

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 3 (d) of the provisional agenda

**Work on the Globally Harmonized System of Classification and
Labelling of Chemicals: Classification of skin sensitizers
using the results of local lymph node assays test methods
in accordance with OECD Test Guideline 442B**

Comments on ST/SG/AC.10/C.4/2022/19 “Clarification of the criteria for classification for skin sensitization using animal studies” and consequential amendments to ST/SG/AC.10/C.4/2022/14

**Transmitted by the experts from the United States of America and
Canada**

Introduction

1. Canada and the United States of America would like to thank the expert from Japan for the working document ST/SG/AC.10/C.4/2022/19 “Clarification of the criteria for classification for skin sensitization using animal studies”, for the hard work that has gone into developing this proposal and for thoughtfully revising the proposal in accordance with feedback from the GHS Sub-Committee.

Background

2. Local Lymph Node Assay (LLNA) sub-categorization first appeared in GHS Rev.3 after being introduced in informal document INF.3 (15th session) and working paper ST/SG/AC.10/C.4/2008/18 (16th session). The criteria for LLNA data in the GHS have remained largely unchanged since Rev.3, even though multiple updates to the OECD test guidelines (OECD TG 429, 442A, 442B, 442C) have occurred since 2008.

Discussion

3. Generally, in the GHS, health hazard criteria is only included if it has been agreed internationally (GHS 1.3.2.4.3). Validated test methods that have yet to be internationally agreed upon have been referenced without the explicit inclusion of criteria. For example, please refer to the recently revised Chapter 3.3 (informal document INF.3 (40th session).

4. The recently developed sub-categorization criteria for the BrdU-ELISA (OECD Test Guideline 442B) while scientifically validated (informal document INF.4 (42nd session) has yet to be agreed to internationally.

5. The existing sub-categorization criteria in the GHS for OECD Test Guideline 429 and OECD Test Guideline 406, though not written in the Test Guidelines, was developed by the OECD (see INF.13 (15th session), ST/SG/AC.10/C.4/2008/18, ST/SG/AC.10/C.4/2008/18/Add.1, informal document INF.3 (16th session) and

ST/SG/AC.10/C.4/32, paragraph 23). Therefore, it can be considered to be internationally agreed. The present proposed note in paragraph 17 and 18 of ST/SG/AC.10/C.4/2022/19 may unintentionally dissociate the relationship of the sub-categorization criteria for OECD Tests Guidelines 429 and 406 with the OECD.

6. Furthermore, we wish to provide clarification in the proposed note in paragraph 17 and 18 regarding the effective concentration. In part, the language can be more aligned with that in the proposed guidance of Chapter 3.4 (informal documents INF.3/Rev.1 and INF.8 (43rd session)).

7. Collectively, to address these concerns and facilitate discussion at the Sub-Committee session, we have set out proposals in paragraphs 8 to 11. The intent is to allow the use of the BrdU-ELISA sub-categorization criteria at the discretion of a competent authority, without including the sub-categorization criteria directly in the criteria.

Proposal

Amendments to ST/SG/AC.10/C.4/2022/19

8. Amend the note in paragraphs 17 and 18 of ST/SG/AC.10/C.4/2022/19 as follows (new text is shown in bold underlined; text that is deleted from the proposal is shown with strikethrough; existing text in the proposal in ST/SG/AC.10/C.4/2022/19 is shown in italics):

*“Note: The EC3 and EC1.6 values are estimated concentration of a chemical expected to produce positive responses in each assay method. **Sub-categorization for the LLNA is performed based on the effective concentration (EC), a linear interpolation to estimate the concentration causing an increase in stimulation index of exactly the critical magnitude.**”*

Although no sub-categorization criteria have yet been described in OECD test guideline Nos. 406, 429 and 442B, validated sub-categorization criteria may still be accepted by some competent authorities. A competent authority may decide which sub-categorization criteria, if any, should be applied for these test methods.

For the LLNA: BrdU-ELISA, sub-categorization criteria (1A: EC1.6 value \leq 6%, 1B: EC1.6 value $>$ 6%, Maeda and Takeyoshi, 2019; Kobayashi et al., 2020) have been proposed and validated by the OECD, but no sub-categorization criteria have yet been agreed internationally. Validated sub-categorization criteria may still be accepted by some competent authorities. A competent authority may decide which sub-categorization criteria, if any, should be applied for this test method.

As for the LLNA: DA and LLNA: BrdU-FCM, there are currently no validated and internationally agreed criteria for subcategorization of skin sensitizers. Therefore, these test methods can only be used to conclude on either classification in category 1 or no classification.”

9. In paragraph 17 of ST/SG/AC.10/C.4/2022/19 delete the following instructions for amendment:

“Under the first column ‘Assay’, after the row for ‘Local lymph node assay’, insert a new row: **‘Local lymph node assay: BrdU-ELISA’**.”

Under the second column ‘Criteria’, for the new row for **‘Local lymph node assay: BrdU-ELISA’**, insert **‘EC1.6 value \leq 6%’**.”

10. In paragraph 18 of ST/SG/AC.10/C.4/2022/19 delete the following instructions for amendment:

“Under the first column ‘Assay’, after the table entry for ‘Local lymph node assay’, insert a new table entry: **‘Local lymph node assay: BrdU-ELISA’**.”

Under the second column ‘Criteria’, for the new entry for **‘Local lymph node assay: BrdU-ELISA’**, insert **‘EC1.6 value $>$ 6%’**.”

Consequential amendments to ST/SG/AC.10/C.4/2022/14

11. Insert the following references in alphabetical order in the references list of ST/SG/AC.10/C.4/2022/14:

“Kobayashi T., Maeda Y., Kondo H., Takeyoshi M. (2020) Applicability of the proposed GHS subcategorization criterion for LLNA:BrdU-ELISA (OECD TG442B) to the CBA/J strain mouse. *Journal of Applied Toxicology*. 40(10):1435-1439

Maeda Y., Takeyoshi M. (2019) Proposal of GHS sub-categorization criteria for LLNA: BrdU-ELISA (OECD TG442B). *Regulatory Toxicology and Pharmacology*. 107:104409”.

Action requested

12. The Sub-Committee is invited to consider the proposed amendments to the proposals in ST/SG/AC.10/C.4/2022/19 and ST/SG/AC.10/C.4/2022/14 as modified by informal document INF.8.
