Joint NGO comments regarding MOCS and introduction of hazard classes for endocrine disruption in the CLP Regulation as follow-up to CASG-ED6.

18 February 2022

CHEM Trust, Client Earth, the European Environmental Bureau (EEB), and the Health and Environment Alliance (HEAL) welcome the opportunity to provide follow-up comments to the discussions in relation to the application of mixture rules for classifying MOCS, and on the updated draft proposal on hazard classes for endocrine disruptors in CLP, which took place at the CASG-ED6 meeting on 24th January 2022.

Comments in response to agenda point 3 on MOCS

To ensure consistency in legislation, we support an approach similar to that applying to CMRs, so that the classification of a mixture containing endocrine disrupting substances cannot be based on the testing of the mixture. Rather, it should be based on calculations of the content of the ED substances in the mixture.

Comments in response to agenda point 5 on new hazard classes for endocrine disruptors in the CLP regulation

Overall, we can support the proposed reorganisation of the text for the hazard classes and the proposed text for Category 1 ED.

However, **we are very concerned that the proposed criteria text for Category 2 ED still entails an excessive burden of proof for identification**. This is because it is required that one of the criteria either a) for adverse effects or b) for endocrine activity should meet the requirements for Category 1 ED. This is not consistent with the CMR approach and results in requesting a higher level of evidence for the identification of EDs than for the identification of CMR substances. Treating EDs differently than CMRs, and in particular differently than mutagens, cannot be justified. This approach will limit the number of substances to be identified as Suspected EDs, in particular in the current situation of overall lack of data on chemicals' ED properties and where many studies are conducted without relevant

ED endpoints, as well as in light of the shortcomings of validated test methods with relevant ED endpoints. The development of horizontal ED criteria has been delayed for nearly 10 years now, and the health of humans and the environment is not at all properly protected against exposure to endocrine disruptors.

It is also important that the criteria text is coherent with the data that are available today and will become available in the future. Therefore, the text should keep the possibility for inclusion of other data than from humans/animals open, in order to be prepared for future new assessments methods. Likewise, the criteria should allow for the increased use of grouping of chemicals for classification purposes in the future.

Considering how contentious and complex this issue is, it is essential to minimise the possibility for differences in interpretations and avoid any confusion in the terminology used. Unfortunately, section 3.11.1.1 creates confusion: it uses the word 'consequently', which does not reflect accurately the full definition of what endocrine disruptors are and as set by Category 1, which rightly uses the concept of "biologically plausible link". The word 'consequently' implies a different level of certainty than the latter and could create grounds for judicial dispute. Therefore, the text must be changed. A definition simply omitting the word 'consequently' would be fully aligned with the current interpretation of the WHO definition under EU law.

Furthermore, we recommend that section 3.11.2.3.5 about exclusion from classification is deleted, as this information seems odd in this context and is more relevant for a guidance document.

Setting generic concentration limits is a method widely used. However, it has severe limitations when it comes to non-threshold substances, and especially to EDs. The usual principles for toxicology cannot always be applied due to ED specificities: non-threshold substances, low dose effects and NMDRs. If generic concentration limits are included, the text should at least foresee a review of the relevance of using the approach in the next 4 years.

We do understand the reasons for not suggesting a pictogram for the ED hazard classes at this stage while awaiting negotiations under the GHS. However, a pictogram showing the ED hazard is a very important warning signal to the public and the industry. In the short run, many endocrine disruptors for human health may also be classified as Reprotoxicants and/or Carcinogens, and therefore be assigned a pictogram. However, two important aspects should be stressed: first, endocrine disruptors for the environment will not be assigned a pictogram at all. Second, very soon when more data and knowledge emerge, endocrine disruptors for human health will be classified on the basis of other adverse effects than Reprotoxicants and Carcinogens. In fact, Resorcinol is already an example illustrative of such a situation. Therefore, and because ED effects are of equivalent level of concern as those of CMRs, a specific pictogram is already needed now to reflect the ED hazard without awaiting GHS discussions.

Lastly, we strongly recommend that CLP further integrates the concept of grouping of chemicals based on their intrinsic properties, so that the legislation allows for classification of a substance based on grouping of substances.

In the following section, we have indicated specific suggestions for text changes (in yellow) with accompanying comments.

Annex 1.A: Proposal of hazard class for human health

Text proposal	Proposal for text revisions	Our comments
3.11 Endocrine disrupting property for human health	Endocrine ~~disrupting property~~ disruptor for human health	We find it more consistent to use the wording 'endocrine disruptor for human health' as this terminology is used in 3.11.1.1 and table 3.11.1.
3.11.1 Definitions and general considerations		
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.	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.	We strongly recommend deleting the word 'consequently' to avoid creating any confusion. The text for Category 1 and Category 2 clearly defines that there should be a biologically plausible link between the adverse effects and the endocrine activity, therefore, it meets the WHO definition. The proposed wording already deviates from the WHO definition by not including 'exogenous', as well as omitting the reference to potential endocrine disruptors.
3.11.1.2 An adverse effect is defined for the purpose of section 3.11 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.		
3.11.1.3 An endocrine activity is defined for the purpose of section 3.11 as an interaction with the endocrine system that can potentially result in a response of the endocrine system, target organs and tissues. A		

<table>
<tr><td>substance that has an endocrine activity has the potential to alter the function(s) of the endocrine system.</td><td></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 disrupting 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></td></tr>
<tr><td colspan="2">Table 3.11.1
Hazard categories for endocrine disruptors for human health</td><td></td><td></td></tr>
<tr><td>Categories</td><td>Criteria</td><td>do</td><td></td></tr>
<tr><td>CATEGORY 1</td><td>Known or presumed endocrine disruptors for human health

The classification in Category 1 is largely based on evidence from human and/or animal data. Such data shall provide evidence that the substance meets the 3 criteria below:
a) an adverse effect in an intact organism or its progeny; and
b) endocrine activity; and
c) an endocrine disrupting mode of action, i.e. there is a biologically plausible link between the endocrine activity and the adverse effect.

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.</td><td>The classification in Category 1 is largely based on evidence from human and/or animal data possibly supplemented by other data. Such data shall provide evidence that the substance meets the 3 criteria below:
a) an adverse effect in an intact organism or its progeny; and
b) endocrine activity; and
c) an endocrine disrupting mode of action, i.e. there is a biologically plausible link between the endocrine activity and the adverse effect.

do</td><td>We strongly support this new wording for the Category 1.
In addition, we recommend adding a clear signal that human and animal data can be supplemented by other data to strengthen the WoE, and to be prepared for future new alternative assessment methods.</td></tr>
</table>

CATEGORY 2	Suspected endocrine disruptors for human health A substance is classified in Category 2 for endocrine disrupting properties, if: - evidence is available to conclude that the substance meets one of the two criteria (a or b) above; and - for the remaining criterion (a or b), the evidence is not sufficiently convincing to place the substance in Category 1; and - for the third criterion (c), there must be evidence that the endocrine disrupting mode of action is biologically plausible.	A substance is classified in Category 2 for endocrine disrupting properties, if: ~~- evidence is available to conclude that the substance meets one of the two criteria (a or b) above; and~~ - the evidence for the ~~remaining~~ criterion (a or b)~~, the evidence~~ is not sufficiently convincing to place the substance in Category 1; and - for the third criterion (c), there must be evidence that the endocrine disrupting mode of action is biologically plausible.	We strongly recommend revising the text proposal for Category 2. Currently, it still sets a too high burden of proof for identification of Suspected EDs, as it requires that one of the two criteria (a or b) meet the requirements for Category 1 ED. This is not consistent with the CMR approach, and rather requires a higher level of evidence than required to be classified as CMR. Further, if adopted, this approach will limit the number of substances identified as Suspected EDs. It is concerning in the current situation of overall lack of data on substances with ED properties and shortcomings of validated test methods with relevant ED endpoints.
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.		Where there is evidence demonstrating that the adverse effects and the endocrine activity identified are not relevant to humans, the substance should not be considered an endocrine disruptor for human health.	We strongly recommend either adding 'and the endocrine activity', or fully deleting this sentence, as long as all the consequences of endocrine disruption have not been fully explored. Human relevance should be considered by default.
3.11.2.2 Basis of classification			
Classification is made on the basis of the appropriate criteria, outlined above, and an assessment of the weight of evidence of each of the criteria (see section 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 an endocrine-related adverse effect.		Classification is made on the basis of the appropriate criteria, outlined above, and an assessment of the total weight of evidence ~~of each of the criteria~~ (see section 1.1.1). Classification as an endocrine disruptor for human health is intended to be used for	The text should follow the existing CLP approach of Weight of Evidence determination. Please, align the text with the similar text for classification for the environment in 4.2.2.2.

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 effects are considered not to be a secondary non-specific consequence of the other toxic effects.	substances which have an intrinsic, specific property to produce an endocrine-related adverse effect.	
3.11.2.3 Weight of evidence		
3.11.2.3.1 A weight of evidence determination (see section 1.1.1) means that all available relevant scientific data (e.g. 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.		We strongly recommend that CLP further integrates the concept of grouping chemicals based on their intrinsic properties, so that the legislation allows for classification of a substance based on grouping of substances.
3.11.2.3.2 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 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;	Delete this section	We recommend deleting this section. As currently drafted, it only indicates generalities on good scientific practise, which come across as rather superfluous and would be more relevant to include in a guidance document.
3.11.2.3.3 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.		
3.11.2.3.4 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.		
3.11.2.3.5 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 mode of action where an endocrine mode of action can conclusively be excluded; ii. the structural or functional relationship between the key events that result in the specific adverse effect is not understood and considered implausible. (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	Delete this section	We strongly recommend deleting this entire section as detailed in our comments as follow-up to CASG-ED4. Further, we rather recommend adding a section on what evidence is needed for classification as ED. The CLP defines evidence needed for classification of hazardous substances and it seems therefore odd to introduce some examples of evidence that does not support classification because there may be many examples of this. We also find this text very challenging, and it can be the subject of many scientific discussions. Further, this exclusion from classification is based on the current scientific knowledge, without considering the huge knowledge gap on many aspects of endocrine disruption. Knowledge advances continuously and therefore, evidence should not be excluded because it is not yet understood, or be considered implausible with the current state of knowledge. In all circumstances, this text is more relevant

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<tr><td>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.</td><td></td><td></td></tr>
<tr><td>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</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 human health</td><td>Category 2 endocrine disruptor for human health</td></tr>
<tr><td>Category 1 endocrine disruptor for human health</td><td>≥ 0.1 %</td><td></td></tr>
<tr><td>Category 2 endocrine disruptor for human health</td><td></td><td>≥ 1 %</td></tr>
</table>
Note: The concentration limits in Table 3.11.2 apply to solids and liquids (w/w units) as well as gases (v/v units).</td><td>Delete</td><td>As stated in our comments as follow-up to CASG-ED4, it is problematic from a scientific point to introduce generic 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 easily be transferred to endocrine disruptors.</td></tr>
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<tr><td></td><td></td><td></td></tr>
<tr><td>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 shall be conclusive taking into account dose and other 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></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></td><td></td></tr>
<tr><td>3.11.4 Hazard Communication</td><td></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></td><td></td></tr>
<tr><td>Table 3.11.3
Label elements of endocrine disrupting properties for human health
<table><tr><td>Classification</td><td>Category 1</td><td>Category 2</td></tr><tr><td>Symbol/pictogram</td><td>No pictogram is used</td><td>No pictogram is used</td></tr></table></td><td></td><td>We can support the new hazard and precautionary statements.</td></tr>
</table>

	Signal Word	Danger	Warning	However, we strongly support using a pictogram for the ED hazard in line with the CMR approach. Although many ED substances will also be classified as CMR, and therefore be assigned a pictogram, in the future many more substances will be classified as EDs on the basis of other endpoints than CMR, e.g. disruption of the immune or thyroid system and thus, there is a need for a pictogram specific for the ED hazard. Resorcinol is already an example of such a situation. In case it is decided to await the ED criteria discussions under the GHS before deciding on a pictogram, then a clear deadline for introducing a pictogram for the ED hazard should be inserted in the legal text.
	Hazard Statement	EUHXXX: May cause endocrine disruption in humans	EUHXXX: Suspected of causing endocrine disruption in humans	
	Precautionary Statement Prevention	P203 P263 P280	P203 P263 P280	
	Precautionary Statement Response	P308 + P313	P308 + P313	
	Precautionary Statement Storage	P405	P405	
	Precautionary Statement Disposal	P501	P501	

Annex 1.B: Proposal of hazard class for the environment

Text proposal	**Proposal for text revisions**	**Our comments**
4.2 Endocrine disrupting property for the environment	Endocrine ~~disrupting property~~ disruptor for the environment	We find it more consistent to use the wording 'endocrine disruptor for the environment' as this terminology is used in 4.11.1.1 and table 4.2.1.
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.	4.2.1.1 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.	We strongly recommend deleting the word 'consequently' to avoid creating any confusion. The text for Category 1 and Category 2 clearly defines that there should be a biologically plausible link between the adverse effects and the endocrine activity, therefore, it meets the WHO definition. The proposed wording already deviates from the WHO definition by not including 'exogenous', as well as the reference to potential endocrine disruptors.
4.2.1.2 An adverse effect is defined for the purpose of section 4.2 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.		
4.2.1.3 An endocrine activity is defined for the purpose of section 4.2 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.		

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<tr><td>4.2.2 Classification criteria for substances</td><td></td><td></td></tr>
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For the purpose of classification for endocrine disrupting 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.</td><td></td><td></td></tr>
<tr><td>Table 4.2.1
Hazard categories for endocrine disruptors for the environment</td><td></td><td></td></tr>
<tr><td><table><tr><td>Categories</td><td>Criteria</td></tr><tr><td>CATEGORY 1</td><td>Known or presumed endocrine disruptors for the environment

The classification in Category 1 is largely based on evidence from animal data. Such data shall provide evidence that the substance meets the 3 criteria below:
a) an adverse effect in an intact organism or its progeny; and
b) endocrine activity; and
c) an endocrine disrupting mode of action, i.e. there is a biologically plausible link between the endocrine activity and the adverse effect.

However, when there is information that raises doubt about the relevance of the endocrine disrupting mode of action for the environment, classification in Category 2 may be more appropriate.</td></tr></table></td><td>do

The classification in Category 1 is largely based on evidence from animal data possibly supplemented by other data. Such data shall provide evidence that the substance meets the 3 criteria below:
a) an adverse effect in an intact organism or its progeny; and
b) endocrine activity; and
c) an endocrine disrupting mode of action, i.e. there is a biologically plausible link between the endocrine activity and the adverse effect.

do</td><td>We strongly support this new wording for the Category 1. In addition, we recommend adding a clear signal that animal data can be supplemented by other data to strengthen the WoE, and to be prepared for future new alternative assessment methods.</td></tr>
<tr><td><table><tr><td>CATEGORY 2</td><td>Suspected endocrine disruptors for the environment</td></tr></table></td><td></td><td></td></tr>
</table>

A substance is classified in Category 2 for endocrine disrupting properties, if: - evidence is available to conclude that the substance meets one of the two criteria (a or b) above; and - for the remaining criterion (a or b), the evidence is not sufficiently convincing to place the substance in Category 1; and - for the third criterion (c), there must be evidence that the endocrine disrupting mode of action is biologically plausible.	A substance is classified in Category 2 for endocrine disrupting properties, if: - ~~evidence is available to conclude that the substance meets one of the two criteria (a or b) above; and~~ - the evidence for the ~~remaining~~ criterion (a or b)~~, the evidence~~ is not sufficiently convincing to place the substance in Category 1; and - for the third criterion (c), there must be evidence that the endocrine disrupting mode of action is biologically plausible.	We strongly recommend revising the text proposal for Category 2. Currently, it still sets a too high burden of proof for identification of Suspected EDs, as it requires that one of the two criteria (a or b) meet the requirements for Category 1 ED. This is not consistent with the CMR approach for human health, and rather requires a higher level of evidence than required to be classified as CMR. Further, if adopted, this approach will limit the number of substances identified as Suspected EDs. It is concerning in the current situation of overall lack of data on substances with ED properties and shortcomings of validated test methods with relevant ED endpoints.
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 endocrine-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 effects are considered not to be a secondary non-specific consequence of the other toxic effects.		
4.2.2.3 Weight of evidence		
4.2.2.3.1 A weight of evidence determination (see section 1.1.1) means that all available relevant scientific data (in vivo studies or adequately		We strongly recommend that CLP further integrates the concept of grouping chemicals

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.		based on their intrinsic properties, so that the legislation allows for classification of a substance based on grouping of substances.
4.2.2.3.2 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 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; (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;	Delete this section	We recommend fully deleting this section. As currently drafted, it only indicates generalities of good scientific practise, which come across as rather superfluous and would be more relevant to include in a guidance document.
4.2.2.3.3 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.		

4.2.2.3.4 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.		
4.2.2.3.5 Evidence considered not to support classification for endocrine disruption It is recognised that evidence may be seen in 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 mode of action where an endocrine mode of action can conclusively be excluded; ii. the structural or functional relationship between the key events that result in the specific adverse effect is not understood and considered implausible. (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.	Delete this section	We strongly recommend deleting this entire section as detailed in our comments as follow-up to CASG-ED4. Further, we rather recommend adding a section on what evidence is needed for classification as ED. The CLP defines evidence needed for classification of hazardous substances and it seems therefore odd to introduce some examples of evidence that does not support classification because there may be many examples of this. We also find this text very challenging, and it can be the subject of many scientific discussions. Further, this exclusion from classification is based on the current scientific knowledge, without considering the huge knowledge gap on many aspects of endocrine disruption. Knowledge advances continuously and therefore, evidence should not be excluded because it is not yet understood, or be considered implausible with the current state of knowledge. In all circumstances this text is more relevant for a guidance document.
4.2.3 Classification criteria for mixtures		

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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>
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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>Delete</td><td>As stated in our comments as follow-up to CASG-ED4, it makes no sense to introduce generic concentration limits for EDs. The usual principles for toxicology cannot always be used for EDs due to their specificities; non-threshold substances, low dose effects and NMDRs.</td></tr>
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<tr><td>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 shall be conclusive taking into account dose and other 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>
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<tr><td>Table 4.2.3
Label elements of endocrine disrupting properties for the environment
<table><tr><td>Classification</td><td>Category 1</td><td>Category 2</td></tr><tr><td>Symbol/pictogram</td><td>No pictogram is used</td><td>No pictogram is used</td></tr><tr><td>Signal Word</td><td>Danger</td><td>Warning</td></tr><tr><td>Hazard Statement</td><td>EUHXXX: May cause endocrine disruption in the environment</td><td>EUHXXX: Suspected of causing endocrine</td></tr></table></td><td></td><td>We can support the new hazard and precautionary statements.
However, we strongly support using a pictogram for the ED hazard, see also comments to table 3.11.3. When it comes to endocrine disruptors for the environment,</td></tr>
</table>

		disruption in the environment		these cannot be expected to have a pictogram assigned due to other hazards as may be the case for some human EDs that are also classified as CMR. This really underlines the need for a pictogram for the ED hazard. In case, it is decided to await the ED criteria discussions under the GHS before deciding on a pictogram, then a clear deadline for introducing a pictogram for the ED hazard should be inserted in the legal text.
Precautionary Statement Prevention	P203 P273	P203 P273		
Precautionary Statement Response	P391	P391		
Precautionary Statement Storage	P405	P405		
Precautionary Statement Disposal	P501	P501		