

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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Programme of work for the biennium 2023-2024

Addendum to ST/SG/AC.10/C.4/2022/18 - unaddressed hazards: endocrine disruptors

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1. This document provides complementary information on endocrine disrupting properties in support of the proposal for new work on unaddressed hazard classes in the programme of work for the biennium 2023-2024. The new work item would initially cover the following hazards: endocrine disruptors (ED) for human health and the environment; persistent, bioaccumulative, toxic (PBT), very persistent, very bioaccumulative (vPvB); persistent, mobile, toxic (PMT) and very persistent, very mobile (vPvM) substances¹.

Background

2. Over the last 30 years, the endocrine disrupting properties of chemicals have been the focus of increasing scientific research, and the accumulated knowledge identifies EDs as a concern to public and wildlife health². The high and increasing incidence of many endocrine-related disorders in humans³ have important parallels in some wildlife populations. Evidence on the roles played in the disease outcomes by environmental and other non-genetic factors, including chemical exposure, is growing. Despite some links having become apparent⁴, more research is necessary on the associations between EDs and other endocrine-related diseases⁵.

3. The interaction between EDs and other environmental stressors is also under investigation, with some research pointing to potential emerging problems⁶. Importantly, only a small proportion of the chemicals on the market have been tested for endocrine effects and the disease risk due to exposure to EDs may be significantly underestimated⁷. Shaffer *et al.* (2019) identifies EDs as a high priority class of environmental health risk factors for inclusion in the future iterations of the Global Burden of Disease (GBD) study⁸.

¹ ST/SG/AC.10/C.4/2022/18 <https://unece.org/info/Transport/Dangerous-Goods/events/368936>

² WHO/UNEP, 2013. [State of the Science of Endocrine Disrupting Chemicals](#); Vandenberg, L. N. and Turgeon, J. L., 2021. Endocrine-Disrupting Chemicals. *Advances in Pharmacology*, 92.

³ Such as asthma, birth defects, neurodevelopmental disorders, cancer, diabetes and obesity in children and cardiovascular diseases, cancer, diabetes and obesity, allergic and autoimmune diseases in adults.

⁴ E.g. polychlorinated biphenyls' exposure as a risk factor in breast and prostate cancers; relationships between perfluoroalkyl substances and child and adult obesity, impaired glucose tolerance, gestational diabetes, reduced birthweight, reduced semen quality, polycystic ovarian syndrome, endometriosis, and breast cancer.

⁵ WHO/UNEP, 2013; Kahn, L. G. *et al.*, 2020. [Endocrine-disrupting chemicals: implications for human health](#). *The Lancet. Diabetes & endocrinology*, 8(8), 703–718.

⁶ For example, the negative impact on fish populations of the synergetic action of increasing water temperatures due to climate warming and endocrine disruption from plastic pollution has been reported in Wu *et al.*, 2022.

⁷ WHO/UNEP, 2013. [State of the Science of Endocrine Disrupting Chemicals - IPCP-2012](#).

⁸ Shaffer, R. M. *et al.*, 2019. [Improving and Expanding Estimates of the Global Burden of Disease Due to Environmental Health Risk Factors](#). *Environmental Health Perspectives* 127(10).

4. The literature concludes that EDs can mimic or interfere with the body's endocrine system, and associated effects include impacts on male and female reproduction, breast development and cancer, prostate cancer, neuroendocrinology, thyroid, metabolism and obesity, and cardiovascular endocrinology⁹. Vulnerable groups, such as young children, are particularly affected by exposure to EDs, which can have life-long impacts and exhibit in adulthood. Rijk et al. (2016) identified more than 80 different health endpoints which have been potentially associated with exposure to EDs¹⁰.
5. As substances and mixtures with ED properties are currently not systematically identified and classified, these properties are not communicated to downstream users, limiting downstream users' ability to make informed purchase choices and to adopt suitable risk management measures. The lack of identification criteria may also result in the failure to define risk management provisions in downstream legislation referring to hazard classification.
6. Moreover, the hazard of substances suspected of having ED properties may be assessed multiple times according to different regulations in different jurisdictions¹¹, contributing to the inefficient use of limited resources that would be solved by global harmonization of the criteria.
7. Although it is not possible to fully quantify the impact on human health and on the environment of chemicals with the most critical hazards, there is already knowledge that exposure to certain EDs is associated with intelligence quotient loss and intellectual deficiencies with a probability of causation of 70% to 100%, with moderate to high strength of human evidence. EDs are also suspected to cause male infertility, obesity, diabetes, and other health issues with varying probabilities of causation and strength of human evidence¹². The reduction of the costs resulting from identification of EDs for the public health services cannot be fully expressed in monetary terms. However, the impact assessment on the introduction of new hazard classes in the European Union¹³ estimated that preventing 0.62-0.4.97 cases per substance per year would offset the costs to industry triggered by the new hazard classes for EDs¹⁴.
8. A reduction of the emissions of ED substances into the environment would also decrease the costs of depolluting urban wastewater from micro-pollutants, which currently equal €1.2 billion per year in the European Union¹⁵.
9. Studies show that taking the lead in implementing ambitious environmental policies can lead to small, statistically significant adverse effects on trade, employment, plant location, and productivity in the short run, particularly in pollution- and energy-intensive sectors. However, the scale of these impacts is small compared with other determinants of trade and investment location choices such as transport costs, proximity to demand, quality of local workers, availability of raw materials, sunk capital costs, and agglomeration¹⁶.

⁹ <https://www.niehs.nih.gov/health/topics/agents/endocrine/index.cfm>

¹⁰ Rijk, I. *et al.*, 2016. [Health cost that may be associated with Endocrine Disrupting Chemicals — An inventory, evaluation and way forward to assess the potential health impact of EDC-associated health effects in the EU](#), Institute for Risk Assessment Sciences, University of Utrecht.

¹¹ For example, Endocrine Disruptor Screening Program in the framework of the Safe Drinking Water Act in the United States of America; or the EXTEND (Extended Tasks on Endocrine Disruption) 2010 and the [Japan's Chemical Substance Control Law](#).

¹² Kahn, L. G. *et al.*, 2020. [Endocrine-disrupting chemicals: implications for human health](#). *The Lancet. Diabetes & endocrinology*, 8(8), 703–718.

¹³ Impact assessments are carried out during the preparation phase of European Union legislation, before the European Commission finalises a proposal for a new law. They provide evidence to inform and support the decision-making process. They examine whether there is a need for European Union action and analyse the possible impacts of available solutions.

¹⁴ European Commission, 2022. [Impact assessment for the revision of the CLP Regulation](#).

¹⁵ *Idem*.

¹⁶ *Idem*.

10. While many EDs may result in adverse effects on reproductive toxicity, not all adverse effects of EDs — for example the effects of obesogens — can be identified within the current existing hazard classes as GHS focuses on adverse effects¹⁷.

11. Furthermore, several Sustainable Development Goals (SDG) are linked to unaddressed hazard classes such as EDs:

(a) SDG #3 Good health and well-being – Target 3.9 “By 2030, substantially reduce the number of deaths and illnesses from hazardous chemicals and air, water and soil pollution and contamination”. The inclusion of unaddressed hazard classes on EDs will contribute to this goal by better protecting human health.

(b) SDG #6 Clean water and sanitation – Target 6.3 “By 2030, improve water quality by reducing pollution, eliminating dumping and minimizing release of hazardous chemicals and materials, halving the proportion of untreated wastewater and substantially increasing recycling and safe reuse globally”.

(c) SDG #9 Industry, innovation and infrastructure – Target 9.4 “By 2030, upgrade infrastructure and retrofit industries to make them sustainable, with increased resource-use efficiency and greater adoption of clean and environmentally sound technologies and industrial processes, with all countries taking action in accordance with their respective capabilities”: the unaddressed hazard classes will help in the identification of sustainable alternatives.

(d) SDG #12 Responsible consumption and production – Target 12.4 “By 2020, achieve the environmentally sound management of chemicals and all waste throughout their life cycle, in accordance with agreed international frameworks, and significantly reduce their release to air, water and soil in order to minimize their adverse impacts on human health and the environment”: the unaddressed hazard classes will have downstream consequences, which will in the end impact the full life cycle of these products.

12. It is therefore necessary to develop a new hazard class on EDs for human health and one on EDs for the environment. Acknowledging the consequence on Sub-Committee workload for the development of a hazard class on EDs for human health and one on EDs for environment – as expressed during the forty-second session of the Sub-Committee; the following section provides properties for the consideration by the experts developing them at global level for EDs.

Endocrine disruptors at the global level

13. The WHO definition of 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 (IPCS, 2002). Consequently, a classification as an endocrine disruptor requires evidence for an endocrine activity, an adverse effect in an intact organism or its offspring or future generations, as well as for a biologically plausible link between the endocrine activity and the adverse effect.

14. The growing focus on endocrine disrupting chemicals has resulted in the development of a wide range of testing methods, both *in vitro* and *in vivo*, that identify endocrine activity of a substance and detect adverse effects in an intact organism or its offspring that are linked to such endocrine activity, both in mammalian and non-mammalian species. A significant number of such methods have become internationally harmonised and agreed in the form of OECD test guidelines (see the annex to this document). Although the available ED criteria implement the generic nature of the WHO definition⁷, in practice mainly effects caused by oestrogen, androgen, thyroid, and steroidogenesis (EATS) modalities are currently identified. This is because the EATS modalities are currently the pathways for which there is a good mechanistic understanding of how substance-induced perturbations may lead to adverse

¹⁷ Only adverse effects triggered by endocrine activity are already covered by existing GHS hazard classes.

effects via an endocrine-disrupting Mode of Action (MoA). In addition, only for the EATS modalities there are at present standardised test guidelines for *in vivo* and *in vitro* testing available where there is broad scientific agreement on the interpretation of the effects observed on the investigated parameters.

15. The OECD guidance document (GD) 150 on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption¹⁸ lists testing methods and parameters that are considered relevant when investigating the ED properties of substances. In addition, the OECD GD 150 provides guidance on how to interpret parameters relevant for identification of ED properties measured in the standardised test guidelines with respect to EATS modalities. It includes the “OECD Conceptual Framework (OECD CF) for Testing and Assessment of Endocrine Disrupters”, which groups the available studies into five levels according to the kind of information provided.

Endocrine disruptors at the European Union level

16. The European Union has criteria in place to identify EDs under its legislation for biocides¹⁹ and plant protection products²⁰ since 2017 and 2018, respectively. A joint guidance by the European Chemicals Agency (ECHA) and the European Food Safety Authority (EFSA), which describes how to gather, evaluate and consider all relevant information for the assessment, and apply a weight of evidence (WoE) approach, in order to establish whether the ED criteria are fulfilled, is available²¹.

17. The identification of endocrine disruptors follows a stepwise approach. Adverse effects of a chemical are identified, as well as its endocrine activity according to available relevant and acceptable data. Then the endocrine disrupter assessment explores the plausibility of a biological link between the endocrine activity and the adverse effects. Mechanistic information, such as toxicokinetics data, informs on such a link or a possible endocrine mode of action. This mode of action analysis is similar to what one assesses for carcinogens (see GHS 3.6.2.5.2. (k)) and reprotoxicants (see GHS 3.7.2.3.2. and 3.7.2.4.1.).

18. The European Union is currently developing classification criteria for endocrine disruptors for human health (ED HH 1 and ED HH 2) and for the environment (ED ENV 1 and ED ENV 2). Once adopted at European Union level, such classification criteria will be submitted for information to the Sub-Committee developing the criteria in the GHS.

Conclusion

19. Experts are invited to take note of the elements supporting the addition of endocrine disruptors as an unaddressed hazard class in the GHS Sub-Committee programme of work for 2023-2024.

¹⁸ OECD (2018), [Revised Guidance Document 150 on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption](#), OECD Series on Testing and Assessment, OECD Publishing, Paris.;

¹⁹ Commission Delegated Regulation (EU) 2017/2100 of 4 September 2017 [setting out scientific criteria for the determination of endocrine-disrupting properties pursuant to Regulation \(EU\) No 528/2012 of the European Parliament and Council](#). OJ L 301, 17.11.2017, p. 1–5. Available online:

²⁰ Commission Regulation (EU) 2018/605 of 19 April 2018 [setting out scientific criteria for the determination of endocrine disrupting and amending Annex II to Regulation \(EC\) 1107/2009](#). OJ L 101, 20.4.2018, p. 33–36.

²¹ ECHA, EFSA (2018). [Guidance for the identification of endocrine disruptors in the context of Regulations \(EU\) No 528/2012 and \(EC\) No 1107/2009](#). EFSA Journal 16(6):5311

Annex

Available OECD test guidelines

1. The following existing in vitro or in vivo OECD TGs measure parameters that provide mechanistic information on endocrine activity:

- (a) OECD TG 455 [Stably Transfected Human Estrogen Receptor-alpha Transcriptional Activation Assay to detect Estrogen Receptor Agonists and Antagonists](#)
- (b) OECD TG 458 [Stably Transfected Human Androgen Receptor Transcriptional Activation Assay for Detection of Androgenic Agonist and Antagonist Activity of Chemicals](#)
- (c) OECD TG 456 [H295R Steroidogenesis Assay](#)
- (d) OECD TG 493 [Human Recombinant Estrogen Receptor \(hrER\) In Vitro Assays to Detect Chemicals with ER Binding Affinity](#)
- (e) OECD TG 440 [Uterotrophic Bioassay in Rodents. A short-term screening test for oestrogenic properties](#)
- (f) OECD TG 441 [Hershberger Bioassay in Rats. A short-term Screening Assay for \(Anti\)Androgenic Properties](#)
- (g) OECD TG 229 [Fish Short Term Reproduction Assay](#)
- (h) OECD TG 231 [Amphibian Metamorphosis Assay](#)
- (i) OECD TG 230 [21-Day Fish Assay](#)
- (j) OECD TG 248 [Xenopus Eleutheroembryonic Thyroid Assay \(XETA\)](#)
- (k) OECD TG 250 [EASZY assay - Detection of Endocrine Active Substances, Acting Through Estrogen Receptors, Using Transgenic tg\(cyp19a1b:GFP\) Zebrafish embrYos](#)
- (l) OECD TG 251 [Rapid Androgen Disruption Activity Reporter \(RADAR\) Assay](#)

2. The following in vivo tests measure parameters that may contribute to the evaluation of adversity in mammalian or non-mammalian species and that are considered indicative of an EATS Mode of Action. Several of the TG for mammalian toxicity have been revised in recent years to include additional test parameters that are relevant for the detection of endocrine disruption:

- (a) OECD TG 407 [Repeated Dose 28-day Oral Toxicity Study in Rodents](#)
- (b) OECD TG 408 [Repeated dose 90-day Oral toxicity Study in Rodents](#)
- (c) OECD TG 414 [Prenatal Developmental Toxicity Study](#)
- (d) OECD TG 451 [Carcinogenicity Studies](#)
- (e) OECD TG 452 [Chronic Toxicity Studies](#)
- (f) OECD TG 453 [Combined Chronic Toxicity/Carcinogenicity Studies](#)
- (g) OECD TG 416 [Two-Generation Reproduction Toxicity Study](#)
- (h) OECD TG 421 [Reproduction/Developmental Toxicity Screening Test](#)
- (i) OECD TG 422 [Combined Repeated Dose Toxicity Study with the Reproduction/ Developmental Toxicity Screening Test](#)
- (j) OECD TG 443 [Extended One-Generation Reproductive Toxicity Study](#)
- (k) OECD TG 426 [Developmental Neurotoxicity Study](#)

- (l) OECD TG 410 [Repeated Dose Dermal Toxicity: 21/28-day Study](#)
 - (m) OECD TG 411 [Subchronic dermal toxicity: 90-day study](#)
 - (n) OECD TG 412 [28-Day \(Subacute\) Inhalation Toxicity Study](#)
 - (o) OECD TG 413 [Subchronic inhalation toxicity: 90-day study](#)
 - (p) OECD TG 409 [Repeated dose 90-day oral toxicity study in non-rodents](#)
 - (q) OECD TG 234 [Fish Sexual Development Test](#)
 - (r) OECD TG 241 [Larval Amphibian Growth and Development Assay \(LAGDA\)](#)
 - (s) OECD TG 210 [Fish early-life stage \(FELS\) toxicity test](#)
 - (t) OECD TG 240 [Medaka Extended One-Generation Reproduction Test \(MEOGRT\)](#)
 - (u) OECD TG 206 [Avian reproduction test.](#)
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