

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 (d) of the provisional agenda

Work on the Globally Harmonized System (GHS):

Classification of skin sensitizers using the results of local lymph

node assays (LLNA) test methods in accordance with OECD Test Guideline 442B

Clarification of the criteria for classification for skin sensitization using animal studies

Transmitted by the expert from Japan

Introduction

1. This informal paper provides an update on the proposal made by Japan to clarify the criteria for classification for skin sensitization using animal studies at the thirty-ninth session of the Sub-Committee.

Background

2. Currently, three skin sensitization test methods are listed as test methods to classify GHS category 1 chemicals. These include two guinea pig prediction tests (the guinea pig maximization test and the Buehler test), known as the official test guidelines (TG) 406 of the Organization of Economic Cooperation and Development (OECD), and the radioisotopic (RI) LLNA (LLNA-RI), known as OECD TG 429 (OECD, 2010). And these three methods can be further applied for GHS sub-categorization 1A/1B to provide information on the skin sensitization potency of chemicals (United Nations, 2019).

3. The LLNA: BrdU-ELISA listed in OECD TG 442B (OECD, 2018) is another reliable sensitization test method using the same principle as the standard LLNA-RI in TG 429 (OECD, 2010). The LLNA: BrdU-ELISA was scientifically validated and peer-reviewed by ICCVAM in 2010 and is used as a conventional skin sensitization test method worldwide and can be used to classify GHS category 1 versus Not classified.

4. Recently, Japanese researchers re-analysed 32 skin sensitizers data, used in the validation and peer review of LLNA: BrdU-ELISA, that are classified as GHS Category 1A or GHS Category 1B, and attempted to determine optimal criterion for GHS sub-categorization using this method. Consequently, the optimal criterion for the GHS sub-categorization was determined to be 6% when using EC1.6, and the criterion represents almost equivalent GHS sub-categorization performance to the existing criterion of the cut-off of 2% with LLNA-RI data (Maeda and Takeyoshi, 2019). Using this criterion, the correct outcomes (%) for GHS 1A and GHS 1B category chemicals were 92.3 and 84.2, respectively, for all 32 chemicals. When excluding 2-mercaptobenzothiazole which may cause a strain-specific low response in this assay system, the correct outcome (%) for GHS 1A chemicals was 100.

Table 1. Proposed GHS sub-categorization criterion for LLNA: BrdU-ELISA

Category	Criterion
Cat.1	SI \geq 1.6
Cat.1A	EC1.6 value \leq 6%
Cat.1B	EC1.6 value $>$ 6%

5. Further examination to confirm the applicability of the proposed GHS sub-categorization criterion to data derived from the commonly used mouse strain was conducted with fifteen chemicals categorized in GHS Category 1A or Category 1B sensitizers listed in the LLNA performance standard. The results revealed that all GHS Category 1A or Category 1B chemicals could be correctly assigned using the newly proposed criterion. (Kobayashi et al., 2020).

6. The proposal above was discussed by the OECD expert group on alternative methods for skin sensitization at a meeting held in October 2020, and the group decided to support the proposal.

7. Then the proposal was submitted to the 39th session of the Sub-Committee and was agreed to be included in the two-year work plan for 2021-2022. Noting that this issue had been considered by the OECD Expert Group on skin sensitization, the Sub-Committee, as a first step, invited the expert from Japan to report to the Sub-Committee at the 40th session on the discussions on this topic and their outcome at the OECD level. It was also noted that the work led by Japan should be done in parallel and in coordination with the on-going work on non-animal test methods led by the United Kingdom and the Netherlands.

Status report

8. Based on the discussion with the OECD secretariat for the support work to strengthen the rationale for the proposed criterion, an independent review of the data would be desirable. The OECD Secretariat proposed to involve the skin sensitization expert group in the review of the data used to decide the criterion.

9. The proposed criterion is based on two publications (Maeda and Takeyoshi, 2019; Kobayashi, et al., 2020). The first publication (Maeda and Takeyoshi, 2019) supports the establishment of the criterion based on the existing data cited in the peer review report of ICCVAM (ICCVAM, 2010). The second publication (Kobayashi, et al., 2020) confirms the applicability of the proposed criterion to the commonly used mouse strain, based on additional experimental work on 15 skin sensitizers.

10. Accordingly, the objective of the OECD review would be to evaluate (i) the process of setting the criterion used in the first publication, and (ii) the validity of the data and the results presented in the second publication, and finally (iii) the overall robustness of the sub-categorization criterion on the full data set.

11. The OECD support work plan and the timeline (OECD, 2021) was submitted for approval at the 33rd Meeting of the Working Party of the National Coordinators of the Test Guidelines Programme (WNT), and approved. The timeline and anticipated actions in OECD and GHS Sub-Committee are shown in Table 2.

12. After the discussion of the review results with the OECD expert group on alternative methods for skin sensitization at a meeting to be held in October 2021, the interim review results will be reported to the 41st session of the Sub-Committee. Then OECD will complete the support work and preparation of the support document by February 2022.

13. Japan aims to submit the working document for approval of the proposal to the 42nd session of the GHS Sub-Committee with the OECD review report.

Table 2. Timeline and the anticipated actions required for the work plan*

	Events		Actions	
	OECD	UN		
2021	4	33 rd WNT	Approval of the support from the OECD Expert Group on skin sensitisation for the review and timelines	
	5			
	6		Beginning of review work for the proposed criterion for sub-categorisation	
	7		40 th GHS SCE	
	8		Explanation of the proposal from Japan	
	9			
	10	OECD sensitization EG		<ul style="list-style-type: none"> • Submission of an SPSF to the WNT for the project to be included formally in the OECD work plan • Discussion of review progress/outcome
	11			Submission of the Informal paper (IP) reporting the interim review result
	12		41 st GHS SCE	Reporting and discussion of IP for the interim review result
	2022	1		
		2		Finalization of the supporting document based on the review result
		3		Submission of the Working document (WD) to the 42 nd GHS sub-committee with the supporting document of OECD
4		34 th WNT		Reporting of the output from the 41 st GHS sub-committee
5				
6				
7			42 nd GHS SCE	Reporting and discussion of the WD for approval
8				
9				
10		OECD sensitization EG		Reporting of the output from the 42 nd GHS sub-committee
11				
12			43 rd GHS SCE	End of the two-year work plan and approval of all outputs
2023	1			
	2			
	3			
	4	35 th WNT		Reporting of the final output

*cited from the meeting document in the 33rd WNT meeting (OECD, 2021)

References

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