8 December 2014

COMMENTS ON AN ANNEX XV DOSSIER FOR IDENTIFICATION OF A SUBSTANCE AS SVHC AND RESPONSES TO THESE COMMENTS

Substance name: Bis(2-ethylhexyl) phthalate (DEHP)
CAS number: 117-81-7
EC number: 204-211-0

The substance is proposed to be identified as meeting the following SVHC criteria set out in Article 57 of the REACH Regulation: Equivalent level of concern having probable serious effects to human health and the environment (Article 57 f)

Disclaimer: Comments provided during public consultation are made available as submitted by the commenting parties. It was in the commenting parties own responsibility to ensure that their comments do not contain confidential information. The Response to Comments table has been prepared by the competent authority of the Member State preparing the proposal for identification of a Substance of Very High Concern. RCOM has not been agreed by the Member State Committee nor has the document been modified as result of the MSC discussions.

PART I: Comments and responses to comments on the SVHC proposal and its justification

General comments on the SVHC proposal

No	Date	Submitted by (name, Organisation/ MSCA)	Comment	Response
1	2014/10/09	Member State United Kingdom	Specific comments Similar to the earlier alkylphenol dossiers, it would be helpful to present the ecotoxicity data grouped per species, with a judgement made about the most relevant and reliable adverse end point (and L/NOEC) for each species. Otherwise it is rather difficult to make sense of the weight of available evidence as presented (e.g. for Japanese Medaka). Section 3.2 (p. 8): Given our comments on bioaccumulation, it is perhaps not so important to focus on persistence in this case. However, the way that the degradation information has been summarised in this report gives only a partial account of the evidence	Not agreed. Even though we have not structured the text as suggested, it is in our view possible to come to a WoE based conclusion when considering the summaries on adverse effects, endocrine mode of action and plausible link between adversity and endocrine mode of action. A general reference to the EU RAR (2008) has now been made. The information on bioaccumulation and (bio)degradation is indeed very short and only based on the summary of the EU RAR as these fate related properties in our view are not of relevance for identification of substances with ED properties with serious health

			available in the ESR Risk Assessment Report (RAR) (JRC, 2008). The surface water half-life of 50 days quoted in the dossier is actually based on a default assumption related to a decision on ready biodegradation. Several laboratory ready and inherent tests indicate high levels of mineralisation under aerobic conditions, and studies using field samples also suggest more rapid degradation in surface water than implied by this value (with one exception, although that study focussed on mineralisation only and gave no information about primary degradation). Quoted half-lives should also be associated with a temperature. The sediment half-life of 300 days is also an estimate based on a default assumption. The experimental sediment data summarised in the ESR RAR are conflicting. In one study (Johnson and Lulves, 1975) an initial concentration of 2 mg/kg wwt achieved ~60% mineralisation after 28 days' incubation at 22 °C. Another study using a similar concentration and the same temperature (Johnson, Heitkamp and Jones, 1984) found 8.5% degradation after 28 days. There is no discussion in the RAR about the quality of either study or possible reasons for this difference (e.g. organic carbon content of the test sediments). It is unclear if either study would be considered acceptable to modern standards. The assumed sediment half-life is acceptable for risk assessment purposes, since it is possible to request further data if a risk is identified. However, we think we should be cautious about using this information for hazard assessment purposes. The assumed sediment half-life significantly exceeds the Annex XIII vP criterion of 180 days. Whilst adsorption to organic matter (and temperature) is clearly important, this conclusion is contrary to the agreed approach to PBT assessment, where readily biodegradable substances are screened out as not being P/vP.	or environmental effects of ELoC Please refer to our response on the general issue of interpretation of art. 57f (Equivalent Level of Concern, ELoC): in brief, we are of the opinion that the ELoC refers to effects of ELoC as specified in art. 57f (i.e. serious effects of ELoC as CMRs and vPvB/PBTs) – Hence it is for the identification of substances with endocrine disruptive properties according to Art. 57f not relevant to refer to other aspects than evidence of endocrine activity and its likely causal link to serious effects for HH and ENV as specified in the article. Other aspects, such as those addessed here (bioaccumulative properties and peristency) are therefore not considered relevant to consider here. Therefore, in the curerent text persistency and bioaccumulative properties are only mentioned briefly as background information and do not influence the final conclusion. Therefore, no change of the SD (Support Document) text has been made.

			We acknowledge that the substance appears to be persistent in anaerobic sediment (this may be the case for many hydrophobic organic substances).	
			Section 5.1.1 (p. 24): How are primates relevant in an EU context? The same comment applies to Section 5.1.2.3 (p. 37).	Sorry for this (funny) mistake. You are right, no primate wild-life species exist in the EU. Text of SD corrected to mammalian species
			Section 5.1.2 (p. 25-29): In general terms, the information presented in the dossier is very brief and prevents an independent assessment of the relevance of the reported effects. The dossier appears to be based on journal article abstracts, and the level of critical appraisal is unclear. We also think it is good practice to list any studies identified in the literature review that have not been considered in the dossier, along with a reason, to avoid accusations of "cherry picking" data.	All peer reviewed studies where endpoints could be of ED relevance have been included. No studies have been excluded unless by mistake (if overseen in the literature search). The literature search databases and phrases are included in section 5.1.2. Hence, a possible accuastion of „cherry picking" would in our view not be justified.
			The Kim et al. (2002) study with Japanese Medaka (Oryzias latipes) appears to give a NOEC based on a concentration that is not mentioned in the table. Is this a typo? Given the apparent uncertainties in the analytical method for VTG, and the use of test concentrations significantly in excess of the critical micelle concentration, the relevance of this study could be questioned. As noted in the general comments, the available information for each species should be compared and a conclusion drawn about the most reliable NOEC for adverse effects.	Accepted. It was a typo and the text has now been changed to <0.01mg/l. As described in the notes (6 and 7) in table 4, the VTG analysis' are not regarded fully reliable and therefore this endpoint is not used in NOEC determination. The study is included because it was a part of the EU RAR (2008) and hence then considered to contribute with valuable information.
			The Caunter et al. (2004) study detected an increase in VTG in the F2 generation for Fathead Minnow (Pimephales promelas) at the high dose of 500 mg/kg food. Is this concentration environmentally relevant? Presumably no effects were observed on hatchability, survival, growth or sex ratio, and this should be mentioned.	Please refer to our response above concerning ELoC:„environmentally relevant concentration" is a fluffy concept, but for the identification of substances with ED properties this is not relevant (exposure is outside the scope of art. 57f which concerns identification based on serious effect properties due to a certian type of MoA (ED) and not to expsoure related criteria. Note that exposure related criteria are actually mentioed as priority setting criteria in art. 58 (wide dispersive use and high tonnage) for prioritizing SVHCs on

				the Candidate list for inclusion on the Authorization List.
			The Xenopus laevis studies used a repeated weekly application of DEHP at a concentration that would have involved colloids, if not undissolved substance. The exposure of the animals was therefore presumably highly variable. It would be useful to know how much the Holfreter solution retarded development (rather than just stating "to a lesser degree" than DEHP). How does the high frequency of unhatched eggs affect the validity of the study? We doubt whether the results of this study are reliable.	Agree. Note that a solvent (methanol) was used and that organic solvent may change the apparant solubility of test substances significantly. The following sentence has now been included in the dossier: „The time from egg to fully developed frog was 78 days in the control, 96 days in the 1/5 Holtfreter solution and 184 days in the 2 mg/l DEHP group" * assigned to this study (cf. Response below) There were no differences in hatching between treatments and control and the doubling of developmental time in the DEHP group is therefore regarded as reliable even though the hatchability was generally low
			The main conclusion of this section is that there was an effect on sex ratio in Atlantic Salmon (Salmo salar), but that this observation could not be replicated with a more powerful test. This is not obvious from the information provided in the table, which is rather brief. It would be helpful to know the magnitude of the shift, rather than say it is "significant" but the overall message we take from the discussion is that this information is not relevant. In addition, this effect occurred after dosing with 1500 mg/kg (1.5 parts per thousand) food – this seems to be a very high concentration, and we think there needs to be some discussion about its relevance. An analogy can be drawn with aquatic toxicity studies, where effects above 100 mg/L are not considered to be significant. We also note that no effect on either sex ratio or ovo-testis appears to be have been detected at 300 800 mg/kg food (before correction), i.e. it appears that there is a threshold for this "effect" (at least based on the test designs that were used).	The sex ratio change was from 49 % females to 64% in the high exposure group. This has now been mentioned in the SD. It seems likely that the changed sex ratio observed by Norrgren et al (1999) may have been caused by a higher exposure concentration than that used (and measured) in the study by Norman et al (2007). This may be a plausible hypothesis, because ovo-testis, as observed in the study by Normann, can be characterized as a mild form of phenotypic sex reversal which was only observed in the study by Norgrren Agree that the applied concentration in the food is high in both the Norrgren and the Norman studies. Norman reported though a very high survival rate and no dose dependent effect on weight so systemic toxicity seems not to appear. Agree that a sex ratio threshhold has been detected in this study but the apperance of a threshold is a consequence of the binary endpoint (male/female). This does not mean that a phenotypic sex reversal may not occur in individual fish below this threshhold but detection of such changes are also dependent of the
			Section 5.1.2.1.2 (p. 29-33): We note that the dossier reports effects from tests carried out well in excess of the solubility in pure water, on the grounds that if an effect is seen, it must be due to the DEHP present	

			(either as micelles or dissolved). We think this is potentially misleading – not only might there be soluble impurities and/or degradation products present, but adsorption to food might also be significant, leading to greater exposure than is in fact likely when the substance is present below its critical micelle concentration. In addition, the UK view is that the concentration at which an effect occurs is in fact a relevant factor.	number of fish studied and the comprehensiveness of the histopathological investigations performed. It is true that effects recorded only above the water solubility concentrations of DEHP (in some studies solubility of DEHP is also affected by use of different carrier solvents as DMSO and ethanol) may be caused by exposure/uptake of DEHP micells / DEHP adsorped to particulate organic material in the test medium. DEHP may however also under natural conditions be taken up by oral ingestion of DEHP contaminated organic material. Focus here is on hazard identification relative to serious population relevant effects related to ED and not risk assessment where quantification of the DEHP expsoure according to exposure routes might be relevant. Hence ED related serious population relevant effects only found above the water solubility limit of DEHP is therefore regarded as of some relevance. Such studies have been marked with an * in the revised SD. Text to this end has been added in the rev. SD.
			The Zanotelli et al. (2010) study with Guppy (Poecilia reticulata) shows a significant effect on fish growth, although there is no evidence that this was ED-related. Presumably the NOEC is in the range 0.1-1 µg/L (0.0001-0.001 mg/L).	Zanotelli et al: There is no evidence that the significant effects on growth are ED-related –or the contrary. Therefore no definitive conclusions on MoA are drawn in the SD. The results may anyway be relevant because they occur far below other reported toxicity effects in fish and are likely – at least partly – to be ED-related. And as written above - all peer reviewed studies where endpoints could be of ED relevance have been included. We have tried to make the text even more accurate in respect to this in the SD.
			The Ye et al. (2014) study with Marine Medaka (Oryzias melastigma) appears to show some important effects, and as a key study it should be described in more detail than is done in the dossier. For example, it would be helpful to indicate the magnitude of the changes	Ye et al : More details have now been included in the SD as requested and abbreviations are explained: As a general reply to comments on significant changes; changes are described as significant

			observed, and to be clear about which ones were statistically significant (in a number of places "significant increases" are noted in the text, whereas only "increases" in others). What was the exposure regime? The terms MEHHP and MEOHP should also be explained. Were the effects observed at both test concentrations (i.e. is the NOEC below 0.1 mg/L)? This is not a typical test species in OECD test guidelines – is there any information about its suitability for laboratory testing in other national guidelines? Please state whether any adverse apical effects were observed in the Wang et al. (2013) study with Chinese Rare Minnow (Gobiocypris rarus). The Uren-Webster et al. (2014) study may be useful from a mechanistic perspective, but the exposure route and concentrations are not relevant (rather than "not necessarily relevant" as stated in the dossier). Please state whether any adverse apical effects were observed in the Mankidy et al. (2013) and Crago & Klaper (2012) studies with Fathead Minnow (Pimephales promelas). Can a NOEC be derived from these studies?	when p<0.05. When „effects" are mentioned in the referenced studies it means that this significance level at least was observed. We agree that the size oft he P-value e.g. P<0.001 could be of value to report which has ben done in the rev. SD. The reproductive effects occured at 0.1 mg/l DEHP so the NOEC was below 0.1 mg/l – The study will be marked with * (cf. response above). O. melastigma is not a widely used OECD model fish but has been used in some ecotox studies as a marine model – probably because it is closely related to Japanese medaka (Oryzias latipes) which is a well described test model. This will be added in the revised SD. Wang et al: Accepted: The sentence „No endocrine related or systemic adverse effects were investigated nor observed" has been included in the SD. Uren-Webster et al.:Accepted that exposure route is not natural. Text modified to „a study that may be useful from a mechanistic perspective but with a not natural exposure route". As long as severe systemic toxicity is not occuring at the tested doses, the effects related to ED at these doses have been regarded as of some relevance. Mankidy et al. Accepted: In the summary the sentence „DEHP caused cytotoxicity at 10 mg/L (P < 0.01) and in developing fathead minnow embryos Exposure to 1 mg DEHP/L resulted in 30% mortality" has been inserted as well as the sentence: some of the exposure concentrations causing effect exceeded the water solubility of DEHP by several orders of magnitude and exposure via other routes than water may have occurred. .No adverse apical effects were reported by Crago & Klaper. A NOEC cannot be derived for an adverse effect

			Carnevali et al. (2010) and Corradetti et al. (2013) studies with Zebrafish (Danio rerio) appear to be key studies for DEHP, so should be described in more detail than is done in the dossier. For example, it would be helpful to indicate the magnitude and statistical significance of the changes observed, as well as the exposure regime (e.g. renewal period and test concentration maintenance). Please state the NOEC (<0.2 µg/L?), and describe the level of consistency in response between these two studies and others using this species (as relevant). We have a couple of important points requiring clarification: • It appears that the work was conducted by the same research group, so these two studies might not be entirely independent. Are the methods consistent with standard test guidelines? We have some concerns about the data that are presented in the original papers, partly based on the low, and consistent, variation around each mean.	related to ED. Agree that a more detailed description of the two studies regarding renewal period of test substance and test concentration maintenance would be warranted but both studies are based on nominal values and the renewal of test concentration is not described. In Carnevali et al (2010) the informations are limited to the following method description regarding renewal and test concentrations „Females were exposed for three weeks, in semi-static conditions, to nominal 0.02, 0.2, 2, 20 and 40 µg/l concentrations of DEHP. In Coradetti et al (2013) the renewal procedure is also not described. Due to the lack of informations on water renewal period the reliability of the two studies to Klimisch cat 2/(4) – generally acceptable but certain documentation of the test procedure is missing. The results of the studies are therefor considered of some relevance and can contribute to the overall environmental ED evaluation of DEHP". Agree regarding the indication of magnitude of effects. The following informations has now been included: with 50% control group fecundity at 0.02 µg/l down to 1% control group fecundity at 40 µg/l. For the Carnevali et al. (2010) and Corradetti et al. (2013) studies with zebrafish, two of 6 authors were participating in both studies and 4 of 6 were new. The senior author in the Carnevali study is from Department of Biology, East Carolina University, Greenville, North Carolina, United States of America, wheras the senior author from the Corradetti study is from Department of Life and Environmental Sciences, Università Politecnica delle Marche, Ancona, Italy. The studies do not follow standard test guidelines and unfortunately no standard test guidelines investigating fish spermatogenesis are available. Variations are endpoint dependent and we find no

				reason to not believe in the correctness of the presented results.
			In particular, the information about the numbers of fish used in each analysis is not clear. At times the results seem to be based on just 3 or 5 fish despite having experimental groups of 3x30 fish for each treatment group.	Regarding the information on numbers of fish used in each analysis, the experimental design is well presented in both studies describing exactly how many fish were subsampled for each analysis. E.g. the following is taken from Coradetti et al (2013): At the end of the first and the third week of exposure, adult malesfrom each group (n = 7) were anesthetized by immersion in water containing 0.17 mg/mL of tricainemethanesulfonate (Argent Laboratories, Inc., Redmond, WA, USA) and sacrificed by decapitation. The testes were removed carefully from the fish with a pair of fine forceps under a dissecting microscope.One testis was designated for histological analysis and the other for assessment of DNA fragmentation of spermatozoa (TUNEL assay). At the end of the third week of exposure, males from each group (n = 10) were transferred to spawning tanks containing non-contaminated water together with untreated females (ratio 10/7; male/females) in order to evaluate their reproductive performance over 14 days.
			The authors state that some of the data were obtained from at least four experiments but do not say which ones. This should be clarified (if necessary by contacting the study authors), and the results re-presented accordingly.	We agree that the authors should not have used the term „four individual experiments" but instead four individual PCR reactions (as described in the referred article No 24 (Migliarini & Carnevali 2008). The term „four experiments" could lead to a wrong interpretation that the fish exposure experiment had been repeated four times. It has been clarified in the dossier that the PCR reactions were repeated 3-4 times.
			It is also somewhat surprising that seemingly lesser effects occur at higher concentrations for one of the	Regarding concentration dependent effects: Up and down regulation of genes are more transcient than e.g. protein levels and clear dose-response relationships are not directly expectable because feedback mechanisms and saturation also take place. The gene expression data in the Carnevali

			gene expression experiments – this is not noted or discussed. • There is more convincing evidence of an adverse effect and an ED mode of action in females than on males. The authors themselves state that the effects of DEHP may result from DNA damage in addition to oestrogenic effects. The progression from spermatogonia to spermatocytes was concomitant with the increase in DNA fragmentation again, and decreased fertilisation success could similarly be due to DNA damage. The dossier should discuss this possibility in more detail and clearly explain the basis for assuming an ED mode of action in these studies. • Is it surprising that reproductive capacity in males recovered less than two weeks after exposure stopped (e.g. is this type of response seen in mammalian studies)? Section 5.1.2.2.1 (p. 33): What is the relevance of the Planelló et al. (2011) study given the short duration and lack of any apparent biological consequence? Section 5.1.3 (p. 33-35): Given our comments about the Salmo salar studies above, we think these findings should be reconsidered in terms of their relevance to the overall argument. We find the results for both Oryzias melastigma and Danio rerio to be more convincing (although the study of Uren-Webster et al. (2014) is less relevant). The discussion of the role of thyroid disruption in the observed effects on Poecilia reticulata is entirely speculative and we think the statement should be simply that "mode of action is not known". The same applies to the Xenopus laevis studies (which as indicated	experiment show induction of the BMP15 gene from 0.2 µg/l and reduction oft he LHR gene from 0.02 µg/l The DNA-damage results are already presented together with the oestrogenic effects and the studies are included in the WoE together with other studies, so the dossier does not use these data as evidence of clear oestrogenic effects. It is not known whether the male recovery could be linked to an endocrine related effect rather than DNA-damage. All peer reviewed studies with endpoints that could be ED relevant are included. In Planelló et al (2011) the ecdysone (molting hormone) gene was investigated. It has now been clarified in the SD that ecdysone is the insect molting hormone. As mentioned above in the comments to the Zanotelli et al study: There is no evidence that the significant effects on growth were ED-related –or the contrary. Therefore no definitive conclusions on MoA is drawn in the SD based on this study alone. The results may anyway be relevant because the effects on growth occur far below other reported toxicity effects in fish and are likely to be at least partly ED-related. And as written above - all peer reviewed studies where endpoints could be of ED relevance have been included. We have tried to make the text even more accurate in respect to this in the SD and to reflect the WoE based conclusion on fish.

			above might not be wholly reliable).	
11	2014/10/16	Industry or trade association CEFIC ECPI Belgium	11_ECPI_Comments_Annex_XV_SVHC_ELoC_ED_Dossiers_Oct_16_2014.docx 11_ECPI_Comments_Annex_XV_SVHC_ELoC_ED_Dossiers_Oct_16_2014.pdf	See responses in the section ‚Specific comments on the justification', below**.**
12	2014/10/16	Member State Netherlands	NL supports the proposal to include BBP in the candidate list of SVHC in accordance with Article 57(f) of Regulation (EC) 1907/2006 (REACH) due to its endocrine disrupting properties which may cause serious effects to human health and to the environment.	Thank you for your support. No changes made due to this comment.
13	2014/10/16	Company DEZA, a.s. Czech Republic	13_Comments to the Annex XV report of Danish EPA_DEZA.pdf	See responses in the section ‚Specific comments on the justification', below.
14	2014/10/16	Individual	14_GA_ZAK_SA_comments_DEHP_REACH_annexXV.pdf	See responses in the section ‚Specific comments on the justification', below.
15	2014/10/16	International NGO Health and Environment Alliance Belgium	We strongly support the nomination of DEHP to the candidate list as an endocrine disruptor and commend Denmark for its submission	Thank you for your support. No changes made due to this comment.
20	2014/10/16	International NGO European Environmental Bureau (EEB) Belgium	20_EEB_4phthalates_EDC.pdf	Thank you for your support. No changes made due to this comment.

Specific comments on the justification

No	Date	Submitted by (name, Organisation/ MSCA)	Comment	Response
1	2014/10/09	Member State United Kingdom	General comments As an opening remark, until an EU regulatory definition of endocrine disrupters (EDs) has been endorsed by CARACAL, the UK believes that it is premature to propose substances for identification as	We agree that it would be good to have criteria, but unfortunately these are not available. The REACH text does neither refer to, nor require, criteria for inclusion of endocrine disruptors in the candidate list on a case-by-

			endocrine disrupting chemicals (EDCs) under REACH. We also do not accept an interpretation of Article 57(f) which proposes that EDs automatically meet the definition of equivalent concern. The requirement for "scientific evidence of probable serious effects to human or the environment which give rise to an equivalent level of concern" must still be demonstrated case-by-case. The proposal is that di(2-ethylhexyl) phthalate (DEHP) meets the criteria of Article 57(f) on both human health and environmental grounds. Considering these aspects separately we have the following comments; Human health We agree that DEHP meets the WHO definition of an ED and the scientific elements described in the JRC report, but as noted above this is not equivalent to satisfying an EU endorsed regulatory definition. For DEHP the ED effects that are listed as giving rise to an equivalent level of concern are the same effects that have led to classification as R1B, subsequent candidate listing in accordance with Article 57(c) and inclusion in Annex XIV. We therefore consider listing DEHP additionally in accordance with Article 57(f) – equivalent concern for human health, to constitute double-counting and is clearly unnecessary and unjustified. If the perceived added benefit of listing DEHP as an ED for humans is that the socio-economic route for authorisation is to be followed if a threshold cannot be determined, we would like to point out that DNEL values have already been established by RAC for DEHP for the purpose of restriction and authorisation applications. Hence, a regulatory threshold has already been determined, giving a strong indication that the adequate control route for Authorisation is appropriate. This has been accepted for the	case basis. This process has already been applied for 4 substances (nonylphenol + ethoxylates + 4-tert-octylohenol + ethoxylates) identified as endocrine disruptors fulfilling REACH art. 57f with relevance for the environment. The same process can be applied for endocrine disrupters with relevance for human health. We acknowledge that UK agrees that DEHP is an endocrine disrupter fulfilling the WHO ED definition. DK disagrees with UK that DEHP does not fulfill REACH Art. 57f, as the difference between the WHO definition and Art. 57f as regards substances with endocrine disruptive properties are that 1) the WHO definition seems to require a higher proof of causality between endocrine activity and adverse effects (WHO term: „causes") than Art. 57 f (terms: „scientific eviden of probable" and 2) that the WHO def. does not as specifically as Art. 57f detail the seriousness of the apical effects as such of CMRs or vPvB/PBTs. However, as DEHP has a harmonized classification Rep 1B, DEHP does indeed fulfill the Art. 57f more detailed criteria (reproductive toxicity) for the seriousness of the effects caused by the endocrine disruptive properties of the substance as documented in the SD. Based on this we also conclude that we disagree on the "double counting" argument, because ED is a MoA giving rise to the adverse outcome reproductive toxicity. Hence, "ED" and „reproductive toxicity" is not the same phenomenon. RAC has assessed DEHP due to its harmonised classification as Repr. 1B, a type of effect

			applications for authorisation already received by ECHA. In conclusion the UK considers that for candidate listing purposes the additional identification of DEHP as EDC in humans is not appropriate. Environment As indicated in our opening remark, Article 57(f) should not be interpreted as saying that EDCs per se meet the standard of scientific evidence of probable serious effects, etc. but that additional justification is needed to demonstrate "equivalent concern". In addition to the drafting of Article 57(f) itself, the CLP Regulation, for example, clearly explains that environmental hazard cannot be assessed in a meaningful way without taking into account the possible exposure of environmental compartments. Therefore, in addition to information on effects, hazard classification incorporates a limited consideration of exposure-related properties, including (bio)degradability and bioaccumulation. We think the identification of substances of equivalent concern on the basis of endocrine disruption in the environment should follow a similar approach. We took this into account when we agreed with the identification of nonylphenol and octylphenol as SVHCs on the grounds of environmental endocrine disruption, although we noted at the time that we did not consider it appropriate to take a decision in the absence of a definition.	that by default assumes a threshold. The existence of a threshold has not yet been assessed and documented for this substance. If DEHP is listed on the Candidate List due to its ED properties being of ELoC etc., RAC will in future restriction and authorization applications assess, if a toxicological / ecotoxicological threshold for DEHP can be established. Scientific proof for establishment of such a threshold with reasonable certainty for the endocrine disruptive properties has yet to be documented in the context of future authorisation applications or restrictions. Further, identification of DEHP under 57(f) for the environment may lead to a higher level of protection for the environment, since environmental protection measures are not triggered by the identification under 57 (c) for reproductive toxicity. We do not agree as explained above. The ED identification includes other elements than the serious effects, and those elements are not part of the classification evaluation procedure, i.e. the evaluation of whether the substance has an ED mode of action and whether this is likely to cause serious effects of ELoC (cf. art. 57 f). We disagree that the CLP Regulation refers to envionmental exposure in its criteria for aquatic hazard classification. Furthermore, the CLP Regulation is not relevant to consider here, but rather the REACH Regulation Art. 57f. As mentioned in our response above, Art. 57f does neither refer to environmental fate related properties nor to expsure, but rather to the likelihood of serious **effects** of EloC as CMRs/vPvB/PBTs due to endocrine disruptive properties of the substance. Furthermore, exposure considerations (such as wide dispersive use and high tonnage) are dealt with in Art. 58 for priority setting of already identified SVHCs.

			There are two aspects to the proposal: a) We agree that effects in mammals are relevant in an environmental context, provided there is a potential for secondary poisoning leading to a population-relevant impact such as on growth or reproduction. DEHP is readily and inherently biodegradable and therefore expected to mineralise rapidly under aerobic conditions. The half-lives cited in the dossier are open to question, although persistence in anaerobic sediment is likely to be high (see our specific comments). Given the reprotoxic properties of the metabolite MEHP, we agree that it is appropriate to use a fish BCF based on both DEHP and MEHP (840 L/kg) (we also note that the BCF for DEHP alone is above 500 L/kg in some studies). It is therefore plausible that fish, mammals or birds could be exposed via their diet. It would perhaps be helpful to summarise monitoring data showing this, if any are available. For DEHP the lowest relevant, robust mammalian NOAEL for population-relevant end points linked to an ED mode of action (reproductive toxicity) is in the range of 1 10 mg/kg bw/d. We note that here is no information on toxicity to birds. On this basis, we think that there is some potential for food chain accumulation and the substance does have ED-related effects on reproduction in mammals at a relatively low dose. b) DEHP can interact with the endocrine system in fish. Despite the limited descriptions given in the dossier, significant reproductive effects have been reported for two fish species (Marine Medaka Oryzias melastigma and Zebrafish Danio rerio, with NOECs below 0.001 mg/L (1 µg/L) for the latter species,	We note that UK - contrary to DK - is taking environmental fate properties and exposure into account when considering ELoC and that UK agrees that adverse effects in mammals are relevant in an environmental context, but only provided there is a potential for secondary poisoning leading to a population-relevant impact such as on growth or reproduction. Contrary to this DK has the view that environmental fate related properties and exposure are not mentioned in art. 57f. We note that the legal text only refers to „probable serious **effects**." (cf. Earlier responses). In addition exposure related triggers are dealt with in art. 58 , i.e. the next priority setting step for identified SVHCs. It would be odd to include exposure both for identification (Art. 57 f where the term „expsure" is NOT mentioned) and then again for priority setting (art. 58 where indeed expsure related issues are mentioned). We also note that exposure and fate related properties are not part of SVHC identifications of CMRs. For vPvBs/PBTs fate related properties are considered but only because they are explicitely part of the detailed vPvB/PBT criteria in Annex XIII. No such fate related properties are referred to in article 57 f - and they also do not appear in the WHO definition for EDs. The CLP context here is in our view irrelevant to refer to in the context of ED related effects (but in respect to the general issue of whether substances classified in chronic cat 1 we generally agree that such classification – in particular if based on chronic aquatic data – on a case by case basis could be considered as being of ELoC (in accordance with art. 57 f) but generally unrelated to whether the MoA is known or not / what the MoA for the chronic effects are). Chapter 6 in the SD has been re-drafted to conclude on fulfilment of the WHO/IPCS definition of endocrine disruptors and the fulfillment of Article 57f. **Thank you for your support, in principle, that DEHP**

			although we have some questions about this). It seems likely that an endocrine mode of action is at least partly involved based on the evidence of biomarkers. In a CLP context, the substance would be classified as Aquatic Chronic 1 based on the ED-related effects in Zebrafish. We think this hazard level is serious enough to qualify the substance as an equivalent level of concern to a PBT/vPvB or CMR substance. (We note that DEHP does not have a harmonised environmental hazard classification under the CLP Regulation.) In summary, the UK believes that DEHP could be identified as an SVHC on the basis of environmental endocrine disruption. However, we repeat our view that it is not appropriate to take a decision in the absence of an agreed definition.	**could be identified as an SVHC on the basis of environmental endocrine disruption**. We finally note that **UK came to the conclusion of acceptance of the identification of DEHP as an endocrine disrupter causing serious environmental effects of equivalent level of concern as referred to in art. 57 f of REACH**. We also note that the UK view is that it is not appropriate to take an ad hoc decision similar to what has already been done earlier as regards SVHC nomination for nonyl- & octylphenol ethoxylates in respect to their endocrine disruptive properties.
2	2014/10/14	Member State Ireland	According to Article 57(f) of REACH, the identification of specific substances as SVHCs requires scientific evidence of probable serious effects to human health or the environment "which give rise to equivalent level of concern" to substances which have been identified as SVHCs in accordance with Article 57(a) to (e) and that such identifications should be on a case by case basis. The proposal to identify DEHP as a SVHC in accordance with Article 57(f) for equivalent level of concern is based on its endocrine disrupting properties for both the environment and human health. The Irish CA notes that in the absence of agreed EU criteria for the identification of endocrine disruptors, the assessment of the endocrine disruption for DEHP in the Annex XV report is based on the definition of an endocrine disrupter by the IPCS/WHO(1) and criteria identified in report by JRC 2013(2) . It is noted that data presented in the Annex XV report address the factors identified in the JRC 2013 report relating to "identification" of endocrine disrupters, namely adverse effect,	Agreed. The Annex XV report has been updated and the elements considered relevant for hazard identification of EDs in the JRC 2013 report discussed. Not agreed. **The JRC report states factors such as severity of effect, irreversibility, lead toxicity and potency were considered <u>not</u> relevant for the *identification* of a substance as ED.** Rather it is mentioned that these factors could provide information with regard to the *further characterisation* of the hazard, i.e. *after* the substance has been identified as an ED. For example in relation to priority setting (e.g. for inclusion on the Authorisation List). It is nowhere in art. 57f stated that potency or lead effects should be considered in an assessment of 'equivalent level of concern' for substances identified under Article 57(f).Please also note that none of these terms are used in article 57f, which only use the terms *„serious **effects***

			endocrine mode of action, plausible link between adverse effects and endocrine mode of action and human relevance. Based on the data, it is concluded that DEHP should be identified as an SVHC in accordance with Article 57(f) because it is identified as an endocrine disrupter. The Irish CA notes that no specific assessment of "equivalent level of concern" in accordance with Article 57(f) is presented in the Annex XV report for DEHP. In particular, the other factors identified in the JRC 2013 report relating to "characterisation" of endocrine disrupters are not addressed in the Annex XV report namely, severity of effect, irreversibility, lead toxicity and potency. The Irish CA considers that such factors could be used to assess equivalent level of concern with respect to endocrine disrupters. Therefore, the Irish CA considers that as an assessment of equivalent level of concern is missing from the Annex XV report, it is difficult to definitively conclude on whether DEHP should be identified as an SVHC in accordance with Article 57(f). (1) IPCS/WHO 2002. Global assessment of the state-of-the-science of endocrine disrupters. T. Damstra, S. Barlow, A. Bergman, R. Kavlock & G. Van der Kraak. WHO/PCS/EDC/02.2, World Health Organisation, Geneva. (2) JRC 2013. Key scientific issues relevant to the identification and characterisation of endocrine disrupting substances. Report of the Endocrine Disrupters Expert Advisory Group. S Munn & M Goumenou, Joint Research Centre of the European Commission.	*…of equivalent concern as CMRs..* Please see the text in Chapter 6 which has been redrafted to clearer address how DEHP meets the requirements of Article 57(f).
3	2014/10/15	Industry or trade association Japan Plasticizer	October 15, 2014 On the Proposal to Designate DEHP as an SVHC under REACH	

		Industry Association Japan	（PROPOSAL FOR IDENTIFICATION OF A SUBSTANCE OF VERY HIGH CONCERN ON THE BASIS OF THE CRITERIA SET OUT IN REACH ARTICLE 57（DEHP）） Japan Plasticizer Industry Association (JPIA) Preface We, the JPIA, welcome this opportunity given to comment on the above proposal to designate DEHP as an SVHC. The JPIA is an industrial association of Japanese companies manufacturing and marketing plasticizer. The JPIA is very concerned about this Proposal because of our deep connection with the EU through trading Japanese articles containing chemical substances which would be included in the scope of the Proposal. The Proposal suggests that DEHP should be added to the list of SVHC candidates based on its endocrine disrupting properties. The Proposal states that the reason is primarily because DEHP would seriously affect human health and the environment, mainly based on harmful effects to the mammalian endocrine system and wild lives, and therefore falls under article 57 (f) of REACH. The proposition is very problematic for the following two reasons: (i) The European Commission has not yet clarified its official view on the identification, criteria and test methods for endocrine disrupting chemicals (EDCs). (ii) Concerning endocrine disruption (ED), interested parties of the world have deeply debated, but not yet reached any agreement. Given the above points of view, the Proposal based on the endocrine disrupting properties of DEHP is premature and should not be accepted. The key points are as follows: Justification for Position 1. Identification and Criteria of EDC	Re. (i): We agree that it would be good to have criteria, but unfortunately these are not available. The REACH text does neither refer to, nor require, criteria for inclusion of endocrine disruptors in the Candidate list on a case-by-case basis. This process has already been applied for 4 substances (nonylphenol + ethoxylates + 4-tert-octylohenol + ethoxylates) identified as endocrine disruptors with relevance for the environment. The same process can be applied for endocrine disrupters with relevance for human health. Re. (ii): Agreed, but global agreement on endocrine disruption is not a prerequisite for inclusion of endocrine disruptors in the candidate list on a case-by-case basis. Justification for Position Re. 1. Not agreed. The European Commission was required to present criteria for identification of endocrine

			As shown in ROADMAP1) for EDCs published by the DG ENV and DG SANC of the EC in June 2014 and the results from public consultation about it2), the necessity of regulating EDCs is being discussed and not yet decided. Although the above public consultation was mainly aimed at BPR and PPPR, the results may influence REACH in dealing with general chemical substances for regal consistency in EU. As just described, it is premature to identify any chemical as an SVHC based on ED action while the definition, criteria and test method for EDCs have not yet been established. 2. Worldwide Consensus on EDCs Many arguments have continued about EDCs for more than 15 years, with opinions expressed by scientists, regulators, people from industry and NGO activists. No global consensus has yet been achieved, even after these arguments. Examples: 1) WHO/IPCS (2002): Global assessment of the state-of-the-science of endocrine disruptors3) 2) WHO/UNEP (2012): State of the Science of Endocrine Disrupting Chemicals – 2012, Critical comments on the WHO-UNEP State of the Science of Endocrine Disrupting Chemicals – 20124) 3) J.C. Lamb et al.: "Critical Comments on the WHO-UNEP State of the Science of Endocrine Disrupting Chemicals 2012"5) 4) Kortenkamp Report: STATE OF THE ART ASSESSMENT OF ENDOCRINE DISRUPTERS, Final Report of Project 23.12.20116) 5) ED EAG（JRC）Reports i) Key scientific issues relevant to the identification and characterization of endocrine disrupting substances 20137) ii) Thresholds for Endocrine Disrupters and Related Uncertainties 20138) 6) EFSA Report Scientific opinion on the hazard assessment of endocrine disruptors: Scientific criteria for identification of endocrine	disruptors for the BPR and PPPR by, respectively, 13 and 14 December 2013. Hence the necessity of regulating EDCs has been decided. Re. 2. Thank you for your input. The dossier is focussing on ED identifcation according tot he WHO/IPCS definition which is a widely accepted definition. In addition, recommendations from the Report of the Endocrine Disrupters Expert Advisory Group. Several UN and EU organisations and also the EU Commission reports have identified endocrine disruptors as substances of human health and environmental concern – as you have also referenced in your comments. Global agreement on endocrine disruption is not a prerequisite for inclusion of endocrine disruptors in the candidate list on a case-by-case basis. The issues of threshold, low dose effects, NMDR, combination effects and epigenetics have not been addressed as they are not required for identification of endocrine disruptors according to the WHO/IPCS definition. However, it is agreed that in accordance with gaining new knowledge about these complex issues, we will also gain more knowledge about the nature of endocrine disruptors.

			disruptors and for appropriateness of existing test methods for assessing effects mediated by these substances on human health and the environment, EFSA Journal 2013;11(3):31329) 7) COMMISSION RECOMMENDATION of XXXX (Draft) 2013 on defining criteria for endocrine disruptors10) 8) The 5th Ad hoc Meeting of Commission Services, EU Agencies and Member States on Community Strategy for Endocrine Disruptors11) 9) Minutes of the expert meeting on endocrine disruptors 201312) The issues on which the opinions are divided are as follows: - Threshold - Low Dose Effect - Non Monotonic Dose Response (NMDR) - Combined Effect, Cocktail Effect, Combination Effect and Cumulative Effect - Epigenetics 3. Relationship between REACH and Authorisation DEHP is now designated as a substance requiring authorisation; RAC and SEAC of REACH (ECHA) have already finished the review for authorisation of its intended uses, summarized the review results and sent them to the applicants. Under REACH regulation, chemical substances may be designated as SVHC candidates based on plural and different criteria. DEHP requires authorisation due to its reproductive toxicity. The present Proposal is also, after all, based on reproductive toxicity via the endocrine system. We believe that the both are based on one and the same endpoint and the regulations are duplicated. 4. Denmark's Proposal The present proposal is mainly based on a) EU RAR 2008 b) JRC Reports (2013)7) c) Kortencamp Report (2011)6) Although the Proposal refers to the literature after the publication of EU RAR, it attaches weight to anti-	Re. 3. Not agreed. The adverse effects were evaluated as part of the classification as a reproductive toxicant, but the endocrine MoA and the plausible link between adverse effects and ED MoA was not in detail assessed in this classification process. Further, the identification of 57(f) for the environment may lead to higher level of protection for the environment, since this is not included in identification under 57(c) for reproductive toxicity. Cf. Further above in response to similar UK comment. Re. 4 and 5. Cf. Above regarding response to similar UK comments. Phthalates are ubiquitous in the environment and present in almost all urinary samples when included in biomonitoring surveys. Exposure-data and cause-effect relationships are extremely difficult, if not impossible, to establish through population surveys, and not required for the identification of substances with endocrine

			androgenic activity just the same in EU RAR. The conclusion in RAR did not urge further regulations although the need to pay attention concerning children was mentioned. JRC reports provide detailed opinions on scientific issues in relation to EDCs but do not specify legal frameworks. The points of note in these reports are: (i) Endocrinal activity and adverse effect are distinguished (ii) Mechanism verification data are necessary to clarify the mode of action (MoA) (iii) Epidemiological data are fraught with uncertainty (iv) AGD shortening is not considered as indicating adverse effects (v) Distinguishing the primary effects of toxicity MoA of ED from non-MoA-based secondary toxicity is important (vi) Analysis of AOPs (Adverse Outcome Pathways) is useful (vii) Traditional test methods to detect ED have limitations (the methods only detect EAT) (viii) Scientists have different opinions as to ecotoxicity The reproductive toxicity of phthalates is commonly discussed in relation to ED action, but the following is an example of the review of reports addressing the relationship between exposure to environmental EDCs and human health by focusing on human data. Phthalates are included among EDCs.13) This review, indicating the paucity of human data and inconsistencies among studies, concludes that further studies are needed. From here on, molecular epidemiological studies should be conducted for a long period of time and be appropriately designed for exposure assessment. Only such studies of exposure will enable demonstrating the cause-and-effect relationship, determining the most important window period and defining each sensitive factor that	distuptive properties fulfilling art. 57 f However, as regards human relevance of the adverse effects of phthalates which inhibit testosterone synthesis during development has been assessed and evaluated as relevant in the dossier, please also note the **new study by Albert and Jégou (2014) (your reference 15) supports the RAC conclusion (2012) that there is too much uncertainty in the available data to allow a conclusion on humans being less, equally or more sensitive than rats. Furthermore, a.o., it states that phthalate anti-androgenicity is plausible in adult men** and that epigenetic and germ cell changes should be interpretated with great caution as there are still many unknowns. The text in the dossier has been updated with the new Albert and Jégou (2014) reference (your article 15: Albert O and Jégou B. 2014. A critical assessment of the endocrine susceptibility of the human testis to phthalates from fetal life to adulthood. Human Reproduction Update, Vol. 20(2):231-249.) Further, epidemiological studies are generally difficult to interpret with enough certainty to dismiss robust findings in comprehensive, reliable animal studies. Please note that epidemiological studies referred to have only been used as supportive information in the SD.

			damages masculine health. Given the above points, Denmark's proposal is fraught with problems. 5. Epidemiological results 1) The validity of epidemiological studies conducted are questioned.14) 2) According to the latest review by O. Albert et al.15), (i) Although studies conducted on humans are limited in number, the results are quite different from those of studies using animals. (ii) Some differences in response to phthalates have been noted among rats, mice, primates and humans. Further investigations are needed to clarify why. 3) An epidemiological review of phthalate esters by CHAP (Chronic Advisory Health Panel) of the U.S. CPSC (Consumer Products Safety Commission)16) indicated the following problems: (i) Exposure misclassification: exposure timing during pregnancy and chemical stability of phthalate metabolites (ii) Inter-study inconsistencies (though using one and the same endpoint) (iii) Lack of replication (iv) Residual confounding (questionnaire of parents, confounding factors: age, sex, ethnic group, race, mother's height and body weight before pregnancy, smoking history, education, IQ, marital history, asthma, hypertension, diabetes, contents of each meal, etc.) (v) Weak association: statistical analyses are associated with uncertainty and limitation due to the limited number of samples (vi) Multiple comparison: Due to various phthalates and responses evaluated, the results from statistical analyses, particularly assessment of neurodevelopmental effects, are questionable 4) Current state of human exposure According to a human bio-monitoring study conducted recently in Norway, the exposure is sufficiently lower than TDI and does not cause any	

			risk for human health.17) Another bio-monitoring study conducted in Canada also reported that the exposure remained at the level of not having any problems.18) 6. Risk assessment In December 2013, the European Commission released an implementation plan in which using risk management option analysis (RMOA) was announced for future evaluation of SVHC candidates.19) Corresponding analyses are considered necessary when making proposals such as the present one. For examining the Authorisation Application of DEHP, RAC and SEAC conducted risk and socioeconomic analytical assessment; these results should be considered well. 7. Species differences The Proposal comments on the literature that reports the difference in expression of toxicity between rodents and monkeys or humans, but the effects on juvenile and fetal marmosets20) are not referred to. In the study using such marmosets, toxic effects on reproduction were not observed, even in the most fragile fetuses. The JPIA has conducted tests and studies on the reproductive toxicity of DEHP to verify the existence of differences in action mechanisms between rodents and primates, and therefore humans, for more than 10 years jointly with the European Council for Plasticisers and Intermediates (ECPI) and American Chemical Council-Phthalate Ester Panel (ACC-PEP). Studies have been conducted using marmosets as primate species, and studies have administered d4-labeled DEHP to human volunteers and directly analyzed the urinary level of its metabolites as well as their conjugates with glucuronic acid or glucuronides. These studies have shown that the metabolic profile of DEHP such as the excretion pattern and excretion rate differs between primates including human beings and rodents. The absorption rate is lower in the former, demonstrating that	Re. 6. Noted. Preparing RMOA's before preparing a proposal for uptake on the candidate list is not a legal requirement under REACH. Nevertheless, the Danish EPA has informed the CARACAL meeting (incl. industry stakeholders) that the regulatory benefit is that future applications for authorisation may need to be addressed under the socio-economic route unless a toxicological threshold is documented. Furthermore, RAC and SEAC have conducted their analytical assessments on the reproductive toxicity of DEHP, not the elements included in the identification of DEHP as an endocrine disrupter (cf. Also response above) Re. 7. Thank you for this new information. The dossier already contains the references 21-24 but references 25-26 will be added to the report.

			primates have a much stronger defensive function against the toxic effects of DEHP than rodents.21), 22) Recent studies23), 24), 25), 26) reported differences in expression mechanism and more of reproductive toxicity between humans and rodents, suggesting that DEHP does not cause toxic effects on reproduction in human beings. 8. Results from ED tests for potential EDCs including phthalates in Japan The Ministry of Environment in Japan conducted a large-scale investigation about EDCs and published the results obtained. Apparent ED activities of DEHP were not observed in a one-generation test using rats, vitellogenin production test using MEDAKA (killifish) and partial life cycle test.27), 28) As mentioned above, the proposal by Denmark to classify DEHP as an SVHC candidate should not be accepted because the necessity of EDC regulations is still being discussed and the European Commission not yet decided on this issue. References 1)http://ec.europa.eu/smart-regulation/impact/planned_ia/docs/2014_env_009_endocrine_ disruptors_en.pdf 2)http://ec.europa.eu/dgs/health_consumer/dgs_consultations/food/consultation_20150116_endocrine-disruptors_en.htm 3) http://www.who.int/ipcs/publications/new_issues/endocrine_disruptors/en/ 4) http://unep.org/pdf/9789241505031_eng.pdf#search='WHP+UNEP+Endocrine+2013' 5) J C Lamb; P Boffetta; W G Foster; J E Goodman; K L Hentz; L R Rhomberg; J Staveley; G Swaen; G Van Der Kraak; A L Williams, "Critical Comments on the WHO-UNEP State of the Science of Endocrine Disrupting Chemicals ・2012", Regulatory Toxicology	Re. 8. Thank you for providing the informations on the two Japanese studies that were not included in the dossier. In relation to ref 27. It is a brief summary of 61 chemicals undergoing investigation in different assays. It is correct that a medaka vitellogenin assay was performed as well as partial and full lifecycle studies with medaka: The conclusions in the report were as follows: Frequency is low, but the appearance of testis-ova was confirmed. There did not appear to be a negative effect on fertilization rates. Clear endocrine disrupting effects were not recognized. As no details on test concentration, number of animals etc is provided it is not possible to evaluate these studies in the current dossier. The text above has been included in the SD. Ref 28 does not provide new experimental data and is more or less a description of the Japanese testing strategy. Therefore assigned Klimish 4 (unassignable) Not agreed. REACH does not foresee specific criteria for identification and inclusion endocrine disruptors on the candidate list in accordance with Art. 57(f) (cf. Also responses above).

			and Pharmacology vol 69 issue 1 (2014) 22-40. DOI Number : http://dx.doi.org/10.1016/j.yrtph.2014.02.002 6)http://ec.europa.eu/environment/chemicals/endocrine/pdf/sota_edc_final_report.pdf#search='Kortenkamp+state+og+the+art+assessment+endocrine+disrupters+final+report' 7)http://ihcp.jrc.ec.europa.eu/our_activities/food-cons-prod/endocrine_disrupters/jrc-report-scientific-issues-identification-endocrine-disrupting-substances 8)https://ec.europa.eu/jrc/en/publication/eur-scientific-and-technical-research-reports/thresholds-endocrine-disrupters-and-related-uncertainties 9) http://www.efsa.europa.eu/en/efsajournal/pub/3132.htm 10)http://www.environmentalhealthnews.org/ehs/news/2013/pdf-links/2013.06.11%20EDC_Recommendation%20Commission%20Draft.pdf#search='EU+COMMISSION+RECOMMENDATION+of+XXXX++%28Draft%29+2013' 11)http://www.endseurope.com/docs/121207a.pdf#search='5th+Ad+hoc+meeting+of+Commission+Services%2C+EU+Agencies+and+Member+States' 12)http://ec.europa.eu/commission_2010-2014/president/chief-scientific-adviser/documents/minutes_endocrine_disruptors_meeting_241013_final.pdf#search='EU+Minutes+of+the+expert+meeting+on+endocrine+disruptors+2013' 13)John D. Meeker、Maturiatas 66(2010)236-241 Review Exposure to environmental endocrine disrupting compounds and men's health 14)Michael A. Kamrin、Journal of Toxicology and Environmental Health, Part B, Volume 12, Issue 2 February 2009, pages 157-174 Phthalate Risks, Phthalate Regulation, and Public Health: A Review 15)Océane Albert,Bernard Jègou.Human Reproduction Update Advance Access published September 29,2013、Vol.0,No.0pp.1-19,2013 "A critical assessment of the endocrine susceptibility	

			of the human testis to phthalates from fetal life to adulthood"(doi: 10.1093/humupd/dmt050 First published online: September 29, 2013) 16)http://www.cpsc.gov/PageFiles/126370/tetaa.pdf#search='Exponent+Reviwe+Phthalate+Epidemiology+2010 17) A K Sakhi; I T L Lillegaard; S Voorspoels; M H Carlsen; E B Loken; A L Brantsaeter; M Haugen; H M Meltzer; C Thomsen, "Concentrations of phthalates and bisphenol A in Norwegian foods and beverages and estimated dietary exposure in adults", Environment International vol 73 (2014) 259-269. DOI Number : http://dx.doi.org/10.1016/j.envint.2014.08.005 18) V R Kay; M S Bloom ; W G Foster, "Reproductive and developmental effects of phthalate diesters in males", Critical Reviews in Toxicology vol 44 issue 6 (2014) 467-498. DOI Number : http://dx.doi.org/10.3109/10408444.2013.875983 19)http://echa.europa.eu/documents/10162/19126370/svhc_roadmap_implementation_plan_en.pdf#search='SVHC+Roadnap+2013 20) Kurata Y, Makinodan F, Shimamura N, and Katoh M.,"Metabolism of di(2-ethylhexyl phthalate (DEHP):comparative study in juvenile and fetal marmosets and rats ", The Journal of Toxicological Sciences, 37, 33-49, 2012. 21)Kurata Y, Kidachi F, Yokoyama M, Toyota N, Tsuchitani M, Katoh M.,Toxicological Science, 42, 49-56, 1998. 22)Tomonari Y, Kurata Y, David R M, Gans G, Kawasuso T, Katoh M., Journal of Toxicity and Environmental Health A., 69(17), 1651-1672, 2006. 23) E.Heger,et al.,Environmental Health Perspectives,120(8),1137-1143,2012 Human fetal testes xenografts are resistant to Phthalate-induced Endocrine disruption 24) Mitchel RT,et al.,J.Clinical Endocrine & Metabo. 97(3):E341-E348(2012) Phthalates affect steroidogenesis by the Human Fetal Testis?:Exposure of Human Fetal Testis Xenografts	

			to Di-n-ButylPhthalate. 25) Kurata,et al.,The Journal of Toxicological Science Vol.37,No.1,34-39,2012. Metabolisom of di(2-ethyl hexyl)phthalate(DEHP):comprative study in juvenile and fetal marmosets and rats. 26) Kurata,et al.,Ibid,Vol.37,No.2,401-414,2012. Metabolite profiling and identification in human urine after single oral administration of DEHP. 27) http://www.env.go.jp/en/chemi/ed/extend2005_full.pdf 28) http://www.env.go.jp/en/chemi/ed/extend2010_full.pdf 6	
4	2014/10/15	Industry or trade association Japan Plasticizer Industry Association Japan	October 15, 2014 On the Proposal to Designate DEHP as an SVHC under REACH （PROPOSAL FOR IDENTIFICATION OF A SUBSTANCE OF VERY HIGH CONCERN ON THE BASIS OF THE CRITERIA SET OUT IN REACH ARTICLE 57（DEHP）） Japan Plasticizer Industry Association (JPIA) Preface We, the JPIA, welcome this opportunity given to comment on the above proposal to designate DEHP as an SVHC. The JPIA is an industrial association of Japanese companies manufacturing and marketing plasticizer. The JPIA is very concerned about this Proposal because of our deep connection with the EU through trading Japanese articles containing chemical substances which would be included in the scope of the Proposal. The Proposal suggests that DEHP should be added to the list of SVHC candidates based on its endocrine disrupting properties. The Proposal states that the reason is primarily because DEHP would seriously affect human health and the environment, mainly based on harmful effects to the	Comments appear to be identical to comment no. 3, above. We refer to RCOM for comment number 3, above.

			mammalian endocrine system and wild lives, and therefore falls under article 57 (f) of REACH. The proposition is very problematic for the following two reasons: (i) The European Commission has not yet clarified its official view on the identification, criteria and test methods for endocrine disrupting chemicals (EDCs). (ii) Concerning endocrine disruption (ED), interested parties of the world have deeply debated, but not yet reached any agreement. Given the above points of view, the Proposal based on the endocrine disrupting properties of DEHP is premature and should not be accepted. The key points are as follows: Justification for Position 1. Identification and Criteria of EDC As shown in ROADMAP1) for EDCs published by the DG ENV and DG SANC of the EC in June 2014 and the results from public consultation about it2), the necessity of regulating EDCs is being discussed and not yet decided. Although the above public consultation was mainly aimed at BPR 2 and PPPR, the results may influence REACH in dealing with general chemical substances for regal consistency in EU. As just described, it is premature to identify any chemical as an SVHC based on ED action while the definition, criteria and test method for EDCs have not yet been established. 2. Worldwide Consensus on EDCs Many arguments have continued about EDCs for more than 15 years, with opinions expressed by scientists, regulators, people from industry and NGO activists. No global consensus has yet been achieved, even after these arguments. Examples: 1) WHO/IPCS (2002): Global assessment of the state-of-the-science of endocrine disruptors3) 2) WHO/UNEP (2012): State of the Science of Endocrine Disrupting Chemicals – 2012, Critical	

			comments on the WHO-UNEP State of the Science of Endocrine Disrupting Chemicals – 20124) 3) J.C. Lamb et al.: "Critical Comments on the WHO-UNEP State of the Science of Endocrine Disrupting Chemicals 2012"5) 4) Kortenkamp Report: STATE OF THE ART ASSESSMENT OF ENDOCRINE DISRUPTERS, Final Report of Project 23.12.20116) 5) ED EAG（JRC）Reports i) Key scientific issues relevant to the identification and characterization of endocrine disrupting substances 20137) ii) Thresholds for Endocrine Disrupters and Related Uncertainties 20138) 6) EFSA Report Scientific opinion on the hazard assessment of endocrine disruptors: Scientific criteria for identification of endocrine disruptors and for appropriateness of existing test methods for assessing effects mediated by these substances on human health and the environment, EFSA Journal 2013;11(3):31329) 7) COMMISSION RECOMMENDATION of XXXX (Draft) 2013 on defining criteria for endocrine disruptors10) 8) The 5th Ad hoc Meeting of Commission Services, EU Agencies and Member States on Community Strategy for Endocrine Disruptors11) 9) Minutes of the expert meeting on endocrine disruptors 201312) The issues on which the opinions are divided are as follows: - Threshold - Low Dose Effect - Non Monotonic Dose Response (NMDR) - Combined Effect, Cocktail Effect, Combination Effect and Cumulative Effect - Epigenetics 3 3. Relationship between REACH and Authorisation DEHP is now designated as a substance requiring authorisation; RAC and SEAC of REACH	

			(ECHA) have already finished the review for authorisation of its intended uses, summarized the review results and sent them to the applicants. Under REACH regulation, chemical substances may be designated as SVHC candidates based on plural and different criteria. DEHP requires authorisation due to its reproductive toxicity. The present Proposal is also, after all, based on reproductive toxicity via the endocrine system. We believe that the both are based on one and the same endpoint and the regulations are duplicated. 4. Denmark's Proposal The present proposal is mainly based on a) EU RAR 2008 b) JRC Reports (2013)7) c) Kortencamp Report (2011)6) Although the Proposal refers to the literature after the publication of EU RAR, it attaches weight to anti-androgenic activity just the same in EU RAR. The conclusion in RAR did not urge further regulations although the need to pay attention concerning children was mentioned. JRC reports provide detailed opinions on scientific issues in relation to EDCs but do not specify legal frameworks. The points of note in these reports are: (i) Endocrinal activity and adverse effect are distinguished (ii) Mechanism verification data are necessary to clarify the mode of action (MoA) (iii) Epidemiological data are fraught with uncertainty (iv) AGD shortening is not considered as indicating adverse effects (v) Distinguishing the primary effects of toxicity MoA of ED from non-MoA-based secondary toxicity is important (vi) Analysis of AOPs (Adverse Outcome Pathways) is useful (vii) Traditional test methods to detect ED have limitations (the methods only detect EAT) (viii) Scientists have different opinions as to ecotoxicity	

			The reproductive toxicity of phthalates is commonly discussed in relation to ED action, but the following is an example of the review of reports addressing the relationship between exposure to environmental EDCs and human health by focusing on human data. Phthalates are included among EDCs.13） This review, indicating the paucity of human data and inconsistencies among studies, concludes that further studies are needed. From here on, molecular epidemiological studies 4 should be conducted for a long period of time and be appropriately designed for exposure assessment. Only such studies of exposure will enable demonstrating the cause-and-effect relationship, determining the most important window period and defining each sensitive factor that damages masculine health. Given the above points, Denmark's proposal is fraught with problems. 5. Epidemiological results 1) The validity of epidemiological studies conducted are questioned.14) 2) According to the latest review by O. Albert et al.15), (i) Although studies conducted on humans are limited in number, the results are quite different from those of studies using animals. (ii) Some differences in response to phthalates have been noted among rats, mice, primates and humans. Further investigations are needed to clarify why. 3) An epidemiological review of phthalate esters by CHAP (Chronic Advisory Health Panel) of the U.S. CPSC (Consumer Products Safety Commission)16) indicated the following problems: (i) Exposure misclassification: exposure timing during pregnancy and chemical stability of phthalate metabolites (ii) Inter-study inconsistencies (though using one and the same endpoint)	

			(iii) Lack of replication (iv) Residual confounding (questionnaire of parents, confounding factors: age, sex, ethnic group, race, mother's height and body weight before pregnancy, smoking history, education, IQ, marital history, asthma, hypertension, diabetes, contents of each meal, etc.) (v) Weak association: statistical analyses are associated with uncertainty and limitation due to the limited number of samples (vi) Multiple comparison: Due to various phthalates and responses evaluated, the results from statistical analyses, particularly assessment of neurodevelopmental effects, are questionable 4) Current state of human exposure According to a human bio-monitoring study conducted recently in Norway, the exposure is sufficiently lower than TDI and does not cause any risk for human health.17) Another bio-monitoring study conducted in Canada also reported that the exposure remained at the level of not having any problems.18) 6. Risk assessment In December 2013, the European Commission released an implementation plan in which using risk management option analysis (RMOA) was announced for future evaluation of SVHC candidates.19) Corresponding analyses are considered necessary when making proposals such as 5 the present one. For examining the Authorisation Application of DEHP, RAC and SEAC conducted risk and socioeconomic analytical assessment; these results should be considered well. 7. Species differences The Proposal comments on the literature that reports the difference in expression of toxicity between rodents and monkeys or humans, but the effects on juvenile and fetal marmosets20) are not referred to. In the study using such marmosets,	

			toxic effects on reproduction were not observed, even in the most fragile fetuses. The JPIA has conducted tests and studies on the reproductive toxicity of DEHP to verify the existence of differences in action mechanisms between rodents and primates, and therefore humans, for more than 10 years jointly with the European Council for Plasticisers and Intermediates (ECPI) and American Chemical Council-Phthalate Ester Panel (ACC-PEP). Studies have been conducted using marmosets as primate species, and studies have administered d4-labeled DEHP to human volunteers and directly analyzed the urinary level of its metabolites as well as their conjugates with glucuronic acid or glucuronides. These studies have shown that the metabolic profile of DEHP such as the excretion pattern and excretion rate differs between primates including human beings and rodents. The absorption rate is lower in the former, demonstrating that primates have a much stronger defensive function against the toxic effects of DEHP than rodents.21), 22) Recent studies23), 24), 25), 26) reported differences in expression mechanism and more of reproductive toxicity between humans and rodents, suggesting that DEHP does not cause toxic effects on reproduction in human beings. 8. Results from ED tests for potential EDCs including phthalates in Japan The Ministry of Environment in Japan conducted a large-scale investigation about EDCs and published the results obtained. Apparent ED activities of DEHP were not observed in a one-generation test using rats, vitellogenin production test using MEDAKA (killifish) and partial life cycle test.27), 28) As mentioned above, the proposal by Denmark to classify DEHP as an SVHC candidate should not be accepted because the necessity of EDC regulations is still being discussed and the European	

			Commission not yet decided on this issue. 6 References 1)http://ec.europa.eu/smart-regulation/impact/planned_ia/docs/2014_env_009_endocrine_ disruptors_en.pdf 2)http://ec.europa.eu/dgs/health_consumer/dgs_consultations/food/consultation_20150116_endocrine-disruptors_en.htm 3) http://www.who.int/ipcs/publications/new_issues/endocrine_disruptors/en/ 4) http://unep.org/pdf/9789241505031_eng.pdf#search='WHP+UNEP+Endocrine+2013' 5) J C Lamb; P Boffetta; W G Foster; J E Goodman; K L Hentz; L R Rhomberg; J Staveley; G Swaen; G Van Der Kraak; A L Williams, "Critical Comments on the WHO-UNEP State of the Science of Endocrine Disrupting Chemicals ・2012", Regulatory Toxicology and Pharmacology vol 69 issue 1 (2014) 22-40. DOI Number : http://dx.doi.org/10.1016/j.yrtph.2014.02.002 6)http://ec.europa.eu/environment/chemicals/endocrine/pdf/sota_edc_final_report.pdf#search='Kortenkamp+state+og+the+art+assessment+endocrine+disrupters+final+report' 7)http://ihcp.jrc.ec.europa.eu/our_activities/food-cons-prod/endocrine_disrupters/jrc-report-scientificissues- identification-endocrine-disrupting-substances 8)https://ec.europa.eu/jrc/en/publication/eur-scientific-and-technical-research-reports/thresholds-end ocrine-disrupters-and-related-uncertainties 9) http://www.efsa.europa.eu/en/efsajournal/pub/3132.htm 10)http://www.environmentalhealthnews.org/ehs/news/2013/pdf-links/2013.06.11%20EDC_Recomm	

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5	2014/10/15	National NGO The Danish Ecological Council Denmark	We support inclusion of DEHP in the REACH candidate list based on its EDC properties.	Thank you for your support. No changes made to the document due to this comment.
6	2014/10/15	Member State Belgium	We want to thank DK for their annex XV dossier for DEHP. Belgium supports the identification of DEHP as a substance of very high concern according to article 57(f) of REACH. The substance is an endocrine disruptor according to the IPCS/WHO (2002) definition. Clear adverse effects are found in rodents	Thank you for your support. No changes made to the document due to this comment.

			and fish, which can be linked to demonstrated ED mode of action. Such data on development and reproduction enable us to identify the substance as an ED for the HH and the ENV (relevance at the population level).	
7	2014/10/16	Member State Finland	The Finnish CA agrees that Bis(2-ethylhexyl)phthalate (DEHP) meets the criteria as SVHC according to Article 57 f as giving rise to an equivalent level of concern because of its endocrine disrupting properties and scientific evidence of probable serious effects to human health and the environment. Human health: The Finnish CA has concern about the value in terms of risk management ("added value") of this approach including such entry to the candidate list. The substance has been previously identified in the CL in accordance with Article 57 (c) as being toxic for reproduction (Repr. 1B). The substance is included in Annex XIV (with sunset date in February 2015) and first authorization applications have been addressed in the ECHA committees (RAC and SEAC) and Commission level. The Finnish CA considers that before including such entry to the candidate list it would be important to evaluate further whether existing candidate list entry (Art. 57 c) and ongoing authorization process already covers sufficiently endocrine disrupting effects and concerns from a human health point of view. The RAC`s risk assessment in opinion making on application for authorization appears to cover at some extent endocrine disrupting properties because anti-androgenic mode of action seems to be mechanistic background of reproductive toxic effects which are basis for the RAC`s risk assessment.	Thank you for your support. We note that **Finland agrees that DEHP meets the criteria as SVHC according to Article 57 f as giving rise to an equivalent level of concern because of its endocrine disrupting properties and scientific evidence of probable serious effects to human health and the environment.** Re. Human health. RAC has assessed DEHP based on its classification as a reproductive toxicant. RAC does acknowledge that the adverse effects seem to follow from an anti-androgenic mode of action. However, classification for reproductive toxicity traditionally by default assumes a threshold. The link between the adverse effects and the endocrine mode of action of DEHP has not yet been formally addressed. If DEHP is listed as an ED, the added value will be that future applications for authorisation may need to be addressed under the socio-economic route unless a toxicological threshold is documented. Further, identification of DEHP under Art. 57(f) for the environment may lead to a higher level of protection for the environment, since this is not included in identification under 57(c) for reproductive toxicity. Reference: RAC – establishing reference DNELs for DEHP: http://echa.europa.eu/documents/10162/13579/rac_24_dnel_dehp_comments_en.pdf We also refer to RCOM to UK comments p. 13-17 for further elaborations on the REACH context.

8	2014/10/16	National NGO WECF - Women in Europe for a Common Future Germany	WECF supports the additional nomination of Bis(2-ethylhexyl) phthalate (DEHP) as a substance of equivalent concern according to article 57 f given its endocrine disrupting properties.	Thank you for your support. No changes made to the document due to this comment.
9	2014/10/16	National NGO CHEM Trust United Kingdom	CHEM Trust supports the nomination of Bis(2-ethylhexyl) phthalate (DEHP) as a substance of equivalent concern based on its endocrine disrupting properties according to REACH article 57 f. Even though the substance is already identified as SVHC based on its reprotoxicity it is important to add the clearly described endocrine disrupting properties. Without being able to determine a toxicological threshold, future authorisations will have to be granted through the socio-economic route, according to Art. 60(3)(a).	Thank you for your support. No changes made to the document due to this intervention.
10	2014/10/16	Member State Germany	General comment: The German CA is of the opinion that REACH Article 57(f) is not intended to simply act as a measure for classification of chemical substances as endocrine disrupters, but rather to identify hazardous substances with equivalent level of concern when benchmarked to Article 57 a)-e) substances. For substances other than CMR 1A/B, PBT and vPvB substances the relevant effects and the equivalent level of concern needs to be demonstrated. In this respect we would like to refer to the case made for the issue SVHC identification e.g. of respiratory sensitizers. We are aware that the Danish CA holds the view that documenting that a substance has endocrine disrupting properties is in itself sufficient to document and conclude that Article 57(f) is fulfilled and there is no need for additional discussion on whether this gives rise to an ELoC (see CA/64/2014). However, we are of the opinion that this view does not meet the legal interpretation of the text of REACH Article 57 (f) in consent with COM (see also CA/64/2014). We would like to point to MSC-27, when a congeneric case – SVHC identification of methoxyacetic acid – was discussed. The need for a general discussion on	DK agress with the first two statements (sentences). DK EPA does not as basis for the current proposal hold the alleged view that a substance having endocrine distruptive properties in itself fulfill art. 57f. DK EPA has earlier presented two possible interpretations of art. 57f one of which holds that view (referred to in our discussion documenta s „the legal interpretation" cf. DK comments ED review letter to CARACAL May 2, 2014). DK EPA also presented an alternative interpretation (referred to as the „scientific interpretation") that there are *very large commonalities between art. 57f as regards substances with ED properties and ELoC and the WHO definition of Endocrine distupters.* **The basis for the current proposal to identify DEHP (and the other three pthalates) as SVHCs is in accordance with the latter Art. 57(f) interpretation.** The proposal has been revised and now concludes on both fulfilment of the WHO definition and the ELoC requirements. (as explained more in detail elswhere in our responses). We agree that different opinions were expressed at this particular MSC meeting as also referred to in the minutes and also that a further discussion and conclusion/ agreement has not yet taken place. In lack of agreed criteria proposed by the Commission and agreed by the EU MS we however think MSCAs have to proceed *ad hoc* for substances with ED

			issues related to the identification of SVHCs under Article 57 (f) concomitant with other criteria set out in points (a) to (e) of article 57 was realised. For example it is stated in the minutes that "One outstanding question is if the adverse effect/intrinsic property mentioned under Article 57 (f) ….may be the same adverse effect already applicable to identify the substance as SVHC under other Article 57 criteria, e.g. 57 c (toxic for reproduction)." To our knowledge, this discussion, which we consider necessary before deciding on the current and further proposals, has not yet taken place so far. Human health: The German CA does not support the additional identification of DEHP as a substance of very high concern for human health in accordance with Article 57(f) of Regulation (EC) 1907/2006 (REACH) as an endocrine disruptor. Environment: The data presented in the dossier give strong hints that DEHP acts as endocrine disruptor in fish and mammalian wildlife species according to the WHO/IPCS definition of endocrine disrupting substances. Thus, independently on the question how to deal with reprotoxic effects that might be evoked by an endocrine disruption pathway or another mode of action for human health (identification according 57 (c) vs. 57 (f)) as mentioned above, identification of DEHP as a 57 (f) substance for the environment seems adequate since a new concern would be addressed by this option. This environmental concern must then additionally be addressed by applicants during authorisation. Hence, we recommend focusing the dossier on the environmental concern for justifying the 57 (f) identification of DEHP. Specific comment on Chapter 4.2: DEHP causes adverse effects on the reproductive organs in adult and developing male rodents, and	properties in respect to their identification of SVHCs in accordance with their interpretation of art. 57 f, - similar to what has been done before (e.g. by the DE CA. - see also RCOM to DE). We note that DE curently does not support the proposal as regards the endocrine distuption for human health because DEHP already has a harmonized classification Rep 1B. We have elswhere responded on the alleged „double counting argument" and the „no added regulatory value arguments - see please those responses (RCOM to UK). We note that DE recommends to focus on the endocrine disruption as regards the concern for the environment and that DE is of the opinion that*‚identification of DEHP as a 57 (f) substance for the environment seems adequate since a new concern would be addressed by this option'.* Re. Specific comment on Chapter 4.2 RAC has assessed DEHP based on its classification as a reproductive toxicant. RAC does acknowledge that the adverse effects seem to follow from an anti-androgenic mode of action. However, **classification for reproductive toxicity is**

			these adverse effects are attributed to the anti-androgenic mode of action of DEHP. Based on this evidence DEHP is classified as toxic to reproduction establishing DEHP as CMR substance. The existence of LOAEL and NOAEL values allow to conclude that thresholds exist for the adverse effects. DEHP has already been added to the candidate list due to its reprotoxic properties. Therefore, the added value of an additional SVHC identification according to REACH Article 57 (f) is highly questioned. Specific comment on Chapter 6.1: In the conclusion of the Substances of equivalent level of concern assessment it is stated: "… (DEHP) is proposed to be identified as a substance of very high concern in accordance with Article 57(f) of Regulation (EC) 1907/2006 (REACH) because it is an endocrine disruptor, …, and this gives rise to an equivalent level of concern to those of other substances listed in points (a) to (e) of article 57 REACH." In our view an appropriate ELoC assessment cannot be replaced by matching whether elements of the WHO/IPCS definition are met. We therefore recommend adding some data on environmental exposure to strengthen the ELoC part and to clearly work out the observed and/or possible endocrine mediated adverse effects on the population level. Additionally, the question of a safe threshold under an environmental point of view (inter-species variability, differing modes of action etc.) should be discussed in more detail to support the ELoC part.	**an effect that *by default assumes* a threshold**. We disagree that the determination of a NOAEL and a LOAEL allow to scientifically conclude that a biological (toxicological) threshold does exist. Furthermore RAC has not formally addressed the link between the adverse effects and the endocrine mode of action of DEHP. If DEHP is listed as an ED, the added value will be that future applications for authorisation may need to be addressed under the socio-economic route unless a toxicological threshold is documented. Further, identification of DEHP under 57(f) for the environment may lead to a higher level of protection for the environment, since this is not included in identification under Art. 57 (c) for reproductive toxicity. As mentioned in our response to UK above we don´t find it necessary to add more background data on environemtal exposure or fate as we don´t interprete art. 57f as requiring such considerations for endocrine disruptors . Such exposure related issues are rather needed in accordance with art. 58 when **prioritising** already identified SVHCs due to their endocrine disruption related properties
11	2014/10/16	Industry or trade association CEFIC ECPI Belgium	ECPI comments on the Annex XV dossiers proposing the identification of DEHP, DBP, DIBP and BBP as SVHC (Substances of Equivalent Level of Concern having probable serious effects to human health and the environment based on Endocrine Disrupting properties) as defined under Article 57(f) Note: Since the Annex XV dossiers for the four substances are very similar in content, a single set of comments has been prepared for the four substances, and with specific references to the individual substances where relevant. This same set	Acknowledged.

			of comments is then being submitted via the ECHA web pages for each of the substances. Key comments CEFIC ECPI is committed to the protection of human health and the environment and we believe that chemical regulations should be based on a thorough, systematic and objective evaluation of current science. As such, CEFIC-ECPI has identified significant short-comings in the approach used by the Danish Environmental Protection Agency in the evaluation of these substances as endocrine disruptors. The major short-comings identified are as follows: Major comment relating to the REACH regulation and the Candidate List : Double identification and listing of these four classified phthalates as SVHCs is not justified DEHP – pages 3 – 4 / DBP pages 3 -4 / DIBP pages 3 – 4 / BBP pages 3 -4 These substances are already on the Candidate List for reproductive effects (based on their classification as CLP Category 1B). *The reproductive effects are the adverse endocrine effects* and in addition a threshold does apply for these effects. Given that the existing SVHC identification and listing already covers the adverse reproductive effects which may be related to an endocrine mechanism and for which there is data to show a *threshold*, a *second listing* as an endocrine disruptor for what are the same adverse effects is *not justified or necessary. No new additional relevant human health data are presented* in these Annex XV reports which were not in the detailed evaluation carried out by the ECHA Risk Assessment Committee (RAC) on DEHP and the other three LMW classified phthalates. When setting the DNELs for DEHP in their opinion on the Danish restriction proposal in 2012 and again in 2013 for the purpose of Authorisation, RAC evaluated in detail the reproductive toxicity data available for DEHP and adopted a concept of a threshold for its evaluations. No justification can be envisaged to *subject a substance twice to Candidate Listing and*	We note that ECPI acknowledge that repotox (Repr. 1B) is the adverse outcome / serious effect of the ED properties of these four pthalates. In general cf. The RCOM to some of the similar comments made by UK, DE & FI in relation to the „double counting", „regulatory added value"-, alleged „threshold"- arguments and regarding the assessment made of RAC due to the harmonised Repr. 1B classification. Noted. These four substances are classified as reproductive toxicants, but the endocrine MoA and the plausible link between adverse effects and the ED MoA was not assessed in respect to the harmonized classification and consequently not when evaluating the restriction proposal.. The REACH legal text does neither refer to, nor require, specified criteria for inclusion of endocrine disruptors in the candidate list on a case-by-case basis. No new data need to be presented for evaluating the ED MoA of SVHC substances. Furthermore, evaluation of substances with ED properties of equivalent level of concern in the meaning of art. 57 f of REACH (ELoC) has already been applied for 4 substances (nonylphenol + ethoxylates + 4-tert-octylohenol + ethoxylates) identified as endocrine disruptors with relevance for the environment. The same process can be applied for endocrine disrupters with relevance for human health. RAC has assessed the effects of these substances leading to their classification as reproductive toxicants, a type of effect that by default assumes a threshold. The existence of a threshold has however not yet been formally assessed for this substance. Regulatory relevance is out of scope for the MSC in relation to identification of SVHC substances if the

			Authorisation on the basis of the same health data. In addition the regulatory consequences of being listed on the Candidate List and Annex XIV are already being applied for these substances (requirement for Authorisation of uses; for DEHP and DBP Authorisation applications are in progress; for DBP and BBP no Authorisation applications have been made and all REACH regulated uses will be phased out as of February 2015). It should also be noted that there is no need to demonstrate *equivalent level of concern* when that level of concern is already agreed for the reproductive effects which are the adverse endocrine effects. While the lack of justification for a *double identification* and listing of these four substances as SVHCs as outlined above should provide a sufficient basis for rejecting the proposals, ECPI is also providing additional comments in relation to the science on these substances in view of the potential precedent setting nature of the justification provided by the Danish EPA in the Annex XV dossers. These additional comments are: (These comments apply to the full Annex XV dossiers for DEHP, DBP, DIBP and BBP. Specific pages numbers are provided in the detailed comments attached). 1. While the WHO/IPCS (2002) definition is used, the Annex XV reports fail to apply a scientifically robust process to integrate various kinds and lines of evidence and to gauge how, and how well, the collective evidence supports the conclusion. 2. A formal framework for assessing adversity, mode of action, human relevance and causation is not used. 3. Although the report cites the WHO/IPCS (2002) definition of an endocrine disruptor, its conclusions include the potential ability of substances to interact with the endocrine system. As such, the important distinction between endocrine active and endocrine disruptive is overlooked. 4. There is no discussion of potency or threshold in the report.	substances in accordance with art. 55 are relevant to consider for phase out. We disagree in respect to the statements under point 1 and 2. Re. point 3: we are of the opinion that such a distinction has been made. Re. point 4: Potency is not mentioned in neither the WHO definition nor in Article 57f (both texts refer to "effects"). Neither is potency used for classification for

			5. Previous ecotoxicological studies have demonstrated a clear threshold for known ED compounds in fishes (e.g. estradiol) 6. Identification of these substances as being hazardous for top predators, primates and other larger animals is not justified The proposals from the Danish EPA are for the identification of the four classified phthalates as SVHCs (substances of equivalent level of concern) for endocrine disrupting effects for both human health and the environment. Reference is made to concerns for wildlife species including top predators, primates and other larger animals (including endangered species). For substances to be considered as of concern to higher trophic levels (i.e. top predators) it must be demonstrated that they are persistent in the environment and/or biomagnify. Studies in vertebrates have clearly shown a lack of bioaccumulation and biomagnification studies have shown biodilution for these substances. Additionally the substances have been shown to be readily biodegradable in the environment and hence they do not persist. The use of rodent models as a surrogate for top predators in the environment is not an appropriate method for hazard determination. In addition there are specific primate studies on DEHP which show a lack of reproductive effects even at very high doses. Taking these points into account the statement in the Annex XV dossiers that the effects observed in rats are of particular concern for wildlife including top predators, primates and other larger animals are not supported by the scientific data. 7. Several aquatic ecotoxicological studies identified suffer from methodological deficiencies including: testing above water solubility, not employing replicates within treatment groups and unnatural exposure concentration in feed. The weight of evidence shows a lack of endocrine disrupting effects for the four classified phthalates. The lack of adherence to key principles of scientific inquiry for evaluating cause and effect for endocrine-	reproductive toxicity. Re. point 6: "Primates" have been removed from the SD (because no wildlife primate species exist in the EU - besides in the zoos). We *disagree that environmental fate related properties should be considered for identification of ED substances of ELoC according to Art. 57f* and note that such exposure related intrinsic properties are not mentioned for EDs. Instead, *potency, fate related properties and other exposure related issues* are considered in relation to the prioritization of the Candidate List substances for inclusion in Annex XIV in accordance with Art. 58. It is in this respect noted that *art. 58* (the *following paragraph* after Art. 57) mentions that exposure related issues / properties such as as PBT ness, wide dispersive use and high tonnage normally should be of priority for inclusion on the *Authorisation List* – indicating that indeed *fate related properties and exposure (surrogates) should be used – but not for identification of SVHCs but for priority setting of already identified SVHCs for inclusion into the Authorisation List.* For more detailed responses to the comments 1-7, please see below, where the full ECPI comments for points 1-7 have been inserted in the RCOM table and addressed.

			mediated toxicity raises doubt about the scientific validity of the conclusions presented in the reports. Considering the significant regulatory implications the Annex XV SVHC proposals have on the availability of a particular chemical in the market, the significant short-comings call into question the appropriateness of this approach for the identification of a substance of very high concern according to the criteria set out in REACH Article 57(f) on the basis of endocrine disruption. In the attached document we have included further details to substantiate our comment of significant short-comings in the scientific approach taken in the Annex XV SVHC proposals and provide recommendations for improving the scientific merit in the evaluation of substances for endocrine disruption activity and considerations for understanding a level of concern.	
11			**1. While the WHO/IPCS (2002) definition is used, the Annex XV reports fail to apply a scientifically robust process to integrate various kinds and lines of evidence and to gauge how, and how well, the collective evidence supports the conclusion.** In addition to utilizing the WHO/IPCS (2002) definition in the EU, the Danish EPA proposed assessment of the following four topics to clarify if BBP, DBP, DEHP, and DIBP fulfill the definition of being an endocrine disruptor (Danish EPA 2014a; 2014b; 2014c; 2014c section 4.2.1) 1. Adverse health effects 2. Mode of action 3. Causality/plausible link between adverse effects and mode of action 4. Human relevance of experimental data. The provided bases for the chosen topics were the widely accepted definition of an endocrine disruptor by the WHO/IPCS (2002) and the elements for identification of an endocrine disruptor agreed upon by the European Commission's Endocrine disrupters Expert Advisory group (JRC, 2013). While these	We note that CEFIC ECPI considers the WHO/IPCS definition and the four elements agreed upon by the European Commission's Endocrine disrupters Expert Advisory group as very critical components of a science-based conclusion on endocrine disruption. We agree to this observation. We do not agree to these statements. We believe, the approach used for the identification of the four phthalates as endocrine disruptors is a transparent, systematic, weight-of-evidence approach based on peer-reviewed literature and compares the scientific findings with the widely agreed WHO definition and the justified

			four topics are very critical components of a science-based conclusion on endocrine disruption, these topics were insufficiently evaluated by the Danish EPA. Considering the significant regulatory implications the SVHC proposals have on the availability of a particular chemical in the market, it is critical the analysis go beyond mere descriptions of patterns in data that are considered possible manifestations of endocrine disruption and include assessment of the basis for evaluating whether the observed patterns should be regarded as real and robust, whether explanations for them other than endocrine disruption could be possible, and what might be the state of toxicological evidence for attributing them to an interference with endocrine-mediated control by the chemical at environmentally relevant concentrations. To do so, requires application of a scientifically robust process that employs a weight-of-the evidence methodology to integrate various kinds and lines of evidence and to gauge how, and how well, the collective evidence supports the conclusions. To accomplish this is not easy, as it requires a thoroughly reasoned and documented evaluation of the data and the uncertainties. However, it is crucial for mitigating an alarmist hazard-based approach and propagates a more balanced and scientifically-informed approach for identifying endocrine disruptors and informing the level of concern. Furthermore, methods that provide a more systematic approach and greater transparency are necessary to avoid regulation based on superficial or potentially biased evaluations and are in line with the proportionality principle (i.e. the EUs obligation to act only when, and to the extent, necessary and without imposing an unnecessary burden on the industry). Structured, objective and systematic approaches for evaluating mode of action and human relevance of endocrine active chemicals have been proposed by a multitude of individuals and organizations. In fact, weight of evidence was identified as a key	legal and scientific interpretation of Art. 57(f). Further, the available documentation on adverse effects, mode of action, plausible link between adverse effects and mode of action and human/environmental relevance for the four phthalates indicate the required probable serious concern to human health and the environment as defined in Art. 57f. As Article 57(f) requests identifcation on a case-by-case basis, substances can be identified based on available data and does not require a certain approach to be agreed in advance.

			component in the evaluation of endocrine disruptors in the two key reports that served as the basis for the Danish-EPA evaluation approach (WHO/IPCS, 2002; JRC, 2013). The 2002 WHO/IPCS "Global Assessment of the State-of-the-Science of Endocrine Disruptors" presented an objective and transparent framework for assessing the relationship between potential endocrine disruptors and health outcomes. Likewise, the ED EAG supported use of weight of evidence approaches to reach a conclusion and outlined a "*basic scheme for building evidence on endocrine disrupting properties of substances*" (JRC, 2013). Considering the Danish EPA "assumed" the substance should fulfill the definition provided by the WHO/IPCS (2002) and the ED EAG (JRC, 2013) to be identified as an endocrine disruptor (Section 4.2.1), it follows that the recommended reliance on a weight of evidence approach should also apply. The Danish EPA, however failed to objectively, transparently and adequately weight the data in support of adverse health effects, mode of action, causality and human relevance in the SVHC proposals for BBP, DBP, DEHP, and DIBP. The implications of the SVHC proposals to the existence of a substance in the market, calls for a higher standard of scientific evaluation, particularly given the controversy and undetermined path forward with respect to the regulation of endocrine disruptors under REACH. Below we have included further detail to substantiate our claim of insufficient evaluation of the scientific evidence presented by the Danish EPA on adverse health effects (section 4.2.2 for DEHP/DBP/DIBP/BBP), mode of action (section 4.2.3 for DEHP/DBP/DIBP/BBP), causality (sections 4.2.4 and 4.2.5 for DEHP/DBP/DIBP/BBP), and human relevance (4.2.6 for DEHP/DBP/DIBP/BBP).	
11			**2. A formal framework for assessing adversity, mode of action, human relevance and causation is not used.** ***Insufficient evaluation of adverse health effects (section 4.2.2):***	Re. Section 4.2.2.: The phthalates are classified on the basis of effects considered as adverse. The same

			The concept of "adverse" versus "adaptive" is controversial. Therefore evaluation of adverse effects requires a transparent and objective approach to avoid the perception of arbitrary determinations. For example, the Danish EPA failed to provide a concrete definition of what may be considered adverse in section 4.2.2 of their SVHC proposals for BBP, DBP, DEHP, and DIBP. In particular, the Danish-EPA did not adopt the IPCS (2004) definition for adverse health effects: *a change in morphology, physiology, growth, development, reproduction or life span 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 influence.*" Certain endocrine mediated adverse effects- such as impacts on fertility-can clearly be judged as adverse. For other endpoints-such as alteration in hormone levels-it is more difficult to delineate an adaptive response that is within the limits of homoeostasis from one that has gone beyond those limits for a sufficient period of time, and therefore, capable of causing an adverse effect. Thus, the mere presence of change does not necessarily mean that the outcome is adverse. Failing to differentiate between observations considered adaptive or inconsequential from those deemed to be adverse misleads the reader about the weight of evidence for an endocrine disruptive effect. For this reason, the authors should indicate the definition of adversity that provides the basis for their determinations and subsequently articulate how this definition was applied to distinguish between the end points they are considering to be adverse from those that they consider to be adaptive or mere biomarkers of change. It is important to acknowledge we are not refuting nor supporting the conclusions on the presence of adverse effects in the toxicology studies for these substances. We are, however, emphasizing the care that needs to be taken when characterizing observed outcomes as adverse and systematically presenting	adverse effects are reported in the SDs and are also the main serious effects relevant for identificaton as endocrine disruptors. We disagree with these statements as we are of the opinion that the relevance and severity of the adverse effects have been considered in the SDs We note that *CEFIC ECPI are neither refuting nor supporting the conclusions on the presence of adverse effects in the toxicology studies for these substances.* In respect to adversity a reference has now been included in respect to the findings of reproductive effects refered to as adverse mentioned in the OECD reproductive Toxicity Guidance Document (Series on testing and assessment No 43: „Guidance document on mammalian reproductive toxicity testing and assessment" (Paris 2008). Furthermore, the adverse reproductive effects were all regarded in respect to the agreed harmonized classification as Repr. 1B. Finally, uncertainties and the studies concerning human relevance are discussed in the report (and in respect to the latter a new study have been added) Re. 4.2.3: Not agreed. The SDs do not state that altered endocrine hormone activitity is adverse in itself. However, the consistently observed adverse effects are substantiated by consistent *in vivo* mode of action data showing effects on steroidogenesis, e.g. effects on testosterone production, further substantiated by mechanistic *in vivo* data showing changes in activity of steroidogenic enzymes and effects on gene pathways of

			the evidence in support of that characterization. Although the IPCS (2004) definition for adversity provides some bounds on interpretation of data, as pointed out by EFSA (2013), scientific criteria for the assessment of adversity have not been generally defined. Therefore it is not possible to point to endocrine-specific criteria for adversity and expert judgment is needed to assess the biological impact of experimental observations on endocrine systems. As these SVHC proposals for BBP, DBP, DEHP and DIBP represent the first of those to propose a substance of very high concern in accordance with Article 57 (f) on the basis of "*endocrine disrupting properties*", the level of evidence as well as the approaches used to weigh and evaluate the evidence may set precedence for future proposals. Therefore, it is critical that robust approaches based on key and accepted principles of scientific inquiry for evaluating and identifying adverse effects provide the foundation for expert judgments presented in section 4.2.2 of these reports. Furthermore, it is important the uncertainties are articulated so as not to mislead the decision makers about the confidence in the conclusions. ***<u>Insufficient evaluation of mode of action (4.2.3)</u>*** In the SVHC proposal for DBP (section 4.2.3 p14), the authors provide the following justification as support of an endocrine MOA, "*several rodent studies have demonstrated an endocrine mode of action in vivo, which is substantiated by mechanistic data from in vivo studies. Several of the studies showed decreased testosterone levels, indicating an anti-androgenic mode of action of DBP due to effects on steroidogenesis. It is biologically highly plausible that the suggested anti-androgenic mode of action give rise to the adverse reproductive effects of DBP reported in the previous section*". A similar, if not identical, statement was provided in the SVHC reports for DEHP (section 4.2.3 p17), DIBP (section 4.2.3, p19) and BBP (section 4.2.3 p16) as support for an endocrine mode of action. For all reports, this	steroidogenesis. The *in vivo* mode of action and mechanistic evidence available for these substances are sufficient to show an endocrine mode of action. The conclusion in 4.2.3 does not state that the observed adverse effects are <u>possibly</u> linked to the endocrine mode of action. It states that it is highly biologically plausible (i.e. probable) that altered gene expression and decreased testosterone production leads to the serious adverse reproductive effects observed.Or in other words that a sufficiently robust discrimination has been provided between correlative mechanisticaly unrelated observations and relationships which are correlative but in addition biologically highly plausible and indicating that the adverse developmental/reproductive toxicity effects observed are indeed caused by endocrine disruption. For response to the mentioning of the HR/IPCS framework, we refer to RCOM Re. 4.2.4, 4.2.5, below.

			concluding quote was preceded by a very brief (approximately one-half page in length) discussion which merely reiterated the observation of endocrine activity and the statement of biologically plausibility. However, for regulatory decisions that can potentially lead to the phase-out and/or market deselection of substances, asking whether it is *possible* that an adverse outcome can be attributed to an endocrine pathway is not the critical question; rather, the relevant question is does the weight of evidence support the interdependence between the endocrine pathway *and* the adverse outcome. Phrasing the question as "*is it* possible" allows the Danish EPA to conclude that conditions have been met in support of an MOA, while avoiding a properly constructed, scientifically robust discrimination between correlative observations and causal observations. As highlighted in the IPCS/WHO (2002) 'Global Assessment of the State-of-the-Science on Endocrine Disruptors' report, "*[e]ndocrine disruption is not considered a toxicological end point per se but a functional change that may lead to adverse effects*". As such, endocrine disruption is considered a specific mechanism or mode of action that <u>may</u> lead to a potential developmental toxicity, reproductive toxicity, cancer, or ecologic effect. This means that not all substances that elicit endocrine activity (i.e. endocrine active) will lead to an adverse effect (i.e. endocrine disruptive). Furthermore, "*it is important to discriminate between endocrine toxicity as a primary effect of an endocrine mode of action and endocrine toxicity secondary to other toxic effects not mediated by an endocrine mode of action*" (JRC, 2013). Therefore, to conclude a substance is an endocrine disruptor, the case needs to be made that the interference with the endocrine system actually *leads to* the adverse effect. This requires a scientific evaluation that goes beyond summarizing an association observed in the data to include a logical integration of the data in support of the interrelationships between those observations. The need for this type of scientific evaluation in support	

			of MOA for regulatory decisions has been internationally recognized by the WHO/IPCS,(Sonich-Mullin, 2001; Boobis, 2006, 2008, 2009; Meek, 2014a, 2014b). It is unclear how holding the evaluation of endocrine disruption to a lower standard of scientific evaluation will result in "science-based regulatory decision-making". Both the IPCS/WHO (2002) and ED EAG (JRC, 2013) recognize the essentiality of a weight-of-evidence approach to assess if observed effects occur via an endocrine mode of action. As these reports provide the foundation for the evaluation of endocrine disrupting potential in the SVHC proposals for BBP, DBP, DEHP and DIBP (as indicated in 4.2.1), the Danish EPA should also rely upon the recognized essentiality of a weight-of evidence approach to establish the relationship between endocrine activity and adverse outcomes. However IPCS/WHO (2002) and ED EAG (JRC, 2013) seemingly disagree in their recommendations on the appropriate "level" of evidence needed in support of an endocrine mode of action. This is not surprising as there is a general lack of consensus in the scientific community over the meaning of the term "weight" of evidence (Kortenkamp, 2011; NRC, 2014). This is further complicated by the confusion between the terms, for example "strength" of evidence in support of an adverse outcome (i.e. the degree of positive evidence from a subset of key studies demonstrating a statistically significant result; Weed, 2005) versus "weight" of evidence in the evaluation of a hypothesized MOA (i.e. evaluating the strength of evidence to infer causation; NRC, 2014). As endocrine disruption is not a hazard but a mode of action, the absolute need to evaluate how well the evidence supports the interdependence of the key and adverse outcome cannot be overlooked. In other words, a causal relationship between the chemical exposure, the changes in endocrine-mediated events, and the outcome of concern needs to be established in addition to establishing case for a causal link between the outcome of concern (e.g.	We agree to this statement: endocrine disruption is defined as a type of Mode of Action i.e. endocrine activity leading to adverse (WHO) or serious effects of ELoC (REACH art. 57 f) – but the statement could be read as if this is not evident from the SDs. If that is the meaning of the statement we disagree. We feel that the same could be said in respect to most other statements here.

			adverse effect) and the chemical exposure as is done in hazard identification. As such, certain weight of evidence frameworks are much more scientifically robust for the purpose of evaluating mode of action than others. The IPCS mode of action human relevancy (MOA/HR) framework (Boobis, 2006, 2008, 2009; Meek, 2014a, 2014b) is one such framework and represents an evolution of the framework for assessing endocrine disruptors as proposed in the WHO/IPCS report (2002), both of which were adapted from the Hill considerations (Hill, 1965). According to the IPCS framework, establishing support for or rejection of a hypothesized mode of action requires an evaluation of the evidence in the context of a number of considerations including dose-response and temporal concordance between specified key events and adverse outcome(s), consistency of the evidence (of, for example the data in different biological contexts), biological concordance, essentiality of key events, and analogy (consistency of observations across chemicals) (Meek, 2014b). While these considerations can be thought of as principles and standards of proof in the evaluation of mode of action, the application of the MOA/HR framework is still heavily reliant on expert judgment. Therefore the bases for interpretations and articulation of how conclusions are established also need to be included in any application of this framework. Having consistent principles and standards of proof from case to case that is applied in a transparent and objective way is necessary so that conclusions are not seen as arbitrary. Short-cutting this will merely result in uninformed decisions based on assumptions and unarticulated uncertainty, rather than scientific evidence. Only through a robust and thorough approach, can all parties, in particular, those without a strong scientific background, be confident in the evidence-based conclusions that arise from such an approach Again, is important to acknowledge we are not refuting nor supporting the conclusions on the presence of an endocrine mode of action for these	We note that *ECPI is "neither refuting nor supporting the conclusion on the presence of an endocrine mode of action for these substances"*. We also note that ECPI is "emphasizing the need for the application of scientifically robust approaches based on key and accepted principles of scientific inquiry that prove the foundation for expert judgments on an endocrine mode of action". Overall, we are of the opinion that this is what has been done in these SDs.

			substances. We are, however, emphasizing the need for the application of scientifically robust approaches based on key and accepted principles of scientific inquiry that prove the foundation for expert judgments on an endocrine mode of action. ***<u>Insufficient evaluation of causality/plausible link between adverse effects and mode of action (sections 4.24, 4.25)</u>*** In deconstructing the elements of the WHO/IPCS (2002) definition of an endocrine disruptor and the elements for identification of an endocrine disruptor agreed upon by the ED EAG (JRC, 2013), evaluation of causality is critical in the evaluation of an endocrine disruptor. Evaluation of a causal relationship between the chemical exposure, the changes in endocrine-mediated events, *and* the outcome of concern is also key in the evaluation of mode of action. In sections 4.24 and 4.25 of the SVHC proposals for BBP, DBP, DEHP, and DIBP (Danish EPA 2014,a b, c, d,), the Danish EPA used an informal approach weighted in professional judgment rather than an objective, structured weight of evidence approach for assessing causation. While CEFIC-ECPI recognizes that expert judgment is integral to scientific analysis, it is our opinion the authors provided insufficient documentation of the analyses that led to their conclusions. Specifically, evidence was presented in a manner that infers the information demonstrates endocrine disruption without evaluation of the data in the context of "causal criteria" or full consideration of alternative explanations for the observed effects. As the SVHC proposals did not apply an objective, operational, transparent weight of evidence methodology in their judgments, a distinction cannot be made on whether the authors reached conclusions based on their own perceptions; versus conclusions representative of the larger body of scientific evidence In the SVHC proposal for DBP (section 4.2.4 p14), the authors provide the following justification as support of an endocrine MOA, "*it is biologically plausible that the observed adverse effects are linked*	Re. 4.2.4, 4.2.5 Criteria for evaluating causality are not available. Principles do exist however. They include evaluation of correlative findings, which based on general basic understandings of causality with the field of science, together with various forms of hypothesis testing makes it possible to establish sufficient scientific evidence for the hypothesized mode of action. This has been attempted and we have carefully referred to and evaluated major relevant scientific publications as cited in the SDs.

			to the endocrine disrupting mode of action". A similar, if not identical, statement was provided in the SVHC reports for DEHP (section 4.2.4 p17), DIBP (section 4.2.4, p19) and BBP (section 4.2.4 p16) as support for an endocrine mode of action. While altering the concentrations of hormones is one of a few different mechanisms by which endocrine disruptors may function, simple observation of altered hormones is not itself evidence that the change is responsible for the adverse event (e.g.. the hormone changes may not be causing the adverse effect, but a secondary or unrelated consequence). Furthermore, the consideration of biological plausibility merely encompasses the possibility that something *can* happen and does not provide scientific evidence that something *will* happen or *is* happening. Phrasing the question as "*is it* possible" allows the Danish EPA to conclude that conditions have been met in support of a causal link, while avoiding a properly constructed, scientifically robust discrimination between correlative observations and causal observations. While "*absolute proof of causation might be too high*" (JRC, 2013) a requirement, the mere "plausibility" of causation is absolutely too low a requirement if indeed, decisions are to be based on science. As discussed in the prior section on mode of action, the Danish EPA provided the widely accepted definition of an endocrine disruptor by the WHO/IPCS (2002) and the elements for identification of an endocrine disruptor agreed upon by the ED EAG as the basis for their evaluations (section 4.2.1). While these reports both point to the utility of the IPCS MOA/HR framework and modified Bradford Hill considerations, they seemingly disagree on the necessity of all of the Bradford Hill considerations. The recommendations made in Chapter 7 of the WHO/IPCS (2002) report are largely in agreement with the level of evidence recommended by the IPCS MOA/HR framework. Conversely, the ED EAG considered the level of evidence "*too high a requirement for the identification of an ED for*	Comment noted. The sentence for all four phthalates has been amended to read: "*it is biologically <u>highly</u> plausible that the observed adverse effects are linked to the endocrine disrupting mode of action*". „Highly pausible" is considered similar to „probable" (cf. Art. 57 f) The SDs do not ask whether it is „possible",- so the comment is addressing something not stated in the SDs. We are of the opinion that the sentence above referring to „highly pausible" with the understanding that this indicates „probable causality" is both in accordance with the requirement of Art. 57f but also appropriate in respect to the rather unreflected wording of the WHO definition („causes") because , providing an **absolute** proof of causation might really never be possible, as also indicated in the JRC 2013 report. We believe, the recommendation in JRC 2013 report can be used as the basis for identification of endocrine disrupters, e.g. under REACH Article 57(f). We note that ECPI disagrees.

			regulatory purposes" particularly considering it was "*developed within the context of relevancy of adverse effects in animals to humans where a high degree of confidence is required".* As such the ED EAG reduced the recommended "level" of evidence to observation of "*endocrine activity in vitro, along with evidence of an in vivo biomarker of endocrine activity and adverse effect coupled with a biologically plausible relationship between the measured parameters*" as sufficient to conclude a causal link for endocrine disruption (JRC, 2013). While the Danish EPA did not specify the approach they followed in their evaluation of the evidence in support of causality, based on the information provided in sections 4.2.4 and 4.2.5 of the SVHC proposals for DBP, DIBP, BBP and DEHP, it seems they relied upon an evaluation approach that more closely resembled the scheme recommended by the ED EAG (JRC, 2013) rather than the WHO/IPCS (2002) framework. This is reflected in the incredibly brief evidence analysis provided in sections 4.2.4 and 4.2.5, the lack of any articulated weight of evidence criteria anywhere in the report, a lack of any evaluation of the interdependence of the observed endocrine activity with the adverse outcome, and a conclusion on causality established on the mere plausibility of biological possibility. However, the justification for the reduction in the "level" of evidence proposed by the ED EAG (JRC, 2013) and seemingly applied by the Danish EPA in the SVHC proposals on BBP, DBP, DEHP and DIBP, is scientifically indefensible. The ED EAG provided the following two reasons (section 3.1.2, p14 JRC, 2013) for reducing the level of evidence needed for supporting the sequence of key events leading to adversity: 1) the "*level of evidence required by the [IPCS MOA/HR] framework might be too high a requirement for the identification of an ED for regulatory purposes*" and 2) the IPCS MOA/HR framework was "*developed within the context of relevancy of adverse effects in animals to humans where a high degree of confidence is*	We disagree. Overall, we believe the presented data in 4.2.3, 4.2.4 and 4.2.5 is sufficient and convincing for demonstrating that the observed adverse effects of the phathalates are caused by an endocrine mode of action. We refer to the text of these sections having been modified in the SD due to comments received.

			required". CEFIC-ECPI finds this justification indefensible for a number of reasons. First, the IPCS MOA/HRF does not make requirements on the "level" of evidence in support of an MOA. In fact, publications on this framework explicitly state "the MOA/HR framework is not designed to address the question of "how much information is enough to support a hypothesized MOA" (Meek et al., 2014b). Instead, the framework aims to guide the application, evaluation and integration of evidence in a manner appropriate for discriminating between associated observations and observations that are causally linked. As stated before, the framework can be considered to provide principles and standards of proof for the scientific logic by which the data inform one another in the evaluation of causality. The "level" of evidence needed to support a regulatory decision is not to be informed by science, however the standards of proof and principles should be. To reduce "standards of proof", as suggested by ED EAG (JRC, 2013) will result in causality conclusions based on assumptions and unarticulated uncertainty, rather than scientific evidence. Second, the IPCS MOA/HR framework was developed for the specific purpose of informing regulatory decisions. As articulated in early publications on this framework, a need was identified to harmonize approaches used in the evaluation of MOA data and the subsequent application of these evaluations to hazard characterization and understanding risk (Sonich-Mullin, 2001, Boobis, 2006). The continuous adoption of this framework into international regulatory guidance (Meek, 2014a) demonstrates regulators find this useful and do not consider this approach to be "too high" a requirement to inform regulatory decisions. As such it is not at all clear why endocrine disruption should be held to a standard that is lower than the standard for other non-cancer modes of action when it comes to the robustness of the evaluation required to reach a conclusion intended to inform regulatory decisions,	The disagreement by CEFIC ECPI to the conclusions by ED EAG (JRC, 2013) on the relevance of IPCS/HR framework is beyond the scope of these documents. However, we agree that the WHO/IPCS framework on mode of action/species concordance analysis is useful and similar considerations have been made in the SDs when evaluating mode of action and human relevance for the current reports. The evaluation of evidence has been performed in consideration of dose-response and temporal concordance between specified key events and adverse outcome(s), consistency of the evidence, biological concordance, essentiality of key events, and analogy (consistency of observations across chemicals with structural similarities), as currently suggested by the ECPI and in agreement with Meek et al., 2014. (Meek ME, Boobis A, Cote I, Dellarco V, Fotakis G, Munn S, Seed J, Vickers C. 2014. New developments in the evolution and application of the WHO/IPCS framework on mode of action/species concordance analysis. J Appl Toxicol. 2014 Jan;34(1):1-18). These considerations are all a part of the "expert judgement" of the weight of evidence The IPCS MOA and HR framework is listed as literature used as reference material by the ED EAG (JRC, 2013) and hence was evaluated and assessed in their deliberations to agree on recommendations for identification of substances as endocrine disruptors.

			particularly when the consequences of the regulatory decision the analysis is intended to inform can potentially lead to the phase-out and/or market deselection of substances. Third, while the IPCS MOA/HR framework does aim to assess human relevancy with some degree of confidence, this framework first and foremost provides a scientifically sound approach for evaluating whether there are sufficient data to support, with an acceptable level of confidence, a mode of action for a suspected toxicological outcome in animals (Sonich-Mullin et al., 2001). As pointed out earlier, the weight of evidence to support an interdependence of the key event and the adverse effect (i.e. causality) for a hypothesized mode of action should draw on the modified Bradford Hill considerations. By eliminating the need to evaluate the data in the context of these considerations a scientifically-informed conclusion on causality in the animal data will not even be established, resulting in regulatory decisions informed largely by assumptions and not scientific evidence. Finally, the brushing off of the utility of the IPCS MOA/HR framework by the ED EAG (JRC, 2013) appears contradictory to the emphasis they place on the importance of evaluating human relevance. Specifically, the ED EAG states "*it was often difficult to demonstrate convincingly the non-relevance of adverse effects observed in the animal models and that the usual approach was to assume relevance unless non relevance to humans could be convincingly demonstrated by, for example, applying the guidance provided by the IPCS mode of action human relevancy framework*". They go on to note "*relevance to humans should be assumed by default in the absence of appropriate scientific data*". The recommendation to ignore the IPCS mode of action human relevancy framework and rely on mere consideration of "*endocrine activity in vitro, along with evidence of an in vivo biomarker of endocrine activity and adverse effect coupled with a biologically plausible relationship*" as proposed by the ED EAG	Not agreed. We find largely that the statemenmts made here are unsubstantiated relative to the content of the SDs. For example we do find that the SDs include sufficient information to the causal links between the observed endocrine activity and the adverse developmental/reproductive effects

			and seemingly applied by the Danish-EPA, will never result in an assessment that is robust enough to inform human relevance, therein leading to many more conclusions based on default assumptions of human relevance than informed, science-based evaluations. The MOA/HR framework specifically assists in framing the question of how animal studies constitute evidence for human hazards in terms of whether the underlying biological processes are shared, this provides a powerful basis for assessing the bearing of such studies on inferences about human hazard potential and the level of concern. CEFIC-ECPI firmly believes the informal evaluation of causality in the SVHC reports for BBP, DBP, DEH and DIBP, is not scientifically robust enough for the identification of an endocrine disruptor in the identification of a chemical as a substance of equivalent level of concern according to Article 57(f) of REACH on the basis of "endocrine disrupting properties". *Th*e reason Bradford Hill proposed his considerations was to inform upon what basis we should proceed from a verdict of association to one of causation (Hill, 1965). While consideration of biological plausibility is one of the key considerations in the evaluation of causation, it is not the only consideration. The consideration of biological plausibility merely encompasses the possibility that something *can* happen and does not provide scientific evidence that something *will* happen or *is* happening. To draw a conclusion about causality with any degree of confidence demands a thorough evaluation of the evidence that includes consideration of the suite of modified Bradford Hill considerations (WHO/IPCS, 2002; Meek, 2014a, 2014b). Reliance on anything less, substantially weakens the scientific robustness of the evaluation and calls into question the legitimacy of the conclusions. ***<u>Insufficient evaluation of Human relevance:</u>*** The implications of the SVHC proposals to the fate of the chemical in the market demands a systematic, robust and transparent assessment of the data resulting in evidence-based conclusions on human	Re. 4.2.6 Phthalates are ubiquitous in the environment and present in almost all urinary samples when included in biomonitoring surveys. Exposure-data and cause-effect relationships are extremely difficult, if not impossible, to establish through population surveys, and not necessarily required for regulatory action. However, human relevance of the adverse effects of phthalates which inhibit testosterone synthesis during development

			relevance. As with mode of action and causality, the Danish EPA seemingly favored the opinion of the ED EAG (JRC, 2013) that *relevance to humans should be assumed by default in the absence of appropriate data demonstrating non relevance"* (JRC, 2013). This is exemplified in the conclusion statement on thyroid effects in the SVHC report for BBP (section 4.2.6, p20) "[i*]t is therefore assumed that these effects may also be relevant to humans, as no data demonstrate non-relevance*"; and in the conclusion on relevance of effects on steroidogenesis-" *the current knowledge on species differences is not sufficient to disregard the human relevance of phthalate effects*" Identical conclusion statements can be found in the SVHC proposal for DBP (section 4.2.6 p18), DEHP (section 4.2.6 p22) and DIBP (section 4.2.6 p21). Important key literature regarding differentiation of direct and indirect thyroid effects (De Sandro et al. (1991)) is missing from the Annex XV dossiers; the full reference is provided in the reference list at the end of these comments. To default to human relevance may be reasonable when there is not enough certainty in the evidence to do otherwise. However, to default to human relevance on the basis of a lack of appropriate data demonstrating non-relevance, requires a systematic, robust and transparent assessment to demonstrate that indeed "appropriate data demonstrating non relevance" do not exist. It is only by putting the basis for inferring potential human risk explicitly forward that one can then evaluate evidence for and against the proposition. This is particularly important in this case, where animal study outcomes disagree with one, another as this raises the question of whether humans ought to be assumed to be like responding species or resistant ones. Therefore the potential reasons for the species difference and how they might inform on the relevance to humans becomes part of the evidence evaluation. Furthermore, the authors should articulate how the uncertainties and inconsistencies in the data that they themselves raised, fail to support non-relevance	has been assessed and evaluated as overall relevant in the dossier. *A new study by Albert and Jégou (2014) supports the RAC conclusion (2012) that there is too much uncertainty in the available data to allow a conclusion on humans being less, equally or more sensitive than rats.* We find that careful interpretation of data regarding relevance to humans has been presented. A review of the available data showing similarities and differences between species is made. As noted in the Annex XV report, the *studies by Tomonari (2006) and Kurata (1998) were in adult marmoset, and therefore did not include the more sensitive perinatal period. A recent publication provides a critical assessment of in vivo and in vitro studies exploring phthalate effects in humans (Albert and Jegou 2014). This paper highlights the variation among species in the window of susceptibility to the effects of phthalates and variation among species in timing of the development of the testis*. Another conclusion of this literature study is that the *indications of species differences found in e.g xenografting studies have methodological limitations and that "Caution before concluding that phthalates are innocuous in the human feta testis should be kept until these issues have been addressed*" Furthermore, a.o., it states that *phthalate anti-androgenicity is plausible in adult men and that epigenetic and germ cell changes should be interpretated with great caution as there are still many unknowns.(*Albert and Jegou 2014). The text in the dossier has been updated with the new Albert and Jégou (2014) reference. (Albert O and Jégou B. 2014. „A critical assessment oft he endocrine susceptibility oft he human testis to phthalates from fetal life to adulthood." Human Reproduction Update, Vol. 20(2):231-249). Regarding interactions with the thyroid system it is merely stated in these SD that this is not addressed in the report.

			in a more thorough and robust manner and/or acknowledge the assumptions that are required for the default human relevant conclusion to hold true. Uncertainty alone is not reason to default to a position of human relevance, as uncertainty will almost always impose itself on scientific conclusions. Therefore it is important to clearly articulate the uncertainty in a manner that demonstrates more or less support of human relevance, to ultimately allow the nature of the uncertainty to substantiate a default conclusion. Of the data that was discussed, the human relevance section was seemingly selective in the dismissal of studies that did not support human relevance and the general acceptance of studies that seemingly supported human relevance. Furthermore, additional information on interactions with the thyroid system and impacts on germs cells that have no apparent link to the hypothesized mode of action presented in section 4.2.3 were provided as support for human relevance. Overall, this subjective approach misleads and confuses the reader about the weight of evidence supporting a human relevant endocrine mode of action. The following was taken from the report on DEHP to exemplify these points, however similar if not identical approaches were taken in the SVHC proposals for BBP, DBP, and DIBP. In section 4.2.6 of the SVHC proposal for DEHP, species differences were discussed in a broader context. Particularly, the contradictory observations in non-human primates (marmosets) were discussed in light of the findings in rats. The authors refer inter alia to the study by Tomonari et al. (2006), (section 4.2.6, p19) which did not reveal reproductive effects of DEHP in concentrations up to 2500 mg/kg bw/d in male marmosets. Additionally the negative findings described by Kurata et al. (1998) in male marmosets receiving up to 2500 mg/kg bw/d were reported (section 4.2.6 p19). Also the mechanistic discussions of Johnson et al. (2012) were cited who concluded that "it appears the human fetal testis responds more	We find it relevant to mention the human relevance of germ cell changes, although implications of these effects are not yet not fully known. We do not find that this statement confuses the reader, but that it is in fact a note to clarify the limits of the report. Not agreed. Overall, the RAC in the conclusion as given above; the JRC (2013) in stating that '*relevance to humans should be assumed by default in the absence of appropriate data demonstrating non relevance*'; and the Albert and Jégou (2014) study - agree that based on available current data, human relevance of the adverse effects of the 4 phthalates has to be assumed.

			like a mouse than a rat", i.e. the most sensitive animal model (rat) does not seem to be a good model for the human situation (section 4.2.6 p21). Despite this experimental evidence of obvious species differences the Danish EPA concluded that the available adverse, endocrine related effects observed in rats are relevant for humans Interestingly, to detract from these findings, the authors emphasize the similarities seen between species (including mice) on germ cell proliferation in favor of their conclusions stating even though they are of uncertain significance and not relevant to the mode of action discussed in section 4.2.3, nor the adverse effects discussed in section 4.2.2- "*in vitro studies on phthalate exposure of fetal testis tissue have shown comparable changes in germ cells whether using testes from rats, mice or humans. This clearly supports the possibility that reproductive effects of phthalates are relevant to humans*"(section 4.2.6 p20). The proposed endocrine mode of action for DEHP in section 4.2.3 referred to "*decreased testosterone levels, indicating an anti-androgenic mode of action of DBP due to effects on steroidogenesis"*, leading to the adverse effects identified in section 4.2.2, which included "*increased nipple retention, decreased anogenital distance, reduced number of spermatocytes, and testicular changes, including multinucleated gonocytes, tubular atrophy and Leydig cell, hyperplasia*". Accordingly, evidence demonstrating species differences on testosterone weight or any of these identified adverse effects weight much more heavily in the evaluation of the human relevance of the proposed endocrine disrupting mode of action then changes in germ cells. The human relevance question should be addressed in the context of the hypothesized mode of action. Presentation of data that is not relevant to the mode of action misleads the reader about the weight of evidence to support or refute human relevance.	
11			**3. Although the report cites the WHO/IPCS (2002) definition of an endocrine disruptor, its**	Not agreed. Endocrine disruption is defined as a type of mode of

			conclusions include the potential ability of substances to interact with the endocrine system. As such, the important distinction between endocrine active and endocrine disruptive is overlooked. In the SVHC proposals for DBP, DIBP, BBP and DEHP the Danish EPA relies upon the definition of endocrine disruptors adopted by the WHO/IPCS (2002) as the basis for assessing whether or not these substances have endocrine disrupting properties (section 4.2.1). According to this definition an "endocrine disruptor" is "*an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations*." Integral to this definition are three important components 1) the substance must act through an endocrine mode of action; 2) the substance must cause an adverse health effect; and 3) that adverse effect must be causally related to and occur as a consequence of the altered endocrine function. All three of these components are necessary to demonstrate that a chemical is an endocrine disruptor. This requires the differentiation between endocrine-mediated effects from other known modes of action, the differentiation between endocrine active versus endocrine disruptive (EFSA, 2013), and the linking of an observation of an adverse effect to that hypothesized endocrine mode of action. While CEFIC-ECPI agrees the WHO/IPCS (2002) definition provides an appropriate basis for characterizing an endocrine disruptor, it is our opinion the evaluation of these substances by the Danish EPA focused on only parts of this cited definition as the basis of their conclusions. By failing to consider a clear link between the reported adverse effects and endocrine activity, the possibility of endocrine active versus endocrine disruptive is left unaddressed.	action i.e. endocrine activity leading to adverse (WHO) or serious effects of ELoC (REACH Art. 57f) . The SDs do not state that altered endocrine hormone activity is adverse in itself. However, the consistently observed adverse effects are substantiated by consistent *in vivo* mode of action data showing effects on steroidogenesis, e.g. effects on testosterone production, further substantiated by mechanistic *in vivo* data showing changes in activity of steroidogenic enzymes and effects on gene pathways of steroidogenesis. The *in vivo* mode of action and mechanistic evidence available for these substances are sufficient to show an endocrine mode of action.
11			**4. There is no discussion of potency or threshold in the report.**	Not agreed. Potency is not part of the definition or the recommendations from the ED EAG (JRC 2013) for a

			Potency is important for informing a level of concern. The approach taken by the Danish-EPA in the SVHC proposals for evaluating an endocrine mode of action ignores potency. Potency refers to the range of doses over which a chemical produces increasing responses. Potency is therefore a measure of a substances activity or strength to produce the effects and is part of the dose response considerations. Ignoring potency assumes that all chemicals are equally capable of eliciting a given adverse outcome. Consideration of potency is important in the identification of an endocrine disruptor for regulatory purposes because this relates to the potential level of concern for the substance.. If the identification of SVHCs on the basis of endocrine disruption is to be based on a level of concern, then whether or not this level of concern is reached must include consideration of dose response and potency. Therefore, potency should be considered as part of the weight of evidence assessment to decide whether a substance requires specific regulatory action on the basis of endocrine disruption. It is important to note that at the whole organism level, potency relates to the ability of a substance to produce a biological effect and may be substantially different from the potency measured with in vitro assays (EFSA, 2013). Therefore, potency should be based on the ability of a substance to produce an adverse health effect in vivo and not be determined on the basis of in vitro studies. This ability will depend not just on a substance potency at its molecular initiating site, but also on its disposition in the body, the timing the exposure and the dose and duration of exposure. Therefore dose remains an important factor in assessing the potency of potential EDCs to cause an adverse health effect. ***Inhibition of testosterone synthesis is a threshold effect*** According to Article 60, paragraph 2 of the REACH regulation, for substances meeting the criteria in	substance to be identified as an endocrine disruptor. Further, in the minutes of the expert meeting on endocrine disruptors on 24/10/2013 at the office of Anne Glover, Chief Scientific Adviser, European Commission it was agreed that consideration of potency, together with exposure, is a matter for the *risk* assessment process – hence exposure considerations are not appropriate to include for the hazard *identification* of endocrine disruptors but we acknowledge that for priority setting purposes in relation to proposing substances on the candidate list for inclusion on Annex XIV such issues are relevant and appropriate to consider (cf. Also REACH art. 58 & . http://ec.europa.eu/commission_2010-2014/president/chief-scientific-adviser/documents/minutes_endocrine_disruptors_meeting_241013_final.pdf) No changes have therefore been made to the SDs. Re. Inhibition of testosterone synthesis Noted. Thank you for your view on this issue. Cf. The issue of threshold is not within the scope of the dossiers to identify substances with endocrine disrupting properties of EloC in the meaning of Art. 57 f. For discussion of Art. 57(f) we refer to RCOM to UK; DE, IE and FI. No changes therefore made to the SDs.

			Article 57(a), (b), (c) or (f) for which it is not possible to determine a threshold can only be Authorised if it is shown that socio-economic benefits outweigh the risk to human health or the environment arising from the use of the substance and if there are no suitable alternative substances or technologies accordance with Section 6.4 of Annex I. This section is in support of the existence of threshold values for endocrine disrupting substances should the current applicable rules for authorization according to Article 57(f) be modified for endocrine disruptors to allow only the socio-economic route. It is general knowledge that hormone levels fluctuate in response many environmental stimuli (*e.g.,* sunlight, stress, exercise, and food availability) (Gamble et al 2014). By their very nature endocrine systems are robust to such fluctuations. It can be generally accepted that humanity does not experience adverse effects because the lights are turned off in a room, is surprised by a sound, goes for a jog, or sees a plate of cookies. All these stimuli alter the endocrine system, but do not cause adverse effects. Simultaneously we can recognize that chronic, high exposure to the above can result in adverse effects. The unifying explanation is the existence of thresholds for adverse effects in endocrine systems. Borgert et al. (2013) provided a well-articulated explanation for why thresholds exists for endocrine effects 2013. In addition, good references are also available to explain fundamental concepts related to reproductive endocrinology (Chedrese, 2009). Generically, ligands and receptors interact in a continuous association-dissociation scenario (*i.e.,* the law of mass action is in effect). At any given moment some ligand-receptor complex dissociates, ending a signal, while at another location in the cell a ligand and receptor associate, initiating a signal (Foreman and Johansen 2002). In endocrine systems the all these fluctuating signals are integrated at the genomic level, resulting in a coherent and	

			coordinated cellular response. If the endocrine system were disrupted by such small fluctuations it is difficult to see how any organism could survive, yet nature proves to us every day how robust the endocrine system is as we draw another breath. Endocrine systems are dynamic. These dynamic, robust systems come about via mechanisms such as regulation of receptor number, sensitivity, and feedback controls. In response to overstimulation they can reduce receptor number, engage posttranslational modifications (*e.g.,* phosphorylation) to reduce receptor sensitivity, or activate negative feedback to reduce genomic signal. Conversely, in under stimulated environments system can respond by increasing receptor number, sensitivity, or activating positive feedback to increase genomic signal. The examples above allow endocrine systems adapt at both cellular and tissue levels, but adaptive responses of endocrine systems also occur at organ and organism wide levels (Norris and Carr 2013). Thresholds for altering the endocrine system are intuitively obvious when one considers the familiar example of the "combined pill" as an oral contraceptives for controlling fertility. To achieve purposeful "endocrine disruption" (reduction in fertility) requires profound, consistent alteration in the endocrine system. To this end, women ingest high affinity estrogen and progesterone ligands regularly to pharmacologically manipulate the endocrine system. The difference in oral contraceptive effectiveness under "perfect" and "typical" conditions is telling as it pertains to thresholds. Under "perfect" conditions 1-year unintended pregnancy rates are reduced approximately 85% to 0.3% or less. However, "typical" conditions considers scenarios where users do not always remember to take their medication. This can be thought of as circumstances when purposeful endocrine disruption temporarily falls below the threshold for reduction in fertility (*i.e.,* the threshold for adverse effect if this were an	

			unintentional exposure). Under "typical" conditions the 1-year unintended pregnancy rates increase from 0.3% to 9% (Trussell 2011). When one performs straightforward reality-checks such as above, it is clear that evidence supports the existence of thresholds for adverse effects in the endocrine system. Thus considering all the above, evidence supports that alterations in testosterone synthesis have a threshold for adverse effects because: 1. The masculinizing effects of testosterone operate via a receptor-dependent mechanism (*i.e.,* the effects of testosterone depend on the androgen receptor). 2. The inherent behavior of receptor based biological systems is threshold-based (*i.e.,* the androgen receptor mediated effects have thresholds). In standard toxicology studies of low molecular weight (LMW) phthalates effects on the male rat reproductive system readily show thresholds. As doses of LMW phthalates escalate, observations shift from biological effect to adverse effect . Initially a biological decrease in testosterone can be observed. At higher doses there are markers of biological effect in decreased AGD and retained nipples. Only at very high doses does one begin to observe a low incidence of adverse effects like hypospadias and cryptorchism. This effect is clearly observable when considering the dose-response data from multiple studies on DBP (Barlow et al 2004; Clewell et al 2009; Howdeshell et al 2008; Johnson et al 2011; Lehmann et al 2004; Mylchreest et al 2000). The results show reductions in StAR precede testosterone decreases, which in turn precede epididymal and androgen-dependent organ weight changes, and only at doses above those that cause alterations in the endocrine system does one observe adverse effects on the male rat reproductive tract.	
11			**5. Previous ecotoxicological studies have**	

			demonstrated a clear threshold for known ED compounds in fishes (e.g. estradiol) Five potentially endocrine disruptive compounds clearly showing a threshold level for the activation of vitellogenin (VTG) in fish have been identified: estradiol (Kang et al 2002), 4-tert-pentylphenol (TPP) (Gimino et al. 1998), nonylphenol (Jobling et al. 1996), octylphenol (Jobling et al. 1996) and bisphenol A (BPA) (Sohoni et al. 2011). VTG is a yolk precursor protein, which is found in both male and female fish but is in greater concentration in females as it is involved with egg development. As such, increased levels of VTG are frequently evaluated in male fish as an indicator for exposure to natural and synthetic estrogens and other endocrine active substances. Briefly the threshold, expressed as Lowest Observed Effect Concentration (LOEC) values, for VTG induction ranged from 0.0557 µg/L for the highly potent hormone estradiol to 1000 µg/L for TPP. Additionally the duration of exposure in the studies varied from 14 days (nonylphenol) to 164 days (bisphenol A) indicating that the threshold is not influenced by the temporal range examined. These chemicals were selected partly due to data availability in a growing field, but also because each study included sufficient exposure concentrations to demonstrate a dose response and threshold for the induction of VTG, a highly responsive biomarker for estrogen receptor agonists. A threshold exists even for the highly potent natural hormone estradiol.	Noted. Thank you for your view on this issue. . Cf. Also our responses on the issue of thresholds elsewhere in these responses to comments. The issue of threshold is not within the scope of the dossiers to identify the substances as endocrine disrupting prperties of ELoC in the meaning of Art. 57f. No changes have therefore been made to the SDs. Not agreed. With regard to immunoassays - the threshold is often just the the detection limit of normally rather insensitive immunoassays. Not agreed. LOEC was 27 and 104 µg/l in two studies from the OECD validation of TG 234 (http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO(2011)23&doclanguage=en).
11			6. Identification of these substances as being hazardous for top predators, primates and other larger animals is not justified The proposals from the Danish EPA are for the identification of the four classified phthalates as SVHCs (substances of equivalent level of concern) for endocrine disrupting effects for both human health and the environment. Reference is made to concerns for wildlife species including top predators, primates and other larger animals (including endangered	As mentioned earlier exposure related issues should not be considered in the identification of SVHCs due to their ED properties. Therefore this has not been included in the SDs. Anyway:According to e.g. Vorkamp K and Rigét F. 2009 (A review of new and current-use contaminants in the Arctic environment: Evidence of long-range transport and indications of bioaccumulation. Chemosphere 111 (2014) 379–395), phthalates are found in arctic animals, indicating that a continuous exposure to the environment is occurring. "Phthalates

			species). For substances to be considered as of concern to higher trophic levels (i.e. top predators) it must be demonstrated that they are persistent in the environment and/or biomagnify. Studies in vertebrates have clearly shown a lack of bioaccumulation and biomagnification studies have shown biodilution for these substances. Additionally the substances have been shown to be readily biodegradable in the environment and hence they do not persist. The use of rodent models as a surrogate for top predators in the environment is not an appropriate method for hazard determination. In addition there are specific primate studies on DEHP which show a lack of reproductive effects even at very high doses. Taking these points into account the statement in the Annex XV dossiers that the effects observed in rats are of particular concern for wildlife including top predators, primates and other larger animals are not supported by the scientific data. Due to relatively low BCF values and the demonstration that DEHP biodilutes through tropic levels and empirical data showing all three phthalates to be readily biodegradable, there is minimal potential for bioaccumulation and for a hazard to top predators. Substances of concern to higher trophic levels (i.e. top predators) must demonstrate they are persistent in the environment and/or biomagnify. In this case, BCF data for fishes demonstrates DEHP, BBP and DBP are of low risk to bioaccumulate. As all top predators are vertebrates, the use of invertebrate BCFs is not appropriate as metabolic processes are not as developed. In addition, biomagnification studies have demonstrated DEHP to biodilute through increasing trophic levels (MacKintosh et al. 2004). Additionally, all three substances are shown to be readily biodegradable in the environment and not persist thereby reducing bioavailability. The use of rodent models as a surrogate for top predators in the environment is not an appropriate method for hazard determination. There is no empirical data demonstrating rodent models	were below detection limits in sediment from Svalbard, but diethyl phthalate (DEP), butylbenzyl phthalate (BBP), DBP and DEHP were detected in sediment from Greenland, in locations far away from human settlements (Vorkamp et al., 2004;Evenset et al., 2009). Xie et al. (2007) analyzed air and seawater of the Arctic and showed that phthalates were transported with the atmosphere to the Arctic and transferred to the oceans by net deposition. Regarding bioaccumulation, DEHP and other phthalates were found in a variety of fish and wildlife samples, but the data did not suggest food chain biomagnification. " DEHP was detected in the following species: Polar bear (Greenland), Minke Whale (Greenland), Pilot whale (Faroe Islands), Ringed seal (East Greenland), Ringed seal (west Greenland), Shorthom sculpin (East Greenland), Shorthom sculpin (West Greenland), Northern fulmar (Faroe Island), Sediment (Greenland). Generally, the overall trend for all sample types seemed to be:DEHP > DEHA > BBP DEP >DnHP =DBP =DnOP > DMP. It has to be noted that the analyses were based on liver samples, with the exception of fulmer (one of the Faroe Islands). Due to the hydrophobic and lipophilic properties of the phthalates, they may also be detected in blubber samples (Vorkamp et al. 2004). (Vorkamp, K., Dam, M., Riget, F., Fauser, P., Bossi, R., Hansen, A.B., 2004. Screening of ''new'' contaminants in the marine environment of Greenland and the Faroe Islands. National Environmental Research Institute, Denmark. NERI Technical Report No. 525 Evenset, A., Leknes, H., Christensen, G.N., Warner, N., Remberger, M., Gabrielsen, G.W., 2009. Screening of new contaminants in samples from the Norwegian Arctic. Akvaplan-niva report 4351-1. (Xie, Z., Ebinghaus, R., Temme, C., Lohmann, R., Caba, A., Ruck, W., 2007. Occurrence and air-sea exchange of phthalates in the Arctic. Environ. Sci. Technol. 41, 4555–4560) Fate related properties such as potential for (bio)degradation and bioaccumulation are to be

			superiority over current animal models, and significant uncertainty prevents its use for environmental assessment. Laboratory rats are inbred or genetically similar. This is in contrast to current aquatic models which use wild-type fish species that may more accurately reflect natural populations. Additionally, the toxic form of each substance needs to be identified. As substances move upwards through trophic levels, substantial biochemical transformation will alter the potency and reactivity of the ultimate chemical to which the top predator is exposed. Finally, routes of exposure may be significantly different in laboratory species from those encountering the substance naturally. **DEHP** The range of BCFs is quite variable, but is generally lower for vertebrates than invertebrates. The EU RAR uses a value of 840 for fish (EU RAR DEHP). This is on the high end for fishes, which generally ranged from 50 – 250. The BCF selected is however still below the bioaccumulation cutoff of 1000 used by the EU in PBT assessments. Additionally, biomagnification factor (BMF) values were quite low for studies ($\leq$ 0.07) reported in the EU RAR (EU RAR DEHP). MacKintosh et al. (2004) calculated the food web magnification factor (FWMF) as 0.25 for DEHP. This value demonstrates that each trophic level will have only ¼ the DEHP as the one below and indicates biodilution in the environment. Reported BCF values for invertebrates are considerable higher than vertebrates and are often over 1000. However, many of the reported studies used DEHP values above water solubility which may skew results. Those values reported for exposures closer to water solubility more closely matched BCF values reported for fishes (EU RAR DEHP). Additionally, Annex XV-Identification of DEHP as SVHC section 3.4 does indicate that a lack of biomagnification may be due to a more developed metabolic pathway in vertebrates (Annex XV, Identification of DEHP as SVHC; Pg 8). Additionally DEHP has been shown to be readily biodegradable. Taking all the data together, there is	considered later, *after* the identification of SVHCs with ED properties, in relation to inclusion on the Authorisation List. Please refer to RCOM to UK p. 15-17. Please note that the infomation on persistency and bioaccumulation in the SDs were just included as background information and Not because those fate related properties are needed for identification of SVHCs with endocrine disruptive properties according to art. 57 df. This has now been clarified in the SDs

			minimal potential for bioaccumulation and a hazard for higher trophic level predators. **DBP** BCF values for DBP are low. Some studies have reported values in the 1000's; however these used radiolabeled compounds and so my be artificially inflated due to detection of metabolites. Hüls, (1996) followed OECD guidelines and calculated a BCF = 1.8. Similarly, Ray et al (1983), demonstrated a lack of bioaccumulation (BCF < 1) in sediment dwelling fauna. This indicates a very low potential to accumulate through the food web, and a minimal risk to top predators. In addition, DBP is readily biodegradable and will therefore not persist in the environment. Taking all the data together, there is minimal potential for bioaccumulation and a hazard for higher trophic level predators. **BBP** BCF values for BBP or moderate to low. Reported values have been as low as 12; however the EU RAR for BBP raises concerns that metabolites may also have ED characteristics, for this reason a more conservative BCF = 449 was selected. This value is still below the bioaccumulation cutoff of 1000 used by the EU in PBT assessments and is not expected to magnify through the food web. Additionally DBP is readily biodegradable and not expected to persist in the environment. Taking all the data together, there is minimal potential for bioaccumulation and a hazard for higher trophic level predators.	
11			**7. Several aquatic ecotoxicological studies identified suffer from methodological deficiencies including: testing above water solubility, not employing replicates within treatment groups and unnatural exposure concentration in feed. The weight of evidence shows a lack of endocrine disrupting effects for the four classified phthalates.**	In general, we refer to RCOM to UK comments as many are of similar nature.

			The lack of adherence to key principles of scientific inquiry for evaluating cause and effect for endocrine-mediated toxicity raises doubt about the scientific validity of the conclusions presented in the reports. Considering the significant regulatory implications the Annex XV SVHC proposals have on the availability of a particular chemical in the market, the significant short-comings call into question the appropriateness of this approach for the identification of a substance of very high concern according to the criteria set out in REACH Article 57(f) on the basis of endocrine disruption. In the attached document we have included further details to substantiate our comment of significant short-comings in the scientific approach taken in the Annex XV SVHC proposals and provide recommendations for improving the scientific merit in the evaluation of substances for endocrine disruption activity and considerations for understanding a level of concern. **<u>DEHP</u>** The low water solubility (~3µg/L) of DEHP poses unique challenges for aquatic toxicity testing. This challenge can be minimized by using a solvent carrier (i.e. methanol) to increase substance solubility. This however can drastically alter the exposure scenario and is not representative of naturally occurring conditions. However, many of the studies listed in the ER RAR for DEHP include solvents to achieve DEHP concentrations well above normal water solubility. Conclusions drawn from these studies are not reliable as they artificially inflate the amount of substance to which fishes/invertebrates would normally be exposed. "Annex XV – identification of DEHP as SVHC" identifies several studies it notes as supporting DEHP as an ED compound published after the EU RAR (Pg 33 – 35). Many of these studies however are flawed in methodology and therefore caution must be taken	Re. The technical comment on use of solvents:. The use of a solvent is not desirable but sometimes necessary and therefore recommendations are given in OECD guideline on how to use solvents if needed. Test results from studies significantly above the water solubilty are not informing about the effects / bioaccumulation by only the aqueous exposure route. Adsorptive substances like the phthalates may occur as micells and/ or adsorbed on to organic particulate matter in the test medium. Which however may also be taken up by aquatic organisms like fish by the dietary route. Test results under such circumstances may indicate the potential of the test substance to cause efffects when not only exposing the organsm via the aquous route. Norrgren et al. (1999) was included in the RAR and hence previously considered relevant in an EU context. Cf responses to UK The present Annex XV dossier is not a risk assessment. However, salmon eat continuously so a longer exposure period could be argued for. Cf. Also responses to UK The phrase "may possibly also have" It is now also mentioned more transparently that this is a possibility considered because no relevant studies on fish have been published – but that thyroidal activity of DEHP has been observed in amphibians and often thyroidal effects are seen across vertebrate classes such as between fish and amphibians due to a higly conserved thyroidal system. This view is supported by a critical review by

			when drawing conclusions. For example, Nerrgren et al. (1999) is cited as a dietary exposure study which demonstrates a change in sex ration when salmon are fed DEHP at a concentration of 1500 mg/Kg food for 4 weeks. However, predicted concentrations in prey items as listed in the EU RAR generally range between 1 – 10 mg/Kg, with one worst-case example of 100 mg/Kg. Therefore, the dietary exposure study uses concentrations at least one order of magnitude higher than expected environmental concentrations. The four week exposure period is also not environmentally appropriate given the high degradation rate for DEHP. Additional studies fail to use realistic exposure concentrations. Finally, in the "Annex XV – identification of DEHP as SVHC", inappropriate conclusions are drawn related to mode of action. Despite no studies being presented which definitively link growth effects to thyroid disruption in fish, it is stated that: " DEHP may also have thyroid effects in fish and/or amphibian species" (Pg 35). While there some studies on DEHP showing the possibility weak estrogenic effects, the vast majority of studies reported here have inherent methodology flaws and should not be used for hazard identification. Overall, the weight of evidence shows a lack of adverse endocrine disrupting effects in ecotoxicology studies. **<u>DBP</u>** As with DEHP, the "Annex XV – Identification of DBP as SVHC" cites several ecotoxicological studies that contain significant flaws. For example, on page 22 Jarmolowicz et al. (2013) is referenced as showing a significant alteration in sex ratio for DBP exposed fish. This study however uses a small number of fish (240 total over 6 treatments, and no replicates). A laboratory based exposure study with no replicates violates the most basic principles of hypothesis testing and cannot be deemed valid. Different authors also report conflicting effects (anti-androgenic vs. anti-estrogenic) and in some cases no	Weltje et al 2013 (Comparative acute and chronic sensitivity of fish and amphibians: a critical review of data. Environ Toxicol Chem. 2013 Apr;32(5):984-94. The SD text does not conclude on thyroid effects. It summarizes that: The MoA for the reduced growth cannot be definitively concluded but the findings are not in contradiction to an anti-thyroid effects hypothesis supported by the *in vitro* anti-thyroid effects of DEHP observed by Sun et al. (2012). And that: Thyroid disrupting effects were not confirmed in any of the *in vivo* studies but could be the MoA causing effects on growth and development in both amphibians and fish (Dumpert & Zietz, 1983; Zanotelli et al., 2009). Mechanistic studies *in vitro* support a possible thyroid disrupting mode of action of DEHP. We disagree with the concluding statement on DEHP Agree that replication should have been included but the results are very clear and conc.-dependent and 40 fish per exposure concentration is a higher number than that imployed in any OECD TGs (E.G. TG 229 and TG 230). If a trend test was applied to the data, the LOEC would probably decrease to 0.5 mg/kg. This does not have to be conflicting. It depends on the receptor- and hormonal status of the organism. In relation to the adverse effects caused by DEHP we (as summarized in the SD) think that when looking at the studies overall, it is biologically highly plausible that the adverse effects on the phenotypic sex and reproductive output in both male and female fish are induced by an estrogenic MoA (Norrgren et al., 1999; Norman et al.,

			effect of DBP on biological endpoints (Mankidy et al. 2013; Pg. 22). As with DEHP, conclusions related to anti-thyroid MoA are drawn in lieu of experimental data, and in fact one researcher reports an inability to replicated perceived in vitro anti-thyroid effects in vivo. While some reported studies demonstrated possible effects (i.e. increases in vitellogenin), none demonstrated these to be adverse effects. Additionally, several studies suffered from methodological flaws such as testing above water solubility, using intraperitoneal injections or not including replicates. A lack of adverse responses and no definitive MoA indicates that DBP's role as an endocrine disruptor is not conclusive. **BBP** In "Annex XV – identification of DBP as SVHC" section 5.1.2.3 states: no adverse effects were observed in the available studies (Pg. 26). This includes studies cited in the ER RAR (2007) and all subsequent publications (13 total studies covering acute and chronic effects to fish, invertebrates and amphibians). However, despite this, section 5.1.2.3 (Pg. 26) recommends read across from DEHP and DBP. Read across from DEHP and DBP is not appropriate in this case. There is sufficient literature on which to determine if BBP is an ED compound to aquatic organisms. Additionally there is a lack of structural similarity between BBP and DEHP/DBP to warrant read across. Therefore based on available data, it is not appropriate to identify BBP as a SVHC based on endocrine disruption to aquatic organisms.	2007; Carnevali., et al 2010; Corradetti et al 2013). The estrogenic MoA of DEHP is further supported by observations of ovotestis (Norman et al., 2007), affected Vtg and steroidogenesis in vivo, and mechanistic studies in vitro. In relation to Jarmolowicz et al 2013, please see response to UK above Regarding different MoA of DEHP such results do not have to be conflicting as also seen from in vitro studies where chemicals can affect different endocrine systems. So these observations do not have to be conflicting. It depends on the receptor- and hormonal status of the organism. Regarding the adverse effect of significant changed sex ratio in fish and sex reversal in amphibians (Rana rugosa) these are adverse effects according to the WHO ED definition
			11_ECPI_Comments_Annex_XV_SVHC_ELoC_ED_Dossiers_Oct_16_2014.docx 11_ECPI_Comments_Annex_XV_SVHC_ELoC_ED_Dossiers_Oct_16_2014.pdf	
13	2014/10/16	Company DEZA, a.s. Czech Republic	Comments to the Annex XV report: PROPOSAL FOR IDENTIFICATION OF A SUBSTANCE OF VERY HIGH CONCERN ON THE BASIS OF THE CRITERIA SET OUT IN REACH ARTICLE 57 for bis(2-ethylhexyl) phthalate (DEHP)	In general: cf. Response to similar comments from DE, UK, IE and FI. Re. Introductory remarks: RAC has assessed DEHP based on its classification as a reproductive toxicant. RAC does acknowledge that the adverse effects seem to

			by the Danish Environmental Protection Agency, Denmark (dated 26 August 2014) Introductory remarks As an introductory remark to our comments on the Annex XV report by the Danish EPA we would like to highlight that anti-androgenic activities of DEHP are discussed since long as a possible or likely mechanism for reproductive toxic effect of DEHP and were as such subject to the detailed evaluation carried out by RAC in relation to the authorization procedure just completed. No additional relevant human health data were presented in this Annex XV report. No justification can be envisaged to subject a substance twice to the authorization regimen on basis of the same data. When setting DNELs for DEHP in their opinion on the Danish restriction proposal in (2012) and again in 2013 for the purpose of authorisation RAC evaluated in detail the reproductive toxicity data available for DEHP and adopted the concept of a threshold for its evaluations. No relevant new data emerged since then to justify a re-evaluation of the same database. Comments on the human health part In the absence of harmonised criteria on the identification of endocrine disrupting chemicals the Danish EPA follows the proposal of the ED EAG (JRC, 2013) which suggested that the elements for identification of an ED are 1) Adverse health effects 2) Endocrine mode of action 3) Plausible link between adverse effects and endocrine mode of action 4) Human relevance **Criterion 1) Demonstration of adverse health effect** The Danish EPA summarized information from rodent studies on adverse effects. They mainly refer to studies already discussed in the EU RAR and documented in Annex 1 of the Annex XV report.	follow from an anti-androgenic mode of action. However, classification for reproductive toxicity by default assumes a threshold. The link between the adverse effects and the endocrine mode of action of DEHP has not yet been formally addressed. If DEHP is listed as an ED, the added value will be that applications for authorisation may need to be addressed under the socio-economic route unless a toxicological threshold is documented. Further, identification of DEHP under 57(f) for the environment may lead to a higher level of protection for the environment, since this is not included in identification under 57 (c) for reproductive toxicity. When DK established the DNELs, and also the reference-DNEL established by RAC,for reproductive toxicity of DEHP, only the classification and NOAEL for reproductive toxicity was considered. At that time no formal agreement had been obtained that DEHP is also an endocrine disruptor. **Re. Criterion 1:** Agreed. The adverse effects of DEHP leading to classification as Repr. 1B have been demonstrated in many studies.

			Further in Table 3 of the Annex XV report studies documenting effects on male reproductive system published after data collection for the EU RAR – according to the Danish EPA – were documented. But some of these Table 3 studies have already been discussed in the EU RAR (Akingbemi et al., 2001; Arcadi et al., 1998; Li et al., 2000; Parks et al., 2000). Effects on the male reproductive system are e.g. reduced anogenital distance, increased nipple retention, cryptorchidism, effects on Leydig cell steroidogenesis and testicular changes observed in adult and developing males. All these adverse effects have already been addressed in the evaluation carried out by RAC in relation to the authorisation procedure just completed. **Criterion 2) Endocrine mode of action** The Danish EPA argues that some of the in vivo studies indicate an endocrine mode of action of DEHP by showing effects on steroidogenesis like effects on testosterone production additionally supported by in vivo studies showing changes in activity of steroidogenic enzymes and effects on gene pathways of steroidogenesis. They further argue that "studies on testosterone production and steroidogenesis in fetal male rats indicate an endocrine disrupting mode of action of DEHP and its monoester metabolite methylhexyl phthalate (MEHP) in vivo". In fact, the studies documented in Table 3 of the Annex XV report do not document an effect of MEHP on testosterone synthesis in vivo. There was only one study included in Table 3 using MEHP as test item (Li et al., 2000) where histological changes of the gonocytes in the presence of MEHP were described, but no information on the effects of MEHP on testosterone synthesis was presented. Only the in vitro data on MEHP referred to by the Danish EPA in Annex 1 show that MEHP influences testosterone synthesis in Leydig cells (Jones et al., 1993). These data are not sufficient to argument that • the in vivo data on MEHP provide information on an endocrine mode of action of MEHP, because there are	Studies included in Table 3 are key studies showing adverse effects and/or showing an in vivo endocrine mode of action of DEHP. Some of these were also available at the time of the EU RAR. Table 3 has been slightly modified in the SD grouping studies showing adverse effects in vivo and studies showing an endocrine in vivo mode of action. **Re. Criterion 2:** Agreed. We agree that the issue of metabolites could be presented more clearly. This section of SD has been revised We are presenting available information on possible mode(s) of action of DEHP. The conclusion of section 4.2.3. is: *In conclusion, several rodent studies have demonstrated an endocrine mode of action in vivo which is substantiated by mechanistic data from in vivo and in vitro studies. Several of the studies showed decreased testosterone levels, indicating an anti-androgenic mode of action of DEHP and the metabolite MEHP due to effects on steroidogenesis. It is biologically highly plausible that the suggested anti-androgenic mode of action gives rise to the adverse reproductive effects of DEHP reported in the previous section.* Partly agreed. The SD includes mentioning of thyroid and the female reproductive system for completeness. The text in section 4.2.1 has been modified to reflect this. This is a citation from the EU RAR. It is correct that there was no in vivo study on MEHP and that sertoli cells

			no in vivo data on MEHP effects on sex hormones in the Annex XV report; • "DEHP and MEHP produce similar changes both in vivo and in vitro both in Leydig cells and in Sertoli cells" (argumentation in Annex 1 with reference to Jones et al., 1993), because, in this study no in vivo investigations have been performed with MEHP and in vitro experiments were only performed in Leydig cells, but not in Sertoli cells. Contradictory results e.g. on the binding of DEHP in different assays and on the binding of DEHP and MEHP on the androgen receptor were not discussed. Moreover it is implied that there is a logical association between DEHP exposure, its metabolism to MEHP and the observed anti-androgenic effects. But the data provided do not strengthen this conclusion, but leave several unsolved questions: no additional information was provided to indicate how MEHP might inhibit testosterone synthesis (apart from referring to Jones et al., 1993). Additional information on possible interactions with estrogens and the thyroid system were provided in an inconsistent and rudimentary way, but convincing data are missing that DEHP affects the thyroid. In conclusion, no new data or aspects were added to the discussion on the possible anti-androgenic mode of action of DEHP, but the studies selected for the argumentation are regarded as partially inappropriate/insufficient to support the argumentation. **Criterion 3) Demonstration of a biologically plausible causal link between the adverse effect and the endocrine MoA** The Annex XV report claims that the documentation provided of adverse effects on reproductive organs in combination with effects on the hormonal system by DEHP in vivo support the argumentation that there is an association between adverse effects and endocrine mode of action. But several contradictory experimental results were not addressed: The Danish EPA refers to the	were not studied in vitro. The intention of that sentence is probably that the effect seen with DEHP in vivo is similar to the effect of MEHP in vitro. This concluding sentence is now omitted from Annex 1 for clarity. **Re. Criterion 3** As above, we agree that the issue of metabolites could be presented more clearly. This section of the report has been revised. However, we do not agree that it is implied that binding of DEHP to the androgen reptor could be „**the** MoA" for the observed adverse effects. It is correct if implied by the comments here that full knowledge about all aspects of the AOP for the ED related reproductive toxicity pathways of DEHP has not *fully* been elucidated, i.e there is currently not full knowledge about all possible MIEs and Key Events of this Moa/AOP: But this is not a

			inhibition of the testosterone synthesis by DEHP and MEHP in vivo and in vitro, respectively. By reporting studies which observed a binding of DEHP to the androgen-receptor it is implied that this could be the MoA. The Danish EPA further argues that DEHP is absorbed as monoester and/or rapidly metabolized to the monoester which is transported across the placenta and is mainly responsible for the observed effects. But the information that MEHP does not interact with the receptor (David, 2006) leaves the question open by which MoA MEHP might influence the testosterone synthesis. The conclusion "it is biologically plausible that the observed adverse effects are linked to the endocrine disrupting mode of action of DEHP and the metabolite MEHP" is not obvious from the presented data, because no data were presented which revealed effects of MEHP on apical endpoints and endocrine endpoints in vivo. **Criterion 4) Demonstration of the relevance of the data to humans** In this section the data used for the documentation that DEHP causes adverse effects causally linked to an endocrine mode of action were discussed in a broader context. Especially, the contradictory observations in non-human primates (marmosets) were discussed in light of the findings in rats. The authors refer inter alia to the study by Tomonari et al. (2006), which did not reveal reproductive effects of DEHP in concentrations up to 2500 mg/kg bw/d in male marmosets. Additionally the negative findings described by Kurata et al. (1998) in male marmosets receiving up to 2500 mg/kg bw/d were reported. Also the mechanistic discussions of Johnson et al. (2012) were cited who concluded that "it appears the human fetal testis responds more like a mouse than a rat", i.e. the most sensitive animal model (rat) does not seem to be a good model for the human situation. Despite this experimental evidence of obvious species differences the Danish EPA concluded that the available adverse, endocrine related effects observed in rats are relevant for humans. The	prerequisite to refer to MoA or to AOP for these pathways. Changes have been made in the SD to clarify this. The SD mentions available peer reviewed in vitro studies investigating possible other modes of action than on steroid synthesis. However, it is stated in the SD that the adverse effects of DEHP are considered to be primarily related to effects on steroidogenesis. We finally also note that existence of more than one MoA seems often to be the case for substances, but that this does not mean that conclusions cannot be drawn if sufficient knowledge exist about significant MoAs and their link to adverse effects have been established. **Re. Criterion 4.** Human relevance of the adverse effects of phthalates which inhibit testosterone synthesis during development has been discussed and evaluated as relevant in the SD. We find that careful interpretation of data regarding relevance to humans has been presented. A review of the available data showing similarities and differences between species is made. As noted in the Annex XV report, the studies by Tomonari (2006) and Kurata (1998) were in adult marmoset, and therefore did not include the more sensitive perinatal period. **A new study by Albert and Jégou (2014) supports the RAC conclusion (2012) that there is too much uncertainty in the available data to allow a conclusion on humans being less, equally or more sensitive than rats. The publication provides a critical assessment of in vivo and in vitro studies exploring phthalate effects in humans (Albert and Jegou 2014). This paper highlights the variation among species in the window of susceptibility to the effects of phthalates and variation among species in timing of the development of the testis. Another conclusion of this literature study is that the indications of species differences found in e.g xenografting studies have methodological limitations and that "Caution before concluding**

			authors interpreted the effects seen on germ cells in marmosets exposed during gestation ("unusual clusters of undifferentiated germ cells") (McKinnell et al., 2009) in favour of their argumentation, although they are of uncertain significance. Due to the observed interspecies differences the rat data should be interpreted more carefully with respect to their relevance to humans. **Comments on the environmental part** **1. Reliability of reported new data** DEHP is an organic substance of low water solubility. In the EU Risk Assessment Report (ECB, 2008) the data are summarised and discussed, with the conclusion that the true water solubility is 3 µg/L. Higher concentrations measured consist most certainly of colloidal forms of DEHP in water. All new ecotoxicity studies presented in the Danish Annex XV report use solvents such as DMSO or ethanol to prepare stock solutions, which are further diluted for the experiments. As concentrations were not analytically confirmed the true concentrations used in the experiments are unknown. Inhomogeneous distributions of colloidal material might have occurred. In addition to the lacking analytical verification of exposure concentrations, several reported studies are hampered by a study design not adequate for the assessment of DEHP's aquatic toxicity. For example, a study by Uren-Webster et al. (2010) is reported in the Annex XV report. The authors investigated the reproductive toxicity of DEHP to male zebrafish by applying the substance at doses up to 5 g/kg body weight (!) for a period of 10 days via intraperitoneal injection. This study received a reliability score of 2 (according to Klimisch) by the authors of the Annex XV report. Other deficiencies relate to the proper documentation of basic and relevant information to assess the study outcomes. For example, in the study by Zanotelli et al. (2010) (see below) effects of DEHP on growth (size and weight) of fish larvae were assessed. Apart	**that phthalates are innocuous in the human fetal testis should be kept until these issues have been addressed" (Albert and Jegou 2014).** **(**Albert O and Jégou B. 2014. A critical assessment of the endocrine susceptibility of the human testis to phthalates from fetal life to adulthood. Human Reproduction Update, Vol. 20(2):231-249.) We find it relevant to mention the human relevance of germ cell changes, although implications of these effects are not yet known. **Environmental part** **Re. 1.** Several studies measured concentrations. The Uren-Webster study (2010) also tested lower concentrations than the 5 mg/kg and relevant information – although no definitive conclusions - can also be obtained from studies that do not use environmentally relevant exposure routes – for example information on endocrine mode of action . Further, in the Zanotelli study (2010) weight and length distribution is not possible to measure in one week old guppys and does not flaw the results after 91 days of exposure. No changes were made to the SD.

			from the lacking analytical monitoring, no measurements of dissolved oxygen concentration, no data on the origin of fish and especially neither weight distribution nor length distribution of fish at the start of the test was provided. 2. Discrepancies between studies The Danish EPA divided their review of ecotoxicological data between data already presented in the EU Risk Assessment Report (ECB, 2008) and new data emerged since 2008. But the authors didn't to consolidate or explain contradictory results between studies, thus leaving important questions open: Examples: Zanotelli et al. (2010) (a study first-authored by a pupil of a Zurich grammar school) reported reduced growth of guppies already starting from concentrations of 0.1 µg/L (!). This is in striking contrast to publications reviewed in the EU Risk Assessment Report. For example, Mayer et al. (1977) (reference see (ECB, 2008) investigated the effect on growth in three different fish species (brook trout, fathead minnow and rainbow trout) of various stages of development with long-term exposure to DEHP in concentrations up to 100 mg/L. There was neither mortality nor significant effects on growth observed in this study. Adema et al. (1981) (reference see (ECB, 2008)) observed no effect on mortality or growth in guppies (the same species as used by Zanotelli et al (2010)) at concentrations up to 320 µg/L. Corradetti et al. (2013) observed a dramatic decrease in fecundity of zebrafish at concentrations as low as 0.2 µg/L. Embryo production and hatching rates were reduced by more than 90% at 0.2 and 20 µ/L (without major differences between these two exposure concentrations despite the 100fold difference). Using the same species as well as guppies in their reproduction study Mayer and Sanders (1973)) (reference see (ECB, 2008) did not find any significant effect on reproduction at DEHP concentrations in food up to 100 µg/g food.	**Re. 2** Non-monotonic dose response has been reported in scientific literature for fish exposed to chemicals that interfere with the endocrine system. See for example Örn et al (2003) (Aquat Toxicol. 2003 Dec 10;65(4):397-411) and Phelps and Okoko (2011) (Aquaculture Research. Volume 42, Issue 4, pages 549–558, March 2011). Food and water exposure concentrations cannot be compared. In addition, the zebrafish exposure by Mayer and Sanders had 49% mortality in controls and are therefore considered invalid. Endpoints such as mortality are not relevant in relation to the evaluation of DEHP as SVHC so studies which only investigate such non-endocrine relevant studies can not be used to compare to effects on the endocrine system.

			In conclusion, the Danish EPA did not critically assess discrepancies and caveats in the newly emerged data, but rather focussed on individual observations of high uncertainty. 3. EDC criteria As already mentioned above, in the Annex XV report the following criteria are listed, against which DEHP as an EDC substance has to be evaluated: 1) Adverse health effects 2) Endocrine mode of action 3) Plausible link between adverse effects and endocrine mode of action 4) Human relevance respectively relevance for the environment Criteria 1: Due to the lacking critical assessment of the adverse outcome of the new studies reported in the Annex XV report (see above) confirmation of the first criterion (at least in a relevant concentration range close to the water solubility limit, thus avoiding artificial exposure situations) must be questioned. Criteria 3: The Annex XV report states that two studies are considered fulfilling this criteria (i.e. demonstration of adverse effects clearly linked to an endocrine mode of action: the study by Norrgren et al. (1999) (reference see (ECB, 2008) and Corradetti et al. (2013). Norrgren et al. (1999) reported differences in the sex ratio (higher percentage of females in the high DEHP group) after administering DEHP at a low and a high dose of 300 and 1,500 mg/kg food to Atlantic salmon. In a follow-up of this study the impact on the sex ratio could not be confirmed (Norman et al., 2007). It was speculated that the actual concentration in the first study was higher than the nominal concentration, which could not be substantiated, as no analytical monitoring of the exposure took place in the Norrgren et al. study. The striking discrepancy between the Corradetti	**Re. 3 Criteria 1**: Exposure may also occur after dietary intake of hydrophobic adsorptive substances like DEHP. See response to similar comment from UK. **Re. 3 Criteria 3 and 4:** Cf. Response to similar comment from UK p 1-11. Regarding the two studies on atlantic salmon (Norrgren and Norman) please see response to UK above. It is not clear for the SD authors that there are striking discrepancies between the Corradetti study and the ECB 2008 studies because the exposure routes, species used, endpoints investigated and concentrations tested differ. For example there are no valid zebrafish studies to directly compare with because the Mayer & Sanders study from 1973 was hampered by 49% control mortality.

			study and other studies reported in ECB (2008) is already discussed above. Criteria 4: Environmental relevance, the fourth criterion, was not addressed in the Annex XV report. When doing so, the following information has to be taken into account: - serious adverse effects are reported in reliable studies only in concentration ranges far above the water solubility limit (see ECB (2008)) - DEHP concentrations in surface water in the European Union are reported in INERIS (2014) : according to this evaluation of data reported until 2008 by 16 EU member states for the Water Framework Directive (WFD) the mean of all measured concentrations (in the whole water body including suspended matter) is 1.04 µg/L (median: 0.25 µg/L;) with a 90th percentile value of 1.41 µg/ (n=4377) (DEHP in water bodies is regulated under the WFD; an Environmental Quality Standard for DEHP of 1.3 µg/L was derived under Directive 2008/105/EC) Investigations with solvent-mediated high concentrations DEHP in colloidal form, without analytical control of real exposure conditions, are not of relevance for the real environmental situation. It should be noted that environmental DEHP concentrations are expected to decrease with further decreasing production volumes. In conclusion, the Annex XV report does not conclusively provide evidence for fulfilment of criterion 3 and does not discuss or explain how the reported studies with questionable effect concentrations or concentrations orders of magnitude above the water solubility limit of DEHP and above measured environmental concentrations should be able to prove the relevance for the environment (criterion 4). Summary We ask Member States Committee to reject Annex XV SVHC proposal made by Denmark identifying	

			DEHP as endocrine disrupting chemical. The document does not provide sufficient evidence that DEHP fulfils criteria set out in Article 57f. References Akingbemi, B.T.; Youker, R.T.; Sottas, C.M.; Ge, R.; Katz, E.; Klinefelter, G.R.; Zirkin, B.R.; Hardy, M.P. (2001) Modulation of rat Leydig cell steroidogenic function by di(2-ethylhexyl)phthalate Biology of Reproduction, 65, 1252-1259 Arcadi, F.A.; Costa, C.; Imperatore, C.; Marchese, A.; Rapisarda, A.; Salemi, M.; Trimarchi, G.R.; Costa, G. (1998) Oral toxicity of bis(2-ethylhexyl) phthalate during pregnancy and suckling in the Long-Evans rat Food and Chemical Toxicology, 36, 963-970 Corradetti, B.; Stronati, A.; Tosti, L.; Manicardi, G.; Carnevali, O.; Bizzaro, D. (2013) Bis-(2-ethylexhyl) phthalate impairs spermatogenesis in zebrafish (Danio rerio) Reproductive Biology, 13, 195-202 David, R.M. (2006) Proposed mode of action for in utero effects of some phthalate esters on the developing male reproductive tract Toxicologic Pathology, 34, 209-219 ECB, European Chemicals Bureau (2008) European Union Risk Assessment Report: bis(2-Ethylhexyl)phthalate (DEHP). 2nd Priority List, Vol. 80 EUR 23384 EN. European Commission. Joint Research Centre Johnson, K.J.; Heger, N.E.; Boekelheide, K. (2012) Of mice and men (and rats): phthalate-induced fetal	

			testis endocrine disruption is species-dependent Toxicological Sciences, 129, 235-248 Jones, H.B.; Garside, D.A.; Liu, R.; Roberts, J.C. (1993) The influence of phthalate esters on Leydig cell structure and function in vitro and in vivo Experimental and Molecular Pathology, 58, 179-193 JRC, Joint Research Centre of the European Commission (2013) Key scientific issues relevant to the identification and characterisation of endocrine disrupting substances. Report of the Endocrine Disrupters Expert Advisory Group http://www.fhi.no/dokumenter/623e53f70d.pdf Kurata, Y.; Kidachi, F.; Yokoyama, M.; Toyota, N.; Tsuchitani, M.; Katoh, M. (1998) Subchronic toxicity of Di(2-ethylhexyl)phthalate in common marmosets: lack of hepatic peroxisome proliferation, testicular atrophy, or pancreatic acinar cell hyperplasia Toxicological Sciences, 42, 49-56 Li, L.H.; Jester, W.F.; Laslett, A.L.; Orth, J.M. (2000) A single dose of di-(2-ethylhexyl) phthalate in neonatal rats alters gonocytes, reduces sertoli cell proliferation, and decreases cyclin D2 expression Toxicology and Applied Pharmacology, 166, 222-229 McKinnell, C.; Mitchell, R.T.; Walker, M.; Morris, K.; Kelnar, C.J.; Wallace, W.H.; Sharpe, R.M. (2009) Effect of fetal or neonatal exposure to monobutyl phthalate (MBP) on testicular development and function in the marmoset Human Reproduction, 24, 2244-2254 Parks, L.G.; Ostby, J.S.; Lambright, C.R.; Abbott, B.D.; Klinefelter, G.R.; Barlow, N.J.; Gray, L.E. (2000) The plasticizer diethylhexyl phthalate induces	

			malformations by decreasing fetal testosterone synthesis during sexual differentiation in the male Toxicological Sciences, 58, 339-349 Tomonari, Y.; Kurata, Y.; David, R.M.; Gans, G.; Kawasuso, T.; Katoh, M. (2006) Effect of di(2-ethylhexyl) phthalate (DEHP) on genital organs from juvenile common marmosets: I. Morphological and biochemical investigation in 65-week toxicity study Journal of Toxicology and Environmental Health. Part A, 69, 1651-1672 Uren-Webster, T.M.; Lewis, C.; Filby, A.L.; Paull, G.C.; Santos, E.M. (2010) Mechanisms of toxicity of di(2-ethylhexyl) phthalate on the reproductive health of male zebrafish Aquatic Toxicology, 99, 360-369 Zanotelli, V.R.T.; Neuhauss, S.C.F.; Ehrengruber, M.U. (2010) Long-term exposure to bis(2-ethylhexyl)phthalate (DEHP) inhibits growth of guppy fish (Poecilia reticulata) Journal of Applied Toxicology, 30, 29-33 Please find full version of the document including links in the attachement. 13_Comments to the Annex XV report of Danish EPA_DEZA.pdf	
14	2014/10/16	Individual	Please see the attached document. 14_GA_ZAK_SA_comments_DEHP_REACH_annexXV.pdf	As the comments received from GA ZAK SA (nr 13) are identical to the comments received from Company DEZA. (nr 14) we refer to comments provided to nr 13, above.

16	2014/10/16	Industry or trade association EDMA and Eucomed Belgium	DEHP, DBP, BBP and DIBP are already regulated by REACH as substances of very high concern (SVHC) for being reproductive toxicants Cat 1B. They have been included on the Authorisation list with sunset date in the beginning of 2015, applications for authorisation have been issued and the processes are ongoing or have recently been completed. Now, Denmark is proposing that the substances are additionally identified as an SVHC because of endocrine disrupting properties. At the same time, the Commission is working on the development of harmonised EU-level operational criteria for regulation of Endochrine Disruptors (ED) the Plant Protection Regulation, Biocidal Products Regulation, Medical Devices, Water Framework Directive and REACH. ECHA should note the second stated aim of the European Commission in its roadmap on "Defining criteria for identifying Endocrine Disruptors in the context of the implementation of the Plant Protection Product Regulation and Biocidal Products Regulation": "What are the main problems which this initiative will address"? The first problem addressed in this initiative is the absence of criteria for ED in the [Biocidal Products Regulation] and the [Plant Protection Regulation], while ED are regulated in these pieces of legislation. These criteria have to be operational, i.e. they have to allow for science-based regulatory decision-making. The second problem is that, since ED are referred to in numerous legislation, these criteria should be developed with the aim of enabling their "horizontal" application in the wider legislation covering the regulation of ED in different regulatory settings (see above). The European Commission will soon develop harmonised EU-level operational criteria for ED which bring much-needed regulatory consistency for the group of ED substances. By contrast, addition of ED classification to these substances on the Candidate list will bring legal uncertainty and administrative	Noted. We agree that it would be good to have criteria, but unfortunately these are not yet available. The REACH text does not refer to, nor require, criteria for inclusion of endocrine disruptors in the candidate list on a case-by-case basis. This process has already been applied for 4 substances (nonylphenol + ethoxylates + 4-tert-octylohenol + ethoxylates) identified as endocrine disruptors with relevance for the environment. The same process can be applied for endocrine disrupters with relevance for human health.

			burden on industry, especially on DEHP using sectors like the medical devices industry and on the applicants whose uses which have only recently been granted authorisation by the European Commission. We ask that the decision on identification of DEHP, DBP, BBP and DIBP as endocrine disruptor be postponed until the Commission has finalised the development of harmonised ED criteria, the process for such amendments of the Candidate list and Annex XIV has been clarified, and the legal and socio-economic consequences have been evaluated with due care.	
17	2014/10/16	International NGO ChemSec Sweden	Comments on the proposed SVHC properties summarised on page 3-4 of the Annex XV SVHC report: We fully support the proposal that DEHP is additionally identified as an SVHC because of its endocrine disrupting properties.	Thank you for your support. No changes made to the document due to this comment.
18	2014/10/16	Member State Norway	The Norwegian REACH CA supports the proposal to identify bis(2-ethylhexyl) phthalate (DEHP) as a SVHC in accordance with Article 57(f) of the REACH regulation due to its endocrine disrupting properties. DEHP is already included in the Candidate list as it is toxic for reproduction (Article 57(c)). The Norwegian REACH CA has for a long time paid attention to identify and regulate endocrine disrupting substances and believes that the efforts to reduce their use and releases to a large extent has to come through international work and regulations. The proposal to identify DEHP also as a SVHC according to Article 57(f), both for health and the environment, is therefore supported. Pending the general criteria from the European Union on how to assess whether or not a substance has endocrine disrupting properties and/or is an endocrine disruptor, the approach using the WHO/IPCS definition of an endocrine disruptor and the recommendations from the European	Thank you for your support. No changes made tot he SD due to this comment. Thank you for this input, but we prefer to keep the text

			Commission's Endocrine Disrupters Expert Advisory for a substance to be identified as an endocrine disruptor is considered appropriate. The three criteria for EDC identification is also described in the EFSA scientific opinion on the hazard assessment of endocrine disruptors and could also be referred in the proposal. The Norwegian REACH CA is of the opinion that DEHP fulfills the definition of an endocrine disruptor for health as both adverse reproductive effects is observed in male rats in response to exposure and an endocrine mode of action (anti-androgenicity) has been established that is a likely causal link to this reproductive effect. As is well described in the Annex XV report, rats seems to have a higher sensitivity to phthalate disruption of steroidogenesis than mice, marmosets and humans, whereas these species differences are not seen for the negative effects of phthalates on gametogenesis as observed in organotypic culture and testicular explants. In our opinion, the large amount of data on both male reproductive toxicity and different mechanisms of action justify a classification of DEHP as an endocrine disruptor. Furthermore the Norwegian REACH CA is of the opinion that DEHP fulfills the definition of an endocrine disruptor for the environment. As pointed out in the dossier the results with rodents are of relevance for mammalian wildlife as well, and in particular concerning wildlife species with low reproductive output there may be serious effects at the population level. In general we agree that read across for hazard identification of the endocrine disruptive properties between data from the different well studied phthalates (BBP, DBP and DEHP) seems appropriate. In general, the Annex XV report would benefit from a	as is by reference to the WHO definition and the JRC report (cf. Also responses above). Accepted. The SD has been modified. The definitions of mode of action and mechanisms of action have been

			more stringent use of the terms "mode of action", "mechanisms of action" and "adverse outcome pathways" as the term "mode of action" has a particular meaning in the evaluation of a substance as an endocrine disruptor as described in e.g. the Joint Research Center (JRC) report.	included in section 4.2.3, and further elaboration has now been included in the report. We hope that the already performed revisions of the SD(s) have covered this suggestion sufficiently – if not we are open for discussing possible editorial changes based on specific proposals from rewording of the SD(s) at MSC39
19	2014/10/16	Industry or trade association Verband der Chemischen Industrie e.V. (VCI) Germany	VCI comments on generic aspects related to substances that are already included in the Candidate List and Annex XIV of the REACH regulation and that are additionally proposed to be identified based on the concern "Endocrine Disruptor". (The same comment has been submitted for consultations on DEHP, DBP, BBP and DIBP). Denmark has submitted Annex XV reports for four phthalates DEHP, DBP, BBP and DIBP with reference to Article 57(f) of the REACH regulation. These substances were already identified as SVHCs on the basis that they are toxic to reproduction (Repr. 1B) referring to Article 57(c). In the current consultation with deadline 16 October 2014, Denmark is proposing that the substances are additionally identified as SVHCs because of endocrine disrupting properties. If the proposal would be agreed, the current entry in the REACH Candidate List would be updated to include both reasons for inclusion (i.e. Repr. 1B + endocrine disrupting properties). Because of the following reasons the proposal should be rejected and the additional concern "Art. 57(f) / Endocrine Disruptor" of the substances DEHP, DBP, BBP and DIBP should not be included on the REACH Candidate List: The European Commission just published the Roadmap "Defining criteria for identifying Endocrine Disruptors in the context of the implementation of the Plant Protection Product Regulation and Biocidal Products Regulation" (http://ec.europa.eu/smart-regulation/impact/planned_ia/docs/2014_env_009_e	Noted. We agree that it would be good to have criteria, but unfortunately these are not available. The REACH text does neither refer to, nor require, criteria for inclusion of endocrine disruptors in the candidate list on a case-by-case basis.

			ndocrine_disruptors_en.pdf) and opened up the "Public Consultation on defining criteria for identifying endocrine disruptors in the context of the implementation of the plant protection product regulation and the biocidal products regulation" (http://ec.europa.eu/dgs/health_consumer/dgs_consultations/food/consultation_20150116_endocrine-disruptors_en.htm) Although these criteria are in the first instance in the context of the implementation of the Plant Protection Product Regulation and Biocidal Products Regulation, the Roadmap clearly states: "The first problem addressed in this initiative is the absence of criteria for ED in the BPR and the PPPR, while ED are regulated in these pieces of legislation. These criteria have to be operational, i.e. they have to allow for science-based regulatory decision-making. The second problem is that, since ED are referred to in numerous legislation, these criteria should be developed with the aim of enabling their "horizontal" application in the wider legislation covering the regulation of ED in different regulatory settings (see above)." REACH and its authorisation procedure for SVHC are clearly mentioned in this context in this Roadmap. Therefore, the decision whether the additional concerns "Art. 57(f) / Endocrine Disruptor" of the substances are included or not on the Candidate List should be postponed until an approach for identifying endocrine disrupting properties is agreed on a European level. A decision to include the additional concern on the REACH Candidate List would set an unjustified precedent which would impair the running procedure to set criteria for Endocrine Disruptors. In addition, there are some crucial legal and procedural questions as a process for amending the Candidate List and Annex XIV of the REACH regulation has not been communicated by the Commission and/or ECHA so far. How would an	This process has already been applied for 4 substances (nonylphenol + ethoxylates + 4-tert-octylohenol + ethoxylates) identified as endocrine disruptors with relevance for the environment. The same process can be applied for endocrine disrupters with relevance for human health. Noted. The process for amending the Candidate list and Annex XIV is not specified in REACH, but we assume that COM will amend Annex XIV appropriately. Existing authorisations may be reviewed in accordance with Article 61(2). We also refer to RCOM to comments from UK, DE and FI.

			additional concern included in an entry of a substance in the Candidate List be handled when ECHA prioritises substances for Annex XIV? How will the Annex XIV entry for the substance be amended and what will be the consequences for new applications, submitted applications and granted authorisations? ECHA, Commission and industry require stable and reliable REACH processes and legal certainty. The current SVHC roadmap 2020 activities are intended to improve the SVHC identification process. In contrast the current initiative from Denmark without prior indication of the process and during an ongoing discussion on how to take decisions on endocrine disrupting properties is counterproductive.	
20	2014/10/16	International NGO European Environmental Bureau (EEB) Belgium	The European Environmental Bureau supports the identification of BBP, DEHP, DBP and DIBP as substances of high concern because of their endocrine disrupting properties as proposed by Denmark. The endocrine disrupting properties of these four phthalates have been well described in the scientific literature (see references below), as summarized in the Annex XV dossier presented by Denmark. 20_EEB_4phthalates_EDC.pdf	Thank you for your support. No changes made to the document due to this comment.
21	2014/10/16	National NGO IEW Belgium	IEW supports Denmark's proposal for identification based on the endocrine disrupting properties of Bis(2-ethylhexyl) phthalate. The preferred authorization route for this substance is the "socioeconomic route for authorization" as safe thresholds for EDCs cannot be assumed. This sets a higher incentive for substitution	Thank you for your support. No changes made to the document de to this comment. It is beyond the scope of the SD to address the issue of preferred authorisation route.

PART II: Comments and responses to comments on uses, exposures, alternatives and risks

Specific comments on use, exposure, alternatives and risks

No	Date	Submitted by (name, Organisation/ MSCA)	Comment	Response
5	2014/10/15	National NGO The Danish Ecological Council Denmark	When looking in the RAPEX system, articles have been notified 373 times based on a chemical risk from DEHP (in the period 2013-2014) across all groups of articles. Especially toys (dolls and accessories) seem not to meet the EU chemicals legislation. This indicates that Europeans are still highly exposed to DEHP through everyday consumer articles. The number of notifications on this specific phthalate has been increasing every year since 2005, being fairly stable in 2008-2010 with 99, 102 and 108 notifications respectively. In 2013 the number was 176 notifications. Especially toys are subject for many notifications.	Noted. Thank you for this additional information. This may be useful information in respect to current authorisations.
11	2014/10/16	Industry or trade association CEFIC ECPI Belgium	11_ECPI_Comments_Annex_XV_SVHC_ELoC_ED_Dossiers_Oct_16_2014.docx 11_ECPI_Comments_Annex_XV_SVHC_ELoC_ED_Dossiers_Oct_16_2014.pdf	See responses in the section ‚Specific comments on the justification', above.
13	2014/10/16	Company DEZA, a.s. Czech Republic	13_Comments to the Annex XV report of Danish EPA_DEZA.pdf	See responses in the section ‚Specific comments on the justification', above
14	2014/10/16	Individual	14_GA_ZAK_SA_comments_DEHP_REACH_annexXV.pdf	See responses in the section ‚Specific comments on the justification', above.
20	2014/10/16	International NGO European Environmental Bureau (EEB) Belgium	BBP, DEHP, DBP and DIBP are present in a wide range of consumer articles. They are ubiquitous contaminants that can be found in all European Environment compartments (air, waters -even rain water, soils) as well as in blood and urine samples of all sampled European population (see references below). 20_EEB_4phthalates_EDC.pdf	Noted. Thank you for this additional information. This information may be relevant if DEHP is accepted to be identified as an SVHC on the Authorisation List also due to its ED properties in accordance with art. 57 f of REACH i.e. if and when new authorisation applications are being evaluated also according to the ED properties of DEHP.