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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 **19 November 2024**

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Work on the Globally Harmonized System of Classification and Labelling of Chemicals: Other matters

Reflection on GHS systemic toxicity hazard classes and aiming on higher reliance on information from non-animal methods

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Introduction

1. This informal paper is presented considering ongoing and expected future discussions in the Sub-Committee on systemic health hazards, such as those partly related to activities of the current informal working groups on germ cell mutagenicity (GCM-IWG), on potential hazard issues and their presentation in the GHS (PHI-IWG) and on use of non-animal testing methods for classification of health and environmental hazards (NATMs). There are issues related to both overlap of hazards of concern and those still not covered in the GHS. In the context of germ cell mutagenicity, also somatic cell mutagenicity and the eventual impact on carcinogenicity has been mentioned. Identified potential hazards not explicitly covered by the GHS, relevant to systemic toxicity are: endocrine disruption with regard to human health, immunotoxicity, neurotoxicity, as well as protection of human health with regard to persistent, mobile or bioaccumulating chemicals through environmental exposure. Within the GHS there is the general aim (paragraph 1.3.2.4.6) to protect animal welfare, and where possible and appropriate, tests and experiments should not require the use of live animals. The informal working group on NATMs, which was established to address this concern, has successfully revised chapters 3.2, 3.3 and 3.4 including non-animal information to fulfil the classification criteria, but will run into problems tackling the systemic toxicity classes for human health, chapters 3.5, 3.6, 3.7, 3.8, 3.9 and possibly also 3.1. This is because a one to one replacement of the information from animal testing in the current criteria for these hazard classes is not possible, most probably neither applying defined approaches.

2. This informal paper provides some reflections made by the Joint Research Centre (JRC) of the European Commission based on information collected from the current harmonised classifications legally binding within the European Union through the CLP Regulation[1] implementing the GHS in European Union Member States.

[1] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures (CLP), https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32008R1272.

Overlaps in current harmonised classifications within the European Union and consideration on how to more efficiently classify for human systemic toxicity based on non-animal methods

3. An analysis of the overlaps between different systemic endpoints was made based on the harmonised and within the EU, legally binding classifications listed in Annex VI to the CLP Regulation. The hypothesis was that one intermediate effect, such as endocrine disruption could lead to more than one adverse outcome, for example reproductive toxicity and carcinogenicity[2]. This would then result in overlaps between systemic hazards.

4. There would be two reasons to reduce the overlaps: (i) improved efficiency of hazard classification and (ii) reduced reliance on animal testing. Higher efficiency can be gained as more evidence and time is required to observe possible adverse outcomes, compared to the intermediate effect(s) that can provoke them, especially if several adverse outcomes are triggered by a single intermediate effect. Evidence from animal testing could be reduced if classification were based on information related to intermediate effects, as non-animal methods then are more suitable and could eventually replace the animal testing. The information required for intermediate effects, even if meeting revised criteria not requiring adverse outcome data, should provide the same level of protection as provided by the current GHS criteria, i.e. the scope of the GHS should not change.

5. In the table[3] below the overlaps between the different GHS classes for systemic health effects are listed for the chemicals listed in Annex VI of the European Union CLP Regulation as latest updated[4]. The table provide the number of chemicals in all categories for a certain hazard class.

	TOTAL NUMBER CHEMICALS CLASSIFIED IN THIS CLASS	CHEMICALS ONLY IN THIS CLASS AMONG THE CLASSES RELEVANT TO SYSTEMIC TOXICITY	CHEMICALS CLASSIFIED AT LEAST IN ONE OTHER CLASS RELEVANT TO SYSTEMIC TOXICITY	OVERLAP OF CHEMICALS CLASSIFIED SPECIFIED BY CLASS					
				MUTAGENICITY	CARCINOGENICITY	REPRODUCTIVE TOXICITY	STOT-RE	STOT-SE	ACUTE TOXICITY
MUTAGENICITY	575	18 (3%)	557 (97%)	-	517 (90%)	76 (13%)	88 (15%)	18 (3%)	118 (21%)
CARCINOGENICITY	1151	387 (34%)	764 (66%)	517 (45%)	-	121 (11%)	171 (15%)	58 (5%)	264 (23%)
REPRODUCTIVE TOXICITY	388	96 (25%)	292 (75%)	76 (20%)	121 (31%)	-	163 (42%)	33 (9%)	199 (51%)
STOT-RE	552	74 (13%)	478 (87%)	88 (16%)	171 (31%)	163 (30%)	-	43 (8%)	372 (67%)
STOT-SE	297	113 (38%)	184 (62%)	18 (6%)	58 (20%)	33 (11%)	43 (14%)	-	161 (54%)
ACUTE TOXICITY	1703	985 (58%)	718 (42%)	118 (7%)	264 16%)	199 (12%)	372 (22%)	161 (9%)	-

[2] Madia, F.A.C., Pillo, G., Worth, A., Corvi, R., Prieto Peraita, M.D.P., 2021. Integration of data across toxicity endpoints for improved safety assessment of chemicals: the example of carcinogenicity assessment. Arch. Toxicol. 95 (6), 1971–1993, https://link.springer.com/article/10.1007/s00204-021-03035-x.

[3] From: Andrew P Worth, Elisabet Berggren, A twin transition in regulatory toxicology: moving toward Chemicals 2.0 and phasing out animal testing, *Toxicological Sciences*, 2024; kfae130, https://doi.org/10.1093/toxsci/kfae130.

[4] Commission Delegated Regulation (EU) 2022/692 of 16 February 2022 amending, for the purposes of its adaptation to technical and scientific progress, Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures, http://data.europa.eu/eli/reg/2008/1272/oj.

6. The list of harmonised classifications in Annex VI to the CLP Regulation are mainly based on information from animal testing, but also human data from epidemiological studies and application of read-across. The harmonised classifications were agreed and proposed by dedicated expert groups spanning over a long time period, during which both classification criteria and available information were gradually revised and updated. This hinders a detailed analysis of the overlaps between different systemic toxicity hazard classes. However, certain relationships are obvious, as mutagenic carcinogens are classified also for mutagenicity (category 1 and 2 of germ cell mutagenicity).

7. It could in the future be considered to merge systemic health effects into one class when sufficient evidence and confidence in its protection level is achieved. This common class should provide the same protection level as the current classes and should be explored in parallel to the development of the current classification system to which additional evidence from non-animal methods would continue to be included and additional classes with relevance to systemic toxicity could be introduced, i.e. the current system should continue to be developed as currently envisaged and contemporarily inform the new system.

8. A new systemic hazard class could only be proposed based on evidence that criteria are developed able to capture chemicals classified with the current system. With this informal paper the European Union informs the Sub-Committee on the analysis made on current harmonised classified chemicals within the European Union. In addition, the European Union would like to make the Sub-Committee aware of an initiative lead by the European Partnership for Alternative Approaches to Animal Testing (EPAA), the "EPAA Designathon for human systemic toxicity"[5] aiming at finding an alternative way to classify chemicals for systemic hazards based entirely on non-animal methods. This project is exploring the feasibility of the concept presented as a possible future European Union legal framework Chemicals 2.0[6].

[5] https://single-market-economy.ec.europa.eu/calls-expression-interest/epaa-designathon-human-systemic-toxicity_en

[6] Berggren E, Worth AP. 2023. Towards a future regulatory framework for chemicals in the European Union—Chemicals 2.0. Regul Toxicol Pharmacol. 142:105431, https://doi.org/10.1016/j.yrtph.2023.105431