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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 (c) of the provisional agenda
Classification criteria and related hazard communication: use of non-animal testing methods for classification of health hazards

Consequential amendments to Chapters 1.2 and 3.2 due to the revision of GHS Chapter 3.3 to fully incorporate non-animal test methods

Transmitted by the experts from the United Kingdom and the Netherlands on behalf of the informal working group on the use of non-animal test methods for classification of health hazards*

Introduction

1. In documents ST/SG/AC.10/C.4/2021/4 and informal document INF.3, a revised Chapter 3.3 for the GHS to fully incorporate non-animal test methods is proposed. The proposed changes to Chapter 3.3 also necessitates a number of conforming changes to be made to both Chapter 1.2 and Chapter 3.2, as outlined below in paragraphs 2 to 5.

Proposed conforming changes to Chapter 1.2

2. Amend Chapter 1.2 “Definitions and abbreviations” as follows:

Insert a new abbreviation after the entry for “IARC”, to read as follows:

“***IATA*** means “Integrated Approach on Testing and Assessment”;”

Proposed conforming changes to Chapter 3.2

3. A number of proposed changes to the pH rule in Chapter 3.3 will also require related amendments to be made to sub-sections 3.2.2.5 and 3.2.3.1.3; to Figure 3.2.1; and decision logic 3.2.2 of Chapter 3.2, together with new guidance provided in section 3.2.5.3.6.

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

4. In addition, a new figure and amendments will also be required to the following sub-sections of Chapter 3.2:

- Section 3.2.1.2;
- Amended section headings (3.2.2.1 to 3.2.2.6; 3.2.2.8 (renumbered from 3.2.2.7)) and a new section (3.2.2.7) on overall weight of evidence assessment to align with the presentation in Chapter 3.3;
- New Figure 3.2.2 on classification of mixtures;
- Various minor textual alignments throughout chapter 3.2.

5. The proposed amendments to Chapter 3.2 are provided in the annex to this document.

Action and next steps

6. The Sub-Committee is invited to agree the proposed conforming changes to Chapter 1.2 (as provided in paragraph 2 of this document) and to Chapter 3.2 (as set out in the annex to this document) and as provided in full in informal document INF.4.

Annex

Proposed amendments to 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 Add ***"(Tier 2 in Figure 3.2.1)"*** at the end of the heading.

3.2.2.3.2 Delete the first sentence and replace "test method used" with "test method(s) used".

3.2.2.3.3.1 Add "(see 3.2.5.3.4)" at the end of the paragraph.

3.2.2.3.4.1 Add "(see 3.2.5.3.4)" at the end of the paragraph.

3.2.2.3.4.2 Delete the last sentence.

3.2.2.3.5 (new) Insert a new section heading to read as follows:

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

3.2.2.3.4.3 Amend and renumber to read as follows:

"3.2.2.3.5.1 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 $\leq$ 2 or $\geq$ 11.5) and non-significant acid/alkaline reserve (result considered inconclusive in Tier 4; see 3.2.2.7) 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 $\leq$ 2 or $\geq$ 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.

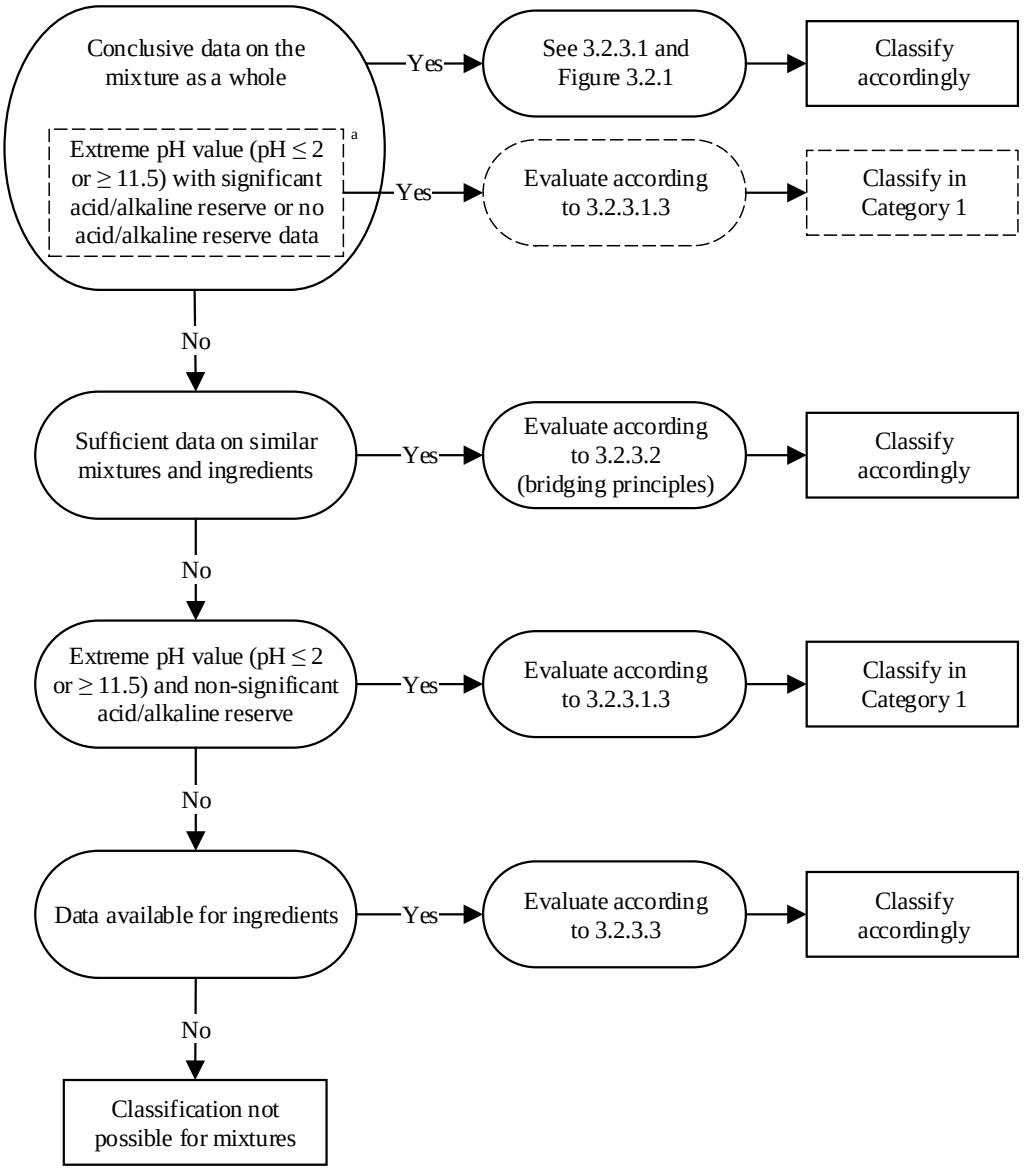
Figure 3.2.1 Amend as follows:

- 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: add "(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.

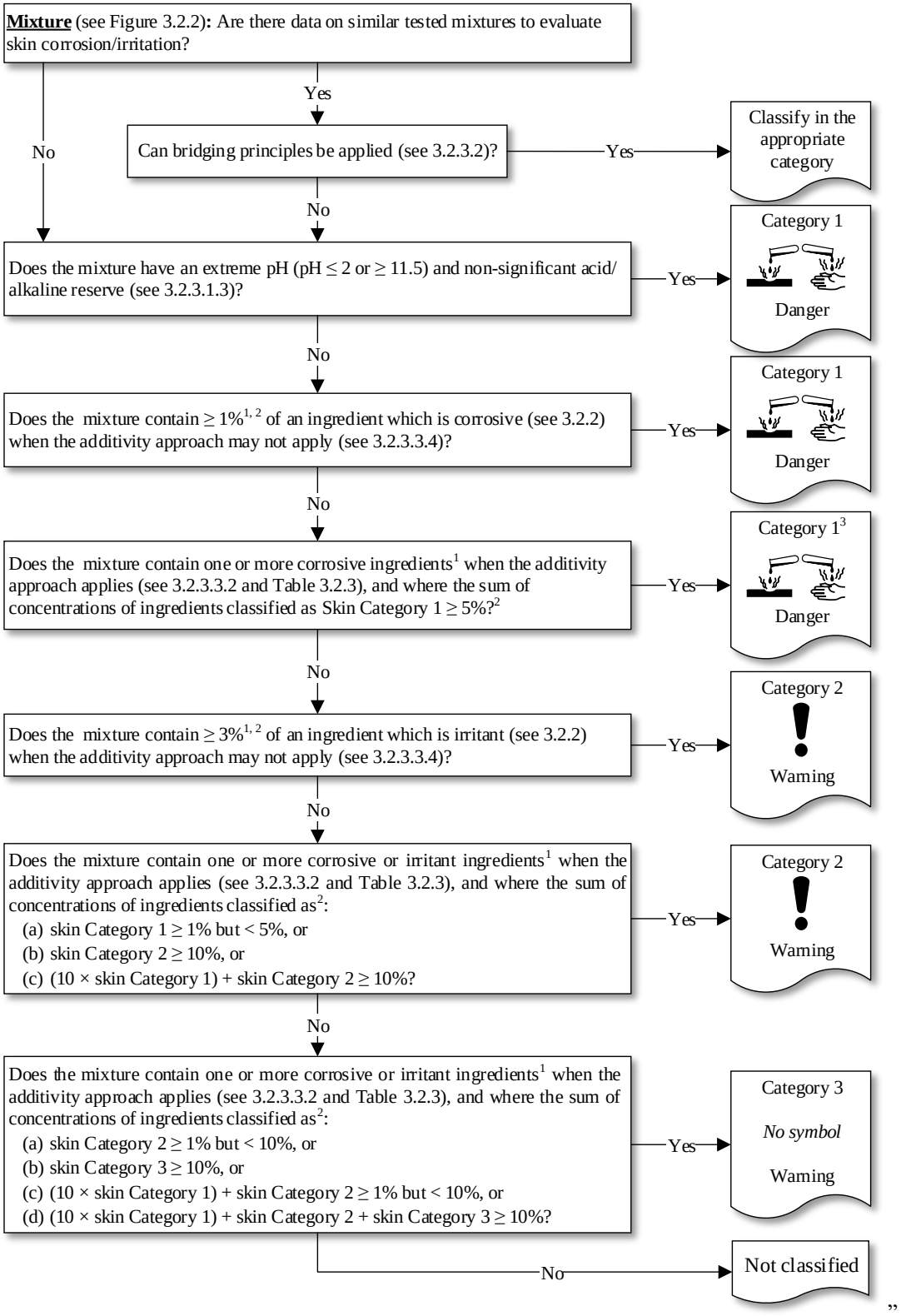
3.2.3.3.4 Amend the middle of the third sentence to read "…the pH should be used as the classification criterion (see 3.2.3.1.3) since extreme pH…".

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 section:

"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."

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* *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.".