Joint Health and Environment Alliance (HEAL) and CHEM Trust comments on draft discussed at 4th CASG ED meeting of 22nd March 2021 on:

European Commission proposal for update of the REACH Annexes in relation to endocrine disruption properties

April 2021

The Health and Environment Alliance (HEAL) and CHEM Trust welcome the opportunity to comment on the European Commission progress proposal to update the REACH annexes in relation to endocrine disruption properties. These written comments complement the oral interventions made during the 4th CASG-ED meeting of 22nd March, in which the European Commission presented its proposal.

In the context of overall lack of data on endocrine disrupting substances and also referring to the European Commission Communication of November 2018[1], we would like to underline that it is crucial that the update of the REACH information requirements takes place as soon as possible. This is the basic condition to fill data gaps and ensure effective identification of substances with endocrine disrupting properties.

Procedural aspects of the current update process

From a procedural point of view, we are surprised by the European Commission's approach to this process. First of all, the basis of the 2 different proposals put forward to the CASG-ED subgroup was never made clear. Second, we had expected a better uptake of the expert advice provided by Member States and stakeholders in the development of the proposals for the update of the REACH annexes.

As highlighted by a large number of Member States at the March meeting, from the 3rd CASG ED meeting in October 2020, we recall a large support in favour of proposal number 2 as a basis for the update process, and we have noticed that the subsequent written comments were filed in this direction as a follow up to it – including those of our organisations.

CASG-ED members were explicitly asked by the European Commission to provide feedback on the proposals including to highlight their favourite option. Therefore, we are very surprised to see that the large feedback provided in support of proposal 2 does not appear to have been appropriately considered in the Commission's preparation for the 4th CASG-ED meeting. It is also not reflected in the documentation that was presented at the meeting. Based on the 3rd CASG ED meeting discussions as well as the submitted written comments, we expected the Commission to present only one option at the 4th CASG-ED, which would form the basis of the further discussions and development.

On the one hand, the Commission has maintained the 2 proposals. On the other hand, it has failed to explain to CASGED members how exactly their feedback was processed, what was taken onboard and

[1] European Commission, Communication COM(2018) 734 final, "Towards a comprehensive European Union framework on endocrine disruptors", 7th November 2018, https://ec.europa.eu/transparency/regdoc/rep/1/2018/EN/COM-2018-734-F1-EN-MAIN-PART-1.PDF

what was not, and for which reasons. Given the large investment of resources members of CASG-ED have spent on and between meetings to provide constructive feedback, this leaves us puzzled.

Moreover, we now understand that the European Commission intends to use the two policy options as presented to the subgroup in the context of a cost-benefit study, which will form the basis of a future impact assessment. We regret that this was not made transparent from the start of the process. It is also unclear what the exact terms of reference of the cost-benefit study contract are – they were neither made publicly available nor to the CASG-ED - and how the cost-benefit analysis will be carried out and with which purpose in mind. The aim for updating the REACH annexes is to gain more knowledge on the endocrine activity of substances. The identification of EDs needs to become more efficient so that companies can fulfil their duty of ensuring safe use of their chemicals under REACH. REACH substance evaluations should only be necessary in difficult cases. Based on the presentation from the Commission at the 4th CASG-ED meeting, we unfortunately expect that the large expert support in favour of option 2 will not be reflected in this process.

The identification of EDs is a complex topic with important scientific challenges, such as an overall lack of data and appropriate test methods, which make expert judgement critical to its success and future improvement. We are therefore concerned about the added-value of the aforementioned cost-benefit study, if it is not framed and carried out properly. In our view, because of the large support in favour of option 2, it would have been much more appropriate to carry out a study based on different options for refinement of this proposal rather than the approach that seems to have been adopted by the Commission.

Finally, we would also like to get clarity about the envisaged timeframe for companies to update the registration dossiers with these new requirements, as this will also be relevant for any impact assessment considerations.

Content aspects of the current update process

Building on comments that we have submitted following the 3rd CASG-ED meeting our organisations would like to emphasise the following points. Adequate information requirements for EDs under REACH need to guarantee that:

- Emphasis is put on triggers rather than waivers in order to adequately address the current overall lack of data on endocrine disrupting properties across substances at all tonnages, and most critically for substances produced at 1-10 tons per annum (about two third of all registered substances).
- The literature screening at the basis of the information requirements covers non-EATS endpoints, even if further regulatory tests are currently limited to EATS modalities.
- The in vitro testing battery proposed under Annex VII is adequately followed up on. A positive result in any of the in vitro tests should trigger appropriate in vivo mechanistic studies under annex VIII. A negative result should be read in conjunction with elements from the literature in order to decide on the next steps. This is critical in the context of lack of data on endocrine disruption and the known risks of false negatives.
- In view of the Commission's and ECHA's current emphasis on the grouping approach to speed up the evaluation of substances, it also needs to be kept in mind that positive in vitro results for one substance can be informative for the assessment of other substances of the same family and contribute to more efficient assessments.
- The data requested on human health and environmental endpoints respectively are properly integrated, since they can inform each other in order to support the provision of the right ED-

related information. Requests for specific tests and waivers for them are considered in the context of the most up-to-date and scientifically accurate knowledge:

- From Annex VII onwards
  - The Toxcast data is not equivalent to a thorough literature review and is neither fit nor sufficient to waive further studies.
  - The Uterotrophic bioassay in rodents (TG 440) regularly encounters problems due to dosing ranges being too low to see any effect. Therefore, it cannot be used as a waiver without guidance on study design.
  - The same holds true for the Hershberger bioassay in rats (TG 441). As we have also mentioned in previous comments, the proposal to use a Hershberger test result as a waiver for the conduct of the AR transactivation assay (TG 458) is not appropriate. There is no validated data showing clear association between AR transactivation and the Hershberger Assay outcomes, and so we are concerned that the 2 tests do not correlate well with each other.
- From Annex VIII onwards:
  - Any Uterotrophic or Hershberger assay requested needs to be accompanied with details about the study design that can support that it is best adapted in order to capture ED-relevant effects.
  - The EOGRTS TG 443 is to date the best designed study in order to capture ED-relevant effects. Authorities should have the flexibility to request it from Annex VIII onwards and to request the addition of DIT and DNT cohorts as they deem relevant and appropriate. Those cohorts are very informative on endpoints such as the immune and developmental neurotoxicity, so they can contribute to a more efficient use of animal studies.

REVISED PROPOSAL 1: NGO comments in blue below and in the right column

General comment on this proposal: We cannot support this proposal. There is currently too much emphasis on waivers for tests and not enough emphasis on triggers.

ANNEX VII

	COLUMN 1 STANDARD INFORMATION REQUIRED	COLUMN 2 SPECIFIC RULES FOR ADAPTATION FROM COLUMN 1	Comments	**Comments from HEAL/CHEM Trust**
11	Information on Endocrine Disruption		Several participants of the CASG ED indicated that a structure assigning information on endocrine disruption to a separate (top level) section as the preferred option. Annex IX and X contain already a section 10. Due to that, a section 11 was introduced.	Unclear
~~8.9.~~11.1	Endocrine Disruption	A weight of evidence determination using expert judgement shall be performed to assess whether there is indication for endocrine disruption for human health or the environment. The weight of evidence determination should take all available information into account, including ~~i~~Information of sections ~~8.9.1~~11.2. and ~~8.9.2~~ 11.3. and other relevant available information~~,~~ ~~including from~~ such as the results of suitable in vitro tests, relevant animal data, information from the application of the category approach (grouping, read-across), in silico methods, (Q)SAR	This section was redrafted based on feedback received from participants of the CASG ED.	

		results, human experience such as occupational data and data from accident databases, epidemiological and clinical studies and well-documented case reports and observations. ~~in silico methods shall be used to assess the endocrine disruptive properties of the substance to the extent it can be derived from that information.~~ Adequate and reliable documentation shall be provided.		
~~8.9.1.~~11.2.	Systematic literature review for endocrine disrupting properties	The systematic review of available literature and studies on mammals and non-mammalian vertebrates shall cover EATS modalities.	The systematic literature review should be carried out for EATS modalities and covering both ED for human health and for the environment. The ED criteria under the BPR and PPPR both include a systematic literature review. Inclusion of such a review in REACH ensures a harmonised approach across legislation. The ED guidance under the BPR and PPPR provide guidance how to perform a systematic literature review. The systematic literature review does not replace but complements the obligation under REACH to	Any literature review should also cover non-EATS modalities. We have some reservations regarding the use of´ systematic literature reviews´ as in the past there were examples of biased review criteria which filtered out potentially relevant studies at a very early stage, and required extensive time and expert resources. The existing obligation under REACH foresee for the registrant to provide all available information and it is clear that these requirements need to be followed and scrutinised.

			provide all available information. At the same time, the systematic review has the advantage of clearly documenting the search, making it possible for the authoriteis to check whether the obligation has been met and to follow up if not.	
~~8.9.2.~~11.3.	*In vitro* mechanistic information	Studies in section ~~8.9.2.~~11.3.1. to ~~8.9.2~~11.3.5. do not need to be conducted if • the substance meets the requirements for classification as endocrine disruptor according to the CLP criteria for ED with regard to humans and the environment, or~~.~~ • the substance has been identified as SVHC with ED properties under REACH	The waiver will need to be adapted depending on the inclusion of hazard classes for ED and one or more categories under the CLP Regulation. [this comment is also valid for similar waivers in other rows].	
~~8.9.2~~11.3.1.	Estrogen receptor transactivation assay (OECD TG 455)	The study does not need to be conducted if: – the output data from the ToxCast ER Bioactivity Model or an Uterotrophic bioassay in rodents (OECD TG 440) are available.		We cannot support the proposed waivers. • Toxcast data is not appropriate to be used as a waiver. • The Uterotrophic assay can also not be used as general waiver without full details on the study design. Further, it seems a very insensitive approach to identify potential estrogenic

				substances by waiving in vitro ER tests no matter the outcome of the Uterotrophic assay.
~~8.9.2~~11.3.2.	Androgen receptor transactivation assay (OECD TG 458)	The study does not need to be conducted if: – a Hershberger bioassay in rats (OECD TG 441) is available.		We cannot support the proposed waiver. The Hershberger assay is not appropriate to be used as a waiver of the AR transactivation assay. Further, it seems a very insensitive approach to identify potential (anti)androgenic substances by waiving in vitro AR tests no matter the outcome of the Hershberger assay.
~~8.9.2~~11.3.3.	H295R steroidogenesis assay (OECD TG 456)		Some participants highlighted performance and validation issues with the (high-through put) steroidogenesis assay, in particular as regards negative predictive values. The CASG ED is invited to comment on that.	
~~8.9.2~~11.3.4.	Aromatase assay (OPPTS 890.1200)			
~~8.9.2~~11.3.5.	<< PLACEHOLDER Thyroid assay >>	The study does not need to be conducted if: – information on the T-modality is available from relevant in vivo mammalian studies.	*In vitro* thyroid assays are foreseen to become available in the near future. ~~An~~ One or more *in vitro* thyroid assays should be included here to complete the screening for EATS modalities. The number and kind of assays has to be further	More than one in vitro thyroid assay will be needed, covering several molecular initiating events e.g. T receptor binding, T hormone transport, TPO inhibition, NIS inhibition, deiodinase inhibition. The waiver should

			assessed, taking into account the availability of validated assays. This issue should be discussed further in the CASG ED.	be more specific e.g. only waiving if in vivo studies have shown altered thyroid hormone levels. Please also clarify that the screening should also cover non-EATS modalities.

ANNEX VIII

	COLUMN 1 STANDARD INFORMATION REQUIRED	COLUMN 2 SPECIFIC RULES FOR ADAPTATION FROM COLUMN 1	Comments	**Comments from HEAL/CHEM Trust**
~~8.9.~~11.4	Endocrine Disruption ~~for human health~~	A weight of evidence determination using expert judgement shall be performed to assess whether there is indication for endocrine disruption for human health or the environment. The weight of evidence determination should take all available information into account, including ~~Appropriate *in vivo* studies in Annex IX or X shall be proposed by the registrant or may be required by the Agency if~~ the assessment in Annex VII Section 8.9~~. indicates the presence of endocrine disrupting properties;~~ and relevant results ~~there is indication of endocrine disrupting properties~~ from the information requirements in Annex VIII, Section 8.6 (Repeated dose toxicity), Section 8.7 (Reproductive toxicity) or from higher tier studies in Annex IX, Section 8.6. or 8.7, triggered by those information requirements. If the WoE determination results in indications for endocrine disrupting properties appropriate in vivo studies in Annex IX or X informing on the relevant endocrine mechanism or adverse effect shall be proposed by the registrant or may be required by the Agency.	The section mentions again, as section 11.1, a weight of evidence (WoE) determination. As an alternative, it appears to be sufficient to simply refer to the WoE determination of this section 11.1. as follows: If the WoE determination in section 11.1 results in indications of endocrine disrupting properties, … ~~OECD TG 407, 408, 409, 414, 421/422, 443, if available.~~ The sentence "If the WoE determination results in indications for endocrine disrupting properties appropriate in vivo studies in Annex IX or X, sections xx, shall be proposed by the registrant or may be required by the Agency" should be understood as	We cannot support the text as it stands. If available information indicates an ED concern, it should be possible for authorities to request in vivo mechanistic information (e.g. well-designed Hershberger, Uterotrophic or Amphibian metamorphosis assays) to further investigate the ED potential. Chemicals falling under Annex VIII are equivalent to a tonnage band of 10-100 tons, which is significant enough to warrant clarifications.

		In vivo ~~S~~studies that inform on endocrine disruption for human health do not need to be conducted if – ~~if~~ the substance meets the requirements for classification as endocrine disruptor according to the CLP criteria for ED with regard to humans , or – the substance has been identified as substance of very high concern with ED properties for human health – ~~a substance undergoes immediate disintegration and there are sufficient data on the cleavage products, or~~ – relevant human exposure can be excluded in accordance with Annex XI Section 3. In vivo studies that inform on endocrine disruption for the environment do not need to be conducted if – the substance meets the requirements for classification as endocrine disruptor according to the CLP criteria for ED with regard to the environment , or – the substance has been identified as substance of	that it is necessary to include studies that cover the relevant mode of actions.	

		very high concern with ED properties for environment		
9.1.	Aquatic toxicity			
9.1.3.	Short-term toxicity testing on fish	If there are any indications for endocrine disrupting properties long-term toxicity testing (Annex IX Section 9.1.6) instead of short-term toxicity testing on fish, shall be proposed by the registrant or may be required by the Agency.	This has to be read in conjunction with the existing text and the Action 2 points on aquatic toxicity. Waivers of this section apply. Endocrine disrupting properties means endocrine activity or adverse effects that might be caused by endocrine activity.	

ANNEX IX

	COLUMN 1 STANDARD INFORMATION REQUIRED	COLUMN 2 SPECIFIC RULES FOR ADAPTATION FROM COLUMN 1	Comments	**Comments from HEAL/CHEM Trust**
~~8.9.~~	~~Endocrine disruption for human health~~			
~~8.9.3.~~11.5	Uterotrophic Bioassay in Rodents (OECD TG 440)	The study does not need to be conducted if: – there is sufficient weight of evidence to conclude on the presence or absence of an estrogenic mode of action. – the output data from the ToxCast ER Bioactivity Model is available, or – there are no indications of estrogen related adversity in a reliable Extended One-Generation Reproductive Toxicity Study (OECD TG 443) – there are indications of estrogenic activity in other *in vivo* studies, e.g. OECD TG 407, 421/422.	Waiver based on text in proposal for update of IR under the BPR. There is overlap of the waivers with the first waiver. Several participants pointed out that the ToxCast ER Bioactivity Model has not been validated. On the other hand, it is noted that the ED guidance under the PPPR and BPR is using ToxCast data as an alternative to the uterotrophic assay for evidencing E-modality. The CASG ED is invited to provide comments. Some participants highlighted a poor reproducibility of the uterotrophic	We cannot support the text as it stands. • We disagree with Toxcast data being used as a waiver for reasons already outlined above. • Further, which endpoints in the TG 443 will be indicative to allow waiving? This test is primarily covering good anti-androgenic endpoints but not sufficient estrogenic endpoints. • The Uterotrophic assay should be adequate and reliable and full details about the study design need to be provided for the interpretation of the results.

			assay. The CASG ED is invited to provide comments.	
~~8.9.4.~~11.6	Hershberger Bioassay in Rats (OECD TG 441)	The study does not need to be conducted if: – there is sufficient weight of evidence to conclude on the presence or absence of an androgenic mode of action. – if there are no indications of (anti-)androgenic related adversity in a reliable Extended One-Generation Reproductive Toxicity Study (OECD TG 443) – If there are indications of (anti)androgenic activity in other *in vivo* studies, e.g. OECD TG 407, 421/422.	Waiver based on text in proposal for update of IR under the BPR. There is overlap of the waivers with the first waiver. Some participants highlighted a high variability of results of the Hershberger assay. The CASG ED is invited for comments.	We cannot support the text as it stands. The results of the Hershberger assay are dependent on a lot of variables. If it is requested, full details about the study design need to be provided for the interpretation of the results.
9.1.	Aquatic toxicity	Other long-term toxicity testing than the tests in Section 9.1.5. or 9.1.6. shall be proposed by the registrant or may be required by the Agency in accordance with Article 40 or 41, if the chemical safety assessment according to Annex I indicates the need to investigate further the effects on aquatic organisms. The choice of the test(s) depends on the results of the chemical safety assessment.	For information only. This will be discussed during the meeting of CASG-IR. The text in the left column corresponds to a current proposal submitted for discussion to the CASG-IR.	
9.1.6.	Long-term toxicity testing on fish The information shall be	The test in section 9.1.6.4 shall be proposed by the registrant or may be required by the Agency if		

	provided for one of the Sections 9.1.6.1, 9.1.6.3 or 9.6.1.4	– there is indication of endocrine disrupting properties, and – a Medaka Extended One-Generation Reproduction Test (OECD TG 240) or a Zebrafish Extended One-Generation Reproduction Test is not available. Fish short-term toxicity tests on embryo and sac-fry stages (OECD TG 212) (Annex IX Section 9.1.6.2) that were initiated before [date of entering into force] shall be considered appropriate to address this standard information requirement in case there is no indication of endocrine disrupting properties from these tests.	For the Zebrafish Extended One-Generation Reproduction Test, please see comments on Annex X, Section 9.7.2.	
9.1.6.1.	Fish early-life stage (FELS) toxicity test (OECD TG 210)			
~~9.1.6.2~~	~~Fish short-term toxicity tests on embryo and sac-fry stages~~		Section 9.1.6.2 should be deleted.	
9.1.6.3	Fish, juvenile growth test (OECD TG 215)		.	
9.1.6.4	Fish Sexual Development Test (OECD TG 234)			
~~9.7.~~	~~Endocrine disruption for the environment~~			
~~9.7.1~~11.7	Amphibian Metamorphosis Assay (OECD TG 231)	The study does not need to be proposed if: – there is sufficient weight of evidence to	Waiver based on text in proposal for update of IR	

		conclude on the presence or absence of a thyroid mode of action in non-mammalian species; – there is no indication for a T-modality – a Larval Amphibian Growth and Development Assay (OECD 241) is available. – a fish study providing information on T-modality is available that has been conducted in accordance with a test method laid down in Council Regulation (EC) 440/2008 or with an international test method recognised by the Commission or the Agency as being appropriate. – the substance can be identified as endocrine disruptor according to the CLP criteria for ED with regard to environment Appropriate *in vivo* studies in Annex IX and/or X shall be proposed by the registrant or may be required by the Agency in case of a positive result in any of the *in vivo* mechanistic studies.	under the BPR. There is overlap of the waivers with the first waiver. Waivers require further guidance. Placeholder to prepare for studies that are in the pipeline. Waiver cover the cases where the substance could be identified as ED for the environment based on the mammalian dataset. XETA only to be discussed in the Guidance in alignment with PPPR and BPR.	

ANNEX X

	COLUMN 1 STANDARD INFORMATION REQUIRED	COLUMN 2 SPECIFIC RULES FOR ADAPTATION FROM COLUMN 1	Comments	**Comments from HEAL/CHEM Trust**
9.7.	Endocrine disruption for the environment	Further testing according to Sections 9.7.2. or 9.7.3. shall be proposed by the registrant or may be required by the Agency if the chemical safety assessment according to Annex I indicates the need to investigate further the endocrine disrupting properties for the environment, unless the substance meets the requirements for classification as endocrine disruptor for the environment.~~, unless the substance meets the requirements for classification as endocrine disruptor for the environment.~~ The choice of the appropriate test depends on the results of the chemical safety assessment.	Alternatively, the obligation for further testing, if information is not sufficient for classification, could include a trigger system that requires the Medaka EOGR (OECD TG 240) in case of EAS modalities and the LAGDA (OECD TG 241 in case of T-modalities. The classification-based waiver option will need to be adapted depending on the inclusion of hazard classes for ED and one or more categories under the CLP Regulation. Further discussions might be required on the waiver as regards a possible need of testing for the derivation of PNECs.	
9.7.2.	Medaka Extended One-Generation Reproduction Test (OECD TG 240) Zebrafish Extended One-Generation Reproduction Test	The study does not need to be proposed if: – a Fish Life Cycle Toxicity Test (OPPTS 850.1500; covering all the 'estrogen-, androgen- and steroidogenic-mediated' parameters foreseen to be measured in the OECD TG 240 study) is available, or – A Fish Sexual Development Test	Several participants of the CASG ED pointed out that a ZEOGRT should be included as alternative to the MEOGRT once the first one is validated and adopted at the OECD-level. A possible wording for column 1 could be: "An extended one-generation	

		(OECD TG 234) is available, or – there is no indication for endocrine activity or endocrine related effects from the mammalian data set or from any other relevant information (e.g. literature) and valid *in vivo* data is available, with no information suggesting that the active substance may elicit endocrine activity or effects potentially related to endocrine activity in either the Fish Short Term Reproduction Assay (OECD TG 229), or the 21-day Fish assay (OECD TG 230) or Fish Sexual Development Test (OECD TG 234) or the Larval Amphibian Growth and Development Assay (OECD 241) If other data are available covering the estrogenic-, androgenic- and steroidogenic- related modalities or parameters investigated in OECD TG 229 or OECD TG 230 or OECD TG 234~~ or OECD TG 241~~, then those data can be used instead.	reproduction test with a fish species" without mentioning the OECD TG. REACH Art. 13(3) requires that test methods are either laid down in the Test Methods Regulation or are in accordance with international test methods recognised by the Commission or ECHA, which should ensure that only validated and adopted methods (such as OECD TGs) can be used. This could be further ensured by providing guidance.	
9.7.3.	Larval Amphibian Growth and Development Assay (OECD TG 241)	The study does not need to be proposed if: – there is no indication for endocrine activity or endocrine related effects from the mammalian data set, or from any other relevant information (e.g. literature), and – valid *in vivo* data is available, with no information suggesting that the substance may	Several participants remarked that the US validation panel during validation of the LAGDA commented: "because chemical exposure begins during embryogenesis in the LAGDA, the effects on development may be manifest as a failure of	In response to the question about the reliability of the LAGDA test, we wish to emphasize that (as presented by the Danish CA at the latest ECHA EDEG meeting) this test is designed to

			have endocrine disrupting properties in an Amphibian metamorphosis assay (OECD 231).	organogenesis independent of thyroid hormone, and any thyroid effects that are seen may be secondary to the teratogenic effects. Therefore, distinguishing an endocrine MOA from a non-endocrine MOA, even if the chemical results in altered thyroid gland development and function, may be difficult." The CASG ED is invited to provide feedback on whether a LAGDA can provide reliable information on the thyroid mode of action.	detect apical effects resulting from both endocrine and non-endocrine mechanisms and it includes endpoints that are partly specific to key endocrine modalities. So it can provide reliable information on the thyroid mode of action through providing evidence of the disruption of the EAT systems in developing amphibians. Because the test covers endocrine and non-endocrine mechanisms, if well designed and well used, it can positively contribute to a smarter use of animals. As regards the proposal wording for the waiver, please make explicit that a LAGDA request can only be waived on the basis of

				a positive AMA result. The current wording is not clear enough.

REVISED PROPOSAL 2:

General comment on this proposal: This proposal is preferred as a basis for developing the information requirements. The emphasis is rightly put on triggers for tests across annexes, and it also provides for a better integration of human health and environment data. Further comments are inserted directly in the table (right column).

ANNEX VII

	COLUMN 1 STANDARD INFORMATION REQUIRED		COLUMN 2 SPECIFIC RULES FOR ADAPTATION FROM COLUMN 1	Comments	**Comments from HEAL/CHEM Trust**
10. ENDOCRINE DISRUPTION					
			If a substance is known to have endocrine disrupting properties for~~on in~~ human health~~s~~, meeting the criteria for classification as an endocrine disruptor for human health category 1: [Hazard code to be inserted] (EUHXXX), and the available data are adequate to support a robust risk assessment, then no further testing for endocrine disruptive properties with regard to humans will be necessary. However, testing for endocrine disruption with regard the environment must be considered. If a substance is known to have endocrine disrupting properties for~~on in~~ the environment, meeting the criteria for classification as an endocrine disruptor for the environment category 1: [Hazard code to be inserted] (EUHXXX), and the available data are adequate to support a robust risk assessment, then no further testing for endocrine disruptive properties with regard to the environment will		

			be necessary. However, testing for endocrine disruption with regard the humans must be considered.		
10.1.	Assessment of ~~the~~ endocrine disruption~~ive properties of the substance~~ to the extent that can be derived from the ~~relevant~~ available information ~~and other relevant information~~, including *in silico* and *in vitro* methods and scientific literature. In all cases, adequate and reliable documentation shall be provided.				The scientific literature review must cover non-EATS modalities.
10.2.	*In vitro* mechanistic information	10.2.	Appropriate *in vivo* mechanistic studies in Annex VIII must be conducted or may be required by the Agency in case of a positive result in any of the *in vitro* mechanistic studies. Studies do not need to be conducted if the substance can be identified as endocrine disruptor according to the CLP criteria for ED with regard to humans and the environment.		
10.2.1.	Estrogen receptor transactivation assay (OECD TG 455)	10.2.1.	The study does not need to be conducted if: – the output data from the ToxCast ER Bioactivity Model or an Uterotrophic bioassay in rodents (OECD TG 440) are available.		Please delete the two waivers. • Toxcast data is not appropriate to be used as a waiver. • The Uterotrophic assay can also not be used as general waiver

					without full details on the study design. Furthermore, it seems a very insensitive approach to identify potential estrogenic substances by waiving in vitro ER tests no matter the outcome of the Uterotrophic assay.
10.2.2.	Androgen receptor transactivation assay (OECD TG 458)	10.2.2.	The study does not need to be conducted if: – a Hershberger bioassay in rats (OECD TG 441) is available.		Please delete the waiver. The Hershberger assay is not appropriate to be used as a waiver of the AR transactivation assay. Furthermore, it seems a very insensitive approach to identify potential (anti)androgenic substances by waiving in vitro AR tests, no matter the outcome of the Hershberger assay.
10.2.3.	H295R steroidogenesis assay (OECD TG 456)	10.2.3.			
10.2.4.	Aromatase assay (OPPTS 890.1200)	10.2.4.			
10.2.5.	<< PLACEHOLDER Thyroid assays >>	10.2.5		*In vitro* thyroid assays, covering several molecular initiating	The screening must include non-EATS modalities

				events e.g. T receptor binding, T hormone transport, TPO inhibition, NIS inhibition, deiodinase inhibition, are foreseen to become available in the near future. ~~These~~ These assays should be included here to complete the screening for EATS modalities.	

ANNEX VIII

	COLUMN 1 STANDARD INFORMATION REQUIRED		COLUMN 2 SPECIFIC RULES FOR ADAPTATION FROM COLUMN 1	Comments	**Comments from HEAL/CHEM Trust**
9.1.	Aquatic toxicity	9.1.			
9.1.3.	Short-term toxicity testing on fish (OECD TG 203). The registrant should consider long-term toxicity testing if the substance is poorly water soluble.	9.1.3.	If there are any indications for endocrine disrupting properties long-term toxicity testing (Annex IX Section 9.1.6) instead of short-term toxicity testing on fish, shall be proposed by the registrant or may be required by the Agency	This has to be read in conjunction with the existing text and the Action 2 points on aquatic toxicity	
10. ENDOCRINE DISRUPTION					
10.2.	*In vivo* mechanistic information	10.2.	Appropriate *in vivo* studies in Annex IX and/or X must be proposed by the registrant or may be required by the Agency in case of a positive result in any of the *in vivo* mechanistic studies. ~~Studies do not need to be conducted:~~ – ~~if the substance can be identified as endocrine disruptor according to the CLP criteria for ED with regard to humans and the environment.~~		Please make explicit that OECD TG 443 is part of the appropriate in vivo studies that can be requested at this stage, including potential additions of DIT/DNT cohorts as seen fit by authorities.
10.2.1.	Uterotrophic Bioassay in Rodents (OECD TG 440) or the output data from the ToxCast ER Bioactivity Model	10.2.1.	The study does not need to be conducted if: – ~~the output data from the ToxCast ER Bioactivity Model is available, or~~ – there are no indications of estrogen related adversity in a reliable Extended One-Generation Reproductive Toxicity Study (OECD TG 443); or – there are indications of (anti)estrogenic		It is unclear why the output from the ToxCast ER bioactivity model has been proposed here, or how it is supposed to add value. Please explain how it can be considered equivalent to the TG 440. Furthermore,

			activity in other reliable *in vivo* studies, e.g. OECD TG 407, 421/422, 443, sufficient to conclude that the substance has (anti)estrogenic activity.		please clarify which endpoints in the TG 443 will be indicative to allow waiving. This test is primarily covering good anti-androgenic endpoints but not sufficient estrogenic endpoints.
10.2.2.	Hershberger Bioassay in Rats (OECD TG 441)	10.2.2.	The study does not need to be conducted if: – if there are no indications of androgen related adversity in a reliable Extended One-Generation Reproductive Toxicity Study (OECD TG 443), or – If there is information are indications of (anti) androgenic activity in other adequate and reliable *in vivo* studies, e.g. OECD TG 407, 421/422, or 443, sufficient to conclude that the substance has (anti)androgenic activity.		
10.2.3.	Fish Short Term Reproduction assay (OECD TG 229)	10.2.3.	The study does not need to be conducted if: – a 21-day Fish Assay (OECD TG 230),; or – a Fish Sexual Development Test (OECD TG 234), or – a Medaka Extended One-Generation Reproduction Test		

			(OECD TG 240), or – a Fish Life Cycle Toxicity test (OPPTS 850.1500; covering all the 'estrogen-, androgen- and steroidogenic-mediated' parameters foreseen to be measured in the OECD TG 240 study) is available.		
10.2.4.	Amphibian Metamorphosis Assay (OECD TG 231)	10.2.4.	The study does not need to be conducted if: – a Larval Amphibian Growth and Development Assay (OECD 241) is available. ~~the substance can be identified as endocrine disruptor according to the CLP criteria for ED with regard to environment~~	XETA only to be discussed in the Guidance in alignment with PPPR and BPR	

ANNEX IX

	COLUMN 1 STANDARD INFORMATION REQUIRED		COLUMN 2 SPECIFIC RULES FOR ADAPTATION FROM COLUMN 1	Comments	**Comments from HEAL/CHEM Trust**
9.1.	Aquatic toxicity	9.1.	9.1. Other long-term toxicity testing than the tests in Section 9.1.5. or 9.1.6. shall be proposed by the registrant or may be required by the Agency in accordance with Article 40 or 41, if the chemical safety assessment according to Annex I indicates the need to investigate further the effects on aquatic organisms. The choice of the test(s) depends on the results of the chemical safety assessment.	For information only. This will be discussed during the meeting of CASG-IR. The text in the left column corresponds to a current proposal submitted for discussion to the CASG-IR.	
9.1.6.	Long-term toxicity testing on fish	9.1.6.		OECD TG 234 should be performed instead of OECD TG 210 if LT testing is triggered. There is an Action 2 (general revision of REACH IR) activity here.	
9.1.6.1.	Fish Sexual Development Test (OECD TG 234) (instead of FELS)	9.1.6.1.	The study does not need to be proposed if: – a Medaka Extended One-Generation Reproduction Test (OECD TG 240) ~~is available~~, or – - a Fish Life Cycle Toxicity Test (OPPTS 850.1500; covering all the 'estrogen-, androgen- and steroidogenic-mediated' parameters foreseen to be		

			measured in the OECD TG 240 study) are available.		

ANNEX X

	COLUMN 1 STANDARD INFORMATION REQUIRED		COLUMN 2 SPECIFIC RULES FOR ADAPTATION FROM COLUMN 1	Comments	**Comments from HEAL/CHEM Trust**
8.6.4.				In contrast to active substances under BPR and PPPR, carcinogenicity studies are normally not available for REACH substances. These studies play an important role in establishing adversity in particular for the T modality. In order to be able to conclude on ED properties for the T modality, there may be a need for additional information which could be requested using 8.6.4., e.g. developmental neurotoxicity (OECD TG 426). However, currently this provision only exists at Annex X. Consider to introduce 8.6.4. also in Annex VIII and IX.	We can support the inclusion of TG 426, However, when used to address adverse effects by the T-modality, TH measurements during sensitive windows of brain development needs to be included to show the plausible link between MoA and adverse effects.
10. ENDOCRINE DISRUPTION					
10.3.1.	Medaka Extended One-Generation Reproduction Test (OECD TG 240)	10.3.1.	The study does not need to be proposed if: – a Fish Life Cycle Toxicity Test (OPPTS 850.1500;	Further consideration on waiver are needed, depending on the risk	

			covering all the 'estrogen-, androgen- and steroidogenic-mediated' parameters foreseen to be measured in the OECD TG 240 study) is available. – there is no indication for endocrine activity or endocrine related effects from the mammalian data set or from any other relevant information (e.g. literature) and valid *in vivo* data is available, with no information suggesting that the ~~active~~ substance may elicit endocrine activity or effects potentially related to endocrine activity in either the Fish Short Term Reproduction Assay (OECD TG 229), or the 21-day Fish assay (OECD TG 230), or Fish Sexual Development Test (OECD TG 234). If other data are available covering all the estrogenic-, (anti)androgenic- and steroidogenic-related modalities and ~~or~~ parameters and relevant life stages investigated in OECD TG 229 or OECD TG 230 or OECD TG 234, then those data can be used instead.	management measures that will be implemented in REACH for substances classified as ED in CLP.	
10.3.2.	Larval	10.3.2.	The study does not need	Further	We cannot

	Amphibian Growth and Development Assay (OECD TG 241).		to be proposed if: – there is no indication for endocrine activity or endocrine related effects from the complaint mammalian data set, or from any other relevant information (e.g. literature) and valid *in vivo* data is available, and – valid *in vivo* data is available, with no information suggesting that the substance may have endocrine disrupting properties in an Amphibian Mmetamorphosis Aassay (OECD 231).	consideration on waiver are needed, depending on the risk management measures that will be implemented in REACH for substances classified as ED in CLP.	support the text as it stands. AMA is only a screening test, while LAGDA is a partial life-cycle test covering chemicals disrupting EAT systems in developing amphibians and it can identify EAT-mediated adversity. Therefore a negative AMA is not enough to support the waiving of request for a LAGDA. We agree a LAGDA request can be waived if a positive AMA result has identified ED properties.