

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

Substance name: 5-sec-butyl-2-(2,4-dimethylcyclohex-3-en-1-yl)-5-methyl-1,3-dioxane [1], 5-sec-butyl-2-(4,6-dimethylcyclohex-3-en-1-yl)-5-methyl-1,3-dioxane [2] [covering any of the individual isomers of [1] and [2] or any combination thereof]

Editorial note: the substance name above was used for the documents submitted for public consultation. As result of the comments the entry name has been changed to name provided below. This change does not constitute actual change in the identity of the entry but is merely an editorial change.

Substance name: 5-sec-butyl-2-(2,4-dimethylcyclohex-3-en-1-yl)-5-methyl-1,3-dioxane [1], 5-sec-butyl-2-(4,6-dimethylcyclohex-3-en-1-yl)-5-methyl-1,3-dioxane [2] [covering any of the individual stereoisomers of [1] and [2] or any combination thereof]

CAS number: -

EC number: -

The substance is proposed to be identified as meeting the following SVHC criteria set out in Article 57 of the REACH Regulation: vPvB (Art. 57 (e))

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. The table does not contain confidential information.

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	Response
4474 2015/04/ 15	Company, Switzerland	Please see attached document	Please consider the responses to your comment in the below section "Specific comments on the justification".
		Attachment: 4474_Letter_of_Response_15_April_2015 FINAL.docx	

4480 2015/04/ 16	International Flavors & Fragrances, Company, Netherlands	- Attachment: 4480_Aurawood_svhc_AnnexXV_IFF_Response.pdf	<p>The SVHC process has been transparent. Indeed initially the focus was on Karanal, but during the process it became apparent that the way forward is to define a group entry that covers all the isomers, and thus also AURAWOOD.</p> <p>The group entry has been clearly defined in response to substance identity information in the Annex XV report. Thus, the eMSCA considers that there should not be any ambiguity on the identity of the substance(s) proposed to be identified as SVHC. Please also consider the responses to comment #4483 (see below).</p> <p>The information on the registrant and tonnage band given in Annex 1 of the Annex XV SVHC report has been included as it is already publically available on the ECHA dissemination website.</p> <p>The C&L inventory contains self-classifications for AURAWOOD. Therefore, the sentence stating that there are no self-classifications for AURAWOOD in ECHA's C&L Inventory database has been removed, and Annex 1 of the Annex XV SVHC report has been adapted accordingly.</p>
4483 2015/04/ 16	Finland, Member State	<p>We support the proposal to identify substance with EC 413-720-9 (Reactio mass of 5-sec-butyl-2-(2,4-dimethylcyclohex-3-en-1-yl)-5-methyl-1,3- dioxane [1] and 5-sec-butyl-2-(4,6-dimethylcyclohex-3-en-1-yl)-5-methyl-1,3-dioxane [2], trade name Karanal) and substance with List number 700-927-7 as vPvB substances according to article 57(e) of the REACH regulation. Based on the information available, it seems possible to conclude that these substances fulfil the vP and vB criteria in Annex XIII to the Regulation.</p> <p>The entry as presented in the Annex XV dossier, "5-sec-butyl-2-(2,4-dimethylcyclohex-3-en-1-yl)-5-methyl-1,3-dioxane [1], 5-sec-butyl-2-(4,6-dimethylcyclohex-3-en-1-yl)-5-methyl-1,3-dioxane [2] [covering any of the individual isomers of [1] and [2] or any combination thereof]", needs to be, however, further clarified. We recognise the need to cover also other similar substances</p>	<p>The eMSCA would like to thank the Finnish CA for their support.</p> <p>Regarding the comment questioning the scope of the group entry, please note that the two names 5-sec-butyl-2-(2,4-dimethylcyclohex-3-en-1-yl)-5-methyl-1,3-dioxane and 5-sec-butyl-2-(4,6-dimethylcyclohex-3-en-1-yl)-5-methyl-1,3-dioxane refer indeed to two groups of stereoisomers and as included in the comment, the wording [covering any of the individual isomers of [1] and [2] or any combination thereof] means that the group entry would cover any possible individual stereoisomer of the two positional isomers</p> <ul style="list-style-type: none"> ▪ 5-sec-butyl-2-(2,4-dimethylcyclohex-3-en-1-yl)-5-methyl-1,3-dioxane and ▪ 5-sec-butyl-2-(4,6-dimethylcyclohex-3-en-1-yl)-5-methyl-1,3-dioxane

		<p>(isomers of these structures) with this entry. What does, however, "covering any of the individual isomers of [1] and [2] or any combination thereof" mean? Does this refer to, for instance, stereo isomers of the two positional isomers [1] and [2]?</p> <p>In addition, please add information on the test substance identity for the key studies presented in the report.</p> <p>The Finnish CA notes that no Risk Management Option Analysis (RMO) Conclusion Document on these substances has been published on the ECHA website. The Finnish CA considers that after inclusion of the substance in the Candidate List (for eventual inclusion in the Annex XIV) it still needs to be further considered which risk management measures would be the most appropriate.</p>	<p>and would cover also any of the possible combinations of these stereoisomers. In order to avoid misunderstandings about the coverage of the group entry, we have specified the entry name by adding the word "stereo" to the word "isomers" in the entry name. This specification is not introducing any actual change to the identity of the entry. The information included in the entry name in square brackets is limited to an explanation of what is defined by the name of the entry and is not meant for expanding the scope of the entry.</p> <p>For example the substance corresponding to the specific stereoisomer 5-[(2R)-butan-2-yl]-2-[(1R,2R)-2,4-dimethylcyclohex-3-en-1-yl]-5-methyl-1,3-dioxane would be covered by the entry.</p> <p>In response to the comments given by the Finnish CA in relation to the inclusion of information on the test substance identity. All available information on the test substance is presented for both key and supporting studies in the confidential annexes to the Annex XV SVHC report.</p> <p>In response to the comments given by the Finnish CA in relation to the RMO analysis. A RMO analysis has previously been conducted for Karanal and is available in the respective IULCID dossier. Following inclusion of this group entry in the Candidate List, further consideration of the most appropriate risk reduction measures may need to be conducted.</p>
4484 2015/04/ 16	Health and Environment Alliance (HEAL), International NGO, Belgium	HEAL supports the nomination of this substance to the candidate list.	The eMSCA would like to thank HEAL for their support.

Specific comments on the justification

Number / Date	Submitted by (name, submitter type, country)	Comment	Response
4467 2015/04/08	Sweden, Member State	<p>Comments on Part 1 section 3-6:</p> <p>Persistence The Swedish CA agrees that the substance meets the criteria for very persistent substances as stated in Annex XIII of REACH, and the proposed substance is considered vP. Netherlands has provided sufficient data and scientific evidence to to meet the vP criterion.</p> <p>Bioaccumulation The Swedish CA agrees that the substance meets the criteria for very persistent substances as stated in Annex XIII of REACH, and the proposed substance is considered vB. Netherlands has provided sufficient data and scientific evidence to to meet the vB criterion.</p> <p>Toxicity The Swedish CA agrees that the substance does not meet the criteria for toxicity as stated in Annex XIII of REACH, and the proposed substance is not considered a T. Netherlands has provided sufficient data and scientific evidence to show that T criterion is not fulfilled even if the overall conclusion is that it is a borderline case. The available aquatic toxicity tests of fish, algae and daphnia show NOECs >0.01 mg/L and therefor do not meet the T criterion for aquatic organisms (NOEC < 0.01 mg/L) that is stated in Annex XIII of REACH. The proposed substance has been self-classified by many notifiers in the ECHAC&L inventory as a STOT RE2 substance having specific target organ toxicity after repeated exposure. This would suffice as evidence of chronic toxicity, if the classification was harmonised. The evaluating MSCA concluded that the available repeated dose toxicity study would most likely be insufficient to pursue a harmonised classification of the proposed substance as STOT RE 2. Therefore, the proposed substance cannot be considered T based on the available data. Thus while there are indications that the proposed</p>	The eMSCA would like to thank the Swedish CA for their reanalysis and their support.

		<p>substance is toxic, the T assessment for the proposed substance is inconclusive.</p> <p>Summary and overall conclusions on the PBT and vPvB properties In conclusion the Swedish CA agrees with Netherlands, that the proposed substance is identified as a vPvB substance according to Art.57(e) of REACH by comparing all relevant and available information listed in Annex XIII of REACH with the criteria set out in the same Annex, in a weight-of-evidence determination. In addition, it should be noted that the proposed substance is considered to be borderline T.</p>	
4468 2015/04/ 08	Germany, Member State	<p>DE would like to thank NL for the preparation of the Annex XV dossier for 5-sec-butyl-2-(2,4-dimethylcyclohex-3-en-1-yl). Concerning the assessment of persistence we have no specific comment and support the final conclusion that the substance is vP. Regarding the bioaccumulation we would like to point out that the strong variation of the BCF values derived in the OECD 305 study using two substance concentrations is indeed unusual and no sufficient reason is given.</p> <p>However, the higher BCF values from the higher substance concentration are more reliable and all the other given data (estimated and experimental from OECD 317) support these higher BCF values. Therefore, we support the final conclusion that 5-sec-butyl-2-(2,4-dimethylcyclohex-3-en-1-yl) is vB.</p>	<p>The eMSCA would like to thank the German CA for their support. The German CA interpretation of the bioaccumulation study led to the same conclusion as the eMSCA reached in the Annex XV SVHC report.</p> <p>Regarding your comment on the strong variation of the BCF values derived in the OECD 305 study using two test concentrations, please refer to response to comment #4474 (see below).</p>
4471 2015/04/ 13	Germany, Member State	<ul style="list-style-type: none"> • In section 1.1 of the IUCLID file beside the IUPAC name the given reference substance dataset does not include any information about the substance(s) that shall be covered by the group entry. It might be useful to incorporate at least the information on the substance identity given in section 1.1 of the Annex XV report in the reference substance dataset in section 1.1 of the IUCLID file. Furthermore, the information given in table 2 "Non-exhaustive list of substances covered by the group entry*" in section 1.2 of the Annex XV report should be included in the reference substance dataset as related CAS information. 	<p>In response to your comment in relation to the information included in section 1.1 and 1.2 of the IUCLID dossier:</p> <p>As long as the scope of the proposal in terms of Substance identity is clearly defined in the Annex XV report and there is no contradicting information with the information reported in IUCLID section 1, the eMSCA considers that there should not be any ambiguity on the identity of the substance(s) proposed to be identified as SVHC. For this specific case, the scope of the proposal is clear. Duplicating the information from the Annex XV report in IUCLID section 1 would not appear to provide an added value.</p>

	<ul style="list-style-type: none"> • In section 1.2 of the IUCLID file the given composition does not reflect the whole group entry but only "An example of composition covered by the group entry". In order to make the IUCLID file more comprehensible it would be useful to include a more representative composition for the group entry in the IUCLID file covering all possible substances/compositions of it. • In table 1 in section 1.1 of the Annex XV report for the molecular weight range the corresponding molecular weight unit is missing. Please add the missing information. The same applies to table 7 and 10 in the confidential part of the report. • In table 3 in section 1.5 of the Annex XV report for the vapour pressure the following value is stated: "0.091 ± 0.01 Pa at 20 °C". This information is not in accordance with the information given in the corresponding study report in the IUCLID file. The given value should be replaced using "0.09 ± 0.01 Pa at 25 °C" instead. • In table 3 in section 1.5 of the Annex XV report for the water solubility the following value is stated: "0.61 ± 0.06 mg/L at 20 °C; pH 7.7-8.1". This information is not in accordance with the information given in the corresponding study report in the IUCLID file. The given value should be replaced using "0.61 ± 0.06 mg/L at 19.7-20.2 °C; pH 7.7-8.1" instead. • In table 3 in section 1.5 of the Annex XV report for the partition coefficient n-octanol/water two values together with two references are given. The first value "6.8 - 7.3 at 22 °C" and the corresponding study report (reference [6]) are not included in the IUCLID file and can therefore not be reviewed/checked. The corresponding endpoint study record should be included in the IUCLID file. Furthermore, for the confidential reference [7] the wrong study report number is stated in the Annex XV report. The study number should be replaced using the study report number given in section 4.7 of the IUCLID file instead. 	<p>Regarding the composition information in section 1.2, considering the number of possible stereoisomers and the number of possible combinations of these isomers, a representative composition for the group entry cannot be established. Therefore reporting only an example of a possible composition in IUCLID section 1.2 seems appropriate.</p> <p>In response to the comments in relation to the information presented in table 1 in section 1.1, table 3 in section 1.5, and tables 7 and 10 in the confidential annex. The tables have been changed accordingly.</p> <p>Concerning the log K_{ow} studies, the study report of reference [6] has previously been evaluated, but is no longer available, and thus cannot be added to the IUCLID dossier. Details on the study are available in the IUCLID dossier of substance with EC No. 700-927-7. The study number of reference [7] has been corrected.</p>
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4473 2015/04/ 14	Belgium, Member State	p.5 Belgium supports the proposal to identify 5-sec-butyl-2-(2,4-dimethylcyclohex-3-en-1-yl)-5-methyl-1,3-dioxane [1], 5-sec-butyl-2-(4,6-dimethylcyclohex-3-en-1-yl)-5-methyl-1,3-dioxane [2] [covering any of the individual isomers of [1] and [2] or any combination thereof] as SVHC, based on article 57(e) of the REACH Regulation. vP criterion is fulfilled (degradation half-life in fresh water > 60 days). vB criterion is fulfilled (bioconcentration factor > 5000 L/kg).	The eMSCA would like to thank the Belgian CA for their support.
4474 2015/04/ 15	Company, Switzerland	Please see attached document Attachment: 4474_Letter_of_Response_15_April_2015_FINAL.docx	<p>The Registrant(s) comments on the persistence, bioaccumulation and toxicity assessment of the proposed substance. The response to these comments is given below in a structured way that follows the order of these comments as they appeared in the Registrant(s) letter. The Registrant(s) included specific comments in an annex to the response. Response to these specific comments is presented below the relevant section, and is indicated with "P, B or T (annex)"</p> <p>PERSISTENCE The objections are noted, but not agreed upon by the eMSCA as it is clear from the followed weight-of-evidence approach that the proposed substance meets the vP criterion. Responses to the specific objections are given below.</p> <p>P(i): In response to the comment given by the Registrant(s) in relation to the use of 12°C as a testing recommendation:</p> <p>In REACH guidance Chapter R.16 (version 2.1, October 2012), paragraph R.16.5.4.5. named "Biodegradation in surface water, sediment and soil" the following is stated: <i>"Temperature influences the activity of microorganisms and thus the biodegradation rate in the environment. When biodegradation rates or half-lives have been determined in simulation tests, it</i></p>

			<p><i>should be considered to recalculate the degradation rates obtained to reflect an average EU outdoor temperature by Equation R.16-9.</i> In Table R.16-9 the typical realistic temperature in the EU is given as 12 °C.</p> <p>In REACH guidance Chapter R.11 (PBT/vPvB assessment; version 2.1; November 2014), paragraph R.11.4.1.1 named "Persistence assessment (P and vP)" the following is stated: <i>"Please note that since its 32nd meeting the Member State Committee has started to require new simulation degradation studies to be carried out around neutral pH values and at 12°C, which is understood as the mean temperature of European surface waters. Accordingly, temperature correction of degradation half-lives from already available study results to 12°C is recommended. In the absence of equations/models reflecting temperature dependence of biodegradation, the Arrhenius equation as provided under the section on "Temperature dependence of hydrolysis" of this Guidance (or a similar appropriate equation designed to normalise physico-chemical degradation rates) can be used as a possible means of normalisation."</i></p> <p>It is clear that 12°C represents the mean temperature of European surface waters, while already available degradation half-lives should be corrected to 12°C, as was done by the eMSCA in the Annex XV SVHC report. Therefore, the objections by the registrant are not considered to be founded.</p> <p>P(ii): In response to the comment given by the Registrant(s) in relation to the use of 12°C for hazard assessment:</p> <p>This comment is not specifically focused on the current Annex XV SVHC report. Nevertheless, the eMSCA would like to note that REACH guidance Chapter R.11 for the PBT/vPvB assessment (version 2.1; November 2014) is considered clear as it is (see previous response).</p>
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			<p>P(iii): In response to the comment given by the Registrant(s) in relation to the necessity to validate and adopt approaches by the appropriate OECD study guideline, to become official requirements, and the adaption of Table R.11-5 – ECHA:</p> <p>Within the EU, REACH (Regulation (EC) No 1907/2006) is the legal framework for the assessment of industrial chemicals, and OECD test guidelines are used in support of this framework. That said, OECD test guideline 309 is already very clear as under section 5 named "General principle of the test", the following is stated: "<i>The test flasks are incubated in darkness at an environmental temperature under aerobic conditions and agitation</i>". Within the EU, the environmental temperature has been set at 12 °C (see previous response).</p> <p>The eMSCA would like to note that REACH guidance Chapter R.11 for the PBT/vPvB assessment (version 2.1; November 2014), including Table R.11-5, is considered clear as it is.</p> <p>P(iv) part 1: In response to the comment given by the Registrant(s) in relation to the deficiencies in the OECD 309 simulation study and the appropriate DT₅₀ value:</p> <p>The eMSCA agrees with the registrant that this study should have followed the OECD test guideline 309 more strictly. The omissions by the registrant were assessed as follows. A positive control was lacking, but a viable microbial population could be presumed as the test was conducted with freshly sampled natural water from an unpolluted site. A GLP-compliant enhanced ready biodegradability study [11] showed that the proposed substance is not toxic to microbial inoculum, which addresses the lack of a toxicity control. The concentration of the solvent carrier was 0.01% (v/v), which is in line with the OECD test guideline 309 validity criteria, and</p>
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			<p>thus a negative solvent effect is considered highly unlikely. Finally, OECD test guideline 309 does prescribe the testing of two test concentrations. The reasoning being that especially at higher test concentrations, there is a risk that degradation will not follow first order kinetics and that the first order degradation constant and half-life cannot be estimated. Fortunately, in this study, degradation did follow first order kinetics, and a half-life could be derived for the proposed substance.</p> <p>Thus, careful consideration by the eMSCA led to the conclusion that the identified deficiencies did not invalidate the study. They merely lowered the reliability of the data. The eMSCA took this limitation into account, and calculated in addition to a realistic degradation half-life of 145 days at 12 °C, a best-case degradation half-life of 74 days at 12 °C. The latter value was compared to the vP criterion of 60 days in freshwater.</p> <p>Further, it should be taken into account that this analysis is part of a weight-of-evidence analysis as prescribed by Annex XIII of REACH. The data from the simulation test do not stand on its own, but confirm the results that were already available from ready and inherent biodegradability tests that showed limited degradation or even no degradation at all.</p> <p>P(iv) part 2: In response to the comment given by the Registrant(s) in relation to the biodegradation screening tests:</p> <p>The GLP-compliant ready biodegradability study according to OECD test guideline 301B was assessed as reliable with restrictions in the confidential part of the Annex XV SVHC report. Section 3.1.2.1.2. was erroneous, and has been amended accordingly. As the biodegradation amounted to 34% after 28 days, which is far below the trigger of 60%, the proposed substance is considered not ready biodegradable, and should thus be considered as potentially (very) persistent.</p>
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			<p>Biodegradability amounted in the inherent biodegradability study according to OECD test guideline 302C to 12% after 28 days, and 18% after 50 days. As this is below 20% there is no evidence of inherent, primary biodegradation (OECD, 2006). This in itself is already sufficient evidence to conclude on persistence without the need for further simulation testing as stated in REACH guidance paragraph R.11.4.1.1 under the subheading “tests on inherent biodegradation”.</p> <p>Therefore, it is not agreed with the registrant that the biodegradation studies indicate any advanced stage of biodegradation. Moreover, the registrant does not provide a rationale for the claim that primary degradation would stop after mono-oxygenation. This is unlikely, and therefore, the theoretical oxygen demand of 2.13% should only be considered as hypothetical.</p> <p><i>Reference</i> <i>OECD (2006): Revised introduction to the OECD guidelines for testing of chemicals, Section 3. OECD Guidelines for the Testing of Chemicals, Section 3. OECD Publishing, Paris. Available at http://dx.doi.org/10.1787/9789264030213-en</i></p> <p>P(annex): In response to the comment given by the Registrant(s) in relation to hydrolysis:</p> <p>The registrant did not present new information concerning hydrolysis of the proposed substance.</p> <p>A detailed assessment of these two hydrolysis studies has been provided by the eMSCA in the confidential annex of the Annex XV SVHC report, in which the supporting hydrolysis study was considered unreliable, and the more recent key study reliable with restrictions.</p> <p>In the key study, the registrant reported for the proposed substance a DT₅₀ of 738.9 h (=30.8 days) at pH 4 following extrapolation to 25 °C. The eMSCA reassessed</p>
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			<p>the data and calculated a DT₅₀ of 1830 h at pH 4 following extrapolation to 12 °C. This shows that even at acidic conditions hydrolysis of the proposed substance is very slow at an EU relevant environmental temperature and exceeds the criterion for very persistent in fresh surface water. For pH 7 and 9, DT₅₀ values could not be extrapolated to 12 °C, due to the irregularities of the log (relative) concentration versus time curves. For river water with pH 8.2, a DT₅₀ of 241 h was calculated at 50 °C, demonstrating that at 50 °C dissipation in the hydrolysis test occurs almost a factor two slower at pH 8.2 compared to pH 4.</p> <p>P(annex): In response to the comment given by the Registrant(s) in relation to photolysis:</p> <p>The registrant does not present any evidence to support the claim of photolytic degradation of the proposed substance.</p> <p>P(annex): In response to the comment given by the Registrant(s) in relation to atmospheric degradation:</p> <p>The proposed substance has a high potential for adsorption to organic matter (HPLC estimated log K_{oc} of 3.61). In the Annex XV SVHC report, paragraph 3.2.3. on distribution modelling it has been shown with a level III fugacity model calculation (LEV3EPI in EPIsuite) that the proposed substance will predominantly be in soil and water, and to a lesser extent in sediment. Distribution to air is very limited (<0.27%) when emission is not solely to air. Therefore, estimated atmospheric degradation will not be included in the Annex XV SVHC report.</p> <p>P(annex): In response to the comment given by the Registrant(s) in relation to biodegradation:</p> <p>It is agreed with the registrant that the outcome of the</p>
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			<p>water simulation study would have been easier to interpret if the test substance was C₁₄-labeled. Nevertheless, as stated above, careful consideration by the eMSCA led to the conclusion this did not invalidate the study. These and other identified deficiencies merely lowered the reliability of the data. The eMSCA took this limitation into account, and calculated in addition to a realistic degradation half-life of 145 days at 12 °C, a best-case degradation half-life of 74 days at 12 °C, taking account of the remaining uncertainties. The latter value was compared to the vP criterion of 60 days in freshwater. The result of this test was used together with the results from the ready and inherent biodegradability test and the hydrolysis tests to reach the conclusion very persistent.</p> <p>P(annex): In response to the comment given by the Registrant(s) in relation to screening tests:</p> <p>In addition, the registrant is reminded that the test methodology of ready, and, to a lesser extent, inherent biodegradability studies is stringent and hence they contribute information at a screening level, as do QSAR estimates (e.g. OASIS-CATALOGIC). When substances, such as the proposed substance, are neither ready nor inherently biodegradable, simulation studies are conducted that address the fate and behaviour of a substance as it may be expected in the environment. In this case, the water simulation study clearly showed that the proposed substance should be considered as very persistent, based on the residual levels of the parent compound.</p> <p>The registrant refers to the limited bioavailability in ready biodegradability tests. However, it should be noted that the dossier already contains several modified ready biodegradability tests to overcome the issues of reduced bioavailability. These modifications did however not improve the biodegradability at all.</p>
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			<p>P(annex): In response to the comment given by the Registrant(s) in relation to simulation tests:</p> <p>The registrant is referred to the response on the water simulation study given above under comment (IV). Further, in the Annex XV dossier it is explained that the inclusion of the lag phase (no degradation at the start of the test) and the inclusion of a residual mass (i.e. not all substance disappears at the end of the test, is erroneous, with reference to the OECD 309 guideline. Besides that, determining a half-life from three time points (and this ignoring the other time points) is highly uncertain.</p> <p>BIOACCUMULATION</p> <p>The objections are noted, but not agreed upon by the eMSCA as it is clear from the followed weight-of-evidence approach that the proposed substance meets the vB criterion. Responses to the specific objections are given below.</p> <p>B(i): In response to the comment given by the Registrant(s) in relation to the reliability of the BCF value obtained at the higher test concentration:</p> <p>In OECD TG 305 paragraph 51 the following is stated: <i>"The concentration(s) of the test substance should be selected to be below its chronic effect level or 1% of its acute asymptotic LC50, within an environmentally relevant range and at least an order of magnitude above its limit of quantification in water by the analytical method used. The highest permissible test concentration can also be determined by dividing the acute 96 h LC50 by an appropriate acute/ chronic ratio (e.g. appropriate ratios for some chemicals are about three, but a few are above 100)".</i></p> <p>The registrant refers to an acute fish toxicity test with the proposed substance that was assessed as unreliable by the eMSCA. Therefore, as a reliable 96 h LC50 value is not available, a comparison cannot be made. Furthermore, it</p>
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			<p>is deemed more appropriate to compare test concentrations applied in the OECD 305 study with chronic effect levels, instead of dividing an acute LC₅₀ value by 100, which represents an acute-to-chronic ratio. For the proposed substance, a GLP-compliant fish-early life stage toxicity test (OECD 210) is available that reported a reliable NOEC of 0.03 mg/L, and LOEC of 0.056 mg/L (both based on mean measured concentrations). Since the higher test concentration (0.03 mg/L) applied in the OECD 305 study was below the chronic effect level (0.056 mg/L), the eMSCA considers the BCF value of 9893 L/kg reliable without restrictions.</p> <p>Furthermore, it should be noted that in the OECD 305 study no mortalities or sub-lethal effects were observed in the solvent control, the lower and higher test concentrations, throughout the duration of the test.</p> <p>B(ii): In response to the comment given by the Registrant(s) in relation to the variation between the BCF values:</p> <p>The eMSCA agrees with the registrant and the German CA that the strong variation of the BCF values derived in the OECD 305 study using two test concentrations is indeed unusual.</p> <p>As discussed above, the higher test concentration is below the chronic LOEC, so sub-lethal effects affecting the physical and metabolic behavior of the exposed fish are highly unlikely. The actual water concentrations in the higher test concentration varied slightly, with the standard deviation amounting to 23%. Therefore, the BCF value of 9893 L/kg is considered reliable without restrictions (R_i=1). In contrast, the actual water concentrations in the lower test concentration varied considerably over time, i.e. the standard deviation of the actual water concentrations in the low concentration was as high as 48%, which is far above the OECD 305 validity criterion of 20%. This could have resulted in an erroneously high average water concentration, and thus</p>
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			<p>an erroneously low BCF value. Therefore, the BCF value of 1892 L/kg is considered less reliable and can only be used with restrictions ($R_i=2$).</p> <p>In support of the higher BCF value of 9893 L/kg are the other bioaccumulation data. i.e. the QSAR estimates and the very high lipid and organic carbon corrected $BSAF_k$ of 15.76 kg OC/ kg lipid that was obtained for the earthworm.</p> <p>B(iii) part 1: In response to the comment given by the Registrant(s) in relation to the metabolization of the proposed substance in fish:</p> <p>The submitted information is not sufficient to evaluate the reliability and the actual relevance of the <i>in vitro</i> trout liver S9 study. For a more detailed assessment, the Registrant is referred to the response on the additional information presented in the statement Annex to this letter concerning the <i>in vitro</i> trout liver S9 study.</p> <p>The eMSCA would like to stress that even if the S9-test could have been assessed for reliability, the estimated BCF values could not refute a conclusion that has been drawn based on reliable <i>in vivo</i> aquatic bioaccumulation test results. The eMSCA is of the opinion that the conversion of <i>in vitro</i> to <i>in vivo</i> metabolism data, and the use of $\log K_{ow}$ values to generate estimated BCF values is not as straightforward as is suggested by the Registrant(s). Such an approach may instead be useful in the future as a cheap bioaccumulation screening tool for certain substance groups (as was discussed in the CEFIC bioaccumulation workshop held in ECHA in September 2014).</p> <p>B(iii) part 2: In response to the comment given by the Registrant(s) in relation to the $\log K_{ow}$ of the proposed substance and the use of an <i>in vitro</i> - <i>in vivo</i> extrapolation model to obtain QSAR estimated BCF values:</p>
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			<p>The log K_{ow} of the proposed substance has not been determined adequately, i.e. by the slow-stirring method according to OECD TG 123.</p> <p>Only log K_{ow} estimates are available. Two studies are available that used the HPLC method to estimate the log K_{ow} of the proposed substance as being between 6.8 and 7.3 at 22 °C (NOTOX, 1989), and more recently between 6.3 and 6.7 at 35 °C (Givaudan, 2013). QSAR estimates, which are considered to be as reliable as the HPLC estimates, indicate lower K_{ow} values of 5.28, 5.36 and 5.89 by Bio-Loom ClogP (v1.5), ACD/logP (v2.0) and KOWWIN (v1.68), respectively. The eMSCA considers it more appropriate to consider the log K_{ow} of the proposed substance as 5.3 – 7.3. This will be amended in the Support Document.</p> <p>As can be seen from the Registrant's table that depicts the estimated BCF values, the log K_{ow} has a strong effect in the applied <i>in vitro</i> - <i>in vivo</i> extrapolation model. For both peak 1 and 2, the estimated BCF values differ practically a factor two when the log K_{ow} is set at 7.1 or 6.5. As indicated by the Registrant(s) the parabolic relationship between log K_{ow} and BCF suggests a higher BCF at a log K_{ow} of around 6. Considering that QSAR's estimate log K_{ow} values between 5.3 and 5.9, it cannot be excluded that the estimated BCF of the proposed substance will be far greater than the highest reported estimated BCF value of 5834 L/kg in the table (shown below), which already exceeds the vB criterion.</p>
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Log K _{ow}	BCF estimates calculated with the <i>in vitro</i> – <i>in vivo</i> extrapolation model ^a			
	Karanal (peak 1, Cl _{int, in vitro} = 0.24 ml/h/mg protein)		Karanal (peak 2, Cl _{int, in vitro} = 0.13 ml/h/mg protein)	
	F _u =1 ^b	F _u calc ^c	F _u = 1 ^b	F _u calc ^c
6.5	235	3816	308	5834
6.8	168	2827	220	4354
7.1	111	1940	108	3000

^a Nichols, J. W.; Huggett, D. B.; Arnot, J. A.; Fitzsimmons, P. N.; Cowan-Ellsberry, C. E. Towards improved models for predicting bioconcentration of well-metabolized compounds by rainbow trout using measured rates of *in vitro* intrinsic clearance. *Environ. Toxicol. Chem.* 2013, 32 (7), 1611–1622.

^b f_u, plasma binding correction term; "f_u = 1.0", hepatic clearance is calculated assuming equal *in vitro* and *in vivo* binding by setting f_u = 1.0

^c f_u, plasma binding correction term; "f_u calc", hepatic clearance is calculated taking into account a theoretically calculated difference between *in vitro* and *in vivo* binding

Furthermore, this table shows a large difference between the estimated BCF values of peak 1 and 2 that amount to 150% for all three log K_{ow} values. The proposed substance has many more isomers that might be even less metabolized and that could potentially yield even higher estimated BCF values.

Considering all the uncertainties associated with the proposed BCF estimates, the eMSCA considers the approach of the Registrant(s) to conclude on bioaccumulation not appropriate. Especially, as reliable *in vivo* aquatic and terrestrial bioaccumulation test results are available that clearly show that the proposed substance exceeds the vB criterion

B(iv): In response to the comment given by the Registrant(s) in relation to the use Arnot-Gobas BCF method (incl. biotransformation rate estimates) instead of the regression based BCF model:

As stated above, the submitted information is not sufficient to evaluate the reliability and the actual relevance of the *in vitro* trout liver S9 study. Therefore, metabolism of the proposed substance in fish cannot be confirmed, and the presented regression based BCF values are considered valid.

			<p>B(v): In response to the comment given by the Registrant(s) in relation to use the BCF value obtained with the lower test concentration, as it is more relevant with respect to the predicted environmental concentrations for the freshwater compartment:</p> <p>The PBT character of any substance is an intrinsic property of the substance and the identification of such PBT or vPvB substances is independent of measured or estimated concentrations in environmental compartments, as stated in the Guidance on information requirements and chemical safety assessment, introduction on chapter R.11.</p> <p>B(vi): In response to the comment given by the Registrant(s) in relation to the use of the test concentration measured in the non-centrifuged water samples to calculate the BCF value from the OECD 305 study, instead of the centrifuged water samples:</p> <p>The eMCSA disagrees. The original study report calculated the BCF values based on the water concentrations that were determined following a centrifugation step. Bioconcentration is defined in OECD TG 305 (version 2012) as: <i>"the increase in concentration of the test substance in or on an organism (or specified tissues thereof) relative to the concentration of test substance in the surrounding medium"</i>. Therefore, it is agreed with the testing laboratory to use the centrifuged water concentrations, as this is the fraction that is bioavailable. The corresponding BCF values are not considered conservative, but realistic.</p> <p>It is worth nothing that even the best-case approach that is suggested by the Registrant(s) and that uses non-centrifuged water samples, would yield a BCF value for the reliable higher test concentration that exceeds the vB criterion of 5000 L/kg.</p> <p>B(annex): The Registrant(s) included specific comments in</p>
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			<p>an annex to the Letter. Points (i), (ii), (iv), (v) and (vi) from this annex correspond to a large extent to the comments presented in the letter. The Registrant(s) are referred to the responses given above.</p> <p>The annex to the letter did contain additional information concerning point (iii), i.e. the <i>in vitro</i> metabolism of the proposed substance in fish liver S9 fractions. A response is given below:</p> <p>The Registrant(s) reported limitedly on the <i>in vitro</i> trout liver S9 study. In fact, the only results that were available for the eMSCA are the four figures presented in the annex to the letter. From these figures, the eMSCA cannot conclude if the data are reliable. For example, from figure 1 and 2 it appears that the heat treated control was tested at the start and end of the test, while the controls with no S9 and with no cofactors were only measured at the end of the test (t=120). The karanal concentration of the heat treated controls also seem to decrease (although limitedly) over time. It is unclear if the clearance rates were corrected for this. Two Karanal peaks were tested and the reported <i>in vitro</i> intrinsic clearance rates differ considerably, i.e. 0.24 and 0.13 mL/h/mg protein for peak 1 and 2, respectively. It should be kept in mind that there are many more isomers. What about their clearance rates? How many replicates were taken along? Furthermore, since raw data is not available we can't check the statistics either. Taken altogether, the reliability of this study cannot be assigned (Ri=4).</p> <p>The Registrant(s) indicated the following concerning the <i>in vitro</i> study : "The corresponding IUCLID dossier will be updated prior to the 24th April 2015 to include the comprehensive overview of the elements presented herein". However, the IUCLID dossier was updated only at April 29th 2015, which is considered too late. In addition, the update contained the same information as the annex to the letter, with the addition that more details were presented on the test conditions and setup.</p>
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			<p>The update did not include the study report, nor did the Registrant(s) present other data than the four graphs that were already included in the annex to the letter. As stated above, the submitted information is not sufficient to evaluate the reliability and the actual relevance of the <i>in vitro</i> trout liver S9 study.</p> <p><u>TOXICITY</u> The objections are noted, but not agreed upon by the eMSCA.</p> <p>T(i): In response to the comment given by the Registrant(s) in relation to the statement that the proposed substance is borderline T. The applicant considers this not only misleading, but also false:</p> <p>The eMSCA considers it relevant to report the available toxicity data for the proposed substance. As indicated in the Annex XV SVHC report, the available data are not sufficient to conclude that the proposed substance is T. The reported NOECs do not meet the T criterion (NOEC < 0.01 mg/L), and there is no harmonised classification for the proposed substance.</p> <p>However, the proposed substance has been self-classified by many notifiers in the ECHA C&L inventory as a STOT RE2 substance having specific target organ toxicity after repeated exposure. Re-assessment of the available repeated dose toxicity study by the eMSCA led to the conclusion that this study would most likely be insufficient to pursue a harmonised classification of the proposed substance as STOT RE 2. Nevertheless, there are signs of chronic toxicity. Therefore, the T assessment for the proposed substance is inconclusive. This has been communicated to the Registrant(s) in 2013. It is therefore concluded that the proposed substance is borderline T.</p> <p>T(annex): The toxicity part of the Annex to the letter did not contain additional arguments. Therefore, the</p>
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			Registrant(s) are referred to the response given above.
4476 2015/04/ 15	National NGO, United Kingdom	General comment: CHEM Trust supports the inclusion of 5-sec-butyl-2-(2,4-dimethylcyclohex-3-en-1-yl)-5-methyl-1,3-dioxane [1], 5-sec-butyl-2-(4,6-dimethylcyclohex-3-en-1-yl)-5-methyl-1,3-dioxane [2] [covering any of the individual isomers of [1] and [2] or any combination thereof] in the REACH candidate list according to article 57 e) due to its vPvB and borderline T properties. The Annex XV dossier presents a well-documented justification using a weight of evidence approach.	The eMSCA would like to thank you for your support.
4479 2015/04/ 15	Norway, Member State	The Norwegian CA supports that 5-sec-butyl-2-(2,4-dimethylcyclohex-3-en-1-yl)-5-methyl-1,3-dioxane [1], 5-sec-butyl-2-(4,6-dimethylcyclohex-3-en-1-yl)-5-methyl-1,3-dioxane [2] [covering any of the individual isomers of [1] and [2] or any combination thereof] should be identified as a substance of very high concern and should be included in the Candidate List.	The eMSCA would like to thank the Norwegian CA for their support.
4480 2015/04/ 16	International Flavors & Fragrances, Company, Netherlands	IFF questions the need for a vPvB/PBT assessment on AURAWOOD. This substance has been registered for a volume that is 1-10 tons. ECHA has furthermore decided on an IFF inquiry that AURAWOOD is dissimilar to Karanal (ECHA letter 9th December, 2012, GB349025-60). IFF notes that a PBT assessment is only prepared at > 10 tons in accordance with Article 14 (3) when also a CSR is needed and recommending risk reduction measures when needed (heading of Article 14). This means that at < 10 tons classification and labelling, which is needed for all marketed substances will present risk reduction measures for substances of concern. This has been further acknowledged in the CARACAL meeting (Caracal, 2015 and Doc CA/16/2015, section 2.1). Article 58(2) also states that restrictions should be in proportion to risk. Although Article 59 presents that an Annex XV report can be limited to an entry in Annex 1, its section 0.1 presents again the need to take the risks into account. Also in the ECHA guidance on R11, in the introduction, it is highlighted that the PBT assessment is carried out when the volumes are > 10 tons in a CSA.	In response to the comment given by IFF in relation to the need for a vPvB/PBT assessment: The eMSCA agrees that a registrant in the tonnage band < 10 tpa does not have an obligation to carry out a chemical safety assessment and therefore neither a PBT assessment. We would like to note that the referred communication on the dissimilarity of two substances is only related to the identity and sameness assessment of the registered substances and not related to further registration obligations. It should be noted that dissimilarity of two substances does not exclude the possibility that substances would belong to such substance group where read across is justified. If a substance is identified in the Candidate List as a PBT/vPvB, all actors in the supply chain (regardless of whether they have registered), have to comply with Title IV of REACH by communicating about the PBT/vPvB properties of the substance in the supply chain.

	<p>Therefore IFF is of the opinion that at this tonnage level classification and labelling for this substance (H410) presents sufficient risk reduction measures and putting the substance on the candidate list for authorization is disproportional to the risk anticipated. In addition, substances with these characteristics on persistency and toxicity will be restricted by the PEC /PNEC ratios in the aquatic and terrestrial environment when exceeding the 10 tons level.</p> <p>In view of the above IFF considers the process unclear and unjustified.</p> <p>IFF disagrees with the scientific conclusions of the MSCA leading to this Annex XV report</p> <p>IFF does not agree with conclusions on the vPvB properties of Karanal in the MSCA Annex XV report.</p> <p>The vPvB/PBT assessment is considered a hazard assessment (ECHA guidance C and R.11) and this means that the result of the OECD TG guidelines as such are leading for the vPvB assessment:</p> <ul style="list-style-type: none"> - For the vP assessment: IFF considers the temperature recalculation for persistency in the Annex XV dossier in conflict with the Annex XIII requirements and the vP being a hazard type assessment. - For the vB assessment: IFF considers the BCF of 1898 the key value and a worst case when applying the WoE approach; <p>This BCF value has been derived with a 0.003 mg/l concentration being 1/100th of the LC50 (0.3 mg/l) in accordance with the OECD TG 305 guideline. The 0.03 mg/l is therefore considered too high, because it may present effects which are not necessarily recorded e.g. metabolic overloading. In addition, the result indicates that the 0.03 mg/l concentration is overloading the metabolic capacity of the fish exposed and therefore presents unrealistic exposure concentrations.</p> <p>vPvB/PBT assessment</p> <p>The PBT assessment is considered mainly a hazard assessment (Guidance C pathfinder and ECHA R.11,</p>	<p>The SVHC-identification is a process identifying certain properties of the substance. The tonnage and other considerations related to the potential risk are generally addressed in the steps after the SVHC-identification.</p> <p>In response to the comment given by IFF in relation to the vPvB/PBT assessment</p> <p>The objections raised by IFF are noted, but not agreed upon by the eMSCA as it is clear from the followed weight-of-evidence approach that the proposed substance meets the vPvB criteria. Responses to the specific objections are given below.</p> <p>Within the EU, REACH (Regulation (EC) No 1907/2006) is the legal framework for the assessment of industrial chemicals, and OECD test guidelines are used in support of this framework.</p> <p>Regarding the objection raised by IFF concerning the temperature at which persistence should be assessed, please consider the responses to comment #4474 (see in particular paragraphs P(i) and P(ii) of the response).</p> <p>Please consider the responses to comment #4474 concerning the assessment of bioaccumulation.</p> <p>The specific comments raised by IFF:</p> <ol style="list-style-type: none"> i. The BCF value obtained at the higher test concentration is considered reliable without restrictions as the test concentration was below the chronic effect level. For details, see response to comment B(i) of comment #4474. ii. The original study report reported BCF values based on centrifuged water samples, as this is the bioavailable fraction. This is not considered conservative, but realistic. For details, see response to comment B(vi) of comment #4474. iii. The BCF value obtained at the lower test concentration was assessed as less reliable due to
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	<p>pathfinder) which means that the result of the OECD TG guidelines as such are leading for the PBT assessment.</p> <p>vP/P - In accordance with Annex XIII (1.1) the assessment of the persistency in the environment shall be based on available half-lives collected under adequate conditions. In the OECD TG 309, the half-life of Karanal resulted in 56-days as agreed by the MSCA. This half-life is below the cut off criteria for vP. The test has been performed at 20°C in accordance with the criteria in this guideline. In the MSCA Annex XV report the half- life has been recalculated to 12°C to express 'European conditions' which is a region based assessment and thus risk based rather than a hazard based argument. IFF therefore views the 20°C result of the OECD TG 309 as leading for the vP/P assessment.</p> <p>IFF concludes that the P criterion is met but not the vP criterion based on the REACH Annex XIII criteria.</p> <p>vB/B – In accordance with Annex XIII the assessment of the vB criterion is fulfilled when the BCF is >5000. In addition, in the PBT guidance document (R11) it is explicitly mentioned that a weight of evidence (WoE) should be used, which is outlined below:</p> <p>The OECD TG 305 (2006) that has been performed has several results. The MSCA presents two BCF values. According to the MSCA one is a BCF value of 1892 and one being 9893 based on measured concentration derived from centrifuged analysed data but leaving out the non-centrifuged analysed water consideration without justification (personal communication with Lead Registrant for Karanal).</p> <p>The following WoE is presented in which the BCF of 1892 is considered a worst case result:</p> <ol style="list-style-type: none"> i. The low concentration used in this test (0.003 mg/l) is in accordance with the OECD TG 305 being 1/100 below the LC50 and 1/10 of the NOEC; the concentration of 0.03 mg/l being at the NOEC is considered to be out of the prescribed range and therefore unreliable. ii. The MSCA derived BCF values which are based on water concentrations which are derived from centrifuged samples while also analysis were available from non-centrifuged samples. No justification is presented why the centrifuged samples were used. The centrifuged samples showed circa 	<p>fluctuating water concentrations. Concerning, metabolism of the proposed substance, this could not be verified by the eMSCA as insufficient information was submitted on the <i>in vitro</i> study. For details, see response to comments B(ii) and B(iii) part 1 of comment #4474.</p> <ol style="list-style-type: none"> iv. See above response to (ii). v. As stated above metabolism of the proposed substance could not be verified. Nevertheless, for completeness the Annex XV SVHC report has been amended depicting estimated BCF values calculated using the regression based model and the Arnot-Gobas method and using the full range of estimated log K_{ow} values. For details, see response to comment on B(iii) part 2 and B(iv) of comment #4474 . <p>Please consider the responses to comment #4474 regarding your comment on the toxicity of the proposed substance.</p>
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	<p>40% of the nominal values while the non-centrifuged ones presented circa 60% of the nominal values. This means that the derived BCF values are considered conservative. In view of the substance concentrations being clearly below the water solubility there is no need to take preference of the centrifuged water concentration samples.</p> <p>iii. The BCF value derived at a concentration of 0.003 mg/l is considered reliable because at this concentration the fish are capable of metabolising Karanal, while at higher dosing the metabolic pathway is overloaded as indicated by the study author (personal communication with the lead registrant for Karanal) further confirming that the dose of 0.03 mg/l is out of the domain of the method.</p> <p>iv. Despite the 0.003 mg/l concentration of the substance showing somewhat more variability compared to the 0.03 mg/l, the fish concentrations were limitedly affected by this variability and therefore this variability is not considered to have influenced the BCF results.</p> <p>v. The BCF of the 0.003 mg/l (1892) supports the predicted metabolism of the substance as is presented in the BCFWIN calculation and Arnot and Gobas of upper trophic levels. IFF concludes the substance is not B and not vB according to the Annex XIII criteria.</p> <p>Furthermore, IFF disagrees with the substance being borderline T as presented in the conclusion of the summary and in section 6.2.1.3 where it is presented as inconclusive. The STOT RE is not applicable (as presented by the MSCA) and the lowest NOEC is 0.03 mg/l being clearly above the 0.01 mg/l threshold for aquatic toxicity.</p> <p>Therefore IFF is of the opinion that at this tonnage level classification and labelling for this substance (H410) presents sufficient risk reduction measures and presenting the substance on the candidate list for potential authorization is disproportional to the hazard and the risk anticipated. In addition, a substance with these characteristics on persistency and toxicity will be restricted by the PEC /PNEC ratios in the aquatic and terrestrial environment when exceeding the 10 tons level.</p> <p>IFF concludes the substance is not T.</p> <p>IFF disagrees with the substance being borderline T as presented in the conclusion of the summary and in section</p>	
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		6.2.1.3 where it is presented as inconclusive. The STOT RE is not applicable (personal communication with the Lead Registrant for Karanal and presented by the MSCA in this Annex XV report) and the lowest NOEC is 0.03 mg/l being clearly above the 0.01 mg/l threshold for aquatic toxicity.	
		Attachment: 4480_Aurawood_svhc_AnnexXV_IFF_Response.pdf	
4486 2015/04/ 16	ChemSec, International NGO, Sweden	ChemSec supports the identification of the substance as a Substance of Very High Concern, according to the evidence laid out in the dossier, and the placement on the REACH candidate list.	The eMSCA would like to thank ChemSec for their support.

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	Response
4474 2015/04/ 15	Company, Switzerland	Please see attached document Attachment: 4474_Letter_of_Response_15_April_2015_FINAL.docx	See response to comment #4474 in PART I, Section "Specific comments on the justification".
4480 2015/04/ 16	International Flavors & Fragrances, Company, Netherlands	- Attachment: 4480_Aurawood_svhc_AnnexXV_IFF_Response.pdf	Please consider the responses to comment #4474 in PART I, Section "Specific comments on the justification".