Assessment of endocrine disruption (ED) properties of co-formulants in biocidal products – instructions for applicants

The UK has proposed the following instructions for applicants when preparing a dossier for submission, in order to assess the endocrine disrupting (ED) potential of each coformulant in a biocidal product. Members of the Coordination Group are invited to comment on the following way forward:

Background

Paragraph 23 of the EU Commission's guidance note on 'The Implementation of scientific criteria for the determination of endocrine-disrupting properties in the content of biocidal product authorisation' (CA-March18-Doc.7.3.b-final) states the following:

> "*Evaluating bodies have to decide whether there is a need to evaluate a specific non-active substance in detail and, if necessary, to ask additional information to the applicant for the appropriate assessment. This should only occur where there are indications that a non-active substance may have ED properties based on the existing knowledge and the available scientific information.*"

To address this requirement the UK CA has produced the following step-wise approach for a targeted determination of whether a non-active substance (AKA 'co-formulant') in a biocidal product is an ED or has "indications" of ED properties, starting with checking whether a decision has already been made within EU programmes of work (part A); if not moving to exclude from any further consideration co-formulants which are food/food stuff materials (part B); and, if necessary, moving on to check whether there is existing information suggesting an 'indication' of ED properties that may need to be further investigated (part C). A schematic representation of the step-wise approach is shown in Figure 1.

A. Checking EU Decisions on ED properties

1. Has the co-formulant been assessed and identified as an ED under Art 57(f) of REACH and included in the Candidate List of SVHCs (https://echa.europa.eu/candidate-list-table)?
   or
   Has the co-formulant been identified as an ED under the BPR (https://circabc.europa.eu/w/browse/e379dc27-a2cc-46c2-8fbb-46c89d84b73d) or PPPR (https://ec.europa.eu/food/sites/food/files/pesticides_ppp_app-proc_cfs_database-201501.xlsx), either when being considered as an active substance or a co-formulant?
   - If Yes, the co-formulant should be considered an ED and the legal consequences outlined in the BPR will apply.
   - If No, proceed to step 2.

B. Excluding from further assessment co-formulants which are food / foodstuff materials

2. Co-formulants which are defined as "food" under Article 2 of Regulation (EC) No 178/2002 do not require to be considered further as these are highly unlikely to possess endocrine disrupting properties.

C. Checking information on 'Indications' of ED properties

3. Has the co-formulant been assessed under REACH Substance Evaluation (https://echa.europa.eu/information-on-chemicals/evaluation/community-rolling-action-plan/corap-table) because of an initial concern about potential endocrine disruption?
   - If Yes, and the conclusion of the assessment was that the substance is not an ED
     - the co-formulant should NOT be considered an ED.
   - If Yes, and the conclusion of the assessment was that the substance is an ED
     - the co-formulant should be considered an ED and the legal consequences outlined in the BPR will apply.
   - If Yes, but a conclusion has not yet been agreed, authorisation can proceed with a post-authorisation condition to, if necessary, reconsider when the conclusion of the ED status has been agreed.
   - If No, proceed to Step 4.

4. Has the co-formulant been included in the EU priority list (any category) (http://ec.europa.eu/environment/chemicals/endocrine/documents/studies_en.htm); EASIS (https://easis.jrc.ec.europa.eu/veil) or the Public authorisation coordination tool (PACT) (https://echa.europa.eu/pact)?
   - If Yes, the product application should include a conclusion as to whether or not the co-formulant is considered to have ED properties, supported by; dedicated testing, read across, justification etc, as appropriate. If considered an ED, the legal consequences outlined in the BPR will apply.
   - If No, proceed to Step 5.

5. If a REACH registration dossier for the co-formulant is available (search co-formulant at https://echa.europa.eu/information-on-chemicals/registered-substances), does information contained within the dossier include data which may provide indications of ED properties of the co-formulant?
   - If Yes, and some positive indication of ED is evident, the product application should include a conclusion as to whether or not that co-formulant is considered to have ED properties. If considered an ED, the legal consequences outlined in the BPR will apply.
   - If Yes, and no concern is evident, proceed to Step 6.
   - If No, proceed to Step 6.

6. Has the co-formulant been considered as an ED or as having concerns over its potential for ED properties under review programmes of other internationally recognised (non-EU) organisations, e.g. World Health Organisation?
   - If Yes, and a concern has been identified, the product application should include a conclusion as to whether or not that co-formulant is considered to have ED properties. If considered an ED, the legal consequences outlined in the BPR will apply.
   - If Yes, and no concern has been identified, proceed to Step 7.
   - If No, proceed to Step 7.

7. Has the co-formulant been screened in either of the following US databases :
   a) USEPA EDSP21 Program (https://www.epa.gov/endocrine-disruption/endocrine-disruptor-screening-program-edsp-21st-century)?
   b) USEPA ToxCast Dashboard (https://www.epa.gov/chemical-research/toxcast-dashboard)?
   - If Yes, and a concern has been identified, the product application should include a conclusion as to whether or not that co-formulant is considered to have ED properties, supported by; dedicated testing, read across, justification etc, as appropriate. If considered an ED, the legal consequences outlined in the BPR will apply.
   - If Yes, and no concern has been identified, proceed to Step 8.
   - If No, proceed to Step 8.

8. a) Specifically in relation to human health, has the co-formulant been assigned (harmonised or self-) classification for reproductive toxicity; STOT-RE (May cause damage to the thyroid or pancreas or adrenals or other endocrine organs, through prolonged or repeated exposure); and/or classification for carcinogenicity under the CLP Regulation in the C&L inventory (https://echa.europa.eu/information-on-chemicals/cl-inventory-database) or in the accompanying Safety Data Sheet (SDS)?
   - If Yes, the product application should include a conclusion as to whether or not the Reprotoxic effects are endocrine-mediated, and therefore whether the co-formulant is considered to have ED properties, supported by dedicated testing, read across, justification, etc, as appropriate. If considered an ED, the legal consequences outlined in the BPR will apply.

   b) Specifically for non-target organisms, a literature search should be carried out to ensure that any current knowledge has been identified and considered. The literature search should encompass at least the last two years, and should include, at a minimum, the following search terms:

"chemical name" OR "IUPAC name" OR "CAS number" OR "EC number" OR "other known alternative nomenclature of the non-active substance" AND
"endocrine disruptor" OR "endocrin*" OR "hormon*" OR "estrogen*" OR "androgen*" OR "thyroid" OR "steroid*" AND
"ecotox*" OR "hazard" OR "environment" OR "wildlife" OR "vertebrat*" OR "fish" OR "amphib*" OR "bird*" OR "avian" OR "mammal*" OR "metamorph*" OR "repro*" OR "embryo*"
(* = Truncation symbol to ensure all wording including the indicated text are included, e.g. "ecotox*" will capture ecotoxicity, ecotoxicology, ecotoxicological)

Alternatively, the search terms for ecotoxicology as detailed in Appendix F of the *Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009* (EFSA Journal 2018;16(6):5311, Adopted 5 June 2018) may be applied, noting that this is more extensive and based on a full regulatory assessment of ED under those regulatory regimes. Likewise this appendix can also be used to help select and justify the literature databases to be searched.

A range of potentially relevant databases should be included in the literature search and all returns should be evaluated for their relevance and reliability to inform the ED assessment of the co-formulant in relation to non-target organisms. The process of the literature search and review should be transparently documented, and the results used to propose a conclusion on whether the co-formulant in a potential ED, which should be included in the submission to the eCA.

- If gathered literature evidence supports an overall judgement that the co-formulant is likely to possess endocrine-disrupting properties, it has to be considered as a Substance of Concern (SoC); other legal consequences, as outlined in the BPR (including document CA March 18-Doc.7.3.b final) must be applied.

  Further details on how to carry out can be found in EFSA (2011)[1]. It should be noted that this guidance is aimed at carrying out a literature review for all aspects of a pesticide active substance; however the search terms should be limited to those outlined above and publications only published in the last 2 years need be considered.

If the co-formulant in question has been considered through the steps above and has been deemed not to be an ED then it is reasonable to conclude that, based on existing knowledge and reasonably available scientific information, there are no indications that the co-formulant has ED potential.

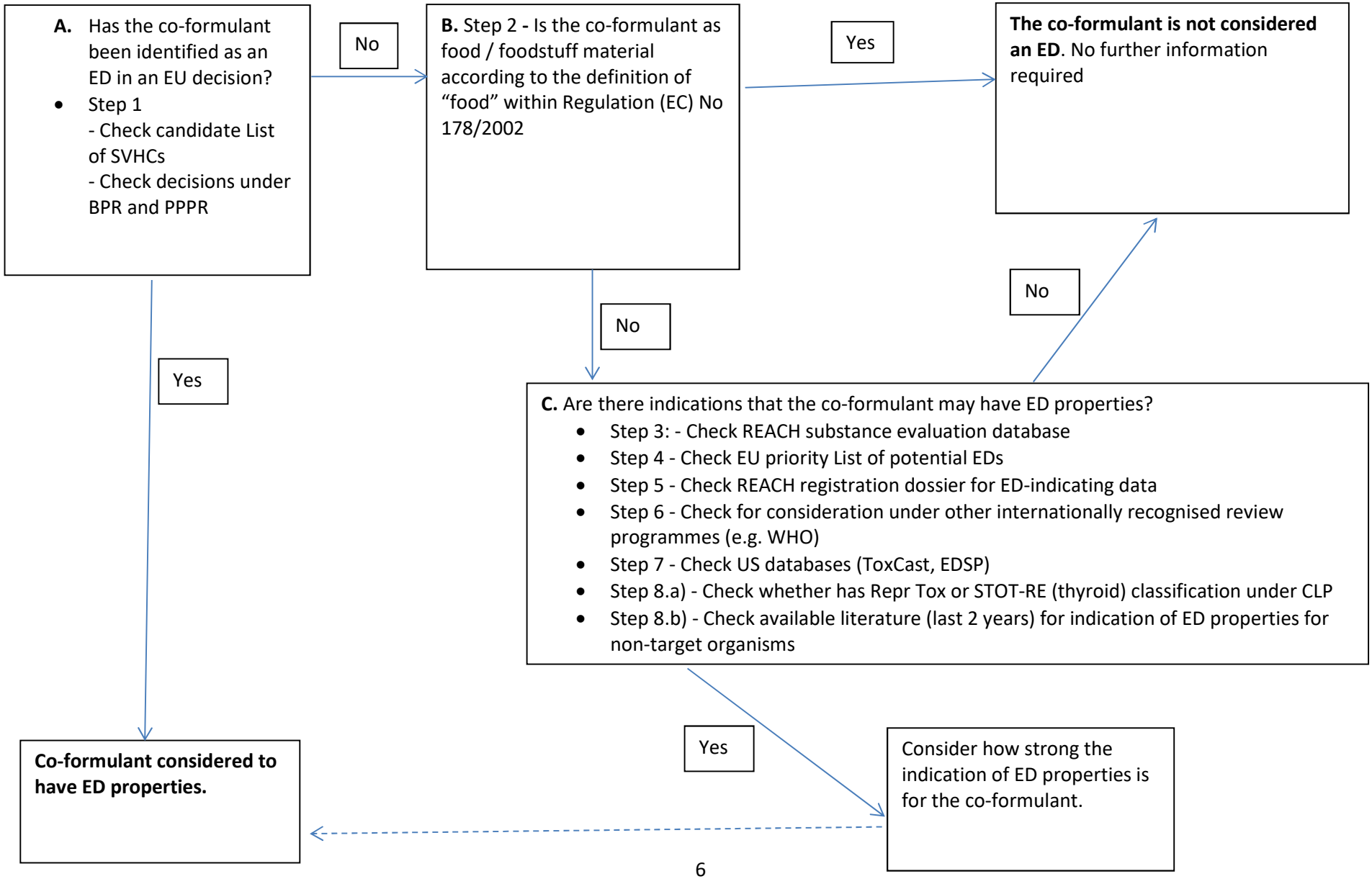
[1] European Food Safety Authority; Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (OJ L 309, 24.11.2009, p. 1-50). EFSA Journal 2011;9(2):2092. [49 pp.]. doi:10.2903/j.efsa.2011.2092. Available online: www.efsa.europa.eu

Summary

The Applicant should follow the steps above and document this for each co-formulant. A summary should be provided to explain how this supports the conclusion as to whether or not each co-formulant within a product is, or is not, considered to have ED properties. A template for reporting the outcome of the different steps for each co-formulant is presented in the Annex to this document.

When ED properties are identified for one or more co-formulants, it has to be considered as a SoC; other legal consequences, as outlined in the BPR (and more specifically in document CA March 18-Doc.7.3.b final), must be applied.

Figure 1 - Decision tree for assessing ED properties of co-formulants in biocidal products



Annex

Suggested reporting template for the assessment of endocrine disruption (ED) properties of co-formulants in biocidal products

Substance name	CAS number	Classification	Identified as ED in				Food/ food stuff?*	ED alert found in			
			BPR/ PPPR	REACH Substance Evaluation	CoRAP	EU priority list		USEPA EDSP21	USEPA ToxCast	REACH registration dossier	Other international review programme

* As defined under Regulation (EC) No 178/2002

12 March 2019