UN/SCEGHS/46/INF.12

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 **18 June 2024**

Forty-sixth session
Geneva, 3-5 July 2024
Item 2 (c) of the provisional agenda
Work on the Globally Harmonized System of Classification and Labelling of Chemicals: Use of non-animal testing methods for classification of health and environmental hazards

Use of non-animal testing methods for classification of health and environmental hazards: progress report

Transmitted by the experts from the United Kingdom and the Netherlands on behalf of the informal working group on the use of non-animal testing methods for classification of health and environmental hazards

Introduction

1. This informal document provides an update on the work performed by the Informal Working Group on "Use of non-animal testing methods for classification of health and environmental hazards" since the last update provided to the Sub-Committee in December 2023 (see informal document INF.8 from the forty-fifth session).

Background

2. At the forty-third session, the Sub-Committee agreed to keep the work on the use of non-animal testing methods (NATM) for classification of health and environmental hazard classes on its programme of work for the 2023-2024 biennium.[1] Updates on the progress of the group's work are provided to the Sub-Committee at each session of the biennium.

3. The informal working group presently has approximately 60 members, reflecting the importance of, and interest in, this work. Its membership includes experts with specialised knowledge of test methods and their application to classification, and experts on national legislation that implements GHS. Discussions are often lively and detailed, but overall are propelled by a strong desire to make progress on the informal working group's mandate and ensure that non-animal testing methods are consistently incorporated in the GHS in a way that reflects their growing importance and scientific relevance, whilst recognising their limitations.

Status report

4. Since the last update to the Sub-Committee in December 2023, the informal working group has continued to work hard on finalising the discussions on the revision of chapter 3.4 via correspondence and virtual meetings (12 December 2024; 2 February 2024; 7 March 2024 and 28 March 2024) with a further meeting currently planned to take place during the July

[1] See informal document INF.16 and report of the Sub-Committee on its forty-third session (SG/ST/AC.10/C.4/2022/86).

2024 session. After each meeting, the Netherlands and the United Kingdom as joint project leads, with the assistance of the Joint Research Centre (JRC), have revised the draft text of chapter 3.4 and drafted meeting notes to keep track of the discussions, taking into account written comments and information on specific topics provided by the members of the group.

5. As a result of this work the group has submitted for the consideration of the Sub-Committee for this session the latest version of the revised chapter 3.4 in documents: ST/SG/AC.10/C.4/2024/10 and INF.5 – "Revision of chapter 3.4 to fully incorporate non-animal testing methods for skin sensitization – mixtures".

6. The group was not able to reach final agreement on the proposed text for paragraph 3.4.5.3.2.3.5 prior to the submission deadline, however the working group is confident that this can be achieved before or during their next meeting. To indicate that this text has not been finalised, it is shown in square brackets (i.e. "[…]") in ST/SG/AC.10/C.4/2024/10 and INF.5. The project leads will provide the outcome of this issue for the consideration of the Sub-Committee at the upcoming July 2024 session.

On-going work

7. The NATM informal working group's project leads are currently considering how to best address a request for collaboration from the informal working group on the clarification of the criteria for classification for germ cell mutagenicity (GCM IWG). The issues to be addressed are described in the annex to informal document INF.16, in particular items 7a (Generic items) and 7b (Specific items related to germ cell mutagenicity) from the December 2023 session (forty-fifth session). The project leads of the two informal working groups met on 7 May 2024 for an initial discussion regarding these issues, with the intention of presenting them to the NATM working group for consideration at their next meeting.

8. In addition, now that work on chapter 3.4 is nearly complete, the group are considering which hazard class or issues to address next. The project leads have drafted a paper, which is provided in the annex of this progress report, to aid the group's discussions at their next meeting. The annex to this informal document is therefore intended as a snapshot of the current issues that the group are considering, and although the specific GCM issues mentioned above have not been included in it, the project leads have considered it is important to flag them as a potential future priority.

Action requested

9. The Sub-Committee is invited to note the progress of the revision of chapter 3.4 for skin sensitization as referred to in paragraphs 5 and 6 above, and to provide views on the on-going work as detailed in paragraphs 7 and 8 above, specifically:

(a) What the next priority (or priorities) should be on the potential next hazard class as outlined in the annex of this document;

(b) Whether the NATM IWG should consider the additional GCM-related issues as a priority ahead of the issues outlined in the annex of this document.

Annex

Suggestions for the next hazard class or other NATM issues to be considered

RIVM, Feb 2024

Introduction

1. The NATM informal working group (IWG) has the mandate to discuss and propose changes to the classification for health hazard and environmental hazard classes for in vitro and in silico methods. The IWG started with chapters 3.2 and 3.3 and is now working on the skin sensitization part of chapter 3.4. These chapters were prioritized without much discussion because there was an obvious need to include the new *in vitro* test methods that were internationally accepted into the criteria. However, it was considered less clear which hazard class to update once the hazard class skin sensitization is finalized. In addition to adapting a new hazard class, other issues could be addressed such as updating in silico criteria for all hazards classes, including an overarching paragraph in chapter 1.3. The same could be done for the defined approaches.

2. Therefore, this document suggests a way forward to prioritize the work of the NATM IWG regarding the next hazard class or other issues to address after work on chapter 3.4 (skin sensitization) of the GHS has been finalized.

Process

3. The NATM project leads developed a table to collect information on which hazard class or issues should be addressed. This included an overall view of remaining GHS hazard classes not yet addressed by the NATM IWG. The table included parameters such as in vitro/in silico methos applied, new in vitro/in silico methods already applied and potential and other issues.

4. The NATM IWG participants were asked to provide information to aid in this discussion.

Collection of information

5. The results of this exercise are shown in table 1. Comments were received from Canada, United States, the United Kingdom and the Netherlands.

6. Information was provided for the following hazard classes: acute toxicity, serious eye damage/eye irritation, respiratory sensitization, germ cell mutagenicity, carcinogenicity, reproductive toxicity, hazardous to the environment and hazardous to the ozone layer.

Next steps

7. As a way forward, the NATM project leads suggested the following four hazard classes/issues for further consideration by the IWG in an attempt to facilitate discussions with the goal of reaching agreement on future work. For these hazard classes/issues, the leads consider that there are new and readily available in vitro methods that could be included in GHS. Adapting chapter 1.3 with general criteria for non-test methods and defined approaches and updating all hazard classes with respect to these concepts would allow consistent application of these concepts within GHS.

- Chapter 3.1 Acute toxicity: introduce the use of non-test methods for substances, option for route-to-route extrapolation and to use vitro 3T3

- Chapter 4.1 Hazardous to the aquatic environment: there is an OECD TG 249 – in vitro method fish cell line acute toxicity available
- Chapter 3.3 Serious eye damage/irritation: update the chapter because there are new OECD test guidelines (OECD 467 and 492b) available allowing identification of category 1, 2 and no classification
- Chapter 1.3 Classification of hazardous substances and mixtures: include paragraph(s) for in silico methods and defined approaches

8. The NATM IWG participants are asked to consider the following:

- Do you agree with the four priorities suggested by the NATM project leads?
- Prioritize the four priority hazard classes / issues by scoring 1 (highest priority) to 4 (lowest priority)

9. Based on comments received, the group should decide on a way forward regarding the next hazard class/issue to be addressed after work has been finalized with regards to chapter 3.4 (skin sensitization) of the GHS.

Table 1

Feedback received from Canada (in red); Netherlands (in blue); USA (in purple); UK (in green); DE (in orange)

Chapter	Hazard class	In vitro methods already applied	New in vitro methods available	In silico already applied	New in silico methods available	Remarks	Scoring	Priority
3.1	Acute toxicity	No Guidance for waiving acute dermal toxicity tests for pesticide formulations and supporting retrospective analysis (US EPA, 2020)	No EURL ECVAM conducted a follow-up validation study demonstrating the usefulness of the 3T3-NRU cytotoxicity assay for the determination of substances with LD 50 > 2000 mg/kg (ECVAM, 2011, Prieto et al., 2013), and published the "EURL ECVAM Recommendations on the 3T3 Neutral Red Uptake Cytotoxicity Assay for Acute Oral Toxicity Testing" in 2013 (EURL ECVAM, 2013). Acute Oral Toxicity: the 3T3 Neutral Red Uptake (NRU) Cytotoxicity assay (europa.eu) Acute dermal systemic toxicity (OECD 402, revised 2017) accepted by EPA and other US agencies) includes provisions for waiving tests and reducing/refining animal use) In vitro dermal absorption methods (OECD TG 428)	Structure-activity relationship (Structure-activity relationship only included for the calculation approach for mixtures)	No The CATMoS model suite is able to accurately classify in all GHS categories. The CATMoS model suite has demonstrated high performance in terms of accuracy and robustness when compared with in vivo results. It is able to accurately classify in all GHS categories. (Mansouri et al 2021: CATMoS: Collaborative Acute Toxicity Modeling Suite https://ehp.niehs.nih.gov/doi/full/10.1289/EHP8495). The model is freely available via the OPERA suite of QSAR models and includes an applicability assessment functionality.	Acute dermal test can largely be waived Route to route extrapolation from oral to dermal could be considered		

Chapter	Hazard class	In vitro methods already applied	New in vitro methods available	In silico already applied	New in silico methods available	Remarks	Scoring	Priority
3.2	Skin corrosion/irritation			Structure-activity relationship		Largely Complete Updated in GHS rev 9		No
3.3	Serious eye damage/eye irritation			Structure-activity relationship		If possible, a reliable test to identify Cat 2 eye irritants would be very helpful – may be addressed but indirectly New OECD TGs (467 and 492b) are available for identifying Cat 2 (and Cat 1 , no cat) substances and mixtures. Updated in GHS rev. 10		No
3.4	Respiratory sensitization	No	OECD: Detailed review paper (DRP) to facilitate the Development of Test Methods to Predict the Respiratory Sensitisation Potential of Substances	Structure-activity relationship		Serious Human Health effect with no reliable predictive animal model The OECD DRP will take probably several years		Yes
3.4	Skin sensitization	No		Structure-activity relationship		Ongoing		No
3.5	Germ cell mutagenicity	Yes In addition to the OECD test methods in GHS Rev.9: -OECD TG 487 (In vitro Mammalian Cell Micronucleus test)		Structure-activity relationship		Update of the criteria by another IWG		No

Chapter	Hazard class	In vitro methods already applied	New in vitro methods available	In silico already applied	New in silico methods available	Remarks	Scoring	Priority
3.6	Carcinogenicity	No In vitro BALB/c 3T3 cell transformation assay; (U.S.: Included on EPA list of alternative methods and strategies considered for use under TSCA (2019); EU: Evaluated by EURL ECVAM (2012)) In vitro mammalian cell gene mutation tests using the thymidine kinase assay; (U.S.: Accepted via OECD Test Guideline 490 (2015, updated 2016); EU: Accepted via OECD Test Guideline 490 (2015, updated 2016)) In vitro mammalian cell micronucleus test (U.S.: Accepted via OECD Test Guideline 487 (2010, last updated 2023); EU: Accepted via OECD Test Guideline 487 (2010, last updated 2023)		Structure-activity relationship		Cell Transformation assays have been proposed for a number of years for identification of non genotoxic carcinogens. (not regarded as very reliable) GHS 3.6.5.3 Background guidance (excerpt from IARC) The IARC criteria included in this paragraph have been updated and contain a new section on mechanistic evidence including in vitro methods. (Preamble-2019.pdf (who.int))		No

Chapter	Hazard class	In vitro methods already applied	New in vitro methods available	In silico already applied	New in silico methods available	Remarks	Scoring	Priority
3.7	Reproductive toxicity Developmental neurotoxicity (DNT)	No	The following studies appear to have some validation by ECVAM: -Mouse (or rodent) embryonic stem cell test (mEST) -Human embryonic stem cell test (hEST) -In vitro rodent whole embryo culture (WEC) assays - Micromass embryotoxicity assay (at the peer review step according to ECVAM's TSAR tracking system) Non-mammalian in vivo assays: -Frog embryo teratogenesis assay (in 2000, ICCVAM had concluded this was not sufficiently validated or optimized for regulatory applications) -Zebrafish embryotoxicity assay (this assay does not appear to be harmonized or optimized yet) Placeholder In vitro battery test for DNT **Link to OECD website**	Structure-activity relationship		Very limited validation in general for all of these methods. The WEC cannot really be considered a NATM as living embryos are removed from dams and allowed to develop further in vitro. The culture system largely uses homologous rat serum from "serum rats" Similarly, the micromass assay is more properly described as an ex-vivo assay requiring embryos to begin with		
3.8	STOT SE	No						
3.9	STOT RE	No						

Chapter	Hazard class	In vitro methods already applied	New in vitro methods available	In silico already applied	New in silico methods available	Remarks	Scoring	Priority
3.10	Aspiration hazard	Yes, viscosity measurements	No	Yes, grouping for hydrocarbons	No	This is assigned on physicochemical properties and does not need an in vitro test.		No
4.1	Hazardous to the aquatic environment		OECD TG 249		yes			
4.2	Hazardous to the ozone layer					No animal tests currently applied		No