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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

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Item 2 (f) of the provisional agenda
Work on the Globally Harmonized System of Classification and Labelling of Chemicals:
Potential hazard issues and their presentation in the Globally Harmonized System

Report of the OECD ad hoc group on potential hazard classes for endocrine disrupters in the Globally Harmonized System

Transmitted by the Organisation for Economic Co-operation and Development (OECD)*

I. Mandate to OECD on identification and unaddressed hazards of endocrine disrupters

1. During its forty-third session in December 2022, the Sub-Committee decided to include work proposed by the European Commission onto its programme of work for the 2023-2024 biennium to consider potential new and yet unaddressed hazard issues under the GHS (ST/SG/AC.10/C.4/2022/18)[1]. To support this work, an informal working group on potential hazard issues (PHI-IWG), coordinated by the European Union, was established based on informal document INF.39)[2].

2. The PHI-IWG developed a mandate (see paragraph 12 of ST/SG/AC.10/C.4/2023/6) to the OECD, to review the science needed for classification and labelling of substances and mixtures that have endocrine disrupting properties for human health and/or for the environment, which was adopted by the Sub-Committee at its forty-fourth session in July 2023.

3. Immediately following the adoption of the mandate in July 2023, an OECD Endocrine Disrupters ad hoc expert group was established to start implementing the mandate. The OECD Secretariat requested nominations of experts in testing and assessment of substances

* A/78/6 (Sect. 20), table 20.5.

[1] Proposal for new work on unaddressed hazard classes in the programme of work for the biennium 2023-2024.

[2] Addendum to ST/SG/AC.10/C.4/2022/18 - unaddressed hazard classes: Updated terms of reference and workplan.

and mixtures for potential endocrine disruption and GHS hazard classification from OECD member countries and stakeholders groups, as well as from delegates of the Sub-Committee. The resulting ad hoc expert group is comprised of fifty-five main members representing twenty-nine organizations (member countries, international organizations, non-governmental organizations (NGOs), industry representatives), as well as another fifty-five experts who are kept informed of these activities. This group has been co-chaired by an expert on endocrine disrupting effects on human health and an expert on ecotoxicology. The online kick-off meeting was held in September 2023, at which time, the scope of the mandate, the workplan and timelines were discussed. In contrast to other OECD expert groups, consensus of the group was not required for the report to be presented to the Sub-Committee.

II. Mandate approach

4. The work of the ad hoc expert group is being approached in three steps:

(a) First step: Identify any gaps regarding the possibility to adequately classify and label under the GHS substances and mixtures that have endocrine disrupting properties for human health and/or for the environment following the WHO/IPCS (2002) definition[3]. A review of the relevant human health and aquatic environment GHS hazard classes was performed;

(b) Second step: Based on the mandate, a review of the state of scientific knowledge to identify available methods that could help identifying endocrine disrupters (EDs) was undertaken. The review considered first, the scientific knowledge on the better understood Estrogen, Androgen, Thyroid, Steroidogenesis (EATS) modalities, then expanded to non-EATS modalities, covering human health. The environmental review of EATS and non-EATS modalities is still being developed with the focus on aquatic vertebrates. The ad hoc expert group agreed to start the gap analysis and review of the scientific knowledge using the currently agreed IPCS/WHO definition; and

(c) Third step: After reviewing the state of the science of methods, the group will discuss the fitness for purpose of the WHO/IPCS definition of EDs for identifying chemicals as EDs under the GHS.

5. The first several meetings of the OECD ad hoc group were devoted to reviewing the mandate detailed in paragraph 12 of document ST/SG/AC.10/C.4/2023/6, which includes the following five points:

(a) Review existing GHS hazard classes (e.g. carcinogenicity, reproductive toxicity, specific target organ toxicity, hazardous to the aquatic environment) that may include endocrine disrupters. The review should:

(i) Identify any gaps regarding the possibility to adequately classify and label under the GHS substances and mixtures that have endocrine disrupting properties for human health (HH) and/or for the environment (ENV);

(ii) Start with knowledge of EATS endocrine pathways and then consider other endocrine pathways for which available methods and scientific knowledge may not be as advanced. Under this task, OECD should use the existing scientific knowledge available, for example OECD Guidance Document 150[4], WHO/UNEP 2013 “State of the Science of Endocrine Disputing Chemicals”[5] and WHO/IPCS (2002)[6]. OECD could also consider in this gap analysis, existing national or regional schemes for identifying endocrine disrupters,

[3] *An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations.* State of the science of endocrine disrupting chemicals 2012 / edited by Åke Bergman, Jerrold J. Heindel, Susan Jobling, Karen A. Kidd and R. Thomas Zoeller.

[4] OECD, 2018. Revised Guidance Document 150 on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption.

[5] WHO/UNEP, 2012. State of the science of endocrine disrupting chemicals.

[6] WHO/IPCS, 2002. Global assessment on the state of the science of endocrine disruptors.

including those identified in the 2017 overview report (III)[7] published by the United Nations Environment Programme (UNEP);

(b) Following the review of gaps, assess whether the existing definition of endocrine disrupters as defined by the WHO/IPCS (2002) is sufficient in the context of the GHS and, if warranted, provide recommendations to the Sub-Committee for adapting the 2002 definition for application under the GHS;

(c) Based on the report from OECD on (a) and (b) above, the PHI-IWG will discuss the next steps as per sub-paragraph 3 (c) of its terms of reference (see informal document INF.39 (forty-third session)[8] and propose recommendations to the Sub-Committee on how to proceed. The Sub-Committee could then task the OECD with a specific request on how to fill any gaps;

(d) Report to the Sub-Committee at each plenary session on the progress made in the implementation on the current mandate. The first report should include a provisional timetable; and

(e) Engage with the PHI-IWG as questions arise and progress warrants.

6. As the language in the mandate to the OECD was interpreted in several ways by the members of the OECD ED ad hoc expert group, following the meeting on 17 October 2023, clarification was requested from the PHI-IWG on the tasks described in paragraph 12.a.i of the mandate and repeated above. Specifically, the OECD ED ad hoc expert group asked the PHI-IWG to clarify if they should be considering:

(a) The state of the science and gap analysis of the current GHS hazard classes regarding the possibility to adequately classify and label EDs under the GHS (i.e. catch the hazard); or

(b) The state of the science and gap analysis of the current GHS hazard classes regarding the possibility to adequately classify and label EDs and identify them as such under the GHS (i.e. catch the hazard and identify the substance as an ED)?

7. To further illustrate, the differences between these two approaches, the PHI-IWG was asked: *if a substance is identified as a reproductive toxicant, does it matter that it is identified as an ED?*.

8. The topic was discussed at the PHI-IWG teleconference on 7 November 2023, where the group clarified that the state of the science and gap analysis should evaluate if existing GHS hazard classes are adequate to classify and label EDs and identify them as such under the GHS (i.e. identify adverse effects as a hazard **and** identify the substance as an ED). This clarification was communicated to the OECD ED ad hoc group by the OECD Secretariat and the co-chair of the PHI-IWG at the teleconference on 13 November 2023.

9. The clarification of the mandate was particularly critical for how the OECD ED ad hoc group approached the work, because identifying an endocrine disrupter under the GHS as such using the WHO/IPCS definition requires that the substance or mixture: (i) alters the function of the endocrine system [through an endocrine mechanism] and (ii) consequently causes an adverse effect in an intact organism or population.

10. Having clarified the mandate, the scope of the work to address the mandate was defined. The aspects listed below were of interest to members of the OECD ED ad hoc group, but due to limited resources, were agreed to be left outside of the initial scope of work:

(a) Non-Monotonic Dose-Responses including essentiality, immunotoxicity, neurotoxicity, and difficult to assess chemicals, and invertebrates will not be included in the state of the science review. It was noted that these aspects are relevant to endocrine disruption, but the timeframe of the work does not allow sufficient time to address them;

(b) the state of the science will not be based on a systematic literature review given the limited time provided to OECD. However, if more robust and science-based reviews are

[7] https://wedocs.unep.org/bitstream/handle/20.500.11822/25636/edc_report3.pdf.
[8] https://unece.org/sites/default/files/2022-12/ST-SG-AC10-C4-86e_0.pdf.

needed, it should be communicated by the PHI-IWG to OECD and the timeline and financial resources to address the mandate should be reconsidered, via a written mandate;

(c) the focus of the group is not to call for new tools or data generation, but to assess the possibilities to identify substances as EDs under the GHS following the WHO/IPCS definition and on current scientific knowledge and available test methods; and

(d) the ad hoc group will not make policy decisions. The recommendations and options proposed by the OECD ED ad hoc group, once they are completed, will be considered by the PHI -IWG and the Sub-Committee.[9]

III. Implementation of the mandate

11. The ad hoc group met via teleconference twelve times between September 2023 and September 2024.

12. The main points discussed during these meetings are presented below. The OECD Secretariat transcribed the main points of each meeting with the chairs and posted the summary record on the OECD community website.

Meeting number	*Date*	*Points discussed*
1	22 Sept. 2023	Discussion of mandate and timeline for work
2	17 Oct. 2023	Review of existing GHS hazard classes; Summary of 2020 European Union ED fitness check
3	30 Oct. 2023	Examples of ED assessments: United States of America , Canada
4	13 Nov. 2023	Clarification of the mandate from the PHI-IWG; agreement by the OECD ED ad hoc group on gaps
5	9 Jan. 2024	Examples of ED assessments: European Food Safety Authority (EFSA)
6	1 Feb. 2024	Examples of ED assessments: European Chemicals Agency (ECHA)
7	10 Apr. 2024	Approach/scope for HH EATS/Non-EATS literature review
8	22 May 2024	Approach/scope for ENV EATS/Non-EATS literature review
9	19 June 2024	Interim overview of HH and ENV literature searches and approach for gathering input
10	11 July 2024	Summary of discussion at the forty-sixth session of the Sub-Committee; Reaffirmation of PHI-IWG clarification of mandate from November 2023; discussion of request for feedback of HH literature review
11	22 Aug. 2024	Responses to state of the science for methods
12	13 Sept. 2024	Discussion of the report to the Sub-Committee for the forty-seventh session

13. The highlights and summary messages from the teleconferences are listed below:

(a) Experts were asked to provide a list of key references to support the identification of ED effects in current chemical legislation frameworks, potential gaps in the

[9] As detailed in paragraph 6 of the mandate to OECD (ST/SG/AC.10/C.4/2023/6).

GHS hazard classes, and to contribute to the state of the science on methods to address the gaps;

(b) The ED ad hoc group reviewed the OECD Conceptual Framework for evaluating EDs and agreed that this approach was helpful for organising the state of the science review; and

(c) The hazard classes likely to be relevant to EDs were summarized and presented to the group (carcinogenicity, reproductive toxicity, target organ systemic toxicity, aquatic toxicity). Some options how to address the hazards of EDs in the current GHS were briefly discussed (e.g. modifying the wording of existing hazard classes, creating a new ED hazard class, modifying annex 11 of the GHS).

14. Given the clarification of the mandate as described above, the group agreed that there is generally a gap in the GHS hazard classes regarding the ability to identify EDs as such, according to the IPCS/WHO definition. In particular, the group acknowledged that the hazard definitions are silent on the inclusion of mechanistic data as part of the identification of most hazards (mutagenicity is an exception), which is considered to be a gap in the current ability to identify chemicals as ED under the GHS according to the IPCS/WHO definition.

15. The next step was to proceed with a targeted literature review to identify ED-relevant methods and provide input on the suitability of methods for classifying and labelling EDs under the GHS. Whereas the EATS pathways and their related adverse effects are well known and limited, the group discussed what should be included for the non-EATS pathways:

> It was agreed to focus the HH literature review on non-EATS modalities where most knowledge exists and where endocrine pathways are known to have a human health impact. Furthermore, the methods identified in the literature review were grouped according to the endocrine pathways addressed and the level of the OECD conceptual framework.

16. Similarly the group agreed to limit the ENV EATS and non-EATS modalities review to aquatic vertebrates (i.e., fish and amphibians), excluding invertebrates. Because less is understood regarding linkages between EDs and environmental hazards, the Adverse Outcome Pathway (AOP) framework was used to organise information, along with the level of the OECD conceptual framework addressed by each method.

IV. State of the science and available methods for identifying endocrine disrupters

17. It should be noted that, due to time limitation, the review of the state of the science of methods to address EDs under the GHS was not a systematic literature review. The review was conducted by two consultants for the disciplines of human health (Karolinska Institute, Sweden) and for the environment (the Norwegian Institute for Water Research). These consultants provided a report of the review to the OECD ED ad hoc group. In addition, following the WHO/IPCS (2002) definition of an ED, the literature search was focused on mechanistic methods measuring endocrine activity (alteration of the endocrine system function) and methods measuring adverse effects. Due to the short timeline available, there was a limited focus on approaches that can help to establish causal links between mechanism and adversity. The review also focused on identifying relevant methods developed and validated after the 2018 revision of OECD Guidance Document 150 on “Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption”[10], as well as methods in the pipeline for validation. If systematic literature reviews are needed to inform the PHI-IWG, the initial timeline and available financial resources should be reconsidered to provide a more in-depth review of the state of the science of methods to address gaps, particularly for non-EATS modalities.

[10] https://www.oecd.org/en/publications/guidance-document-on-standardised-test-guidelines-for-evaluating-chemicals-for-endocrine-disruption-2nd-edition_9789264304741-en.html.

V. Human health

18. The review on methods to address gaps for identification of human health EDs targeted existing reviews articles in scientific literature and reports from the OECD and the European Commission, as well as standardized test guidelines (TGs) relevant for human health, the European Union reference laboratory for alternatives to animal testing (EURL ECVAM) tracking system for alternative methods towards regulatory acceptance (TSAR), the public-private platform for the validation of methods for the characterization of endocrine disrupters (PEPPER), and assays available in the CompTox (ToxCast) database of the United States of America Environmental Protection Agency (US EPA). In addition, methods and models not yet validated from the projects included in the European Cluster to Improve Identification of Endocrine Disrupters (EURION) were considered.

19. Regarding methods to address non-EATS adverse health effects covered by the state of the science review, the focus was on the following health effects considered to be of high relevance for public health and for which there is some general knowledge about links with the non-EATS endocrine pathways of interest:

(a) Metabolic syndrome, including hypertension, obesity, dyslipidemia, insulin resistance, diabetes mellitus and non-alcoholic fatty liver disease;

(b) Female reproductive health effects (polycystic ovary syndrome - PCOS, endometriosis);

(c) Cardiovascular disease (CVD), including thrombosis;

(d) Bone metabolism; and

(e) Effects on development, including skeletal development and developmental neurotoxicity.

20. For the purpose of the review of methods, each health effect cluster was further broken down into specific (adverse) health effects and measurable parameters on the organism and organ/tissue levels. This methods identified in the review will be included in a future OECD document.

21. The feedback from the ED ad hoc group to the state of the science review of methods to address gaps in the identification and classification of EDs for human health was captured using a survey. Fourteen out of twenty-nine organisations replied to the survey questions (four European Union Member Countries, United Kingdom and Switzerland), six industry representatives, two NGOs). There were contradicting views on the possibility to identify substances with endocrine disrupting properties under the GHS, based on the state of the science. Some respondents indicated EDs can be identified (EATS (eight - authorities from four European Union Member States, United Kingdom, Switzerland and two NGOs)), and some non-EATS (five – authorities from four European member states and one NGO), though additional (validated) methods would increase the possibility of identifying Eds. Other respondents (six – industry representatives) indicated current science does not allow ED identification. Some organisations expressed their concerns about potential biases or misinterpretation of the survey outcomes, and thus did not answer it, or did only partially .

22. The main conclusions of the ED ad hoc group relative to the state of the science are summarised below:

(a) EATS:

(i) The group generally agreed that EATS pathways have a number of adequate and validated methods.

(ii) Several members noted the need for additional methods to be developed and/or validated for the thyroid (T) and steroidogenesis (S) pathway.

(iii) The group agreed that additional methods were not needed for the estrogen (E) pathway.

(b) Non-EATS:

(i) Several members noted the need for additional research, method development (for both mechanistic and adverse effects), and validation of methods (for both mechanistic and adverse effects) for all non-EATS.

(ii) Requirements for more research was particularly noted for non-EATS modalities linked to metabolic syndrome, cardiovascular disease, and bone metabolism.

(iii) Several members mentioned the difficulty to establish causal links between alteration of function(s) of the endocrine system (endocrine activity) and adverse effects, as required by the IPCS/WHO 2002 definition.

(iv) Several members mentioned the need to develop a definition of "non-EATS" EDs under the GHS to help define what is in scope for non-EATS endocrine modalities. Several members of the group mentioned that such a definition was not needed.

23. Other comments were made which are not specific to endocrine disruption, such as:

(a) The need to consider species difference/human relevance when evaluating chemicals; and

(b) Available methods may not be applicable to certain types of chemicals, such as metals.

24. Despite the clarification of the OECD mandate by the PHI-IWG that gap analysis and state of the science of methods to address any identified gaps should evaluate if existing GHS hazard classes are adequate to classify and label EDs and identify them as such under the GHS (i.e. identify adverse effects as a hazard and identify the substance as an ED), a few members of the group would like to analyse if known EDs are captured by the existing GHS hazard classes. However, several members disagree with this request because based on the clarification of the scope by the PHI-IWG, the absence of mention of mechanistic data in the GHS hazard definitions is a clear gap with regard to identifying an ED as such according to the IPCS/WHO definition. In addition, the need and appropriateness of adding a potential new hazard class to identify EDs is beyond the scope of the current mandate, and would need to be considered by the PHI-IWG.

VI. Next steps and timeline

25. In the next months (September to December 2024), the work of the ad hoc group will focus on discussing the available methods and their suitability to identify EDs under the GHS in the aquatic environment, as well as the fitness of the IPCS/WHO definition to identify and label EDs under GHS. An update on the discussion on these topics will be provided to the Sub-Committee at its forty-seventh session in an informal document.