Joint Health and Environment Alliance (HEAL) – CHEM Trust comments on EC proposal for CLP hazard class for EDCs

April 2021

The Health and Environment Alliance (HEAL) and CHEM Trust welcome the opportunity to comment on the European Commission draft proposal on hazard classes for endocrine disruptors in CLP, which was presented at the 4th CARACAL subgroup on endocrine disruptors on 22nd March.

Our organisations support the European Commission in its endeavour to improve the hazard identification of endocrine disrupting chemicals (EDCs) in a way that is reflective of available scientific knowledge, allows a coherent approach to those substances across sectors and legislations, and ultimately serves an increase in the level of protection of human health and the environment. As highlighted during the last CASG ED meeting, we have a number of questions and comments about the draft proposal, which we will detail further below. For the sake of clarity, we are using the European Commission table to structure our more specific comments (we have deleted the second column and added a new column on the right side the table for our comments) following some general comments.

We hope those comments will be helpful and we look forward to discussing an improved version of the proposal, as a strong basis for protective and coherent hazard identification of EDCs.

General comments:

- Overall, we find it important that the **specific characteristics of endocrine disruption** are sufficiently taken into account, when establishing horizontal ED criteria under CLP. Further, it is equally important that the same emphasis is put on endocrine activity as part of the ED definition as it is on the adverse effects, and that the hazard is recognised as 'endocrine disruption'.

- We could support having only **Category 1, even though we clearly favour including two subcategories 1A and 1B** in order to properly inform about the kind of the evidence and to ensure consistency in the CLP legislation, see our joint CHEM Trust, ClientEarth and HEAL position paper for more details. Should

category 1 be kept as currently proposed, it is important that it allows taking into account the usual evidence levels required for both Category 1A and 1B, as in the identification of CMR substances.

- We welcome the **inclusion of a Category 2** as this is necessary to ensure ED identification based on the varying degrees of available data and the current scientific level of evidence. We would like to emphasize again that the definition of an ED includes both endocrine activity and adverse effects, and this should also be reflected when allocating substances to Category 2. The inclusion of Category 2 will also ensure consistency in legislation and logic, as several ED substances are already classified as Rep2 or Carc2 under CLP.

- In addition, we propose to **include a Category 3** to identify endocrine active substances based on in vitro data to ensure transparency and reflect that endocrine activity is part of the definition of an ED.

- **We prefer an integrated approach for human health and environment**. This makes sense from a scientific point of view and would help with more efficient identification processes. However, should the currently proposed separation between classification for human health (HH) and environment (ENV) be maintained, the ED categorisation has to allow for good integration of HH-ENV data in the assessment. This is to ensure full utilization of all scientific data available and to simplify the classification and labelling of substances. For example, it makes no sense that the same rodent data lead to separate classifications and results in separate classification and labelling for HH and ENV. An integrated approach to simplify classification and labelling should be established.

- **The classification criteria should be supported by a guidance document**. However, important aspects already recognised in the ECHA/EFSA Guidance Document can and should be spelled out in the legal text, e.g. text about biological plausibility and the role of expert judgement as part of the weight of evidence (WoE).

- As regards the **treatment of mixtures containing EDs**, we find it problematic from a scientific point of view to introduce general concentration limits for EDs. Some of the special characteristics of endocrine disruptors include the fact that protective thresholds cannot be set with sufficient certainty, the existence of low dose effects, and non-monotonic dose responses. Moreover, because substances have various modes of action, the usual principles in toxicology cannot always be used for endocrine disruptors. We therefore propose to refrain from setting a general concentration limit.

Annex I: Proposal of hazard class for human health

EC Text proposal	EC Comments	NGO Comments
3.11 Endocrine disruptionng property for - human health	To follow CLP naming, it should be the name of the hazard (and not the substance) as for example "carcinogenicity"	We would suggest naming this section: Endocrine disruption – human health. This would be more logical and consistent as for example carcinogenicity is not named "carcinogenic property"
3.11.1 Definitions and general considerations	Wording from Repro. 3.7.1	
3.11.1.1 Endocrine disruptor means a substance or a mixture of substances that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations.	Definition from WHO/PCS/EDC/02.2: https://www.who.int/ipcs/publications/en/ch1.pdf?ua=1	
3.11.1.2 A substance is considered to be an endocrine disruptor if it meets the elements of the definition: all of the following criteria : (1) it shows an adverse effect in an intact organism or its progeny; (2) it shows endocrine activity; (3) the substance has an endocrine disrupting mode of action, i.e. there is a biologically plausible link between the endocrine activity and the adverse effect".		We suggest to change the wording of this section as indicated in column 1. What is specific for this new hazard class is the endocrine activity and the plausible link between this activity and an adverse effect.
3.11.1.3 An adverse effect is defined in this context as a change in morphology, physiology, growth, development, reproduction or lifespan of an organism, system or (sub)population that results in	Definition from WHO/IPCS Environmental Health Criteria 240, Principles and Methods for the Risk	

<table>
<tr><td>an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences.</td><td>Assessment of Chemicals in Food. Environmental Health Criteria 240: https://apps.who.int/iris/bitstream/handle/10665/44065/WHO_EHC_240_13_eng_Annex1.pdf?sequence=13 (Glossary)</td><td></td></tr>
<tr><td>3.11.1.4 An endocrine activity is defined as an interaction with the endocrine system that can potentially result in a response of the endocrine system, target organs and tissues. A substance that has an endocrine activity has the potential to alter the function(s) of the endocrine system.</td><td>Definition from the ECHA/EFSA guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009 [1].</td><td></td></tr>
<tr><td>3.11.2 Classification criteria for substances</td><td></td><td></td></tr>
<tr><td>3.11.2.1 Hazard categories
For the purpose of classification for endocrine disruption ~~ng properties~~ for human health, substances are allocated to one of two categories based on strength of evidence and additional considerations in a weight of evidence approach.</td><td></td><td>See proposal for amendment of the text in column 1.</td></tr>
<tr><td>Table 3.11.1
Hazard categories for endocrine disruptors for human health
<table><tr><td>Categories</td><td>Criteria</td></tr><tr><td>CATEGORY 1</td><td>Known or presumed endocrine disruptors for human health</td></tr></table></td><td>Wording adapted from Repro. 3.7.2.1.1 (Table 3.7.1(a))</td><td>Referring to our suggestions made in 3.11.1.2 the requirements for endocrine disruption consists of evidence on adverse effects, evidence on endocrine activity and the existence of a biological</td></tr>
</table>

[1] https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5311

	A substance is classified in Category 1 for endocrine disruptionng properties for human health if it is known or presumed to meet the criteria defined in 3.11.1.2. The classification in Category 1 is largely (but not exclusively) based on evidence from humans and/or on data from animal studies, possibly supplemented with other information (such as read-across data). Such data shall provide clear evidence of endocrine disruption. However, when there is information that raises doubt about the relevance of the endocrine disrupting mode of action for humans, classification in Category 2 may be more appropriate.		plausible link between these two. Therefore, we suggest small amendments in the text (see proposal in column 1). We are in favour of a distinction between category 1A based on evidence from humans and Category 1B based on evidence from animal studies. This is particularly relevant for EDs due to the overall lack of scientific data on hazardous properties of the substances and the shortcomings in validated test methods. Hazard categorisation must be closely reflective of the available scientific evidence and we believe this is best achieved through maintaining of category 1A and 1B. Although the regulatory consequences may be the same, it is still considered highly concerning when evidence comes from human data. Therefore, this information should be clearly indicated, as it may be relevant for other regulatory purposes. The inclusion of subcategories will also contribute to consistency in regulation as this is in accordance with the existing CLP categories for CMR classification. This section could also mention that the list of evidence that can be used to identify substances under the proposed categories can be found in section 3.11.2.4.
CATEGORY 2	Suspected endocrine disruptors for human health A substance is classified in Category 2 for endocrine disruption properties for human health when there is evidence of an adverse effect, which	Wording adapted from Repro. 3.7.2.1.1 (Table 3.7.1(a))	See proposal for amendment of the text in column 1.

~~is a consequence of the endocrine activity~~endocrine disruption, and where the evidence is not sufficiently convincing to place the substance in Category 1.		
~~Where there is evidence demonstrating that the adverse effects identified are not relevant to humans, the substance should not be considered an endocrine disruptor for human health.~~		We suggest deleting this paragraph, which we find concerning in the context of hazard categorisation of EDs, including because there is no reference to endocrine activity. Relevance to humans should be considered by default. Furthermore, the science is not yet fully developed in this area and there are still knowledge gaps regarding all the effects endocrine disruption may lead to.
3.11.2.2 Basis of classification		
Classification is made on the basis of the appropriate criteria, outlined above, and an assessment of the total weight of evidence (see 1.1.1). Classification as an endocrine disruptor for human health is intended to be used for substances which have an intrinsic, specific property to ~~produce~~ induce ~~an~~ endocrine disruption ~~related adverse effect~~. ~~Endocrine-related adverse effects shall have been observed in the absence of other toxic effects, or if occurring together with other toxic effects the endocrine-related adverse effect is considered not to be solely secondary non-specific consequence of the other toxic effects.~~	Wording adapted from Repro 3.7.2.2.1	We suggest to delete the second paragraph of this section. In particular, the first part of the sentence "Endocrine-related adverse effects shall have been observed in the absence of other toxic effects" should be removed, as it appears highly unrealistic. Due to the complex functioning of the endocrine system, it is common for endocrine-related adverse effects to not take place in isolation from other toxic effects. Therefore, excluding such effects may lead to under classification of EDs. See also small wording amendment for paragraph 1 of this section in column 1.
3.11.2.3 Weight of evidence		

Classification as an endocrine disruptor for human health is made according to the criteria on the basis of an assessment of the total weight of evidence, see section 1.1.1. This means that all available relevant scientific data (in vivo studies or adequately validated alternative test systems predictive of adverse effects in humans or animals; as well as in vivo, in vitro, or, if applicable, in silico studies and data from analogous substances using structure-activity relationship (SAR), informing about endocrine modes of action) are considered together, including peer-reviewed published studies and additional acceptable data.	Wording adapted from Repro 3.7.2.3.1 For further information, please refer to ECHA/EFSA guidance on in silico prediction methods and read-across approaches and categories (page 52-53) "peer-reviewed …" from Carc. 3.6.2.2.1	See small wording amendment in column 1.
In applying the weight of evidence determination, the assessment of the scientific evidence shall, in particular, consider all of the following factors: (a) both positive and negative results; (b) the relevance of the study designs, for the assessment of adverse effects and of the endocrine ~~mode of action~~activity; (c) the quality and consistency of the data, considering the pattern and coherence of the results within and between studies of a similar design and across different species; (d) the route of exposure, toxicokinetic and metabolism studies; (e) the concept of the limit dose, and international guidelines on maximum recommended doses and for assessing confounding effects of excessive toxicity;		We suggest to adapt this list to the wording of the ECHA/EFSA-guidance on EDs, including by adding a mention of expert judgement. See also small wording amendment in point b) of column 1.

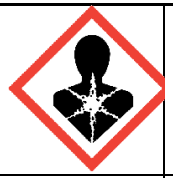
Using a weight of evidence approach, the link between the adverse effect(s) and the endocrine activity shall be established based on biological plausibility, which shall be determined in the light of current scientific knowledge.		
Evidence used for the classification of a substance as an endocrine disruptor for the environment in section 4.2 should be considered to assess the classification of the substance as endocrine disruptor for human health in the current section 3.11.		In this section, we suggest to add a reference to the ECHA/EFSA-Guidance table, summarising the conclusions on biological plausibility.
3.11.2.4 [List of evidences that can be used for classification]	This is a placeholder for a future list of evidence that can be used in the weight of evidence to assess the classification. This list will be developed in a second step on the basis of the discussion on the hazard categories.	We suggest that substances can be allocated to Category 1 based on: • Reliable evidence from humans where it is plausible that the observed adverse effects are endocrine-mediated, or • Experimental studies where it is plausible that the observed adverse effects are endocrine-mediated, or • Experimental studies showing endocrine activity in vivo predicted to have a biological plausible link (e.g. through (Q)SAR, AOPs, analogue and category approaches) to adverse effects in vivo. We suggest that substances can be allocated to Category 2 based on: • Evidence from humans where it is suspected that the observed adverse effect is endocrine-mediated, or • Experimental studies where there is a biologically plausible link that the observed adverse effects are endocrine-mediated but

		where, for example, specific weaknesses in study design (e.g. limitations in relevant ED endpoints), or execution weaken this conclusion, or • Experimental studies in vivo where it is suspected that the observed adverse effects are endocrine-mediated. • Experimental studies showing endocrine activity in vivo which is suspected to be linked to adverse effects in vivo (e.g. through (Q)SAR, AOPs, analogue or category approaches), or • Experimental studies in vivo showing endocrine activity but for which the link to an adverse effect is uncertain, or • Experimental studies in vitro showing endocrine activity, combined with toxicokinetic in vivo data, linked to adverse effects in vivo (e.g. through Q(SAR), AOPs, analogue and category approaches) but for which the link is suspected. In view of an integrated approach for assessing endocrine disruption also data from the environment assessment should be considered.
~~3.11.2.5 Evidence considered not to support classification for endocrine disruption~~ ~~It is recognised that evidence may be seen in humans, animals and/or in vitro that do not justify classification. Such effects include, but are not limited to:~~ ~~(a) evidence on adversity, endocrine activity or biological plausibility such as~~ ~~i. the available information is sufficient to postulate a non-endocrine MoA where~~		We strongly support the deletion of this entire section. These aspects are already included and considered by default in the WoE approach. Further, the text is concerning for the following reasons: <u>Paragraph (a)</u> - As a matter of fact, the demonstration of a mode of action is challenging with the current scientific knowledge and lack of data provided. Therefore, most identification processes will give rise to significant discussions and divergences of views to postulate a mode of action, whether to include or exclude it. - Likewise, most identification discussions will give rise to controversial discussions when it comes to assessing the

~~an endocrine MoA can conclusively be excluded;~~ ~~ii. the structural or functional relationship between the KEs is not understood and considered unplausible.~~ ~~(b) substance-induced species-specific mechanisms of toxicity, i.e. demonstrated with reasonable certainty to be not relevant for human health, shall not justify classification.~~		structural or functional relationships between the KEs and that is exactly where biological plausibility is adding value by allowing a conclusion. Paragraph (b) - Again, human relevance of the toxicity data available for the substance assessment should always be assumed by default. When there are elements suggesting the contrary, they will always be discussed, and taken into account. Therefore, this sub-paragraph is unnecessary and counterproductive.
3.11.3 Classification criteria for mixtures	Wording from Repro	
3.11.3.1 Classification of mixtures when data are available for all ingredients or only for some ingredients of the mixture	Wording from Repro	
3.11.3.1.1 The mixture shall be classified as an endocrine disruptor for human health when at least one ingredient has been classified as a Category 1 or Category 2 endocrine disruptor for human health and is present at or above the appropriate generic concentration limit as shown in Table 3.11.2 for Category 1 and Category 2, respectively.	Wording adapted from Repro	
Table 3.11.2 Generic concentration limits of ingredients of a mixture classified as endocrine disruptor for human health that trigger classification of the mixture	Wording adapted from Repro	
Ingredient classified as: / Generic concentration limits triggering classification of a mixture as:	Wording adapted from Carc. This table defines the GCL (Generic Concentration Limit). However SCL	We would recommend **not to introduce generic concentration limits for classifying mixtures containing EDs**. EDs have specific characteristics (non-threshold substances, low-dose effects and

	Category 1 endocrine disruptor for human health	Category 2 endocrine disruptor for human health	(Specific Concentration Limit) could be set on a case-by-case basis.	NMDRs) which would make a generic concentration limit hard to justify. It should be kept in mind that specific concentration limits can always be considered for each substance present in mixtures on a case-by-case basis.
Category 1 endocrine disruptor for human health	≥ 0.1 %			
Category 2 endocrine disruptor for human health		≥ 1 %		
Note: The concentration limits in Table 3.11.2 apply to solids and liquids (w/w units) as well as gases (v/v units).				
3.11.3.2 Classification of mixtures when data are available for the complete mixture			Wording from Repro	
3.11.3.2.1 Classification of mixtures will be based on the available test data for the individual ingredients of the mixture using concentration limits for the ingredients classified as endocrine disruptor for human health. On a case-by-case basis, test data on mixtures may be used for classification when demonstrating effects that have not been established from the evaluation based on the individual ingredients. In such cases, the test results for the mixture as a whole must be shown to be conclusive taking into account dose and other			Wording adapted from Repro	

<table>
<tr><td>factors such as duration, observations, sensitivity and statistical analysis of endocrine disrupting test systems. Adequate documentation supporting the classification shall be retained and made available for review upon request.</td><td></td><td></td></tr>
<tr><td>3.11.3.3 Classification of mixtures when data are not available for the complete mixture: bridging principles</td><td>Wording from Repro</td><td></td></tr>
<tr><td>3.11.3.3.1 Where the mixture itself has not been tested to determine its endocrine disrupting properties for human health, but there are sufficient data on the individual ingredients and similar tested mixtures (subject to paragraph 3.11.3.2.1) to adequately characterise the hazards of the mixture, these data shall be used in accordance with the applicable bridging rules set out in section 1.1.3.</td><td>Wording adapted from Repro</td><td></td></tr>
<tr><td>3.11.4 Hazard Communication</td><td>Wording from Repro</td><td></td></tr>
<tr><td>3.11.4.1 Label elements shall be used in accordance with Table 3.11.3, for substances or mixtures meeting the criteria for classification in this hazard class.</td><td>Wording from Repro</td><td></td></tr>
<tr><td>Table 3.11.3
Label elements of endocrine disruption - ~~ng~~ ~~propertie~~ human health</td><td>Wording adapted from Repro</td><td>We suggest amending the title of the table.</td></tr>
<tr><td><table><tr><td>Classification</td><td>Category 1</td><td>Category 2</td></tr></table></td><td>Table based on “ozone layer” hazard class before entering into GHS:</td><td>We do not find the wording of the precautionary statements very informative for the public.</td></tr>
</table>

Symbol/pictogram			https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02008R1272-20101201 Section 5.1	A suggestion for alternative wording could be as follows: Category 1: May cause endocrine disruption and harm the unborn child and human health. Category 2: Suspected of causing endocrine disruption and harm the unborn child and human health.
Signal Word	Danger	Warning		
Hazard Statement	EUHXXX: May cause endocrine-~~related~~ disruption and harm the unborn child and ~~adverse effects on~~ human health	EUHXXX: Suspected of causing endocrine disruption and harm the unborn child and ~~-related adverse effects on~~ human health	EUH statement based on similar wording as Carc.	
Precautionary Statement Prevention	P201 P202 P260 P263 P264 P270 P280	P201 P202 P260 P263 P264 P270 P280	P Statements adapted from Repro. P201: Obtain special instructions before use. P202: Do not handle until all safety precautions have been read and understood. P260: Do not breathe dust/fume/gas/mist/vapours/spray. P263: Avoid contact during pregnancy and while nursing. P264: Wash … thoroughly after handling. P270: Do not eat, drink or smoke when using this product. P280: Wear protective gloves/protective clothing/eye protection/face protection. P308 + P313: IF exposed or concerned: Get medical advice/attention.	
Precautionary Statement Response	P308 + P313	P308 + P313		
Precautionary Statement Storage	P405	P405		

	Precautionary Statement Disposal	P501	P501		P405: Store locked up. P501: Dispose of contents/container to …	

Annex II: Proposal of hazard class for the environment

Text proposal	Comments	NGO Comments
4.2 Endocrine ~~disrupti~~disruption ~~- ng property for the~~ environment		We would suggest naming it: Endocrine disruption – environment. This would be more logical and consistent as for example carcinogenicity is not named “carcinogenic property”
4.2.1 Definitions and general considerations		
4.2.1.1 Endocrine disruptor means a substance or a mixture of substances that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations.		
4.2.1.2 A substance is considered to be an endocrine disruptor if it meets the elements of the definition ~~all of the following criteria~~: (1) it shows an adverse effect in an intact organism or its progeny; (2) it shows endocrine activity; (3) ~~the substance has an endocrine disrupting mode of action, i.e. t~~here is a biologically plausible link between the endocrine activity and the adverse effect”.		We suggest changing the text as indicated.
4.2.1.3 An adverse effect is defined in this context as a change in morphology, physiology, growth, development, reproduction or lifespan of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences.		
~~3.11.4.2.~~1.4 An endocrine activity is defined as an interaction with the endocrine system that can potentially result in a response of		Wrong numbering.

the endocrine system, target organs and tissues. A substance that has an endocrine activity has the potential to alter the function(s) of the endocrine system.		
4.2.2 Classification criteria for substances		
4.2.2.1 Hazard categories For the purpose of classification for endocrine ~~disrupting~~ disruption ~~properties~~ for the environment, substances are allocated to one of two categories based on strength of evidence and additional considerations in a weight of evidence approach.		We suggest to change the wording referring to 4.2.
Table 4.2.1 Hazard categories for endocrine disruptors for the environment		

Categories	Criteria			
CATEGORY 1	Known or presumed endocrine disruptors for the environment A substance is classified in Category 1 for endocrine disruption~~ng properties~~ for the environment if it is known or presumed to meet the criteria defined in 4.2.1.2. The classification in Category 1 is largely (but not exclusively) based on evidence from animal species living in the environment ~~human~~ and/or on data from animal studies, possibly supplemented with other information (such as read-across data). Such data shall provide evidence ~~of an adverse effect that is relevant for the (sub-)population level and which is a consequence of the endocrine activity.~~ endocrine disruption.			Referring to our suggestions made in section 4.2.1.1, we suggest small changes in the wording in column 1. We prefer to see a distinction between Category 1A based on evidence from wildlife/field studies and Category 1 B based on evidence from experimental laboratory studies. This is particularly relevant for EDs due to the overall lack of scientific data on hazardous properties of the substances and the shortcomings in validated test methods. Hazard categorisation must be closely reflective of the available scientific evidence and we believe this is best achieved through maintaining of category 1A and 1B as for CMR human health classification. Although, the regulatory consequences may be the same, it is still considered more concerning when evidence comes from wildlife/field studies and this information may be relevant for other regulatory purposes. And this will

	However, when there is information that raises doubt about the relevance of the effect for the (sub-)population level, classification in Category 2 may be more appropriate.		also contribute to consistency in regulation as this is in accordance with the existing CLP categories for CMR classification for human health.
CATEGORY 2	Suspected endocrine disruptors for the environment A substance is classified in Category 2 for endocrine disruption ~~ng properties~~ for the environment when there is evidence of endocrine disruption and ~~an adverse effect that is relevant for the (sub-)population level and which is a consequence of the endocrine activity, and~~ where the evidence is not sufficiently convincing to place the substance in Category 1.		
~~Where there is evidence demonstrating that the adverse effects identified are not relevant at the (sub)population level for non-target organisms, the substance should not be considered an endocrine disruptor for the environment.~~		This paragraph coming from PPP criteria is not relevant for a horizontal system in CLP.	We suggest the deletion of this entire section.
4.2.2.2 Basis of classification			
Classification is made on the basis of the appropriate criteria, outlined above, and an assessment of the total weight of evidence (see 1.1.1). Classification as an endocrine disruptor for the environment is intended to be used for substances which have an intrinsic, specific property to ~~produce an~~induce endocrine disruption ~~-related adverse effect~~. ~~Endocrine-related adverse effects shall have been observed in the absence of other toxic effects, or if occurring together with other toxic effects the endocrine-related adverse effect is considered not~~			We suggest the deletion of the entire second paragraph of this section. In particular, the first part of the sentence "Endocrine-related adverse effects shall have been observed in the absence of other toxic effects" should be removed, as it appears highly unrealistic and risks to miss identifying ED chemicals as dangerous for environmental health. Due to the complex functioning of the endocrine system, it is common for endocrine-related adverse effects to not take place in isolation from other toxic effects.

~~to be solely secondary non-specific consequence of the other toxic effects.~~		
4.2.2.3 Weight of evidence		
Classification as an endocrine disruptor for the environment is made according to the criteria on the basis of an assessment of the total weight of evidence, see section 1.1.1. This means that all available relevant scientific data (in vivo studies or adequately validated alternative test systems predictive of adverse effects in humans or animals; as well as in vivo, in vitro, or, if applicable, in silico studies and data from analogous substances using structure-activity relationship (SAR), informing about endocrine modes of action) is considered together, including peer-reviewed published studies and additional acceptable data.		See small text amendment in column 1.
In applying the weight of evidence determination, the assessment of the scientific evidence shall, in particular, consider all of the following factors: (a) both positive and negative results; (b) the relevance of the study design for the assessment of adverse effects and its relevance at the (sub-)population level, and for the assessment of the endocrine ~~mode of action~~activity; (c) the adverse effects on reproduction, growth/development, and other relevant adverse effects which are likely to impact on (sub-)populations. Adequate, reliable and representative field or monitoring data and/or results from population models shall as well be considered where available; (d) the quality and consistency of the data, considering the pattern and coherence of the results within and between studies of a similar design and across different taxonomic groups;		We would suggest to adapt this list to the wording of the ECHA/EFSA guidance on EDs, including by adding a mention of expert judgement.

(e) the route of exposure, toxicokinetic and metabolism studies; (f) the concept of the limit dose, and international guidelines on maximum recommended doses and for assessing confounding effects of excessive toxicity;		
Using a weight of evidence approach, the link between the adverse effect(s) and the endocrine activity shall be established based on biological plausibility, which shall be determined in the light of current scientific knowledge.		
Evidence used for the classification of a substance as an endocrine disruptor for human health in section 3.11 should be considered to assess the classification of the substance as endocrine disruptor for the environment in the current section 4.2.		In this section, we suggest to add a reference to the ECHA/EFSA Guidance table, summarising the conclusions on biological plausibility.
4.2.2.4 [List of evidences that can be used for classification]	This is a placeholder for a future list of evidence that can be used in the weight of evidence to assess the classification. This list will be developed in a second step on the basis of the discussion on the hazard categories.	We suggest that substances can be allocated to Category 1 based on: • Reliable evidence from wildlife/field studies where it is plausible that the observed adverse effects are endocrine-mediated, or • Experimental studies where it is plausible that the observed adverse effects are endocrine-mediated, or • Experimental studies showing endocrine activity in vivo predicted to have a biological plausible link (e.g. through (Q)SAR, AOPs, analogue and category approaches) to adverse effects in vivo. We suggest that substances can be allocated to Category 2 based on:

		• Evidence from wildlife/field studies where it is suspected that the observed adverse effect is endocrine-mediated, or • Experimental studies where there is a biologically plausible link that the observed adverse effects are endocrine-mediated but where, for example, specific weaknesses in study design (e.g. limitations in relevant ED endpoints), or execution weaken this conclusion, or • Experimental studies in vivo where it is suspected that the observed adverse effects are endocrine-mediated. • Experimental studies showing endocrine activity in vivo which is suspected to be linked to adverse effects in vivo (e.g. through (Q)SAR, AOPs, analogue or category approaches), or • Experimental studies in vivo showing endocrine activity but for which the link to an adverse effect is uncertain, or • Experimental studies in vitro showing endocrine activity, combined with toxicokinetic in vivo data, linked to adverse effects in vivo (e.g. through Q(SAR), AOPs, analogue and category approaches) but for which the link is suspected. In view of an integrated approach for assessing endocrine disruption also data from the human health assessment should be considered.
~~4.2.2.5 Evidence considered not to support classification for endocrine disruption~~ ~~It is recognised that evidence may be seen in humans, animals and/or in vitro that do not justify classification. Such effects include, but are not limited to:~~		We strongly support the deletion of this entire section. These aspects are already included and considered by default in the WoE approach. Furthermore, the text is concerning for the following reasons: Paragraph (a)

~~(a) evidence on adversity, endocrine activity or biological plausibility such as~~ ~~i. the available information is sufficient to postulate a non-endocrine MoA where an endocrine MoA can conclusively be excluded;~~ ~~ii. the structural or functional relationship between the KEs is not understood and considered unplausible.~~ ~~(b) substance-induced species-specific mechanisms of toxicity, i.e. demonstrated with reasonable certainty to be not relevant for human health, shall not justify classification.~~		- As a matter of fact, the demonstration of a mode of action is challenging with the limited current scientific knowledge and lack of data provided. Therefore, most identification processes will give rise to significant discussions and divergences of views to postulate a mode of action, whether to include or exclude it. Likewise, most identification discussions will give rise to controversial discussions when it comes to assessing the structural or functional relationships between the KEs and that is exactly where biological plausibility is adding value by allowing a conclusion. <u>Paragraph (b)</u> Again, human relevance of the toxicity data available for the substance assessment should always be assumed by default. When there are elements suggesting the contrary, they will always be discussed, and taken into account. Therefore, this sub-paragraph is unnecessary and counterproductive. As regards (b): human health should be changed to 'environment'.
4.2.3 Classification criteria for mixtures		
4.2.3.1 Classification of mixtures when data are available for all ingredients or only for some ingredients of the mixture		
4.2.3.1.1 The mixture shall be classified as an endocrine disruptor for the environment when at least one ingredient has been classified as a Category 1 or Category 2 endocrine disruptor for the environment and is present at or above the appropriate generic concentration limit as shown in Table 4.2.2 for Category 1 and Category 2, respectively.		

<table>
<tr><td></td><td></td><td></td></tr>
<tr><td>Table 4.2.2
Generic concentration limits of ingredients of a mixture classified as endocrine disruptor for the environment that trigger classification of the mixture</td><td></td><td></td></tr>
<tr><td>
<table>
<tr><td rowspan="2">Ingredient classified as:</td><td colspan="2">Generic concentration limits triggering classification of a mixture as:</td></tr>
<tr><td>Category 1 endocrine disruptor for the environment</td><td>Category 2 endocrine disruptor for the environment</td></tr>
<tr><td>Category 1 endocrine disruptor for the environment</td><td>≥ 0.1 %</td><td></td></tr>
<tr><td>Category 2 endocrine disruptor for the environment</td><td></td><td>≥ 1 %</td></tr>
</table>
Note: The concentration limits in Table 4.2.2 apply to solids and liquids (w/w units) as well as gases (v/v units).
</td><td></td><td>We would recommend <u>not to introduce generic concentration limits for classifying mixtures containing EDs.</u> EDs have specific characteristics (non-threshold substances, low-dose effects and NMDRs) which would make a generic concentration limit hard to justify.

It should be kept in mind that specific concentration limits can always be considered for each substance present in mixtures on a case-by-case basis.</td></tr>
<tr><td>4.2.3.2 Classification of mixtures when data are available for the complete mixture</td><td></td><td></td></tr>
<tr><td>4.2.3.2.1 Classification of mixtures will be based on the available test data for the individual ingredients of the mixture using concentration limits for the ingredients classified as endocrine disruptor for the environment. On a case-by-case basis, test data on mixtures may be used for classification when demonstrating effects that have not been established from the evaluation based on the individual ingredients. In such cases, the test results for the mixture as a whole must be shown to be conclusive taking into account dose and other factors such as duration, observations,</td><td></td><td></td></tr>
</table>

<table>
<tr><td>sensitivity and statistical analysis of endocrine disrupting test systems. Adequate documentation supporting the classification shall be retained and made available for review upon request.</td><td></td><td></td></tr>
<tr><td>4.2.3.3 Classification of mixtures when data are not available for the complete mixture: bridging principles</td><td></td><td></td></tr>
<tr><td>4.2.3.3.1 Where the mixture itself has not been tested to determine its endocrine disrupting properties for the environment, but there are sufficient data on the individual ingredients and similar tested mixtures (subject to paragraph 4.2.3.2.1) to adequately characterise the hazards of the mixture, these data shall be used in accordance with the applicable bridging rules set out in section 1.1.3.</td><td></td><td></td></tr>
<tr><td>4.2.4 Hazard Communication</td><td></td><td></td></tr>
<tr><td>4.2.4.1 Label elements shall be used in accordance with Table 4.2.3, for substances or mixtures meeting the criteria for classification in this hazard class.</td><td></td><td></td></tr>
<tr><td>Table 4.2.3
Label elements of endocrine disruption - ~~bng properties for the~~ environment</td><td></td><td>We suggest amending the title of the table.</td></tr>
<tr><td><table>
<tr><td>Classification</td><td>Category 1</td><td>Category 2</td></tr>
<tr><td>Symbol/pictogram</td><td>  </td><td>  </td></tr>
<tr><td>Signal Word</td><td>Danger</td><td>Warning</td></tr>
<tr><td>Hazard Statement</td><td>EUHXXX: May cause endocrine</td><td>EUHXXX: Suspected of causing endocrine ~~-~~disruption ~~related~~</td></tr>
</table></td><td></td><td>We do not find the wording of the precautionary statements very informative for the public.

A suggestion for alternative wording could be as follows:
Category 1: May cause endocrine disruption and harm the offspring and the environment.

Category 2: Suspected of causing endocrine disruption and harm the offspring and the environment.</td></tr>
</table>

	disruption and harm the offspring and ~~-related adverse effects on~~ the environment	~~adverse effects o~~n and harm the offspring and the environment			
Precautionary Statement Prevention	P273	P273	P Statements from long-term (chronic) aquatic hazard. P273: Avoid release to the environment. P391: Collect spillage. P501: Dispose of contents/container to …		
Precautionary Statement Response	P391	P391			
Precautionary Statement Storage					
Precautionary Statement Disposal	P501	P501			