CHEMTrust
Protecting humans and wildlife from harmful chemicals

Consultation Response

Consultation on EU Guidance for the identification of Endocrine Disruptors

Comments from CHEM Trust

1 Introduction

The Pesticide (EC 1107/2009) and Biocide (EC 528/2012) Regulations include provisions that substances with endocrine disrupting properties for humans or non-target organisms should not be authorised. CHEM Trust has closely followed the debate on the development of the criteria for identifying endocrine disrupters (EDs). Two European Agencies – the European Food Safety Authority (EFSA) and the European Chemical Agency (ECHA) – and the Commission's Joint Research Centre (JRC) are in the process of drafting a guidance document for identifying endocrine disruptors under EU legislation for pesticides and biocides.

The Guidance Document was open for public consultation until the 31st of January 2018. https://comments.echa.europa.eu/comments_cms/PC_ED_Guidance.aspx

CHEM Trust submitted the following comments in order to improve the guidance document for a better identification of EDs.

2 General Comments (Section 1, Page 1, Line 1)

The Guidance has been improved in certain areas, and there are some parts in particular that we welcome, such as the recognition that if an old version of a test guideline has been used, it will not be sufficient to conclude `no ED properties`. For example, it is vital that lines 96-98 (page 12) are kept as these specify that all mandatory studies should be carried out according to the latest version of the corresponding test guideline. Similarly, for the identification of EDs in non- target organisms, lines 380 -384 (page 26) are important to keep.

Another good point is that lines 325-326 acknowledge non monotonic dose responses may occur. Lines 340-341 are also welcomed as they note that lack of a 'proper' dose response or lack of consistency between species and studies should not be taken to imply there is insufficient justification to conclude that a chemical is an ED as long as this can be justified.

However, CHEM Trust is very concerned about the high level of evidence required in this guidance document which will hinder rather than enable identification of EDs. Our main concerns are:

i) the level of detail that seems to be required for the mode of action (MoA) linking the endocrine activity with the adverse effects and;

ii) the way in which the Guidance proposes to deal with chemicals with multiple endocrine modes of action and;

iii) how false negatives can be avoided and what happens with inconclusive cases due to lack of data.

i) We therefore conclude that the requirement for an overly detailed knowledge of the MoA and key events (e.g. line 538-540; line 809-811) must be changed.

In CHEM Trust`s view it is neither legally required nor necessary to know the details of the steps (KIE/MoA analysis) to conclude whether or not the link is biologically plausible. Indeed, CHEM Trust maintains that if e.g. there seems to be some action on estrogen and/or androgen receptors, and the adverse effects are on reproductive organs which are sensitive to these hormones, then this should be sufficient to conclude that the link between the adverse effects and the endocrine activity is biologically plausible. Therefore, the guidance should make it much more clear, that a 'short-cut MoA analysis' can and should be applied, where possible. Otherwise the task of identifying EDs will fail.

By highlighting the data analysis necessary for an almost detailed knowledge of the mechanism of action, the Guidance seems to err too much on the side of avoiding false-positives, with no apparent recognition for the need to protect against false-negatives. What is needed to comply with the criteria is some confidence that the endocrine action is in some way linked with the adverse effects seen, rather than absolute proof, which will be elusive in many cases. Indeed, experts must be confident that the link is biologically plausible to avoid falsely identifying substances, but this should not be interpreted as requiring the mechanism of action to be known.

The criteria require biological plausibility as it states "using a weight of evidence approach, the link between the adverse effect(s) and the endocrine mode of action shall be established based on biological plausibility".

In some places the Guidance does acknowledge that detailed knowledge of KEs is not necessary. For example, lines 543-547 are good, but then followed by the requirement to describe at least one putative endocrine mediated MoA. Instead, the guidance should clarify that only a basic overview description of the plausible MoA (a short-cut MoA analysis) should be necessary. This is outlined to some extent in what is very good (paragraph 623-633 on page 34, which is essential to keep in the document. However, this concept of a short-cut MoA should become the starting point of the chapter 3.5 to avoid the impression that KE and KERs need to be known and understood in order to conclude a strong biological plausibility. It would be unrealistic to require the knowledge of KEs/KERs which can take many years to generate and meanwhile, an ED identification would be prevented. It needs to be recognised that the aim of the application of the ED criteria is to identify EDs in need of better regulatory control and not to generate more mode of action data.

ii) The Guidance needs to be changed to enable easier identification of ED substances acting via multiple MoAs. Lines 566-568 are good but then additional text as shown in our specific comments below is needed.

In practice, difficulties in concluding on an ED may arise in cases where there seems to be more than 1 endocrine activity, and the adverse effects seen are therefore not classically oestrogenic or anti-androgenic, but rather a hotch-potch of effects on reproductive organs that may be due to a mix of EATS. The Guidance therefore needs to make it clear that due to concomitant E, A and/or T activities and endocrine activity beyond EATS, interaction and convergence may occur resulting in a melee of adverse effects which are not solely related to one endocrine activity. In such cases the data should be able to be looked at together, rather than in all cases trying to analyse each activity in detail in isolation.

iii) The guidance need to ensure that false negatives are avoided and clarify the process for dealing with inconclusive cases due to lack of data.

The guidance seeks to largely avoid false positives, but not necessarily false negatives. There are ambiguities in the document as to what `sufficient data` means and what the consequences of missing data are: For example: Section 3.2.2.1 says that data from old versions of test guidelines cannot be used to rule out ED properties, which is important. Will these studies have to be redone? And will an updated EORGTS now be required? It will need to be clarified how the absence of data impacts on the ED identification and how applicants and regulators are supposed to follow up.

3 Specific comments

Section Glossary of terms, Page VIII, Line 144: References to Klimisch in the definition of relevance and reliability are not necessary, have been discussed controversially and should be removed. Better references to how reliability and relevance can be evaluated are available from SciRAP: http://www.scirap.org/

Section 2, Page 2: Line 192-196: Replace the text with the following 2 sentences: *This guidance should only be used in the contest of identifying ED pesticides and biocides as it is not suitable for other chemicals where less data will typically be available. Moreover, as in all European Union policy on the environment, decisions as to whether or not the criteria are met shall be based on the precautionary principle.*

Section 2, Page 2: Line 223 -224. Delete the sentence starting ´Consequently´ and replace as follows. *´Whether or not these assays and any additional available and relevant information can be the basis for concluding the EDC criteria are met, will depend on a case by case assessment and expert judgement.´*

Section 2, Page 2: Line 234: Add a sentence as follows. *´Nevertheless, all available information shall be considered and it will be for experts to decide whether it can be concluded that a substance is an ED for non-target invertebrates.´*

Section 3, Page 3: Line 277: Replace the words '*does not'* with 'is judged unlikely to'…

Section 3, Page 5: Line 314: Change the title of Table 1 to: ´Factors which MAY be considered in the weight of evidence assessment´. Moreover, please add the following sentence at the end in the 'human' box relating to quality and consistency of the data. *´However, it needs to be recognised that substances may act as agonists at certain doses and antagonists at others.´*

Section 3.1., Page 6: Line 348: The distinction between EATS mediated parameters and endpoints `potentially sensitive to, but not diagnostic of ´is scientifically questionable and unclear. Why is this suggested, can this separation really be made and is it helpful in the present context? Effects may well be due to endocrine disrupting properties, but mediated by glucocorticoid receptor, prolactin, oxytocin, etc. It would be good to give specific substances examples of why this distinction is useful for identifying EDs or otherwise refrain from using it.

Section 3.1., Page 6, Line 373: We propose to drop this differentiation in the assessment strategy: The distinction between "diagnostic endpoints" and endpoints that are "sensitive to, but not diagnostic of, EATS" seems arbitrary and scientific justification is missing. Instead, the guidance should state that any effect on an ED sensitive tissue should be considered diagnostic.

Section 3.1, Page 7: Line 381: Add a sentence as follows. *´Indeed, if the mammalian data are sufficient to conclude the criteria are met for humans, then the only additional consideration for mammals in the environment is whether the adverse effects will cause a (sub) population level effect. ´*

Section 3.1, Page 9, Line Figure 1: Please revise the flowchart and ensure that there is no difference in how guidelines studies and data from the scientific literature are reviewed and assessed. Please also remove the reference to EATS modalities so that it is clear that the identification is always based on all relevant and available data.

Section 3.2.2, Page 11, Line 80: delete "preferably standardized methodology" and replace with 'the methodology used'.

Section 3.2.2.1, Page 12, Lines 96-98: This is an important clarification which should remain in the text.

Section 3.2.2.1, Page 13, Lines 147: Please include references to recently developed systematic and transparent framework for assessing reliability and relevance of data, e.g. the

SYRINA framework for assessing EDs.
https://ehjournal.biomedcentral.com/articles/10.1186/s12940-016-0156-6

Section 3.3.3., Page 18: Lines 320 – 324: This paragraph describes moving beyond hazard identification and introduces elements of hazard characterisation (dose-response). This is neither appropriate nor helpful for this guidance and therefore we propose to delete it.

Section 3.3.3., Page 18, Lines 340-341: This is an important clarification which should remain in the text.

Section 3.4, Page 26: Lines 380-384: This is an important clarification which should remain in the text.

Section 3.4, Page 26, Line 401 (Table 4): This table leads to many more questions than answers and should be revised, taking our following comments on the scenarios into consideration.

Section 3.4.1, Page 28: Line 425: We disagree that a MoA analysis is required to establish the biological plausibility of the link between EATS adversity and endocrine activity. It is neither foreseen in the pesticides/biocides laws nor in the ED criteria and scientifically unrealistic to demand generation of these data. We suggest to change the sentence to: *When adversity is observed based on EATS mediated parameters, it needs to be established whether the adverse effect and endocrine activity and are biologically plausibly linked.*

Section 3.4.2, Page 28: Line 441: Add a sentence as follows. *If data are insufficient to conclude but there are data indicating EATS activity, such as in vitro studies or QSARs etc, then up to date higher tier studies must be undertaken as specified in lines 96-98, p12.*

Section 3.4.2, Page 28: Line 449: Replace 'a MoA analysis is required' by '*a description for the proposed link between adverse effect and endocrine activity should be formulated in line with the legal ED criteria.*

Section 3.4.2, Page 29: Line 491: Replace 'a MoA analysis is required' by '*a description for the proposed link between adverse effect and endocrine activity should be formulated in line with the legal ED criteria. This could be a short-cut MoA analysis.*

Section 3.5, Page 30: Line 499: reword to read: - *a formal MoA analysis may be helpful* … because as commented above, a MoA cannot be made a general prerequisite for describing the plausible link.

Section 3.5, Page 30: Lines 500-504: Delete existing sentence from end of 500. Replace with the following 2 sentences. *However, in some cases, the evidence may be such that judgement can be reached that the criteria are met without recourse to a detailed MoA analysis. For example, when adversity is indicated in EATS mediated parameters, given current toxicological and endocrinological knowledge, such data may often be sufficient to conclude on the overall biological plausibility of the link between endocrine activity and the adverse effect.*

Section 3.5, Page 30: Line 505: Add prior to the start of the sentence: *´In cases where a formal MoA analysis is judged to be helpful, Figure 4 illustrates…. ´*

Section 3.5.1., Page 31, Line 543 – 547: This is an important paragraph which should be amended to say in line 546 that the knowledge should be considered sufficient (instead of `may`). The next sentence requires that at least one putative endocrine mediated MoA should be described. This is a major obstacle for identification and not covered by the legal text of the law and the EDC criteria. Instead, the guidance should clarify that only a basic overview description of the plausible MoA (a short-cut MoA analysis) should be necessary.

Section 3.5.1., Page 32: Line 570: Replace sentences end of 570-575 with: *`However, it needs to be recognised that if multiple endocrine MoA are operating, then these may act simultaneously (concomitantly), such that only analysing one MoA at a time in isolation may not be appropriate. The effects seen may be considered in part like those for E, A, or T disruption as well as beyond EATS modalities but interaction may lead to complexities. In this case,*

expert judgement is required to determine whether there is a plausible link with the endocrine activity.´

Section 3.5.1., Page 33, Line 584-585: This section again requires too much evidence, therefore delete these lines and revise the approach to allow detailed molecular data to be used when available. The guidance task is to provide support for ED identification, not for generation of MoA data.

Section 3.5.1., Page 33: Line 589: Delete sentence end 589-591 and replace with*: ´However, before requiring further data to be generated, it should be carefully considered whether the effects seen are plausibly related to one or more endocrine activity. Experts may reach a judgment as to the biological plausibility of this, without there being an established clear series of biological events leading to the adverse effects. This is because it needs to be recognised that it may take decades to establish beyond doubt the precise mechanism of action and the animal testing required to do so may not be justifiable, particularly when multiple and possibly interacting mechanisms are at play.´*

Section 3.5.1, Page 34: Line 609: Add the following sentence. *As knowledge of the concordance between various parameters and adverse effects increases, it may be possible to determine adverse effects without the need for higher tier 5 testing in some cases. For example, in future, it may be possible to assign adversity to some level of increase in VTG*.

Section 3.5.2, Page 34: Line 623-633: It is vital to retain this paragraph which should become central to the approach but is currently in contradiction with other parts in this chapter.

Section 3.5.2, Page 34: Line 645: After the words 'pair of KEs', add. *In the context of identification of an EDC it is necessary to establish the biological plausibility of the link between the ED activity and the adverse effects, but not between 2 KEs. Therefore, the overall biological plausibility for and endocrine disrupting MoA, will focus on providing credible support for the link between the adverse effect and the endocrine activity.*

Section 3.5.2.1, Page 35, Line 664: not helpful in this guidance document for ED identification, recommend to delete.

Section 3.5.2.2, Page 35, Line 688: not helpful in this guidance document for ED identification, recommend to delete. If it stays, please add in line 702:

However, as noted earlier (line 325-7) some substances may have non monotonic dose response curves, such that agonistic or antagonistic effects may be observed with different administered doses, or when different absorption leads to different internal doses.

Section 3.5.2.4 Page 38: Lines 773-804: Vital to keep these paragraphs.

Section 3.5.2.6, Page 38, Lines 809-811: Requiring too much evidence, delete these lines and revise approach in this chapter. What is needed to comply with the criteria is some confidence that the endocrine action is in some way linked with the adverse effects seen, rather than absolute proof, which will be elusive in many cases. Indeed, experts must be confident that the link is biologically plausible to avoid falsely identifying substances, but this should not be interpreted as requiring the mechanism of action to be known.

Section 3.5.2.6, Page 38: Line 810: effects should, where possible, identify the KEs… Add the words 'where possible' as shown. This should not be a prerequisite for being able to conclude on the strength of the plausible link.

Section 3.5.2.6, Page 38: Line 816: Change MoA to MoA(s) to allow for interactive E, A and/or T or modes beyond EATS as multiple MoA.

Section 3.5.2.6, Page 39: Delete 817-838: We doubt that this section is appropriate and useful for identifying substances with endocrine disrupting properties. It is too detailed and over prescriptive and we would strongly recommend to take it out.

Section 3.5.2.6, Page 39: Lines 839: unclear, corrected phrase:

If the overall pattern of evidence leading to the adverse effect is based on EATS-mediated parameters, then the toxicology and endocrinology knowledge is considered sufficient to assume a clear biologically plausible link between the adverse effect and the endocrine activity, providing that a justification exists that the observed adverse effect is coherent with broadly accepted with pre-existing theory and knowledge. (OECD 2012a; Susser 1991) …. Then delete 843-845 (repetitive).

Section 3.5.2.6, Page 40, Line 848: corresponding to our other comments we recommend to take out table 8 out as not useful for this guidance.

Section 3.5.3, Page 41: Line 854: add sentence: *´In some cases a short-cut MoA analysis will suffice because the adverse effects are in line with the endocrine activity based on the current knowledge of endocrinology.´*

Section 3.5.3, Page 41: Line 856: replace `follow the assessment` with ´If a full MoA analysis has been done then a clear statement´… because a MoA cannot and should not be a requirement (`statement of confidence´: meaning unclear what this would entail).

Section 3.5.3, Page 41: Line 863: add on to line 862, no new para and Replace: *In cases where the biological plausibility for the KERs is weak and the empirical support is weak, then it can be considered that the link between the adverse effect and endocrine activity has not been substantiated.*

Section 3.6 Page 42: Line 908-910: Edit sentence to read as follows. *´If the link between the endocrine activity and the adverse effect(s) is not judged to be biologically plausible for any of the postulated MoA(s), the substance is considered not to meet the ED criteria. ´*

Section 3.6 Page 42: Line 911 -912: Delete sentence and replace as follows. *Where the available information is sufficient to establish a non-EATS endocrine MoA, it will be up to expert judgement to determine whether this is biologically plausibly linked with adverse effects and therefore to conclude whether the ED criteria are met.*

For comments or questions, please contact:

- Ninja Reineke: Ninja.reineke@chemtrust.org
- Gwynne Lyons: Gwynne.lyons@chemtrust.org

For more information on Endocrine Disrupting Chemicals (EDCs), see the CHEM Trust blog & our EDC FAQ:

- http://www.chemtrust.org/tag/edc/
- http://www.chemtrust.org/faq

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