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

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

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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 an update on the work undertaken by the informal working group on clarification of the criteria for classification for germ cell mutagenicity since the forty-fourth session of the Sub-Committee.

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/Add1, 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). The informal working group reported on the progress of work at the forty-first (INF.14), forty-second (INF.15), forty-third (INF.26) and forty-fourth (INF.17) sessions. At the forty-third session the Sub-Committee agreed to carry-over the program of work of the informal working group work into the 2023-2024 biennium. The informal working group is aiming on finalisation of the revision of chapter 3.5 by the end of 2024.

Status report

- 3. As a follow-up to the forty-fourth session, the informal working group progressed the revisions and on-going discussions through written procedure and three online meetings. Items discussed and agreed are summarised in a living working document revised after each meeting. Any issues related to the activities of the informal working group on non-animal test methods were, in agreement with the leads of the other informal working group, listed and shared for further consultation with that group. This list is also annexed to this document for transparency to the Sub-Committee.
- 4. The informal working group agreed to consider replacing the current GHS text on the terms "genotoxic and genotoxicity" with the OECD definition of genotoxicity. While this was supported by several members, some experts objected to the use of "primary DNA"

damage" when referring to indicator tests. This terminology was considered misleading. GTTC/OECD experts were also consulted and it was agreed to replace "primary DNA damage" with "genotoxicity indicator tests". The United States of America proposed a partly new simplified version of the OECD text for consideration, that lead to further revisions in the definition, which are still to be agreed by the group.

- 5. The informal working group discussed the text on non-testing methods carried over from the recently revised chapters 3.2-3.4 to be consistent with those. However, the informal working group discussed this in some length as germ cell mutagenicity is considered a more critical hazard than the health hazards dealt with in the earlier chapters. The text related to non-testing methods is still not finalised, and some issues are referred back to the informal working group on non-animal test methods (see annex).
- 6. Another issue discussed was the introduction of a tiered approach to guide data organization for classification decision-making based on available information. Whether this is useful for germ cell mutagenicity is still under consideration, as often a weight of evidence assessment of all available data is usually made.
- 7. It was agreed that the section on in vitro methods needs to be further elaborated, to better understand how data from these methods can be used also in support to the animal data. The group will also consider whether in vitro data could be used for classification in the absence of additional evidence, in case all underpinning mechanisms to mutagenicity are covered within an in vitro test battery.
- 8. A proposal was made to clarify the category 2 definition being more explicit on the fact that this category includes substances known to induce somatic mutations in cells of humans or to be regarded as if they induce somatic mutations in humans. The current definition only states "Substances which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans". This is not a change in the criteria as such, but clarifies that for germ cell mutagenicity category 2, there is the demonstration of an effect, i.e. mutagenicity in somatic cells. This is different from the category 2 of the hazard classes for carcinogenicity and reproductive toxicity, where category 2 does not comprise enough evidence for classification in category 1. This issue will be further discussed based on a thought starter prepared by the Netherlands.
- 9. The Genetic Toxicology Technical Committee (GTTC) of the Health and Environmental Science Institute (HESI) informed the informal working group on the progress of their extended 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.

Annex

Issues for consultation with the informal working group on non-animal testing methods

- 1. The basis of the work carried out by the informal working group (IWG) on germ cell mutagenicity (GCM) revising chapter 3.5 of GHS, is set out in the terms of reference (as amended in the informal document INF.24, fortieth session). The main task of the IWG is to review the classification criteria, but that should also include revisions to facilitate hazard classification using non-animal methods, where appropriate, and consultation with the IWG on non-animal testing methods (NATM) when relevant.
- 2. The GCM and NATM leads first met in June 2023 to discuss how the two IWGs could best interact and how best benefit from the feedback and expertise of the NATM IWG in the work with chapter 3.5. It was determined that the best way forward was to present a document outlining issues identified by the GCM IWG for consultation with the NATM IWG.
- 3. Three main topics were identified for consultation with the NATM IWG:
 - 1. classification based on non-test methods,
 - 2. the use of a tiered approach, and
 - 3. classification based on in vitro data.

Classification based on non-test methods

- 4. A new section including four paragraphs on non-test methods was imported into chapter 3.5 from chapters 3.2, 3.3, 3.4, in agreement with the terms of reference. The idea is to keep the text as consistent as possible with that of the other chapters and to adapt it only, if specifically needed in the context of germ cell mutagenicity. Generic amendments to the four paragraphs are not in the remit of the GCM IWG, but should be done only if agreed by the NATM IWG.
- 5. At the meeting of the GCM IWG that took place in the margins of the 44th session of the sub-committee, the NATM leads presented the rational for each of the paragraphs, as discussed in the NATM IWG.
- 6. The introduction of the four paragraphs on non-test methods triggered considerable discussion within the GCM IWG and a consultation was launched over the summer to identify items for further discussion with the NATM IWG. The consultation was based on the revised chapter 3.5 version 11.
- 7. Among the identified items, some were of generic nature while other were specific to GCM.
 - (a) Generic items
 - (i) Cite ECHA read-across framework (RAAF guidance)

It was noted that the RAAF is very conservative and restrictive as its aim is to assess compliance with REACH. Other available reference can be cited in the guidance.

<u>Proposal:</u> Add these references in the guidance section of chapter 3.5.

(ii) Paragraph 3.5.2.5.3

For consistency with paragraph 3.5.2.5.1 Germany suggests to change the wording as follows (new text in CAPS): "With respect to reliability, lack of alerts in a SAR or expert system OR ABSENCE OF POSITIVE PREDICTION BY QSAR is not sufficient evidence for no classification."

Proposing such an amendment would require a re-discussion in the NATM IWG as it implies amending chapters 3.2, 3.3 and 3.4, which goes beyond the mandate of the GCM IWG.

<u>Proposal:</u> No action needed by the GMC IWG. NATM IWG to agree whether taking this into consideration for a future proposal to revise the text in all chapters.

(iii) Paragraph 3.5.2.5.2

It was suggested to add "experimental" before "test data", however the notion of "experimental" seems to be redundant and already included in "test data".

<u>Proposal</u>: No action, but consistency with other chapters to be checked prior to conclude on the issue.

(iv) Replace "and" with "or" in paragraph 3.5.2.5.4

Read-across and (Q)SAR do not necessarily need to be considered in conjunction why it was suggested to replace "and" with "or" in this paragraph. Proposing such an amendment would require a re-discussion in the NATM IWG as it implies amending chapters 3.2, 3.3 and 3.4, which goes beyond the mandate of the GCM IWG.

<u>Proposal:</u> No action needed by the GMC IWG. NATM IWG to agree whether taking this into consideration for a future proposal to revise the text in all chapters.

- (b) Specific items related to germ cell mutagenicity
 - (i) Delete the paragraph 3.5.2.5.4 for conclusion on no-classification

It seems unusual that scientific rigour is highlighted exclusively to substantiate "no classification". It was questioned whether the standards for classification and non-classification should be the same. NATM IWG participants clarified that higher standards need to be considered for conclusion on no classification, which represent an integral part of the GHS. However, this paragraph raised concern in the GCM IWG because there is a perception that solely non-test methods could lead to the conclusion not to classify, even when the evidence should rather be regarded as inconclusive. This concern arises from the fact that the GCM is considered a more critical hazard to human health when compared to hazards covered in chapters 3.2, 3.3 and 3.4.

Proposal: Move this paragraph to the guidance section, but do not delete it.

(ii) Deletion of "including the conclusion not classify" in paragraph 3.5.2.5.1

GCM IWG agreed to delete this text. It was explained that this is not in contrast with paragraph 3.5.2.5.4 because in the first paragraph the context is generic, while the 4th paragraph it has a specific purpose as explained above.

Proposal: Deletion of text in paragraph 3.5.2.5.1 as indicated above.

(iii) Can non-test methods, e.g. read-across, be used as stand-alone to classify for germ cell mutagenicity?

This is how they are intended to be used in chapters 3.2-3.4. For instance, it was mentioned that if genotoxicity experimental data are not available read-across could eventually be substantiated by other data. One member suggested that results from an in vitro test should be a prerequisite for read-

across. However, it is the read-across justification itself and the strength of evidence on the source substance that should be decisive for the classification.

<u>Proposal:</u> No action is suggested by the leads. In vitro data can strengthen the justification for read-across but are not necessary.

(iv) Evidence based on QSARs compared to read-across

(Q)SARs are almost exclusively built on in vitro data (especially Ames data) and these data are not always of optimal quality. Moreover, there seems to be no reliable *in silico* models that predict the outcome of in vivo genotoxicity. (Q)SAR should have a clear lower weight than read-across and should therefore not be considered in the same way, as already mentioned in 3.5.2.5.2. In particular, there appears to be more willingness to accept read-across argument rather than (Q)SAR predictions for negative outcomes.

<u>Proposal</u>: Maintain the paragraph on (Q)SAR, also for possible future use, and add clarifications on cautious use of (Q)SAR data in the guidance section.

The use of a tiered approach

- 8. GCM IWG leads invited a member of NATM IWG to present the tiered approach developed in chapter 3.4 for consideration of the concept to be applied also to chapter 3.5.
- 9. Acknowledging that the situation for GCM is much more complex than for skin sensitisation it was agreed to explore in the GCM IWG whether a tiered approach is applicable to GCM classification.

Classification based on in vitro data

10. GCM IWG does not ask for advice on this topic from the NATM IWG as by now.

5