Breast Cancer UK comments on draft guidance for the identification of endocrine disruptors in the context of regulations (EU) No 528(2012) for biocidal products and (EC) No 1107/2009 for plant protection products

The European Chemicals Agency (ECHA) and European Food Safety Authority (EFSA) published draft guidance for the identification of Endocrine Disruptors (EDs) for public consultation. The guidance will directly impact regulatory risk assessment of pesticides and biocides. It is based on the 2002 definition of an ED, published by the WHO /IPCS, and describes how to gather, evaluate and consider all relevant information for assessment; how to conduct a mode-of-action analysis; and how to apply a weight-of-evidence approach, in order to determine whether ED criteria for a particular substance have been met. Breast Cancer UK's submitted response to the consultation is shown below

Submitted to EFSA/ECHA on January 31st 2018

General Comments

Breast Cancer UK is a charity which aims to prevent breast cancer by reducing public exposure to carcinogenic and other hazardous chemicals in the environment. We are concerned about the potential role of exposures to environmental chemicals such as endocrine disrupting chemicals, especially *in utero*, in increasing breast cancer risk. We welcome the opportunity to provide feedback on draft guidelines for the implementation of scientific criteria for determining endocrine disrupting properties for plant protection and biocidal products.

The guidance document is largely based on the WHO/IPCS definition of an endocrine disruptor (ED) which offers potential for the guidance to be applied more generally to EDs in products other than biocides and plant protection products. A general guidance document would be useful, as EDs are present in many other types of products covered by EU regulations (e.g. cosmetics). However, we believe this draft document has too narrow a focus for this purpose.

We welcome recognition that EDs may demonstrate a non-monotonic dose response, and the requirement that studies are carried out according to the latest version of the relevant test guidelines. However, Breast Cancer UK has a number of concerns with the proposed guidance.

Our main concern is that ED assessment is restricted to "EATS modalities". We are also concerned with the amount of evidence that will be necessary to link endocrine activity with adverse effects, and so demonstrate a substance is an ED. There seems to be a disproportionate emphasis on determining the "mode of action" of a substance, and a lack of recognition that certain substances will have multiple modes of action. The identification criteria, as applied to pesticides and biocide regulations, do not state the mode of action must be identified.

Restricting EDs to compounds that only affect oestrogens, androgens, thyroid hormones and steroidogenesis is inadequate, and will exclude many potential EDs. We suggest this should (at the very least) be extended to the full hypothalamus-pituitary-thyroid (HPT) axis. Although EDs mainly act on nuclear and non-nuclear steroid and thyroid receptors, they also act on serotonin, dopamine, adrenaline as well as orphan receptors (e.g. Santos-Silva et al. (2018). Molecular and Cellular

Endocrinology 460: 246-257). Although there may be no *in vitro* assays focusing on disruption of these hormones, the same is true for thyroid disruption, which isn't excluded from the modalities.

Specific comments

Section 2
Page 2, Lines 205-207 the document currently provides guidance on EDs with EATS modalities only. EDs can have many other modalities. These should be included in the guidance. If the guidance document only addresses EATs modalities the title should reflect this (guidance for identification of EDs with EATS modalities …) and a further guidance document would need to be generated.

Page 2, Lines 221-224: standardised tests described by OECD GD 150 should not be excluded, based on "lack of clear interpretation" resulting in lack of "firm conclusions". These statements are imprecise. Lines 221 -224 should be deleted from "However…..endocrine MoAs".

Page 2 Lines 232-234: Similarly, if the focus of this document is on vertebrates only, another guidance document focusing on non-vertebrates is needed

Section 3
Page 4, line 285. This states "all available scientific data must be considered". This emphasises the need for assessing EDs with non-EATS modalities

Page 6, lines 323-361. This grouping of parameters will exclude many EDs e.g. with properties relating to the hypothalamus/pituitary glands

Page 6, line 348. Insert an additional category "non-EATS mediated" Include parameters measured in non-EATS assays and experiments.

Page 9, Figure 1. Should be renamed "flow chart for assessment strategy for EDs with EATS-modalities

Page 12, lines 114-120. It is unclear why limit doses are specified. These sentences could be deleted.

Page 18, line 325-327. Acknowledgement of non-monotonic effects is welcome. Please insert "Furthermore, some EDs may act as hormone agonists or as antagonists, depending on their concentrations.

Page 28, Lines 424-427: This sentence suggests that if EATS mediated parameters are established then a MoA must be described. This is not a requirement of the criteria and means demonstrating a substance is an ED requires documenting its MoA. Line 425 should be changed from "a MoA analysis is required" to "would be useful, but is not essential"

Page 28: Line 449-450: Delete a MoA analysis "is required" and replace with 'would be useful".

Line 29, Line 468: Change "does not meet the ED criteria for humans and non-target organisms" to, "does not meet the ED criteria with EATS modalities for humans and non-target organisms

Page 29: Line 491: Replace "a MoA analysis is required' with "would be useful"

Page 30: Line 499 Replace "a MoA analysis is necessary" with "is useful"

Page 31 Line 526 Replace "a MoA analysis is necessary" with "a MoA analysis is recommended"

Page 32 Line 566-575 EDs often have multiple modes of action and analysing MoAs one at a time may not accurately reflect biological effects. It may be difficult to establish precise mechanisms for many reasons (multiple modes of action, timing of exposures, additive effects/interactions with other EDs etc). The final sentence of this paragraph "it may be necessary to undertake an analysis of each postulated MoA" should be deleted.

Page 33 Lines 587-591. This paragraph should be modified. If adversity is indicated by EATS-mediated parameters there shouldn't be a requirement to conduct further experiments to link adverse outcomes with postulated MoA. Change line 589 "further data must be generated by the applicant" to "further data may be required".

Page 42: Line 908-910: Delete sentence and change to the following: "If the link between the endocrine activity and the adverse effect(s) is not judged to be biologically plausible for any of the postulated MoAs, the substance is considered not to meet the ED criteria.

Page 42, Line 911 -912 Delete sentence. This guidance is focused on EATS modality and doesn't provide guidance for non-EATS endocrine MoA.

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