ^e Measurement of pH alone may be adequate, but assessment of acid or alkali 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 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. Expert judgment should be exercised prior to making such a determination. Negative results from applicable validated skin corrosion/irritation *in vitro* tests are considered in the total weight of evidence evaluation.”.

3.2.3.1.1 Amend to read as follows:

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

3.2.3.1.2 Delete the first sentence (“Unlike...inexpensive to perform”).

In the second sentence replace “strategy” with “approach” and “as avoid” with “as to avoid”.

Amend the beginning of the third sentence to read: “In the absence of any other information, a mixture is considered...”.

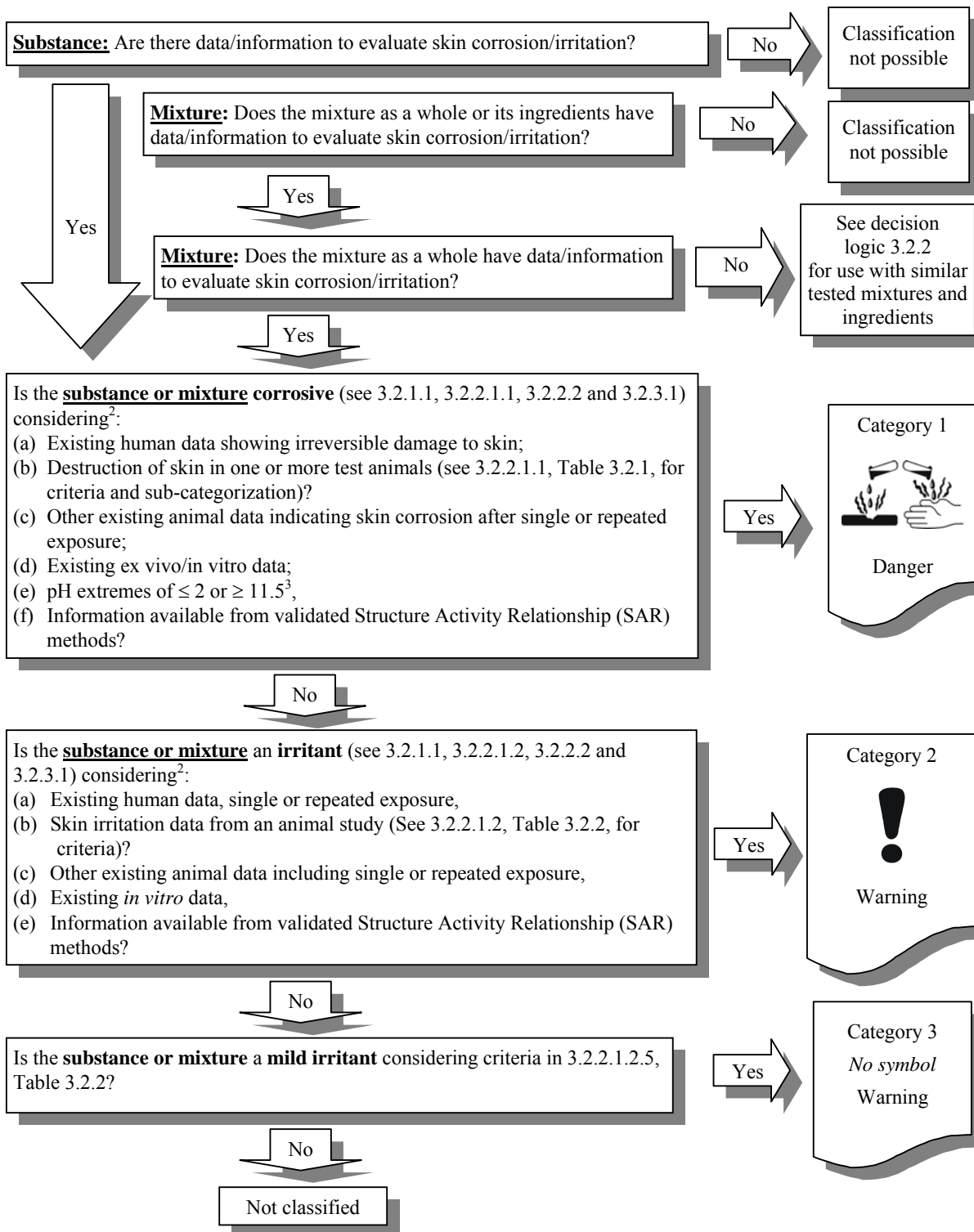
Amend the last sentence to read as follows: “However, if consideration of acid/alkaline reserve suggests the mixture may not be corrosive despite the low or high pH value, this needs to be confirmed by other data, preferably by data from an appropriate validated *in vitro* test.”

- 3.2.3.2.1 In the first sentence, replace “skin irritation/corrosion” with “skin corrosion/irritation potential”.
- 3.2.3.2.3 Replace “irritation/corrosion potential” and “toxicity” with “skin corrosion/irritation potential”.
- 3.2.3.2.4 In the first sentence, replace “for corrosion” with “for skin corrosion”.
- In the second sentence:
- Replace “in the highest category for skin irritation” and “in the highest irritation category” with “for skin irritation (Category 2)”
 - Replace “not contain corrosive” with “not contain skin corrosive”.
- 3.2.3.2.5 In the heading and in the paragraph, replace “toxicity” with “hazard” (twice) and “irritation/corrosion” with “skin corrosion/irritation” (twice).
- 3.2.3.2.6 In (d), replace “irritation/corrosion” with “skin corrosion/irritation” and “toxicity” with “skin corrosion/irritation potential”.
- 3.2.3.2.7 At the end of the paragraph, replace “the irritation or corrosive properties” with “the skin corrosion/irritation properties”.
- 3.2.3.3.1 Replace “skin irritation/corrosion” with “skin corrosion/irritation” (twice).
- 3.2.3.3.2 In the first sentence, replace:
- “mixtures as irritant or corrosive” with “mixtures as corrosive or irritant”
 - “each corrosive or irritant ingredient” with “each skin corrosive or irritant ingredient”, and
 - “overall irritant or corrosive properties” with “overall corrosive or irritant properties”
- 3.2.3.3.3 Replace “be an irritant or a corrosive” with “be corrosive or irritant to the skin”.
- 3.2.3.3.4 In the second sentence, replace “of such substances” with “such substances”.
- In the third sentence, replace “of Table 3.2.3” with “in Table 3.2.3”.
- In the last but one sentence replace:
- “skin Category 1” with “skin corrosion Category 1”; and
 - “skin Category 2/3” with “skin irritation Category 2 or Category 3”.
- 3.2.3.3.5 In the first sentence, insert “limits/” before “cut-off values” and in the last sentence, replace “strategy” with “approach”.
- 3.2.3.3.6 In the first sentence, insert “to skin” after “may be corrosive or irritant”
- Table 3.2.3 Amend the note under the table to read as follows:
- NOTE:** Where the sub-categories of skin Category 1 (corrosive) are used, the sum of all ingredients of a mixture classified as sub-category 1A, 1B or 1C respectively, should each be ≥5% in order to classify the mixture as either skin sub-category 1A, 1B or 1C. Where the sum of 1A ingredients is <5% but the sum of 1A+1B ingredients is ≥5%, the mixture should be classified as sub-category 1B. Similarly, where the sum of 1A + 1B ingredients is <5% but the sum of 1A + 1B + 1C ingredients is ≥5% the mixture should be classified as sub-category 1C. Where at least one relevant ingredient in a mixture is classified as Category 1 without sub-*

categorisation, the mixture should be classified as Category 1 without sub-categorisation if the sum of all ingredients corrosive to skin is $\geq 5\%$.”

- Table 3.2.4 In the title, replace “for which the additivity” with “when the additivity”.
- In the first column, under “Ingredient” for the third and fourth rows, replace “ingredients” with “ingredient” and delete “for which additivity does not apply”.
- In the last column, under “mixture classified as: skin”, for the last row, replace “Category 2” with “Category 2/3”

3.2.5.1 Replace decision logic 3.2.1 and related footnotes with the following:

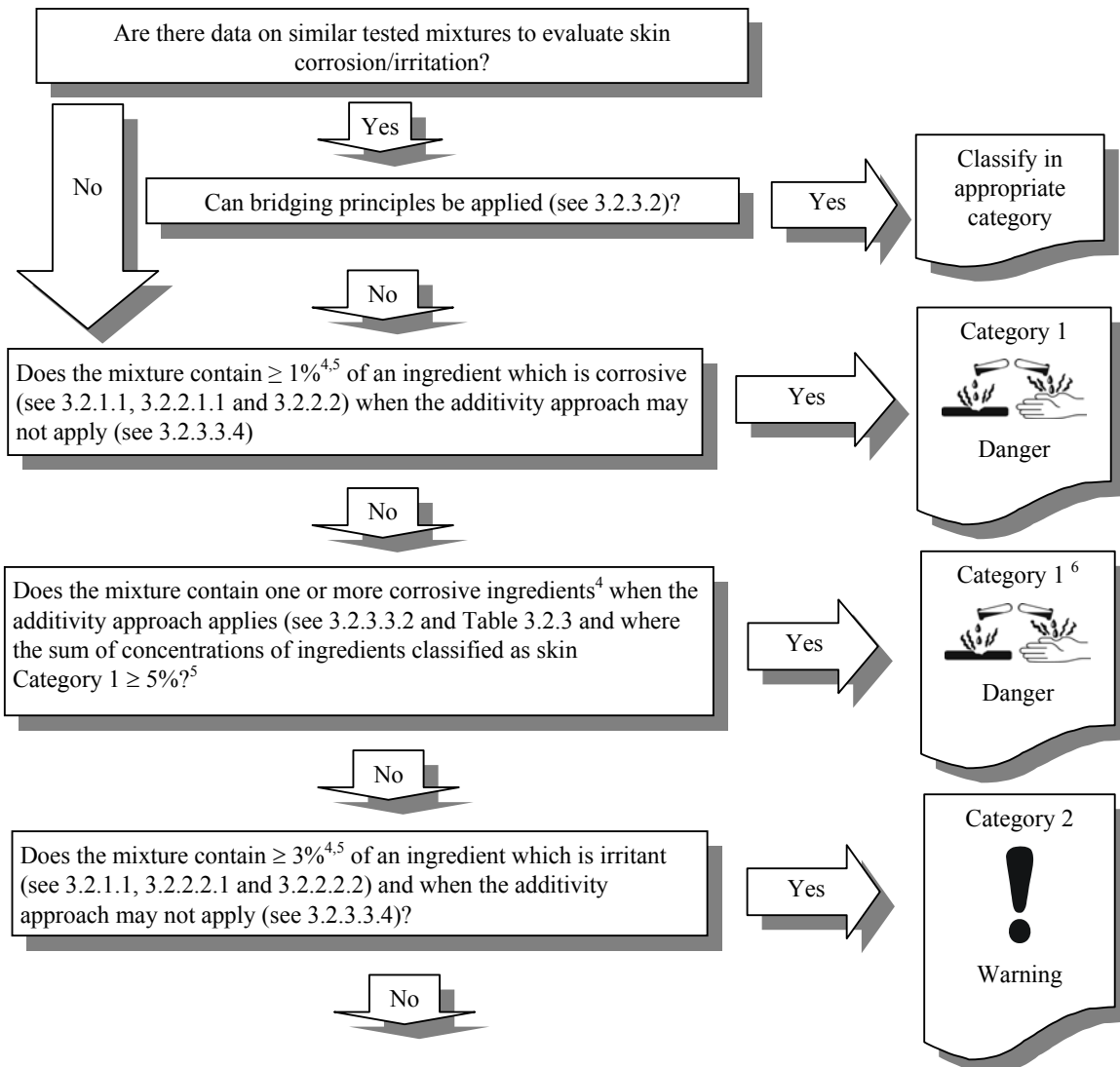


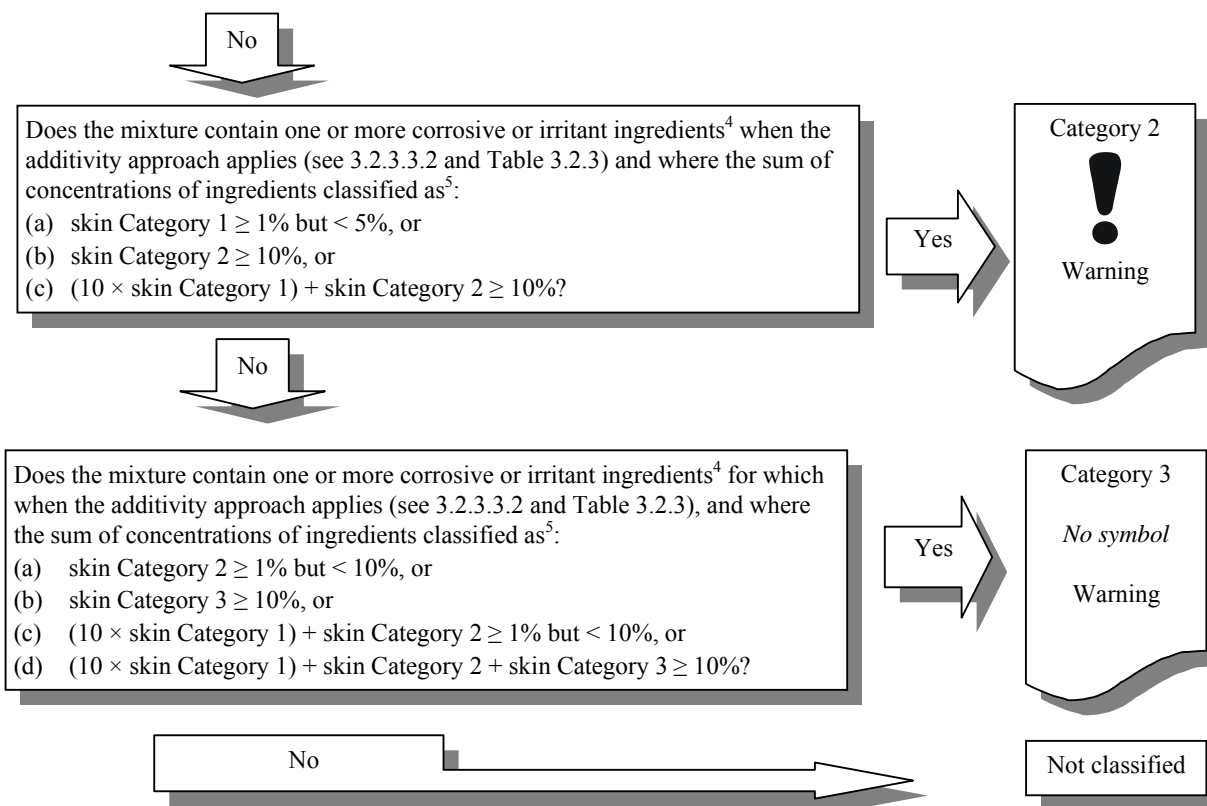
² Taking into account consideration of the total weight of evidence as needed;

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

3.2.5.2 Replace decision logic 3.2.2 and related footnotes with the following:

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





⁴ Where relevant $<$ 1%, see 3.2.3.3.1.

⁵ For specific concentration limits, see 3.2.3.3.6. See also Chapter 1.3, para. 1.3.3.2 for "Use of cut-off values/concentration limits".

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

3.2.5.3 Insert a new sub-section to read as follows:

“3.2.5.3 Background guidance

3.2.5.3.1 Classification criteria for the skin and eye hazard classes are detailed in the GHS in terms of a 3-animal test. It has been identified that some older test methods may have used up to 6 animals. However, the GHS 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.

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

- 3.2.5.3.3 In the case of a study with 6 animals the following principles apply:
- (a) The substance or mixture is classified as skin corrosion Category 1 if destruction of skin tissue (that is, visible necrosis through the epidermis and into the dermis) occurs in at least one animal after exposure up to 4 hours in duration;
 - (b) The substance or mixture is classified as skin irritation Category 2 if at least 4 out of 6 animals show a mean score per animal of ≥ 2.3 and ≤ 4.0 for erythema/eschar or for oedema;
 - (c) The substance or mixture is classified as skin irritation Category 3 if at least 4 out of 6 animals show a mean score per animal of ≥ 1.5 and < 2.3 for erythema/eschar or for oedema.
- 3.2.5.3.4 In the case of a study with 5 animals the following principles apply:
- (a) The substance or mixture is classified as skin corrosion Category 1 if destruction of skin tissue (that is, visible necrosis through the epidermis and into the dermis) occurs in at least one animal after exposure up to 4 hours in duration;
 - (b) The substance or mixture is classified as skin irritation Category 2 if at least 3 out of 5 animals show a mean score per animal of ≥ 2.3 and ≤ 4.0 for erythema/eschar or for oedema;
 - (c) The substance or mixture is classified as skin irritation Category 3 if at least 3 out of 5 animals show a mean score per animal of ≥ 1.5 and < 2.3 for erythema/eschar or for oedema.
- 3.2.5.3.5 In the case of a study with 4 animals the following principles apply:
- (a) The substance or mixture is classified as skin corrosion Category 1 if destruction of skin tissue (that is, visible necrosis through the epidermis and into the dermis) occurs in at least one animal after exposure up to 4 hours in duration;
 - (b) The substance or mixture is classified as skin irritation Category 2 if at least 3 out of 4 animals show a mean score per animal of ≥ 2.3 and ≤ 4.0 for erythema/eschar or for oedema;
 - (c) The substance or mixture is classified as skin irritation Category 3 if at least 3 out of 4 animals show a mean score per animal of ≥ 1.5 and < 2.3 for erythema/eschar or for oedema.”
-