SUMMARY REPORT OF THE 28th ENDOCRINE DISPUTOR EXPERT GROUP MEETING

The 28th ED EG meeting took place on 14 and 15 May 2024. The EG provided scientific advice on ED assessments of one REACH substance, three biocidal substances, one CLH substance and one CLH group of substances.

The meeting was attended by 100 participants representing 18 Member States and EEA countries (AT, BE, CZ, DE, DK, ES, FI, FR, IE, IT, LT, NL, NO, PL, PT, SE, SI, SK), Switzerland, EFSA, the European Commission and six accredited stakeholder organisations (CHEM Trust, Cefic, Concawe, CropLife Europe, Health and Environment Alliance, PETA Science Consortium International e.V.).

Main outcomes of the substance discussions

Closed session

- DEAPA (3-aminopropyldiethylamine) (CLH): Regarding ED properties for human health (ED HH) many members thought that there are ED-mediated adverse effects and, despite some uncertainties, there was general support for an EAS-mode of action (MoA) which could be further specified. The members also suggested to explore a non-EATS MoA due to reduced potassium, and to further consider reliability of the ToxCast analysis, statistical significance of the observed effects, the similarity of the effects observed in several studies and the overall weight of evidence. Many members considered on the basis of available data that the substance may meet the criteria for classification as ED HH Cat 2. Regarding T-modality, a short discussion took place with advice to further refine the assessment. ED properties for the environment could be considered in the future based on the available mammalian data and their population relevance.

- Cypermethrin (α-cyano-3-phenoxybenzyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate) (biocidal active substance): The effects observed in the presented Fish Short-Term Reproduction Assay (FSTRA, OECD TG 229) were not considered sufficient to conclude on the ED MoA in fish, although it was considered well performed and showing clear effects on fecundity. The members remarked that additional *in vitro* and fish studies are available, including a Tier I Endocrine Disruptor Screening Program assessment from the US EPA which indicates potential for interaction with the androgen (anti-androgenic) pathway in mammals and fish. The members suggested to finalise the ED HH assessment and literature review first, as they may already provide sufficient information to conclude on ED ENV. If additional data still needs to be generated, the collected information should facilitate selection of the best approach for further investigations.

Open session

- Chlorfenapyr (4-bromo-2-(4-chlorophenyl)-1-ethoxymethyl-5-trifluoromethylpyrrole-3-carbonitrile) (biocidal active substance): The ED EG concurred with the previous advice of the biocides Working Group on Human Health (WG HH) that the thyroid (T) and estrogen (E) modalities have been sufficiently investigated and do not meet the criteria for concern. Additional assays requested by WG HH were presented: Steroidogenesis Assay (OECD TG 456), Aromatase Assay (US EPA OPPTS 890.1200) and Hershberger Bioassay in Rats (OECD TG 441).

The ED EG members requested more detailed information on the studies presented to draw definitive conclusions on the androgen (A) and steroidogenesis (S) modalities. Specifically, they asked for numerical data on organ weights and information on systemic toxicity, along with an explanation of the apparently inconsistent results observed: equivocal results in the Steroidogenesis Assay, positive results in the Aromatase Assay, and negative results in the Hershberger Bioassay. The ED EG agreed to proceed with a written consultation to further evaluate these findings. To address ED for non-target organisms (NTOs), chlorfenapyr has been assessed in the FSTRA and Xenopus Eleuthero Thyroid Assay (XETA). While no ED relevant effects were observed in either study, the members considered the concentrations tested too low and questioned the choice of the XETA. A written consultation will be launched to provide advice on the testing strategy to address the ED concerns for NTOs.

- Oxybenzone (REACH) (CoRAP): The substance was evaluated in 2014 under the substance evaluation process. The ED assessment presented included also data generated by the US National Toxicology Program and related to both human health and the environment. Regarding human health, there was general agreement that there is enough information on endocrine activity for the EAS modalities. A refinement of the assessment was suggested for adversity, in particular looking at the effects at different doses, life stages and based on the types of studies. There were also some suggestions on how to refine and present the MoA, considering the large data package and the data available on benzophenone-1 (BP-1), the main metabolite of oxybenzone (BP-3). It was noted that the highest sensitivity observed was *via* dermal exposure. With regard to the T modality, the majority of experts were of the opinion that a firm conclusion on the T modality was not possible. Regarding the environment, there was support that there is enough evidence for both endocrine activity and adversity for the EAS modalities and that this is enough for the ED identification without the need to further investigate the T modality. Overall, the experts supported that the substance could be classified as ED ENV Cat 1 and ED HH.

- Group of C4-C6 orthophthalates[1] (CLH): The presented ED assessment focused on seeking early advice from the ED EG on the scope and general approach for the CLH dossier on the group of C4-C6 ortho-phthalates. Regarding HH effects targeted in the analysis, there was support to the approach selected focusing on effects and MoA related to "phthalate syndrome" targeting anti-androgenicity. However, if the information on certain substances would be too scarce more modalities and adverse outcomes could be included. Steroidogenic and neurodevelopmental parameters were mentioned as potentially useful to consider. No clear consensus was expressed on the inclusion of the thyroid modality. The grouping approach proposed was considered acceptable, but the substances with benzyl moiety should be carefully checked to determine if there is supportive data available. Regarding monobutylphthalate (MBP), further publications may need to be looked at to have sufficient support for the read across. Regarding ENV parameters, ED EG agreed on the proposal to investigate a wide array of potential modalities, however, use of ENV behavioral parameters may be challenging. Regarding *in vitro* parameters, ED EG agreed that peroxisome proliferator-activated receptor γ (PPARγ) should be considered. No view was expressed about the need to address AhR.

[1] Mono- and di-phthalate esters with linear and/or branched alkyl moieties with at least one longest continuous carbon chain counted from the ester function corresponding to C4-C6 and/or with C6 cyclic saturated carbon chains and/or with unsaturated hydrocarbyl moieties

- IPBC (3-iodo-2-propynyl butylcarbamate) (biocidal active substance): An Amphibian Metamorphosis Assay (AMA) was submitted to the competent authority for the biocide IPBC in order to address the T-modality for non-target organisms. While the study was well conducted and considered valid, the ED EG members agreed the test concentrations might have been too low to definitely conclude on the ED properties. At the tested concentrations, the AMA study did already show some decrease in developmental stage, Hind Limb Length, body weight and Snout Vent Length, all in the absence of general toxicity. Most experts agreed that these findings, especially in the absence of clear findings on thyroid histology, are not sufficient to already conclude that the substance is an ED. Several experts considered that IPBC already meets the ED criteria due to its degradation to iodine. However, ECHA clarified that according to the BPR, the degradation product iodine is in principle not assessed at the active substance level but rather assessed as part of the biocidal product assessment. The HH discussions on IPBC from ED EG 17 and 18 on T-modality were summarised, and the revised ED assessment according to the group's advice was presented, focusing on findings in studies on rats, mice and rabbits. The experts agreed that the rat is the preferred species for investigating thyroid effects and that the five rat studies presented showed no thyroid effects. In addition, there was no evidence of effects via other ED modalities. On this basis the ED EG advised that IPBC should not be considered an endocrine disruptor for HH.

General ED-related topics

The European Commission provided updates on the Commission roadmap towards phasing out animal testing for chemical safety assessment; developments in the Globally Harmonised System of Classification and Labelling of Chemicals regarding EDs; future United Nations Environment Program reporting on EDs; and on developments in ED evaluation under the biocides and pesticides regulations. ECHA provided further information on ED assessment in the biocides process and on development of the CLH Guidance relating to EDs.

Substances discussed at the 28th ED EG meeting:

MS	EC#	Substance name	Outcome of the discussion	Session	Notes
AT	203-236-4	3-aminopropyldiethylamine (DEAPA)	HH: ED Cat 2 ENV: Refine assessment	Closed	CLH
BE	257-842-9	a-cyano-3-phenoxybenzyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate (Cypermethrin)	Refine assessment	Closed	Biocidal active substance
PT	602-782-4	4-bromo-2-(4-chlorophenyl)-1-ethoxymethyl-5-trifluoromethylpyrrole-3-carbonitrile (Chlorfenapyr)	HH: Refine assessment ENV: Testing needed	Open	Biocidal active substance
DK	205-031-5	Oxybenzone / benzophenone-3	ED HH ED ENV Cat 1	Open	CoRAP 2014
FR		The group of C4-C6 ortho-phthalates	Refine assessment	Open	CLH
DK	259-627-5	3-iodo-2-propynyl butylcarbamate (IPBC)	HH: Not ED ENV: Refine assessment	Open	Biocidal active substance

Written procedures between 27th and 28th meeting

MS	EC#	Substance Name	Notes
FR	939-505-4	Reaction mass of p-t-butylphenyldiphenyl phosphate and bis(p-t-butylphenyl) phenyl phosphate (tBuTPP)	CoRAP 2023
FI	259-978-4	3-(3-biphenyl-4-yl-1,2,3,4-tetrahydro-1-naphthyl)-4-hydroxycoumarin (difenacoum)	Biocidal active substance