



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

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

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Item 2 (i) of the provisional agenda

Classification criteria and related hazard communication:

Other issues

Clarification of the criteria for classification for germ cell mutagenicity in category 1B

Transmitted by the European Union*

Introduction

1. The European Commission wishes to thank the secretariat and all delegates for agreeing to consider and discuss this proposal aimed at clarifying the criteria for classification for germ cell mutagenicity in category 1B.
2. The current criteria have led to diverging opinions between experts when implementing the current GHS. In particular, the requirement for “demonstrating the ability of the substance or its metabolite(s) to interact with the genetic material of germ cells” has caused difficulties in being able to classify for 1B. In our understanding, this requirement was never intended to allow for classification in category 1B only when a substance’s molecular interaction with germ cell genetic material had been proven explicitly, as such data in practice are rarely available. We consider and have evidence that this wording is prone to different interpretations and thus suggest amending it.
3. We consider that indirect information that would demonstrate the ability of a substance or its metabolite(s) to interact with germ cell genetic material should be sufficient to justify classification in category 1B if substances elicit positive results in *in vivo* somatic cell mutagenicity tests in mammals. This could involve a weight of evidence-based assessment, considering all available data, including toxicokinetic data from *in vivo* studies or supporting evidence from other available studies that the substance or its metabolite(s) reaches the germ cells.
4. The smooth implementation of the current criteria has so far been hindered by the lack of accurate test methods for assessment of germ cell mutagenicity, thus the studies have rarely been conducted and only limited data and experience in evaluating these studies has been acquired. Moreover, there are no fully validated tests methods to cover all genotoxicity

* 2020 (A/74/6 (Sect.20) and Supplementary), Subprogramme 2.

endpoints (i.e. gene mutation, clastogenicity and aneugenicity) in all stages of germ cell maturation¹. Another gap is the lack of test methods to analyse the induction of genotoxic alterations in female germ cells.

5. In addition, under the GHS it is preferred to avoid the use of live animals, especially when not necessarily leading to improved safety for workers, consumers and the general public². Therefore, the classification criteria should be set up to avoid additional animal testing, if not expected to lead to a conclusive result.

6. We propose to revise the wording defining the criteria for classification in category 1B in order to permit the use of other types of data as indirect evidence of interaction with germ cells; such as toxicokinetic data from currently accepted *in vivo* studies and/or supporting evidence from other available studies, e.g. effects in gonads in reproductive toxicity studies may demonstrate that the substance has reached the germ cells. Considerable experience already exists in using these types of data in the assessment of pesticides and pharmaceutical products. This approach would then enable classification in category 1B without requiring additional *in vivo* germ cell mutagenicity study(ies), and avoiding classification in category 2 based on possible false negatives from such studies.

7. In addition, we also suggest the following revisions under:

- (a) category 1B (a): delete the word “heritable”, so that the statement would allow the use of any germ cell tests (e.g. OECD TG 488 on Transgenic rodent somatic and germ cell gene mutation assays);
- (b) category 1B (b): to avoid the inconsistent use of the word “mutagenicity” between category 1B and category 2, we suggest to add “or other *in vivo* somatic cell genotoxicity tests in mammals which are supported by positive results from *in vitro* mutagenicity assays”;
- (c) category 1B (b): replace “genotoxic” with “genotoxicity” and “germ cells” with “gonads” as it may be technically challenging to detect a substance or its metabolite(s) in germ cells, especially in the case of female germ cells.
- (d) Note: add “; similarly, substances for which read-across to substances classified in category 1B is applicable, classification in 1B should be considered”, to allow a read-across approach, in line with GHS paragraph 3.2.2.6.2.

¹ F. Marchetti et al., *Environmental and Molecular Mutagenesis* 61 (2020) 42-54; CL. Yauk et al., *Mutation Research* 783 (2015) 36–54.

² See paragraph 1.3.2.4.6 of the GHS.

Proposal

8. We suggest amending Table 3.5.1 as follows: (~~red-stricken-out~~ text is deleted, underlined text is added):

Figure 3.5.1: Hazard categories for germ cell mutagens

<u>CATEGORY 1:</u>	Substances known to induce heritable mutations or to be regarded as if they induce heritable mutations in the germ cells of humans
Category 1A:	Substances known to induce heritable mutations in germ cells of humans Positive evidence from human epidemiological studies.
Category 1B:	Substances which should be regarded as if they induce heritable mutations in the germ cells of humans (a) Positive result(s) from <i>in vivo</i> heritable germ cell mutagenicity tests in mammals; or (b) Positive result(s) from <i>in vivo</i> somatic cell mutagenicity tests in mammals <u>or other <i>in vivo</i> somatic cell genotoxicity tests in mammals which are supported by positive results from <i>in vitro</i> mutagenicity assays</u> , in combination with some evidence that the substance has potential to cause mutations to germ cells. This supporting evidence may, for example, be derived from mutagenicity/genotoxicity tests in germ cells <i>in vivo</i> , or by demonstrating the ability of the substance or its metabolite(s) to interact with <u>reach the genetic material of germ cells</u> ; gonads; or (c) Positive results from tests showing mutagenic effects in the germ cells of humans, without demonstration of transmission to progeny; for example, an increase in the frequency of aneuploidy in sperm cells of exposed people.
<u>CATEGORY 2:</u>	Substances which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans Positive evidence obtained from experiments in mammals and/or in some cases from <i>in vitro</i> experiments, obtained from: (a) Somatic cell mutagenicity tests <i>in vivo</i> , in mammals; or (b) Other <i>in vivo</i> somatic cell genotoxicity tests which are supported by positive results from <i>in vitro</i> mutagenicity assays. NOTE: <i>Substances which are positive in <i>in vitro</i> mammalian mutagenicity assays, and which also show structure activity relationship to known germ cell mutagens, should be considered for classification as Category 2 mutagens; similarly, substances for which read-across to substances classified in category 1B is applicable, classification in 1B should be considered.</i>