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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

Report of the Sub-Committee of Experts on the Globally Harmonized System of Classification and Labelling of Chemicals on its fortieth session

held in Geneva from 5 to 7 July 2021

Contents

I. Attendance

1. The Sub-Committee of Experts on the Globally Harmonized System of Classification and Labelling of Chemicals held its fortieth session from 5 to 7 July 2021, with Ms. Maureen Ruskin (United States of America) as Chairperson and Ms. Nina John (Austria) as vice-chairperson.

2. Experts from the following countries took part in the session: Argentina, Australia, Austria, Belgium, Canada, China, Finland, France, Germany, Italy, Japan, Netherlands, New Zealand, Norway, Poland, Republic of Korea, Russian Federation, South Africa, Spain, Sweden, United Kingdom and United States of America.

3. Under rule 72 of the rules of procedure of the Economic and Social Council, observers from Chile, the Philippines and Switzerland also took part.

4. Representatives of the International Labour Organization (ILO) and the United Nations Institute for Training and Research (UNITAR) were also present.

5. The following intergovernmental organizations were also represented: European Union and Organisation for Economic Cooperation and Development (OECD).

6. Representatives of the following non-governmental organizations took part in the discussion of items of concern to their organizations: Australasian Explosives Industry Safety Group Incorporated (AEISG); Compressed Gas Association (CGA); Croplife International; Dangerous Goods Advisory Council (DGAC); European Chemical Industry Council (Cefic); European Industrial Gases Association (EIGA); Federation of European Aerosol Associations (FEA); Fertilizers Europe (FE); Industrial Federation Paints and Coats of Mercosul (IFPCM); International Association for Soaps, Detergents and Maintenance Products (A.I.S.E); International Council on Mining and Metals (ICMM); International Organization of Motor Vehicle Manufacturers (OICA); International Petroleum Industry Environmental Conservation Association (IPIECA); Institute of Makers of Explosives (IME); Responsible Packaging Management Association of Southern Africa (RPMASA); and Sporting Arms and Ammunition Manufacturers' Institute (SAAMI).

II. Adoption of the agenda (agenda item 1)

Documents: ST/SG/AC.10/C.4/79 and ST/SG/AC.10/C.4/79/Add.1 (secretariat)

Informal documents: INF.1, INF.2, INF.8 and INF.13 (secretariat)

7. The Sub-Committee adopted the provisional agenda prepared by the secretariat after amending it to take account of informal documents INF.1 to INF.25.

8. The Sub-Committee noted that the Economic and Social Council had adopted on 8 June 2021 Resolution 2021/13. The resolution was adopted with no changes on the basis of the proposed resolution submitted by the Committee in December 2020 (ST/SG/AC.10/48, annex IV).

9. As regards status of publications, a member of the secretariat informed the Sub-Committee that the English and French versions of the ninth revised edition of the GHS were already available and that the remaining linguistic versions were expected to be issued later this year.

III. Work on the Globally Harmonized System (GHS) (agenda item 2)

A. Work of the Sub-Committee of Experts on the Transport of Dangerous Goods (TDG) on matters of interest to the GHS Sub-Committee

Informal document: INF.23, paragraphs 4 and 5 (secretariat)

10. The Sub-Committee took note of the outcome of the discussions of the TDG Sub-Committee in paragraphs 4 and 5 of informal document INF.23 on matters related to the review of the definition of explosives and a proposal for alignment of the Model Regulations with the GHS as regards animal species for acute dermal toxicity.

B. Simultaneous classification in physical hazard classes and precedence of hazards

11. The expert from Germany informed the Sub-Committee that due to the work on the review of Chapter 2.1 during the last biennium, experts on physical hazards had been unable to make themselves available to work in parallel on the simultaneous classification and precedence of hazards and as a consequence, little progress had been made on this topic so far.

12. She indicated that she intended to relaunch the work and that she had already started discussions with the Chairperson of the Explosives Working Group of the TDG Sub-Committee on how safety of testing personnel is addressed in the Manual of Tests and Criteria. She invited all experts interested in the work on simultaneous classification in physical hazard classes and precedence of hazards who are not yet on the distribution list of the group to contact her (Ms. Cordula Wilrich) as soon as possible.

C. Use of non-animal testing methods for classification of health hazards

Documents: ST/SG/AC.10/C.4/2021/4 (United Kingdom, Netherlands)

ST/SG/AC.10/C.4/2021/5 (United Kingdom, Netherlands)

Informal documents: INF.3, INF.4, INF.22 and INF.18 (United Kingdom, Netherlands)

13. The Sub-Committee expressed its appreciation for the work done by the informal working group.

14. On a question from the expert from China regarding the absence of criteria for the determination of what can be considered a “significant” acid/alkaline reserve as referred to in 3.3.2.7, 3.3.3.1.3 and 3.3.5.3.7, it was pointed out that in the absence of an internationally agreed single test method, no specific criteria were proposed for the GHS. Noting that there were several methods available (e.g. those described in OECD Test Guideline 122 and Young et al.) and acknowledging the differences between them, the evaluation of the most appropriate method and the assessment of the results was left to the discretion of the competent authority.

15. It was noted that the amendments in informal document INF.22 to update paragraph 3.2.2.3.2 provided a more consistent conforming change with respect to the proposals in Chapter 3.3 while also reaffirming the principle that the GHS is test-method neutral.

16. The Sub-Committee adopted the amendments to Chapter 3.3 in the annex to document ST/SG/AC.10/C.4/2021/4 and the consequential amendments to chapters 1.2 and 3.2 in ST/SG/AC.10/C.4/2021/5, as amended in informal document INF.22 (see annex I).

17. The Sub-Committee took note of the report on the work of the informal working group in informal document INF.18, in particular as regards on-going activities related to the inclusion of non-animal testing methods for skin sensitizers in Chapter 3.4 of the GHS.

D. Classification of skin sensitizers using the results of local lymph node assays (LLNA) test methods in accordance with OECD Test Guideline 442B

Informal document: INF.10 (Japan)

18. The Sub-Committee took note of the results of the study conducted by Japan that confirmed the applicability of the alternative LLNA methods in OECD guidelines 442B

and 429 for classification of skin sensitizers within Category 1. It was also noted that the OECD expert group on alternative methods for skin sensitization had agreed to review the data and overall robustness of the criterion proposed by Japan in accordance with the scope, workplan and timetable in paragraph 10 and table 2 of informal document INF.10.

19. The expert from Japan indicated that he would report on the interim review results at the forty-first session of Sub-Committee and that it was expected that the work be finalised on time for a proposal to be submitted for consideration by the Sub-Committee at its forty-second session.

E. Classification criteria for germ cell mutagenicity (sub-category 1B)

Document: ST/SG/AC.10/C.4/2021/3 (European Union)

Informal document: INF.24 (United States of America)

20. There was general support for the work on the clarification of the criteria for classification for germ cell mutagenicity, with the extended scope and the additional items as contained in document ST/SG/AC.10/C.4/2021/3. It was felt however that there was a need to further clarify in the proposed terms of reference the role and engagement of OECD as regards the review of any changes to the classification criteria. On these grounds, the Sub-Committee considered and adopted the terms of reference as amended by informal document INF.24.

21. The representative of OECD confirmed OECD support for this work. The Sub-Committee noted that, once agreed by the informal working group, the changes on the classification criteria would be sent for review to the OECD Expert Group on Genotoxicity before being considered for final adoption.

22. It was also noted that the details on how to progress with this work at OECD level as regards OECD calendar of meetings and program of work would be discussed at the forthcoming meeting of the informal working group on the clarification of the criteria for classification for germ cell mutagenicity, on Thursday 8 July 2021. The leader of the informal working group indicated that the Sub-Committee will be kept informed about the outcome of the discussions.

F. Practical classification issues (proposed amendments to the GHS)

23. As no proposal for amendment to the GHS had been submitted by the informal group on practical classification issues no discussion took place on this subject. The Sub-Committee considered the status report of the work of the group under agenda item 4 (b) (see paragraphs 68 to 70).

G. Nanomaterials

24. As no document had been submitted under this agenda item, no discussion took place on this subject.

H. Improvement of annexes 1 to 3 and further rationalization of precautionary statements

1. Combination statement amendments to sections 1, 2 and 3 of Annex 3

Document: ST/SG/AC.10/C.4/2021/1 (United Kingdom)

25. There was general support in principle for the proposed amendments to sections 1, 2 and 3 to the GHS. However, the Sub-Committee could not reach a consensus on the proposals as currently drafted. Some experts indicated that it had proven difficult to understand the proposed amendments without an accompanying informal document showing the changes with respect to the current text.

26. On the amendments to current H315+H320, several experts expressed their preference for the alternative proposal outlined in paragraph 17 of document ST/SG/AC.10/C.4/2021/1, i.e. to retain the existing combination statement H315+H320 for skin corrosion/irritation category 2 and serious eye damage/eye irritation 2B and to insert a separate new entry for H315+H319 for skin corrosion/irritation category 2 and serious eye damage/eye irritation category 2/2A. There was also support for including a note indicating that competent authorities should select the applicable statement depending on the categories they implemented (2/2A or 2A/2B).

27. As regards the proposed text for A3.1.2.5, some experts suggested amending it to clarify that hazard statements may be combined where appropriate, as long as all the hazards are conveyed, to provide greater clarity and improve readability.

28. Finally, on the proposal regarding a new P374 and the applicability of P373 to Type A self-reactive substances and mixtures and Type A organic peroxides, it was noted that although they are not explosives in the sense of Chapter 2.1, they do have explosive properties. The appropriateness of fighting a fire until the fire reaches the Type A substances/mixtures as well as explosives was discussed. It was also noted that Type A substances/mixtures would rarely occur on the market as they are not allowed for transport according to the UN Model Regulations. After an exchange of views, the Sub-Committee concluded that this issue needed further consideration and invited the informal working group to further develop the proposal in the light of the comments made.

29. The expert from the United Kingdom informed the Sub-Committee that discussions would continue within the informal working group with a view to submit a revised proposal for the forty-first session that would take account of all the comments made.

2. Amendments to sections 2 and 3 of Annex 3

Document: ST/SG/AC.10/C.4/2021/2 (United Kingdom)

Informal document: INF.19 (Germany)

30. The Sub-Committee adopted the amendments in paragraphs 6 to 9 (amendments to P232, P264 and P270) and 31 to 34 (amendments to the respiratory and skin sensitization entries in Annex 3 of the GHS) in document ST/SG/AC.10/C.4/2021/2 (see annex I).

31. After an exchange of views on the proposed amendments to the matrix tables for flammable gases (paragraphs 25 to 27 in document ST/SG/AC.10/C.4/2021/2), the Sub-Committee concurred with the views expressed by Germany in informal document INF.19 and adopted the proposal to delete the notes to the matrix tables for pyrophoric gases and chemically unstable gases and not to introduce a note to the matrix table for flammable gases, in Annex 3 of the GHS (see annex I).

32. With respect to the proposal to modify P354 to address an ambiguity in the skin corrosion combined statement P302+P361+P354 (“IF ON SKIN: Take off immediately all contaminated clothing. Immediately rinse with water for several minutes.”), several experts considered that the combined statement needed further consideration. Experts provided comments addressing, among other matters, the priority of response actions (e.g: rinsing while removing the clothes instead of removing the clothes and rinsing immediately afterwards) and the need to take a holistic approach to reviewing the combined statement. The Sub-Committee invited the informal working group to revise the proposal to take account of the comments made.

3. Status of the work of the informal working group

Informal document: INF.17 (United Kingdom)

33. The Sub-Committee expressed its appreciation for the work undertaken by the informal working group to further improve the comprehensibility of the hazard and precautionary statements and noted the progress report on its work provided in informal document INF.17.

I. Other matters

1. Alignment of Chapter 2.17 with Chapter 2.1: correction to GHS Rev. 9

Document: ST/SG/AC.10/C.4/2021/6 (Sweden)

Informal document: INF.23 paragraph 6 (Secretariat)

34. The Sub-Committee noted that the Working Group on Explosives of the TDG Sub-Committee had considered the document by the expert from Sweden and delivered a favourable opinion on the proposal. The Sub-Committee adopted the corrections to paragraph 2.17.1.1 and decision logic 2.17.1 as proposed in document ST/SG/AC.10/C.4/2021/6 (see annex II). It was pointed out that these corrections would be included in a corrigendum to the ninth revised edition of the GHS.

2. Amendment to 2.17.2.1

Informal document: INF.6 (Germany)

35. Several experts raised concerns on the unexpected implications that the proposed amendment could have on classification and testing of desensitized explosives (including industrial nitrocellulose) and considered that the question needed further consideration. After discussion, the Sub-Committee invited those who provided comments to work with the expert from Germany on a revised proposal. It was pointed out that the scope of the revised proposal should be limited to address the issue initially raised by Germany in informal document INF.6 as well as the comments made during the discussion as regards industrial nitrocellulose, without entailing a full review of Chapter 2.17.

36. The Sub-Committee agreed that, once finalised, the revised proposal should be submitted for review by the Working Group on Explosives of the TDG Sub-Committee at its next meeting in June 2022, before being submitted for final adoption by the GHS Sub-Committee.

3. French translation of the definition of “Eye irritation” in the GHS

Informal document: INF.7 (Canada)

37. There was no consensus among French speaking delegations on the need to review the French translation of the definition for “Eye irritation”. The expert from France and the representative of Cefic indicated that, in their opinion, the proposal was not justified from a technical point of view. They suggested instead to better align the English version with the French text, but this view was not shared by the Sub-Committee. It was pointed out that the current definition had been reviewed relatively recently by the practical classification issues informal working group and that it might not be appropriate to revisit it again as long as no implementation issues were reported.

38. In view of the comments made, the expert from Canada withdrew the proposal.

4. Proposal for a definition of “toxic”

Informal documents: INF.12 (RPMASA)

INF.23, paragraph 7 (secretariat)

39. The Sub-Committee concurred with the views and conclusions expressed by the TDG Sub-Committee on this topic as contained in informal document INF.23.

40. The representative of RPMASA indicated that she intended to contact those who had expressed an opinion on the proposal to further clarify its intent and explore ways to address the difficulties that, in her view, developing countries were encountering to understand this concept within the framework of the GHS.

IV. Implementation of the GHS (agenda item 3)

A. Possible development of a list of chemicals classified in accordance with the GHS

Informal documents: INF.15 and INF.15/Add.1 (Canada and United States of America)

41. The Sub-Committee took note of the findings of the study conducted by Sweden on "The role of national substance classification lists in the implementation of the GHS".

42. Regarding the activities of the informal working group on the possible development of a list of chemicals classified in accordance with the GHS, the expert from the United States of America informed the Sub-Committee of the development of a survey that was expected to be initiated in July or August 2021. The survey would aim at filling in knowledge gaps with respect to existing national, regional and third-party classification lists that follow the GHS and show how they compare to the guiding principle questions developed by the informal working group in 2020 (see ST/SG/AC.10/C.4/2020/17 paragraph 4). The results of the survey will be presented to the Sub-Committee at its forty-first session.

43. The Sub-Committee was invited to review the information in the annex to informal document INF.15 and provide feedback to the experts from the United States of America and Canada about any other lists that may be worth considering as well as the contact persons administering them that could be interested in participating in the survey.

B. Reports on the status of implementation

1. South Africa

Informal document: INF.5 (South Africa)

44. The Sub-Committee noted the information provided by the expert from South Africa regarding the promulgation into law, on 29 March 2021, of the "Regulations for Hazardous Chemical Agents" under the Occupational Health and Safety Act. The regulations, which are based on the eighth revised edition of the GHS, make GHS classification, safety data sheets and labelling compulsory for hazardous chemicals in the workplace and allow for a 18-month transitional period for implementation from the date of promulgation.

2. Chile and Colombia

45. The Sub-Committee was informed that the Government of Chile had published on 9 February 2021 a "Regulation on classification, labelling and notification of hazardous substances and mixtures". The regulation implements the seventh revised edition of the GHS and allows for the following transitional periods following its publication in the official journal:

- For chemicals intended for industrial use: 1 year for substances and 4 years for mixtures
- For all other chemicals covered by the regulation: 2 years for substances and 6 years for mixtures

46. The Sub-Committee was also informed that in Colombia, the Ministries of Labour and of Health and Social Protection had issued on 7 April 2021 "Resolution No.0733 of 2021" implementing the provisions of the sixth revised edition of the GHS at the workplace. The Resolution entered into force on the day of its publication and allows for a transitional period of 2 years for substances and 3 years for mixtures.

47. It was noted that the information concerning the status of implementation in both countries had already been updated accordingly (including links to both regulations) on the GHS implementation webpage[1].

3. Argentina

48. The Sub-Committee took note of the information provided by the expert from Argentina on past and current activities related to the implementation of the GHS at national level. It was noted that a draft law addressing chemicals' risk management was being finalised and that a proposal to include a chapter addressing GHS implementation was being considered.

49. At the level of the Southern Common Market (MERCOSUR), the Sub-Committee noted that a workplan on hazardous chemicals addressing GHS related activities had been approved for implementation between 2021-2024. The plan includes assessment for the possible establishment of a technical regulation to implement the GHS.

50. In addition, it was also noted that GHS related activities had been included in the updated workplan of the Intergovernmental Network on Chemicals and Waste for Latin America and the Caribbean for 2021-2024.

51. Finally, it was pointed out that a regional virtual working group promoted by the International Council of Chemical Associations (ICCA) had been established to facilitate exchanges between the public and private sector as regards the development of a chemical regulatory framework in the region.

4. New Zealand

Informal document: INF.25 (New Zealand)

52. The Sub-Committee noted that New Zealand had completed the update of its hazardous substance classification framework, which was implemented in 2001 and based on a pre-published version of the GHS. On 15 October 2020, a new legislative instrument (the Hazardous Substances (Hazard Classification) Notice 2020) had been issued, adopting by incorporation by reference, the seventh revised edition of the GHS. The Hazard Classification Notice took effect on 30 April 2021.

53. It was also noted that the new Hazard Classification Notice allowed alignment and updating of the Hazardous Substances (Labelling) Notice 2017 and the Hazardous Substances (Safety Data Sheets) Notice 2017, from the fifth to the seventh revised edition of the GHS. A significant number of approvals for hazardous substances under the Hazardous Substances and New Organisms Act (HSNO) Act had also been updated in accordance with the classification criteria in the seventh revised edition of the GHS.

54. It was pointed out that existing data on the Environmental Protection Authority (EPA) hazardous substance databases were being migrated to the International Uniform Chemical Information Database (IUCLID) and that the process was expected to be completed during the final quarter of 2021.

5. European Union chemicals strategy for sustainability

Informal document: INF.21 (European Union)

55. The Sub-Committee noted with interest the information published on 14 October 2020[2] on the forthcoming developments in the European Union following the adoption of the European Union chemicals strategy for sustainability.

56. It was noted that work to update the Classification, Labelling and Packaging (CLP) Regulation (European Union Regulation 1272/2008) from the seventh to the eighth and ninth

[1] https://unece.org/transport/documents/2021/01/ghs-implementation-implementation-country

[2] https://ec.europa.eu/environment/strategy/chemicals-strategy_en

revised editions of the GHS was due to start soon. In addition, as part of a wider range of actions related to the chemicals' strategy for sustainability, the CLP revision would aim at:

(a) strengthening existing criteria on endocrine disruptors; persistent, bioaccumulative and toxic substances (PBTs); and Persistent, Mobile and Toxic substances (PMTs);

(b) Assessing the need for specific criteria for Immunotoxicity, Neurotoxicity and Toxicity for terrestrial organisms

57. To achieve the objectives described in (a) and (b) above, new hazard classes would need to be developed and included in the CLP, in accordance with the following approach:

(a) For immunotoxicity, neurotoxicity and terrestrial hazards, a proposal to assess the need for specific criteria will be submitted for consideration by the Sub-Committee during the biennium 2023-2024.

(b) For endocrine disruptors, PBTs (including very persistent and very bioaccumulative substances (vPvB)) and PMTs (including very persistent and very mobile substances (vPvM)) a proposal based on existing international standards is already being developed at European level to be implemented first through the CLP Regulation before the end of 2022. Following the adoption of the criteria for implementation at European level through CLP, a proposal to consider these endpoints for inclusion in the GHS would be submitted for consideration to the Sub-Committee for the period 2023-2024.

58. The Sub-Committee took note of the commitment of the European Union to consider revising its regulations to make them compliant with GHS, should the hazard classes already addressed in CLP be incorporated later on in the GHS and addressed differently.

59. It was also noted that the overall impact of the proposals mentioned in paragraph 57 above would be assessed through a study and an impact assessment. Open consultations with stakeholders (within and outside the European Union) would also be conducted. Sub-Committee members were invited to participate in the CLP open online consultation that is expected to be conducted between July and October 2021 through the website of the European Commission[3].

60. The Sub-Committee will continue to be updated on the progress on implementation of the European Union chemicals strategy for sustainability.

6. Study on the role of international trade agreements for the implementation of GHS

Informal document: INF.14 (Sweden)

61. The Sub-Committee took note of the findings of the study commissioned by the Swedish Chemicals Agency (KemI) to investigate whether environmental provisions in regional trade agreements have been used to promote the implementation of GHS, as reflected in paragraphs 7 to 10 of informal document INF.14.

62. The Sub-Committee was informed of an on-going pilot study to investigate to what extent information required for classification and labelling in accordance with GHS is made available for countries importing chemicals. The expert from Sweden indicated that some preliminary results might be available before the end of 2021 in which case they would be communicated to the Sub-Committee during its forty-first session.

7. UNITAR activities to support GHS implementation

63. The representative of UNITAR indicated that background research on country experiences with GHS implementation was being conducted in coordination with the Global Partnership to implement the GHS. Additional outputs expected to be published in 2021 include a study on lessons learnt for implementation and guidance on developing legislation

[3] https://ec.europa.eu/info/law/better-regulation/have-your-say_en

relevant to the GHS. The information will be made available at the global partnership website[4].

64. The Sub-Committee noted that a document on ILO instruments and the GHS developed by ILO was also available.

C. Cooperation with other bodies or international organizations

65. As no document had been submitted under this agenda item, no discussion took place on this subject.

D. Miscellaneous

66. As no document had been submitted under this agenda item, no discussion took place on this subject.

V. Development of guidance on the application of GHS criteria (agenda item 4)

A. Alignment of Annex 9 (section A9.7) and Annex 10 with the criteria in Chapter 4.1

67. The representative of ICMM informed the Sub-Committee about the activities of the informal working group since the thirty-ninth session. She mentioned that two rounds of written comments have been completed and that the informal working group had already considered in depth two of the open issues identified in informal document INF.9/Rev.1 (thirty-ninth session), with two other issues yet to be further explored. The Sub-Committee noted that the informal working group was progressing work with a view to submitting a document for consideration by the Sub-Committee at its forty-first session.

B. Practical classification issues

Informal document: INF.20 (United States of America)

68. The Sub-Committee noted that the informal working group had decided to defer consideration of item (f) of its program of work pending completion of the work on items (c) and (d).

69. On item (c) (guidance on conversion of inhalation toxicity values for test data with exposure times other than 1 hour) the Sub-Committee was informed that the group had reached agreement on several key principles for the guidance and noted that a proposal was expected to be submitted for consideration at its forty-first session.

70. On item (d) (additivity), the Sub-Committee was informed that following completion of the discussions on a thought starter, the European Chemicals Agency was considering the best path forward to propose text for Chapter 1.3 and the need to develop additional guidance.

C. Practical labelling issues

Informal document: INF.9 (Cefic)

71. The Sub-Committee took note of the questions in paragraph 5 of informal document INF.9. One expert suggested that the difficulty in application of digitalization at the workplace should also be considered.

[4] https://unitar.org/global-partnership-implement-ghs

72. The representative of Cefic invited experts to share with the informal working group any experiences they may have with digitalisation of hazard information.

D. Miscellaneous

73. As no document had been submitted under this agenda item, no discussion took place on this subject.

VI. Capacity building (agenda item 5)

74. The representative of UNITAR indicated that work to support Ghana and Kiribati to develop GHS implementing legislation was on-going and that a technical webinar for Spanish-speaking stakeholders on safety data sheets, labelling and data search had been conducted in June 2021. The Sub-Committee noted that the next round of the UNITAR GHS e-learning courses would take place from 20 September to 29 November 2021 (English course) and from 27 September to 6 December 2021 (Spanish course).

75. The expert from Argentina provided a summary of activities conducted in his country in support of GHS implementation. These included for instance, technical assistance to industry for the development of GHS compliant safety data sheets, classification, labelling and testing as well as activities conducted within the framework of a Global Environment Facility (GEF) project.

Informal document: INF.11 (RPMASA)

76. The Sub-Committee took note of the information by RPMASA on capacity building activities in South Africa.

VII. Other business (agenda item 6)

A. Seminar in follow-up to the explosion in the port of Beirut in 2020

Informal document: INF.16 (secretariat to the UNECE Convention on the transboundary effects of Industrial accidents)

77. The Sub-Committee took note of the information regarding the organisation of an online seminar on experiences, good practices and lessons learned following the explosion of a large amount of ammonium nitrate in the port of Beirut on 4 August 2020. Experts interested in participating in the seminar as members of the advisory group, by replying to a survey on existing guidance and good practices or by sharing their expertise were invited to contact the secretariat. It was pointed out that the survey was under development and that it was expected to be available soon.

78. The expert from the United States of America expressed interest in exploring ways to participate and contribute to the seminar.

B. Meeting dates and submission deadlines for the forty-first session

79. A member of the secretariat informed the Sub-Committee that the 2021 meeting calendar planning was being assessed by the Meetings Management Section of the Division of Conference Management on a quarterly basis and that the planning for the final quarter of the year was still under discussion. It was noted that, although unlikely, changes to the meeting arrangements for the forty-first session of the Sub-Committee could not be completely excluded. Pending the outcome of the discussions on the planning at ECE level, the Sub-Committee was invited to note the meeting dates and document submission deadlines for its forty-first session as follows:

- Meeting dates: From 8 to 10 December 2021

- Deadline for submission of official documents: 15 September 2021 (for documents submitted for consideration by the GHS Sub-Committee only) and 6 September 2021 (for documents submitted for consideration by both sub-committees, i.e.: TDG and GHS)

C. Tribute to Ms. Leroy (Cefic)

80. The Sub-Committee was informed that Ms. Marie-Hélène Leroy, who has been participating in its work since 2003 was attending the session for the last time. The Sub-Committee expressed its appreciation for her work as head of the Cefic delegation and as the lead of the informal working group on practical labelling issues and wished her well in her coming retirement.

VIII. Adoption of the report (agenda item 7)

81. The Sub-Committee adopted the report (and its annexes) on its fortieth session on the basis of a draft prepared by the secretariat.

Annex I

[Original: English and French]

Draft amendments to the ninth revised edition of the Globally Harmonized System of Classification and Labelling of Chemicals (ST/SG/AC.10/30/Rev.9)

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.

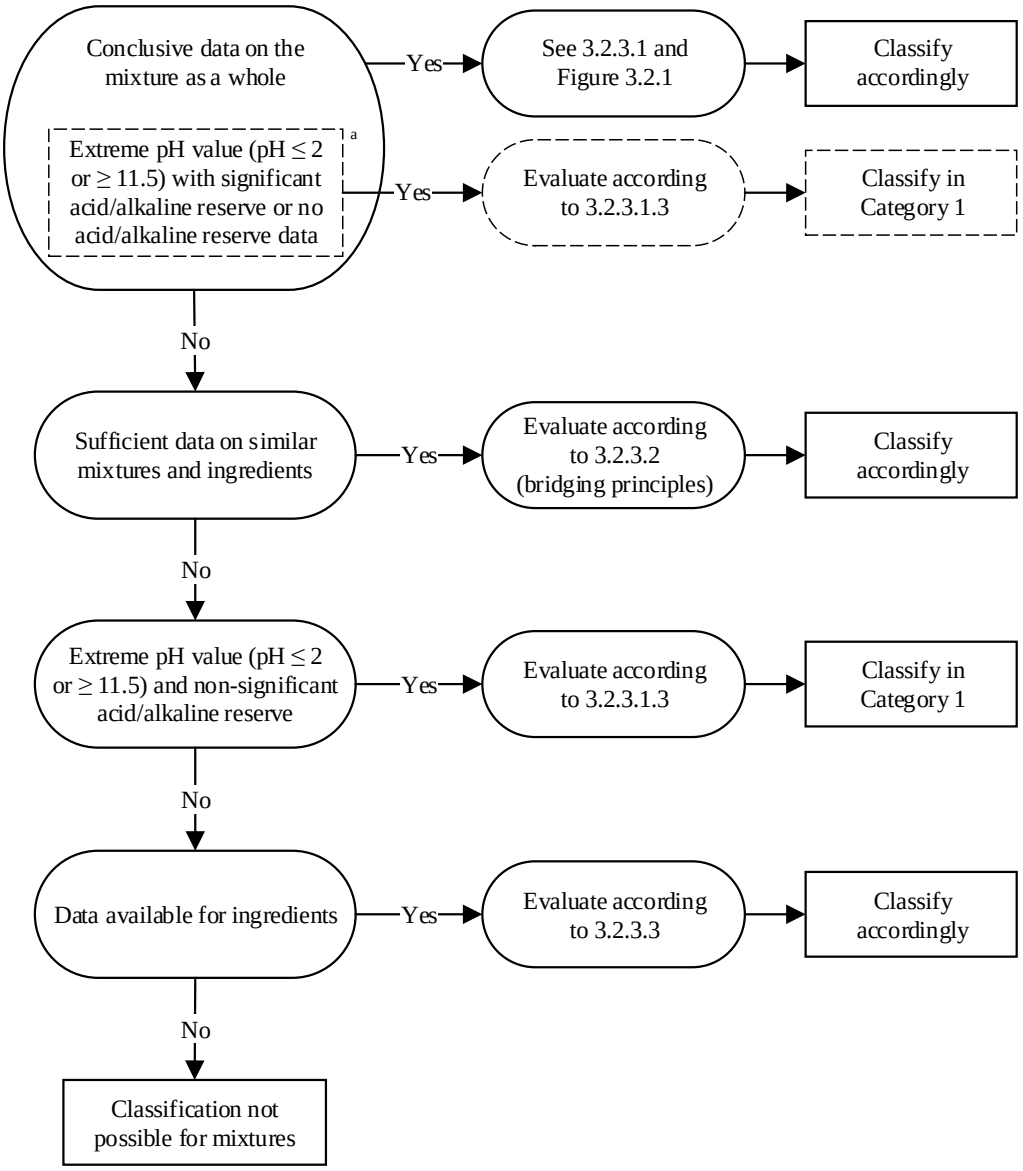
Figure 3.2.1 Amend as follows:

- 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: 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.

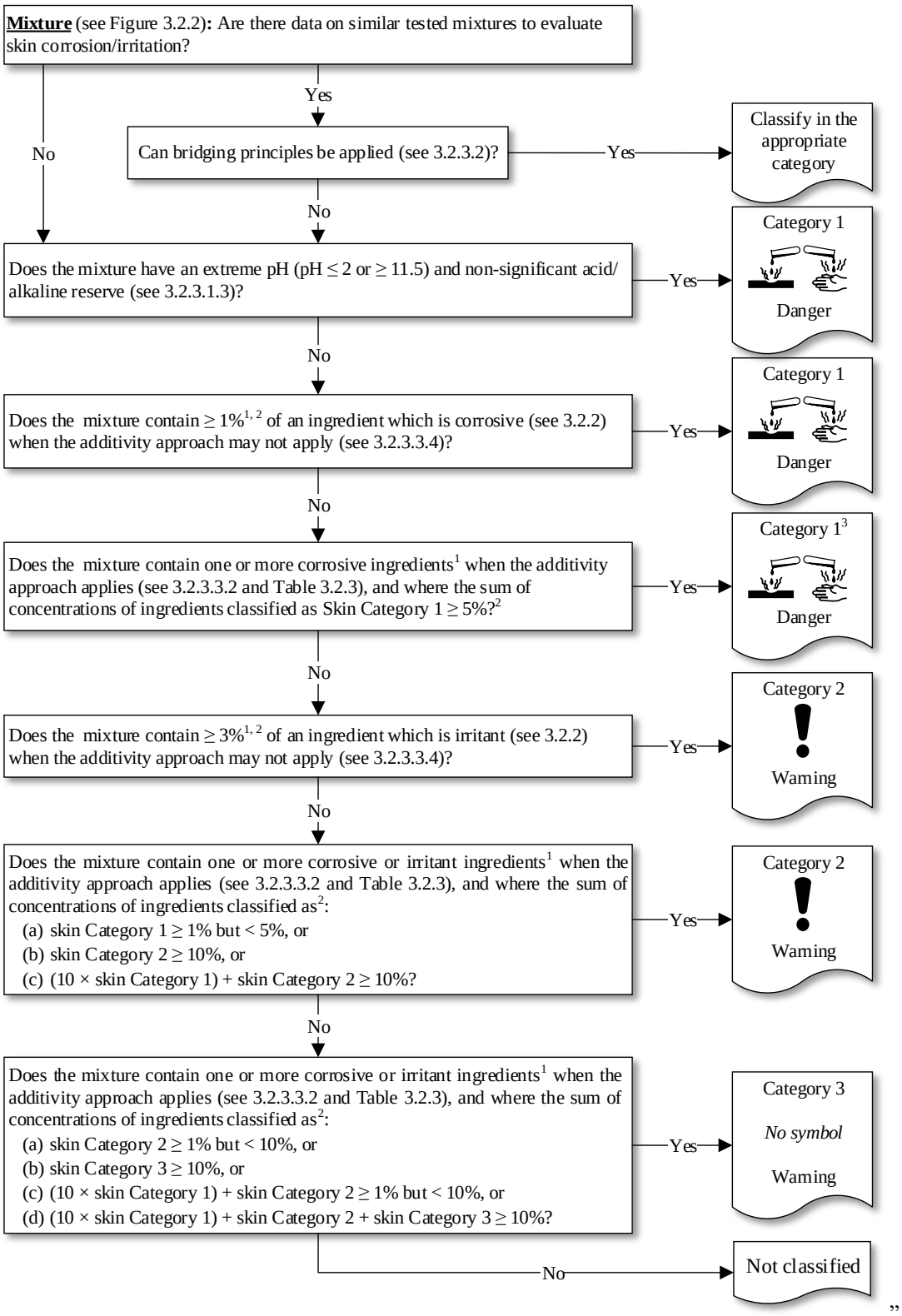
3.2.3.3.4 Amend the middle of the third sentence to read "…the pH should be used as the classification criterion (see 3.2.3.1.3) since extreme pH…".

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 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.".

(Ref. Doc: ST/SG/AC.10/C.4/2021/5 as amended by informal document INF.22)

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.”.

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.".

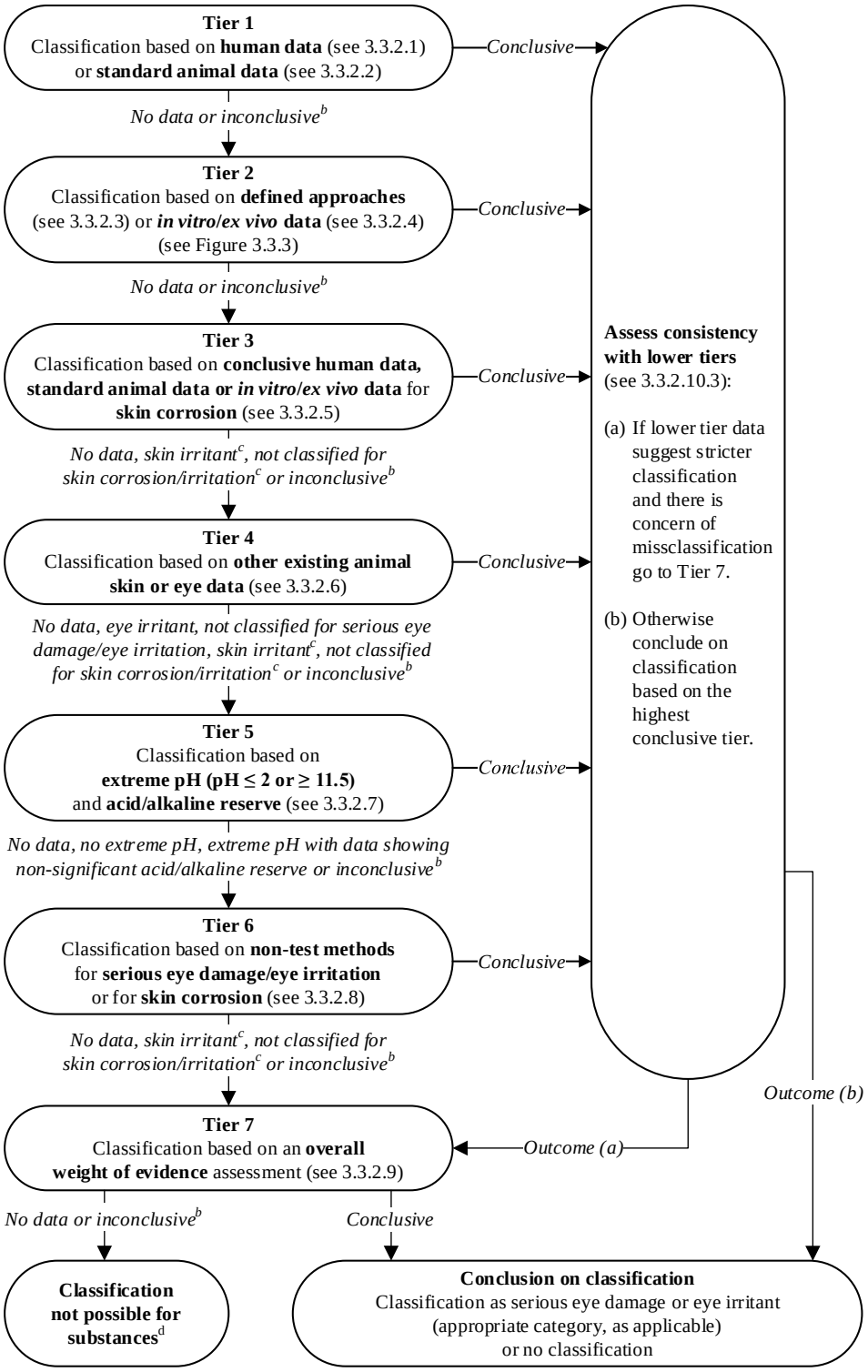
3.3.2.10.2 and 3.3.2.10.3 Insert the following two new paragraphs:

"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.”.*

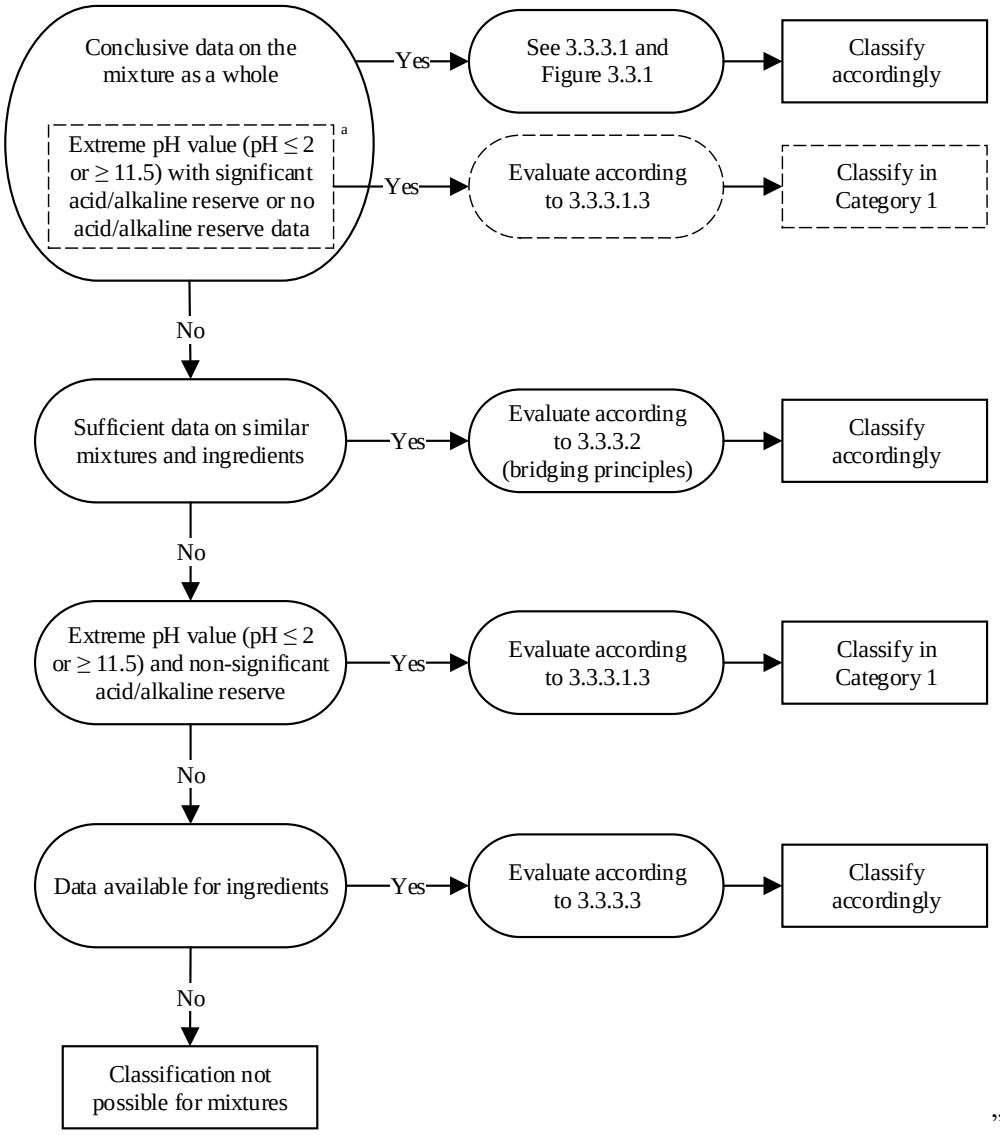
Delete current notes “e” and “f” to Figure 3.3.1.

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.”.

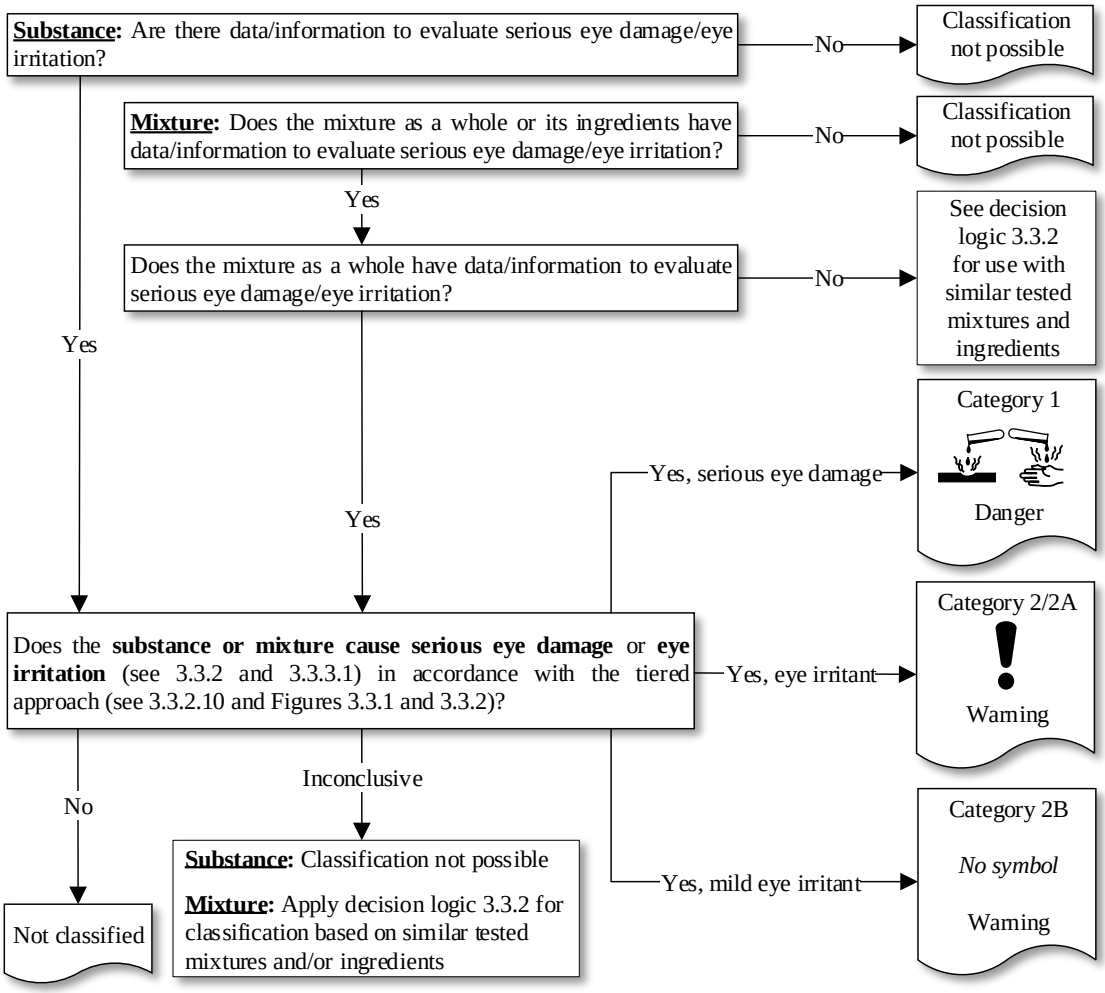
3.3.3.2.7 Replace “aerosolized form of mixture” with “aerosolized form of the mixture”. Renumber footnote 3 as 4.

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:

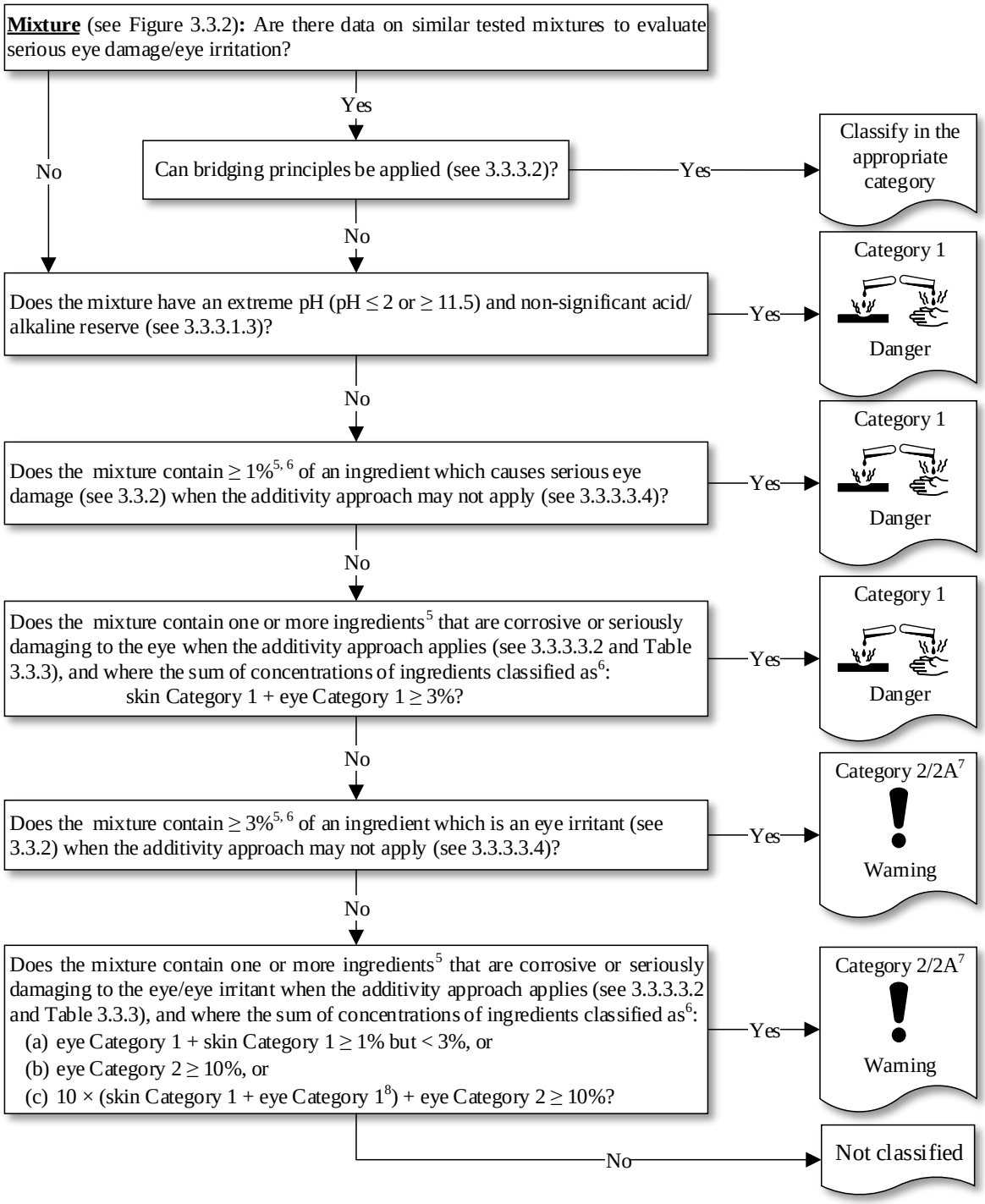
“



”

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.

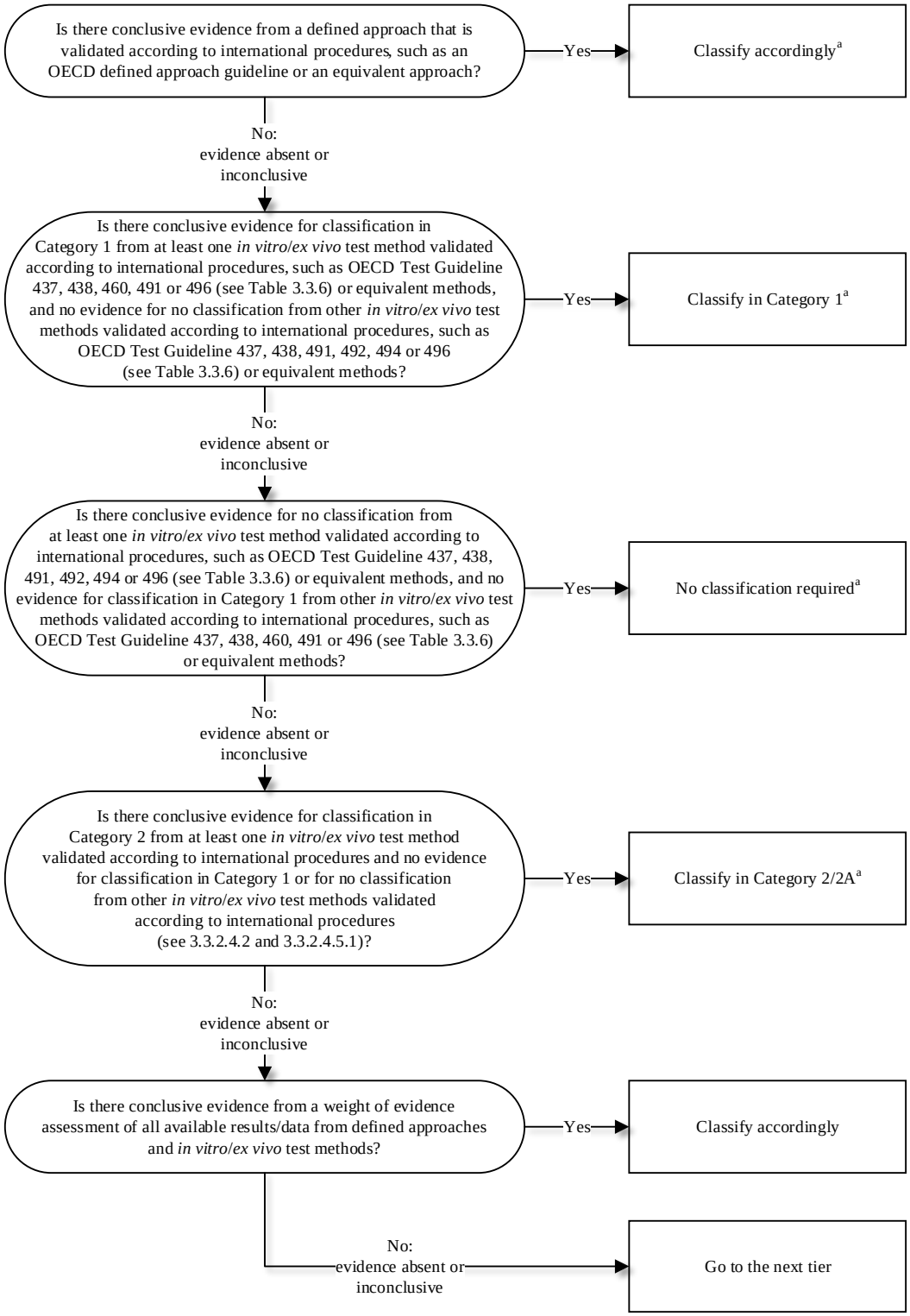
3.3.5.3.4.2 A stepwise approach to the evaluation of information derived from Tier 2 of Figure 3.3.1, i.e. defined approaches and/or *in vitro*/*ex vivo* test methods, should be considered where applicable (Figure 3.3.3), recognizing that not all elements may be relevant. However, all available and relevant 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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* *References:*

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(Ref. Document: ST/SG/AC.10/C.4/2021/4)

Annex 3

Section 1, Table A3.1.2

H317, column (3)

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

(Ref. Doc: ST/SG/AC.10/C.4/2021/2, paragraphs 31 to 34)

H334, column (3)

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

(Ref. Doc: ST/SG/AC.10/C.4/2021/2, paragraphs 31 to 34)

Section 2, Table A3.2.2

P262, column (4)

Insert: “3” after: “1, 2”.

(Ref. Document: ST/SG/AC.10/C.4/2021/2, paragraphs 6 to 9)

P264 and P270, column (4)

For the hazard class acute toxicity (dermal), insert: “3” after: “1, 2”.

(Ref. Document: ST/SG/AC.10/C.4/2021/2, paragraphs 6 to 9)

Section 3

Tables for flammable gases (Chapter 2.2)

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

(Ref. Doc: ST/SG/AC.10/C.4/2021/2 as amended by informal document INF.19)

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.”.

(Ref. Doc: ST/SG/AC.10/C.4/2021/2, paragraphs 6 to 9)

Tables for “Sensitization – respiratory (Chapter 3.4)

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

(Ref. Doc: ST/SG/AC.10/C.4/2021/2, paragraphs 31 to 34)

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

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

(Ref. Doc: ST/SG/AC.10/C.4/2021/2, paragraphs 31 to 34)

Annex II

[Original: English and French]

Corrections to the ninth revised edition of the Globally Harmonized System of Classification and Labelling of Chemicals (ST/SG/AC.10/30/Rev.9)

Chapter 2.17

1. Paragraph 2.17.1.1, last sentence, text between brackets

For see also Note 2 of paragraph 2.1.2.2 *read* see paragraph 2.1.1.2.2

(Reference document: ST/SG/AC.10/C.4/2021/6)

2. Footnote 1 to paragraph 2.17.1.1

The first sentence should read*:*

Explosives that are too sensitive to be assigned Category 2 of Chapter 2.1 can also be desensitized and consequently may be classified as desensitized explosives, provided all criteria of Chapter 2.17 are met.

(Reference document: ST/SG/AC.10/C.4/2021/6)

3. Paragraph 2.17.4.1, decision logic 2.17.1, in the two text boxes on the right-hand side with the "exploding bomb" symbol

For Division 1.1 *read* Sub-category A

(Reference document: ST/SG/AC.10/C.4/2021/6)