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 **24 June 2024**

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Item 2 (d) of the provisional agenda
Work on the Globally Harmonized System of Classification and Labelling of Chemicals: Classification criteria for germ cell mutagenicity

Status of the work of the informal working group on clarification of the criteria for classification for germ cell mutagenicity

Transmitted by the European Union on behalf of the informal working group on germ cell mutagenicity

Introduction

1. This informal paper provides a summary on the work undertaken by the informal working group on clarification of the criteria for classification for germ cell mutagenicity since they started their tasks in 2021. It also informs on currently ongoing discussions and future plans.

Background

2. Reference is made to the proposal contained in ST/SG/AC.10/C.4/2020/13 and ST/SG/AC.10/C.4/2020/13/Add.1, the informal document INF.37 (thirty-ninth session) (European Union) on the Clarification of the criteria for classification for germ cell mutagenicity in category 1B and the report of the Sub-Committee on its thirty-ninth session (ST/SG/AC.10/C.4/78). Based on these documents the Terms of Reference and work programme of the informal working group on the criteria for classification for germ cell mutagenicity were submitted for discussion at the fortieth session (document ST/SG/AC.10/C.4/2021/3). The Sub-Committee adopted the terms of reference as amended by the informal document INF.24 transmitted by the expert of the United States of America as stated in the report of the fortieth session (ST/SG/AC.10/C.4/80).

3. The Sub-Committee agreed at the fortieth session that changes on the classification criteria proposed by the informal working group would be sent for review to the OECD Expert Group on Genotoxicity before being considered for final adoption. At their forty-forth Meeting in April 2022, the OECD Working Group of the National Coordinators of the Test Guidelines Programme agreed to the request submitted by the European Commission and the OECD Secretariat, asking for support for the work on the criteria for classification for germ cell mutagenicity to be included in their work plan.

4. At the forty-third session the Sub-Committee agreed to carry-over the programme of work of the informal working group into the 2023-2024 biennium.

Status report

5. Items discussed and agreed by the working group are summarised in a living working document revised after each meeting. The current state of the revisions to the chapter 3.5 that have been provisionally agreed by the informal working group are summarised in paragraphs

6 to 10 here below. Issues related to the activities of the informal working group on non-animal test methods are, in agreement with the leads of the other informal working group, tabled for discussion at their next meeting held in the margin of the forty-sixth session. This will inform the informal working group on germ cell mutagenicity in particular how to best progress with the carrying over of the paragraphs on non-testing methods from chapters 3.2, 3.3 and 3.4, relevant also to chapter 3.5. Some members of the informal working group suggest that revisions might be necessary to the text agreed in the other chapters due to the considered more severe concern for germ cell mutagenicity compared to these other endpoints. Others state that the suggested revisions lessen protection for germ cell mutagenicity and therefore the text developed by the informal working group on non-animal test methods should be used in this chapter.

6. The following **definitions** were revised: mutation, mutagenicity, gene mutation and genotoxiciy. For genotoxicity the footnote “Epigenetic changes are not included in the definition of genotoxicity.” was added. The following new definitions were introduced to the chapter to provide further clarity: clastogenicity, aneugenicity, genotoxicity, primary DNA damage, heritable mutation and inherited mutation.

7. Consistency and clarification of **terminology** were made through out the chapter, and specifically these changes were noted, the use of: “offspring and future generations” instead of “progeny”, “test” instead of “assay” and “genotoxicity indicator tests” instead of “genotoxicity tests”.

8. The **structure** of the chapter was aligned with the recently revised chapters 3.2, 3.3 and 3.4 where the application of the data on classification is discussed for each type of data originating from human evidence, in vivo, in vitro and non-test methods. In addition, the following new sections were introduced: *Hazard categories*, *Classification based on non-test methods*, *Supportive information*, *Classification based on weight of evidence*, and *Background guidance*. Whereof the following sections include new content: *Classification based on non-test methods* (as referred to in paragraph 5 above), *Classification based on weight of evidence* (see paragraph 9 below) and *Background guidance*.

9. The informal work group agreed to consider including a **tiered approach** to guide data organization for classification decision-making based on available information as outlined in chapters 3.2, 3.3 and 3.4. The informal working group explored this possibility and agreed that this approach was not preferred for germ cell mutagenicity, but that basic guiding principles for an overall **weight of evidence** should be included in the main text of the chapter.

10. The **lists of tests** in chapter 3.5 have been updated to add recently adopted OECD test guidelines. The grouping of the tests has been reorganised as considered adding clarity. In vivo heritable germ cell mutagenicity tests now include also mutagenicity tests in germ cells (i.e. transgenic rodent somatic and germ cell mutation assays and mammalian spermatogonial chromosome aberration test), based on the newly added definition of “heritable”. Information on the type of genotoxic abnormality identified has been added in correspondence to each test, as this may be helpful especially for stakeholders less expert in the area. Additional explanatory text on the relevance of the listed test results and how they can be used either alone or in combination with other data to support classification, needs to be further developed.

11. The Genetic Toxicology Technical Committee (GTTC) of the Health and Environmental Science Institute (HESI) took the initiative in 2021 to conduct a study investigating existing data on germ cell mutagenicity to, if possible, underpin the work of the informal working group to revise the current classification criteria. This analysis has now been finalised and presented to the informal working group. The GTTC is also preparing a manuscript on the analysis for publication. Based on the results collected, the GTTC concluded there is insufficient data and evidence that the presence of somatic mutagens in the blood or gonads is indicative to conclude that the compound is a germ cell mutagen. In addition, the GTTC decided to continue conducting further work in this area and to develop a position paper on

when a positive mutagen in somatic tissue would trigger a concern for germ cell mutagenicity.

12. At their forty-fifth meeting the Sub-Committee noted (ST/SG/AC.10/C.4/90) that the informal working group had initiated discussions of a thought-starter submitted by the Netherlands with a proposal to consider changing the current hazard class "germ cell mutagenicity" to "mutagenicity", which was considered outside the scope of its terms of reference. A rationale for this change is that mutagens in somatic cells are also considered as a human health hazard in itself. The Sub-Committee further noted that the informal working group would continue the discussions to assess the appropriateness of this change as well as its implications, advantages and disadvantages and would submit its findings and recommendations for consideration by the Sub-Committee.

13. Since the forty-fifth meeting of the Sub-Committee, the informal working group met four times with a major emphasis on the discussion related to the considered change of scope of the current hazard class "germ cell mutagenicity" to "mutagenicity". The informal working group further developed and discussed several options how this could be done based on the Netherlands' proposal. There are currently two proposals under discussions, both with similar impacts. One proposal is to keep "germ cell mutagenicity" and "mutagenicity" in the same hazard class, as originally suggested by the Netherlands, but to separate the two effects by different hazard statements. The other proposal by the United States of America elaborates the possibility to identify two separate hazard classes, one for "germ cell mutagenicity" and the other for "mutagenicity". In both cases, there would be substances currently classified for germ cell mutagenicity in Category 2, which would fulfil criteria for somatic cell mutagenicity in Category 1. The working group needs first to conclude the discussion on whether the change of scope of hazard class should be proposed and then provide a recommendation to the Sub-Committee.

14. Due to the complexity of the issues discussed in the informal working group, it will not be possible to finalise the work of the group within the current biennium. The working group discussed the possibility to submit a partial revision of chapter 3.5 by the end of the biennium, but concluded that this is not optimal as it may create inconsistencies with current criteria and would most probably need some fine tuning once the new criteria are developed. Moreover, the work on the guidance section has not been concluded. The informal working group therefore anticipates that it will be necessary to request whether the Sub-Committee agrees to carry-over their work into the 2025-2026 biennium. In addition, the informal working group intends to present its findings and recommendations related to the suggested change of scope of the hazard class and any revision of the terms of reference, if necessary, timely prior to the forty-seventh meeting together with an updated programme of work.