17 May 2016

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

Substance name: 1,7,7-trimethyl-3-(phenylmethylene)bicyclo[2.2.1]heptan-2-one (3-benzylidene camphor)
CAS number: 15087-24-8
EC number: 239-139-9

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 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

Number / Date	Submitted by (name, submitter type, country)	Comment	Responses
4592 2016/04/14	Netherlands, Member State	NL supports the proposal to include 3-BC 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.	We thank the Netherlands for this supportive comment.
4597 2016/04/14	United Kingdom, Member State	• As a general point, data derived from QSARs should include a statement about their reliability as for any other source of data. This applies for example to the physico-chemical, fate and behaviour properties, as well as the non-test information on endocrine disruption. • P. 8, Section 1.2 (Composition): 3-BC is comprised of four stereoisomers. It would be useful to provide further information on the ratio of these isomers in the marketed substance and the tested technical materials in case any isomer is more active than the others. Whether these isomers behave differently in the environment could also be investigated.	We thank the UK CA for their extensive and helpful comments. We agree with the first point stated and amended the Supporting Document respectively. We agree, but unfortunately, information about the isomeric pattern in different test materials is not available to us.

		Editorial - A purity as low as 80% w/w is indicated, but since there are no REACH registrations, presumably this is just a standard substance description entry. It would be helpful to make this clear (as otherwise a reader less familiar with REACH processes might ask what the impurities are).	We agree and the Supporting Document was amended respectively.
		• P. 8, Section 1.3 (Identity of degradation products): Since the dossier discusses the possible role of a hydroxylated metabolite, it would be useful to include the structure here, and an appendix to indicate how this structure is predicted to interact with endocrine receptors using the same QSARs as those mentioned in Section 5.2.2. Also, is it likely to be more rapidly excreted than the parent substance since it is more hydrophilic?	We agree and the structure of the hydroxylated metabolite was added to the document. Unfortunately, the QSAR equations are not accessible for us at the moment, since the exact 3-D QSAR equations for the used pharamacopohre models are not given in the respective publications and the authors so far did not respond to our request for further information. From structure-activity considerations the metabolite should be excreted more rapidly. However, this does not influence its intrinsic endocrine hazard potential.
		• P. 10, Section 1.5: Editorial – vapour pressure is usually expressed as Pascal (Pa).	Thank you for this remark. The dossier was changed accordingly.
		• P. 11, Section 3.1.1 (Abiotic degradation): SCCS (2013) mentions a UV stability study using a "non-ionic emulsion", which suggests that the substance rapidly forms a photostable isomer, followed by very slow irreversible degradation. This information could be added to the summary of photodegradation, since it implies that UV degradation is unlikely to be rapid. However, we do not know what the "photostable isomer" is, and whether this might be formed in aquatic media under laboratory conditions. Is there any information available about this?	Thank you for this comment. We agree and the summary of the photodegradation part was amended accordingly. Unfortunately, we don´t have any further information on the nature of the photostable isomere and the conditions of its formation.
		• P. 11, Section 3.1.2 (Biodegradation): We note that there were substantial losses of 70-80% from test media over 48 hours in the Kunz et al. (2006b) study. The study authors discussed this in terms of adsorption to surfaces and organic matter as well as bioaccumulation in the fish, but can biodegradation be ruled out? It would be helpful to include some discussion of this in this section.	We agree that this issue should be discussed and section 3.1.2 was extended accordingly.
		• P. 12, Section 3.4 (Bioaccumulation): Only a single QSAR estimate for log Kow is provided. Although this exceeds 5, fish may be able to metabolise the	Thank you for this hint. We agree and changed the respective sentence in

		substance (as suggested by the discussion in Section 5.2.2). Without a reliable fish BCF measurement, we cannot conclude that the substance is actually bioaccumulative. The statement "3-BC therefore shows a high potential for bioaccumulation" should be replaced with "3-BC therefore screens as being potentially very bioaccumulative, but definitive data are not available", since it is a clearer statement.	accordance with your proposal.
		A BCF of 314 for 3-BC is included in the training set of the EPISUITE QSAR. The source is Kunz et al. (2006b), which estimates a fish BCF in the range 102 – 493 depending on exposure concentration. Although the data were not derived using standard bioaccumulation test methods, a comment should be included about the relevance of this information for completeness.	We agree and the dossier was amended accordingly.
		• P. 13, Section 5 (Environmental hazard assessment): The estimated water solubility (~0.7 mg/L) is equivalent to about 3 µM (the actual water solubility is unknown and could be higher or lower than this). Several studies reported in this section (e.g. acute toxicity and in vitro studies) include test concentrations significantly in excess of this value. Some comment should be added about the relevance of the results where this is the case (and the concentration should be indicated in all studies in the main text, not just the table; for example, the description of the screens for progesterone activity on p. 23).	We agree and the dossier was amended accordingly.
		In addition, the test substance purity should be stated for all key studies, since it is possible that impurities might also cause (or contribute to) some of the observed effects. Does stereoisomer composition also vary between studies, and can this be a possible explanation for varying effects in different systems?	We agree but unfortunately we don´t have further information about purity and especially about the isomeric pattern of the tested substances.
		• P. 16-21, Section 5.2.2 (in vitro data): Were any of these studies performed in accordance with (or similar to) standard test guidelines? Where positive controls were used, the results should be provided (this is done for some of the studies in Table 7 but not all). Statements such as "nearly full" or "submaximal" dose-response are unclear and should be rephrased. In particular, in the summary of the effects on p. 23, there should be a clear indication of relative potency in comparison with the positive controls. There is some speculation about the possible role of a metabolite, and how this could explain differences between studies (e.g. on p. 21). However, as mentioned above, could differences in purity/composition also affect the results?	Thank you for this comment. Most of the assays were performed according to standard test guidelines (e.g. the YES assays and the E-SCREEN assays). Regarding your further hints, we agree and the text is changed accordingly.
		• P. 27, Table 8: Editorial - Does the first column relate to anti-androgens too (i.e. not just estrogens)?	Thank you for this remark. The column header was extended accordingly.
		P. 31, Section 5.2.3 (in vivo effects in fish): The description of the Kunz et al.	Thank you for this important hint.

		(2006b) study mentions histological examination. A detailed review of a variety of papers that included histopathology end points by an independent expert fish histopathologist for the recent SETAC Pellston Workshop™ found that histopathology data were of low credibility in almost half of the 188 papers examined. Key drawbacks were missing descriptions of how sampling/observational bias was minimized, lack of information on group sizes (sometimes only a couple of fish were analysed), poor histopathology (e.g. sample preparation and incorrect identification of lesions, etc.) and lack of photomicrographs to allow any independent verification of the results. The main message was that it was unwise to accept any histopathology data at face value – an independent expert review should always be considered. Whilst we have no reason to doubt the findings reported, it would be useful to confirm whether the histopathology data have been critically reviewed. Could the reported histological effects also be a result of stress or some other factor? This is not discussed in the dossier but as noted above, it seems odd that some replicates stopped spawning a long time before exposure began. The lack of supporting details makes it impossible to independently judge how histology actually varied with dose. P. 29, Table 10: Editorial – the first column says that 4 males + 2 females were used per replicate – presumably these should be the other way round (i.e. 4 females and 2 males per replicate). • P. 32, Section 5.2.3 (in vivo effects in fish): The summary on p. 32 mentions that the change in growth rate observed in the Kunz et al. (2006a) study is "a further hint for the proposed estrogenic activity of 3-BC in fish that can lead to adverse effects in organisms". However, this study only lasted 14 days, and other mechanisms can also affect growth. We therefore think that it is premature to draw any conclusions about effects on growth and the relevance of this to an endocrine mode of action and would prefer such statements to be removed.	According to the authors of the study "in order to minimize bias, histological sections were first evaluated in a blinded fashion by two histologists and two members of our group. Subsequently, histological sections were reevaluated for each treatment group independently by these two group members and findings of the two evaluations were compared and controlled for bias." Hence, we think that the observed histological changes are reliable. Since the study of Kunz et al., 2006b reports histological changes in a concentration dependent manner (e.g. dose-dependent inhibition of spermatogenesis in the testis of male fish) we think that stress or other factors are unlikely to be the origin of the observed histological changes. Thank you for this hint. You are right and the column was corrected respectively. You are right that growth can be influenced by various factors. However, for fish it was shown that the sexual endocrine system and the growth regulation are highly interrelated and that growth, as an apical endpoint, can be as sensitive as reproduction responding to an exposure against estrogens (see e.g. Schäfers et al., 2007, Journal of Toxicology and Environmental Health, Part A). Regarding your concern, we changed the sentence to "might be a further hint…".

		• P. 33-35, Section 5.2.3 (in vivo effects: Supporting information from mammalian toxicity tests): The uterotrophic assay and reproductive/developmental toxicity study are difficult to interpret due to the lack of clarity in methodologies used and limited presentation of results. There do appear to be effects on sexual maturation, the male reproductive system, oestrous cycling in females as well as effects on sexual behaviour. We therefore think that a more thorough evaluation of the mammalian data is warranted. • P. 37, Section 5.2.4 (Conclusion concerning endocrine disruption): Editorial – the second bullet in the middle column of Table 12 should have the word "females" instead of "males" at the end. • P. 38, Section 5.3 (Aquatic invertebrates): Although not essential for an SVHC conclusion, it would be helpful to mention whether the study with Potamopyrgus antipodarum by Schmitt et al. (2008) complied with the validation criteria of the draft OECD test guideline. As the study involved exposure via sediment, is it better to consider it under Section 5.4?	We agree. Since this dossier is solely focused on the environmental hazard assessment of 3-BC, human health data were not analysed in detail and are only given as supporting information. A detailed assessment of the human health data might be done in a further follow-up action. Thank you for this hint. You are right and the table was changed accordingly. The study by Schmitt et al. does not meet all the validation criteria set out in the draft OECD test guideline since it uses a reduced number of replicates per treatment and it lasted for 56 days instead of 28 days (however, there is a sampling done after 28 days). Since the draft OECD guideline groups this assay under a test for aquatic molluscs we decided not to move the description to section 5.4.
		-	
4612 2016/04/14	Health and Environment Alliance (HEAL), International NGO, Belgium	HEAL supports the nomination of this substance as an SVHC, and notes that with respect to the equivalent level of concern in relation to the environment, unless appropriate data exist demonstrating non-relevance to humans, it should be assumed that the data is relevant to humans, and therefore the endocrine disrupting effects also apply to human health.	We thank HEAL for this supportive comment. We agree that the endocrine disrupting effects evaluated here for the environment might also be relevant to human health. However, this dossier is solely focused on the environmental hazard assessment of 3-BC and human health data were not analysed in detail. This might be done in a further follow-up action.

Specific comments on the justification

Number / Date	Submitted by (name, submitter type, country)	Comment	Responses
4581 2016/04/12	Norway, Member State	The Norwegian CA supports that 3-benzylidene camphor (3-BC) should be identified as a substance of very high concern (SVHC) and should be included in the Candidate List. The Norwegian CA agrees that scientific evidence shows that 3-BC fulfills the criteria in REACH Article 57 f) and the WHO/IPCS definition of an endocrine disruptor for the environment. In vitro data provide evidence for possible estrogenic, antiandrogenic and antiprogesteronic effects. In vivo data available for fish shows significant and dose related increase of the vitellogenin levels in males and females. The vitellogenin levels in males is following adverse effect on histology, fecundancy and secondary sex characteristics. Consequently, there is strong evidence that 3-BC acts as endocrine disruptor in fish, alters the function of the endocrine system, disturbs the natural reproduction cycle and can cause population relevant adverse effects. This is most likely also true for other environmental species, including invertebrate species since the vertebrate hormone receptors are highly conserved through evolution in a broad range of taxa. Consequently, the endocrine mediated effects provide strong evidence that 3-BC is of equivalent level of concern as PBT/vPvB and CMR substances. 3-BC is tentatively identified in krill (marine), mysis and smelt (aquatic) in a non-target Norwegian screening report, see: http://www.miljodirektoratet.no/no/Publikasjoner/2016/Februar-2016/Screening-program-2014/. 3-BC may be included in the Norwegian screening program for 2016.	We thank Norway for this supportive comment and for the hint and link to the monitoring screening report. These findings in marine and freshwater organisms underlines the environmental relevance of 3-BC. Your monitoring evidence was added to the dossier.

4589 2016/04/14	ChemSec, International NGO, Sweden	ChemSec supports the identification of 3-BC as an SVHC due to its endocrine disrupting properties. We already in 2011 identified it as an EDC for the SIN List. In 2012 the Danish EPA again evaluated the substance in the context of their proposed EDC critera, and concluded it to be a Category 1 EDC. We are impressed by the report, which is thorough and takes the relevant scientific studies into account. The evidence for 3-BC being and EDC is well presented and convincing. While UBA has nominated this substance based only as being an EDC for environment we hope for the MSC to extend this to cover also human health. On page 33 a summary of effects on mammals, from the earlier mentioned Danish study, is presented. Although mentioned here only to support the identification as EDC for environment, we believe these studies supports also the identification for human health. We especially want to emphasise the conclusion from the EU Endocrine Disruptors Expert Advisory Group and JRC in the document " Key scientific issues relevant to the identification and characterisation of endocrine disrupting substances, 2013" stating "Relevance of the data to humans should be assumed in the absence of appropriate data demonstrating non-relevance". The fact that the Scientific Committee on Consumer Safety already in 2013 found the substance to be unsafe for use in cosmetics further strengthens the case. In April 2016 it was reported at the conference ENDO 2016 By Rehfeld et al. that 3-BC and 4-MBC interfere with human sperm function by mimicking progesterone https://endo.confex.com/endo/2016endo/webprogram/Paper24339.html	We thank ChemSec for this supportive comment and the provided literature. This further hint for progesterone like activity was added to the dossier. Regarding the human health issue we agree that the endocrine disrupting effects evaluated here for the environment might also be relevant to human health. However, this dossier is solely focused on the environmental hazard assessment of 3-BC and human health data were not analysed in detail. This might be done in a further follow-up action.
4597 2016/04/14	United Kingdom, Member State	• As an opening remark, until an EU regulatory definition has been endorsed by CARACAL, the UK CA believes that it is premature to propose substances for identification as endocrine disrupting (ED) chemicals under REACH. In addition, 3-BC is not yet registered so it does not seem to be a "substance that matters" under REACH.	We agree with your statement that 3-BC not seem to be a substance that matters under REACH. However, given the number of pre-registrations for 3-BC under REACH, the monitoring data documenting its environmental relevance and the fact that 3-BC might gain importance as a substitute for regulated UV filter substances in the near future, we think that candidate listing of 3-BC is an important sign for industry to find safer UV filter alternatives.

			Furthermore, the identification of 3-BC as an ED for the environment would facilitate the parallel identification of the structural analogue 4-MBC, which is actually not even regulated under the cosmetics directive, as an SVHC substance via a read-across approach.
		• We agree that from what little is known of the environmental fate properties of 3-BC (all modelled), there are indications that it might persist and bioaccumulate in the environment.	Thank you for this supportive comment.
		• P. 40-47, Section 6.3 (Hazard and equivalent level of concern): This is a highly unusual case, since there are no measured data for physico-chemical or environmental fate properties, and the only useful evidence of an adverse impact in fish comes from a single OECD level 3 screening test (similar to OECD TG 229). We would normally expect data from a level 4 or 5 test (in accordance with OECD GD 150) before concluding on the relevance of endocrine disrupting potential. OECD TG 229 itself says that "the suite of endpoints … allows inferences to be made with regard to possible endocrine disturbances and thus provide guidance for further testing".	Thank you for this remark. In light of the above-mentioned relevance of regulating 3-BC with respect to our environmental concerns and the inability to request further data at the moment, we think that the total weight of evidence derived from the available in vitro and in vivo studies is sufficient for identifying 3-BC as an endocrine disruptor for the environment.
		We agree that the in silico and in vitro evidence indicates that 3-BC (or a metabolite) can show estrogenic as well anti-estrogenic effects, although it appears to be less potent than 17β-estradiol by three or more orders of magnitude. The in vivo studies also demonstrate VTG formation in male fish, so 3-BC clearly interacts with the fish endocrine system.	Thank you for this supportive comment.
		The key aquatic study presented in the dossier is Kunz et al. (2006b), which is a published academic paper rather than a standard test guideline report. Full details are missing from the article, and so we must be cautious when reviewing it. Fecundity 3-BC appears to affect fecundity, and the true dose-dependency might be masked by the high variability in fecundity seen in the test. However, a closer look at the data suggests that there may have been problems with some of the replicates. The DS mentions the variability in egg production between treatments prior to exposure to some extent on p. 31. We have not been able	Thank you very much for all the detailed and helpful comments of the aquatic key study. Generally, we agree with your point that the study is not performed according to an OECD guideline and has some drawbacks regarding missing details and that thus caution is necessary when interpreting its results. Nevertheless, the study has a sound experimental design and managed to go through a peer

		to review the statistics in detail, but information from Fig. 2 in the original paper needs to be considered: • One of the three replicates (i.e. four females) in the top dose treatment group stopped producing eggs 16 days (>2 weeks) prior to exposure. This replicate failed to produce any more eggs following exposure. A second replicate in this treatment also laid a relatively low number of eggs prior to exposure (compared with all the others). This could suggest a problem with this treatment. • One replicate in each of two other treatments (3 and 74 µg/L) laid no eggs for five days prior to exposure, and these replicates also failed to lay any more eggs for 7-15 days following exposure (i.e. no egg laying at all for a period of 12-20 days). Might this reflect the status of the fish prior to exposure? One of the OECD TG 229 validity criteria is that fish must be actively spawning in all replicates prior to initiating chemical exposure. This criterion does not seem to have been met for at least the top dose treatment, which then raises questions about the conclusion that can be drawn for this particular treatment, as well as the overall validity of the test. OECD TG 229 recommends that technical proficiency studies should be performed by inexperienced laboratories (and also when there is a substantial change, e.g. of fish supplier), which implies that test reliability may depend on the experience of the laboratory. We do not know whether the laboratory in this case was experienced or not. However, a test with better concentration maintenance (e.g. flow-through), better spawning rates prior to exposure and/or more replicates could have provided somewhat different results. Secondary sexual characteristics We know that effects on secondary sexual characteristics are related to changes in hormone levels. Nuptial tubercles are found in spawning male Fathead Minnow, and are often exhibited by only one or a few dominant males. Effects were only measured at the end of the study, and there is no indication of the extent or size of tubercles in fish at the beginning of exposure. Might the factors that affected spawning prior to exposure at the top dose also have affected the males? For example, Kunz et al. (2006b) mention that the standstill of milt production might be a male response to the cessation of spawning activity in females. Could this have resulted in a loss of breeding	reviewing process leading to publication in a highly renowned journal. Thus, we consider this study to fulfil the Klimisch 2 criteria and to be valid to draw sound conclusions on the mode of action and plausible adverse effects of 3-BC in fish species. Regarding some of your specific comments we would like to respond in more detail as follows: • Secondary sex characteristics: As you mentioned, the secondary sex characteristics are related to hormone levels. Thus, even though other factors cannot be ruled out definitively, we think that the loss of tubercles in male fish here is a direct response to the increasing level of vitellogenin in the males. A significant loss of tubercles starts exactly with the same 3-BC concentration significantly raising the VTG concentration in males and shows a concentration dependent trend. In addition, it could be shown for other estrogenic acting chemicals like Bisphenol A that a loss of tubercles in male fish can occur during a period of 14 days (see e.g. Ankley et al., 2010, Aquatic Toxicology). Given this and the histological observations from the key study we think that there is sufficient evidence of a feminisation of male fish after exposure to 3-BC. • Given the overall evidence,

		condition, i.e. if the males were no longer reproductively active, could that also explain the loss of tubercles? This is not discussed in the dossier. It would also be interesting to know which other substances trigger complete loss of male characteristics in this species over 3 weeks. In other words, are these observations consistent with other substances, or are they unusual and/or an artefact? Assuming that the cessation of egg production at the highest concentration was a genuine toxicological response, we cannot be sure of any causal link with the loss of male nuptial tubercles at the same dose (i.e. these two findings could have been caused by different modes of toxic action; OECD TG 229 points out that fecundity and gonad histopathology are [not] intended to unequivocally identify specific cellular mechanisms of action). We note that according to OECD TG 229, secondary sexual characteristics are a biomarker endpoint. Conceptually, effects on secondary sexual characteristics are likely to have implications for behaviour (including competition). However, it is difficult to conclude about their actual population relevance without further information. For example, had the females carried on laying eggs at the highest dose, would the males still have been able to fertilize them (i.e. would the fish still be able to produce viable offspring)? [Comments about histology are provided later.] Conclusion about the results of the Kunz et al. (2006b) study Given the problems observed at the highest test concentration, we do not think the study is reliable. Ideally, we would therefore prefer more detailed information from a reliable higher tier test before agreeing that 3 BC causes adverse population-relevant apical effects mediated by endocrine disruption. Equivalent concern If we were to accept that the relevance of the effects in the Kunz et al. (2006b) study, the next issue is whether they can be considered to be of "equivalent concern" in a REACH context. This is discussed in Section 6.3.2 of the dossier. We do not find the arguments particularly convincing, since they rely on a range of speculative, generic and/or hypothetical statements, rather than any firm evidence for the substance itself: ☐ Shared mode of action with substances already on the Candidate List is not a compelling reason – if it were, then any estrogenic substance would automatically be in scope regardless of how weak the interaction is. ☐ Relative potency is a critical consideration, but comparisons between	we think that a further higher tier study is not necessary to conclude on the SVHC properties of 3-BC with regard to its endocrine disrupting effects in the environment. Thank you for your critical discussion. We agree with your statement that further data from higher tier testing would substantiate the case. However, since we are unable under REACH to request further data and taking together the presented environmental relevance and evidence for the endocrine disrupting potential of 3-BC, we see the equivalent level of concern given. Especially we would like to emphasize the following

		substances should be made on the basis of molar concentrations (which has not been done). ☐ Claims of a lack of safe threshold because of the presence of other substances with similar modes of action is not a valid argument, since this depends on the actual mixture composition involved, and 3-BC might be the least relevant constituent. ☐ "Hints" of possible interactions with progesterone receptors is not sufficient for SVHC identification. ☐ Although effects might occur in a range of species, this is equally true of most chemicals for which we have very little test data. If there is a suspicion that taxonomic groups other than fish will be more sensitive, it would normally be appropriate to seek relevant toxicity data to test the range. Our ability to derive a safe threshold for 3-BC depends on the level of precaution that we are willing to apply in the absence of data. A SETAC Pellston Workshop™ on Environmental Hazard and Risk Assessment Approaches for Endocrine-Active Chemicals was held recently and discussed many of issues that are relevant for the hazard and risk assessment of substances like 3 BC. A series of papers will be published, and we think these should be taken into account for future cases. As indicated in comments for previous SVHC cases involving environmental endocrine disruption (e.g. 4-octylphenol), the UK CA advocates the use of environmental fate properties along with potency to decide whether there is sufficient concern to add a substance to the Candidate List. In the case of 3-BC, a NOEC for fecundity (the only statistically significant adverse population-relevant end point) might lie in the range 0.01 – 0.1 mg/L. This is equivalent to an Aquatic Chronic 1 classification (provided that the substance is not rapidly degradable) and we would support the identification of SVHCs that fall into the highest classification band for environmental hazard. However, Candidate Listing has important consequences, so we need to be very sure of the database before reaching a decision. The NOEC based on nominal concentrations is in the range 0.1 – 0.25 mg/L, which meets the criteria for Aquatic Chronic 2 (i.e. lower concern). The lower NOEC might therefore be an artefact of the loss of test concentration, since a semi-static renewal procedure was used. Can we also conclude that the substance is not rapidly degradable with certainty? We rely on measured rather than predicted data to identify PBT/vPvB substances (unless there are very strong read across arguments), so with only a QSAR prediction and no further justification, we are reluctant to agree that the evidence is sufficiently strong in this case.	aspects: • In our point of view potency, as long as systemic toxicity can be ruled out, should not be taken into account when identifying ED substances. This is in line with the very recently published statement of several scientists (see http://www.bfr.bund.de/cm/349/scientific-principles-for-the-identification-of-endocrine-disrupting-chemicals-a-consensus-statement.pdf) • Owing to specific uncertainties arising from the environmental exposure of ED substances we generally think that a safe threshold of an ED in the environment cannot be derived at the moment. Especially if the ED hazard is combined with likely vBvP properties as it is the case for 3-BC. • An early candidate listing in the case of 3-BC would be a clear sign to industry to avoid a full registration under REACH and to seek for safer alternatives. Hence, resource consuming follow-up processes like authorisation under REACH could be avoided. Thus, we are of the opinion that SVHC identification can and should be done now based on the available scientific evidence. • We agree that identification of 3-BC as a vBvP substance under REACH would

		We are therefore not certain that the substance falls within the highest classification band for environmental hazard, based on both the uncertainty in the concentration causing the apparent effect and the lack of information about actual degradability. A further argument that may lead to identification of an environmental endocrine disrupter is a combination of significant effects in birds or mammals along with fate properties that may lead to food chain impacts. This argument has not been made in the dossier, but we think that the mammalian data should be assessed in more detail (see further comments below). Overall conclusion On balance, we do not agree that 3-BC should be considered to be a substance of equivalent concern at the present time. We think that the case could be improved with measured data (or stronger arguments) for degradability, and we would ideally prefer a higher tier fish test to be sure about the level at which effects occur and their population relevance. We note that the screening data indicate that 3-BC is potentially a vPvB substance. It is unfortunate that this aspect has not been assessed in parallel, since this is agreed to be a non-threshold concern at the policy level. We do, however, recognise the current regulatory inability to request any data for this substance under REACH.	significantly strengthen our case. However, as you already mentioned the available data is not sufficient to conclude on this aspect and at the moment there is no option to request further data.
		-	

4601 2016/04/14	CHEM Trust, National NGO, United Kingdom	CHEM Trust supports inclusion of (3-benzylidene camphor) in the REACH candidate list based on its endocrine disrupting properties as an SVHC of equivalent concern according to article 57 f. The data to show that 3-benzylidene camphor has endocrine disrupting properties is very convincingly presented and well documented. The evidence presented illustrates that 3-benzylidene camphor can have irreversible and long lasting effects on animal populations and that even short term exposures during sensitive life stages of organisms can have adverse effects during the entire life time. Based on the presented evidence 3-benzylidene camphor should be included in the REACH candidate list as an SVHC for the environment and for human health. Given the nature of the endocrine system and the fact it has been conserved throughout evolution, it is also highly likely that chemicals with ED properties in fish will also have ED properties in mammals, including humans. The default position should be to assume endocrine disrupting properties for humans unless the endocrine disrupting active molecule is the parent compound, which is active in fish due to direct transfer via the skin and gills, but not active in humans due to metabolism. Moreover, the data presented from rodent studies illustrate that one cannot assume detrimental effects would be limited to the environment.	We thank CHEM Trust for this supportive comment. Regarding the human health issue we agree that the endocrine disrupting effects evaluated here for the environment might also be relevant to human health. However, this dossier is solely focused on the environmental hazard assessment of 3-BC and human health data, including the possible influence of different uptake routes and metabolism, were not analysed in detail. This might be done in a further follow-up action.
4606 2016/04/14	ANSES, Academic institution, France	ANSES supports the proposal of DE for identification of 3-BC as SVHC, in accordance with Article 57(f) of REACh regulation because of its endocrine disrupting properties associated with probable serious effects to the environment. In light of the in vitro and in vivo studies presented in the Annex XV report of the 3-BC, we agree on the proposed causal relationship for an estrogenic mode of action of 3-BC between in vitro results, biomarker responses (induction of VTG), histological effects (histology of gonads, inhibited development of oocytes and spermatocyte in male and female gonads) and adverse effects in fish (decrease of fecundity, cessation of reproduction, demasculinisation in secondary sexual characteristics of male fish).	We thank France for this supportive comment.
4614 2016/04/25	Finland, Member State	The Finnish CA agrees that 3-benzylidene camphor (3-BC) (EC 239-139-9) shows rather strong screening level indication of endocrine mode of action in the environment in several in vitro and in vivo tests. Estrogenic and antiandrogenic activity is seen in in vitro screens and vitellogenin induction is seen in male fish in three in vivo studies in the absence of indications of systemic toxicity. Observations about reduced fertility and fecundity and depression of male secondary sex characteristics were considered to indicate adverse effects in fish. Some histological changes were also seen but with low statistical significance.	Thank you for your extensive comment. Given the number of pre-registrations for 3-BC under REACH, the monitoring data documenting its environmental relevance and the fact that 3-BC might gain importance as a substitute for regulated UV filter substances in the near future, we think that candidate listing of 3-BC is an

		The fish test results were obtained with short term reproduction assays which are considered to have a low statistical power, and only one of the studies was rated as reliable without restrictions (similar to OECD TG 229, adult fish, realistic exposure method). In the OECD guidance for evaluating endocrine disrupting chemicals (EDs) (OECD 2012) the OECD 229 test is rated as a level 3 screening test which is not sufficient for conclusive evaluation of ED properties. Therefore the Finnish CA considers that some uncertainty remains in the environmental ED identification of 3-BC. The 3-BC has been an allowed UV filter in cosmetic products but this and other possible uses were prohibited in cosmetics in 2015. The substance has not been registered and hence no substance evaluation process has been initiated and no information of other uses is available. The DE CA concludes that 3-BC meets the criteria in Article 57(f) as environmental ED and considers SVHC identification the most appropriate risk management measure, because the banning in cosmetic use may not cover all emission sources. However, it could be considered whether the SVHC identification of 3-BC is necessary at this stage. The banning in cosmetics use may be a sufficient risk management measure for now, and the possible future registrations could bring out the uses other than cosmetics and hence support the risk assessment. In addition a substance evaluation process with additional data requests could be conducted to confirm the ED identification with conclusive higher tier information and other supporting information like data on (bio)degradation and bioaccumulation potential. The Finnish CA notes that a Risk Management Option Analysis (RMOA) conclusion document has been published on the ECHA website.	important sign for industry to find safer UV filter alternatives and an important first step for further regulatory steps outside the cosmetics directive. Furthermore, the identification of 3-BC as an ED for the environment would facilitate the parallel identification of the structural analogue 4-MBC, which is actually not even regulated under the cosmetics directive, as an SVHC substance via a read-across approach. We agree with your statement that further data from higher tier testing would substantiate the case. However, since we are unable under REACH to request further data and taking together the presented environmental relevance and evidence for the endocrine disrupting potential of 3-BC, we see the equivalent level of concern given and think that a further higher tier study is not necessary to conclude on the SVHC properties of 3-BC with regard to its endocrine disrupting effects in the environment.

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

Specific comments on use, exposure, alternatives and risks

Number / Date	Submitted by (name, submitter type, country)	Comment	Responses
4597 2016/04/14	United Kingdom, Member State	• We have no further information on likely use pattern. However, the statement about the annual production volume of UV filters (presumably in the EU?) in Section 7 is not very helpful, because there is no indication of which substances are included, nor what type of information the estimate is based on.	We thank the United Kingdom for this comment. The estimated annual production volume of UV filters was cited from Buser et al., 2006. The citation was made to illustrate that UV filters are of economic importance within the EU. With respect to this 3-BC, even though only pre-registered up to now, might gain significance as a substitute in the near future when taking into account the ongoing regulatory activities of other important UV filters like the group of benzotriazoles.