EUROPEAN CHEMICALS AGENCY

Helsinki, 1 August 2017

Addressee: [redacted]

Decision number: CCH-D-2114368187-40-01/F
Substance name: 3,7-DIMETHYLOCTAN-3-OL
EC number: 201-133-9
CAS number: 78-69-3
Registration number: [redacted]
Submission number: [redacted]
Submission date: 09.03.2016
Registered tonnage band: 1000+T

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA requests you to submit information on

1. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) in rats with the registered substance;**

2. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2., column 2; test method: EU B.31./OECD TG 414) in a first species (rat or rabbit), oral route with the registered substance;**

3. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a second species (rabbit or rat), oral route with the registered substance;**

4. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: EU B.56./OECD TG 443) in rats, oral route with the registered substance specified as follows:**
   - **Ten weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce some toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity); and**
   - **Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation.**

5. **Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: Daphnia magna reproduction test, EU C.20./OECD TG 211) with the registered substance;**

6. **Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.; test method: Fish, early-life stage (FELS) toxicity test, OECD TG 210) with the registered substance; and**

7. **Exposure assessment and risk characterisation (Annex I, Sections 5. and 6.) for environment: generate an exposure assessment for all relevant exposure scenarios and revise the risk characterisation accordingly.**

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI of the REACH Regulation. In order to ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective Annex, and an adequate and reliable documentation.

You are required to submit the requested information in an updated registration dossier by **8 August 2022** except for the information requested under point 1 for a sub-chronic toxicity study (90-day) which shall be submitted in an updated registration dossier by **8 August 2019**. You may only commence the extended one-generation reproductive toxicity study as requested under point 4 after **8 November 2019,** unless an indication to the contrary is communicated to you by ECHA before that date. You shall also update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. Advice and further observations are provided in Appendix 3.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, shall be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under http://echa.europa.eu/regulations/appeals.

Authorised[1] by Kevin Pollard, Head of Unit, Evaluation E1

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Appendix 1: Reasons

TOXICOLOGICAL INFORMATION

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

In the registration, you have adapted the standard information requirements for
- Sub-chronic toxicity study (90-day; Annex IX, Section 8.6.2.);
- Pre-natal developmental toxicity study in a first species (Annex IX, Section 8.7.2.);
- Pre-natal developmental toxicity study in a second species (Annex X, Section 8.7.2.); and
- Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)

by applying a read-across adaptation following REACH Annex XI, Section 1.5.

Grouping of substances and read-across approach

Article 13(1) of the REACH Regulation provides that information on intrinsic properties of substances may be generated by means other than tests. Such other means include the use of information from structurally related substances (grouping of substances and read-across), "provided that the conditions set out in Annex XI are met".

Annex XI, Section 1.5. requires a structural similarity among the substances within a group or category such that relevant properties of a substance within the group can be predicted from the data on reference substance(s) within the group by interpolation. The following analysis presents your justification for the proposed grouping approach and read-across hypothesis, together with ECHA's analysis concerning the justification in both a generic and a property-specific context.

Description of the grouping and read-across approach proposed by the Registrant

You summarise the read-across approach as follows:

"*The structural similarities between the target substance tetrahydrolinalool and the source substances (linalool and dehydrolinalool) and the similarities in their toxicological and physicochemical profiles presented above support the read-across hypothesis. Adequate and reliable scientific information indicates that the source and target substances behave very similar and that data for the source substances reliably predict the behaviour and toxicity of the target substance. This approach is further confirmed by the OECD QSAR toolbox.*

The toxicokinetic profiles of the target and source substances are considered to be similar, therefore systemic toxicity is not affected by potentially different kinetics.

The results of the studies performed with the target substance are consistent with the results obtained from studies on the source substances. Consequently, for endpoints where no experimental data are available for the target substance, data for the read-across substance allow sufficiently valid predictions for the target substance, too."

ECHA understands this as the hypothesis under which you make predictions for the properties listed above.

Support of the grouping and read-across approach

You have provided a read-across justification as a separate attachment in IUCLID section 13.

In summary, you provide the following arguments to support the read-across approach:

Source and target substances are structural similar: *"Target and source substances share structural similarities and functional groups. The alcohols (the target substance tetrahydrolinalool and the source substances linalool and dehydrolinalool) are tertiary, monoterpenic alcohols. The hydroxyl group is positioned at the third atom of the carbon chain. Linalool and dehydrolinalool contain a double bond between the sixth and seventh carbon atom. The only difference between linalool and dehydrolinalool is that linalool possesses another double bond between the first and second carbon atom, whereas in dehydrolinalool these two atoms are connected by a triple bond. Tetrahydrolinalool does not contain double or triple bonds."*

Compounds the organism is exposed to: *"The test organisms are exposed to the compounds themselves as they are not supposed to undergo any reactions before entering the body. The substances are rapidly and completely absorbed after oral or dermal exposure and will be systemically available and metabolised."*

Biological targets of the compounds: *"It is assumed that the source and target substances affect the same biological targets. This assumption is confirmed by the results of the QSAR-toolbox prediction [...]. The repeated dose toxicity studies conducted with dehydrolinalool and linalool confirm that the same target organs are affected: in the higher dose groups lesions were observed in the male kidneys and in the female livers after treatment with linalool. Like linalool, dehydrolinalool led to increased liver weights in male and female animals and to increased kidney weights in the males. The kinetic profiles for the substances are considered to be similar and therefore the biological targets are exposed to a comparable rate and the strength of the effects is similar."*

Toxicokinetics: "The toxicokinetic profiles of the target and source substances are considered to be similar, therefore systemic toxicity is not affected by potentially different kinetics."

QSAR predictions: You have provided predictions based on structural alerts from the OECD QSAR Toolbox.

Data matrix: You have provided a data matrix showing that the source and target substances have comparable physiochemical properties. Furthermore, you have provided a data matrix showing that the source and target substances have similar results with regard to acute toxicity, eye and skin irritation and genetic toxicity. The data matrix also contains the studies which are listed below for repeated dose toxicity, pre-natal developmenal toxicity and toxicity to reproduction.

In the technical dossier you have provided the following endpoint study records:

Repeated dose toxicity

i. Key study; Read-across from supporting substance (structural analogue or surrogate); Reliability 1 (reliable without restrictions); GLP; 1990; similar to OECD TG 407 (Deviations: not specified); conducted in rats via the oral route using linalool; Doses tested equivalent to 0, 117, 292, and 729 mg/kg/day; the study established a NOAEL of 117 mg/kg/day for systemic toxicity based on stomach and liver effects at the mid- and high-doses;

ii. Supporting study; Read-across from supporting substance (structural analogue or surrogate); Reliability 2 (reliable with restrictions); GLP; 1992; according to OECD TG 407 (Deviations: Food consumption not measured); conducted in rats via the oral route using dehydrolinalool; Doses tested equivalent to 0, 200, 400, 900 mg/kg/day; the study established a NOAEL of 200 mg/kg/day for systemic toxicity based on hypersalivation and sedation at 750 mg/kg/day;

iii. Key study; Read-across from supporting substance (structural analogue or surrogate); Reliability 2 (reliable with restrictions); GLP; 1980; similar to OECD TG 411 (Deviations: not specified); conducted in rats via the dermal route using linalool; Doses tested equivalent to 0, 250, 1000, and 4000 mg/kg/day; this dermal sub-chronic toxicity study establishes a NOAEL at 250 mg/kg/day based on local effects;

Pre-natal developmental toxicity

iv. Key study; Read-across from supporting substance (structural analogue or surrogate); Reliability 1 (reliable without restrictions); GLP; 2006; according to OECD TG 414; conducted in rats via the oral gavage using linalool; Doses tested equivalent to 0, 250, 500, and 1000 mg/kg/day; the study establish maternal toxicity at 500 mg/kg/day based on "*nonsignificant reductions in body weight gain*" at 1000 mg/kg/day. In this study no teratogenicity was observed and a NOAEL was established at 1000 mg/kg/day;

Toxicity to reproduction

v. Key study; Read-across from supporting substance (structural analogue or surrogate); Reliability 1 (reliable without restrictions); GLP; 1989; similar to OECD TG 421 (Deviations: Females only); conducted in rats via the oral gavage using linalool; Doses tested equivalent to 0, 183, 365, and 829 mg/kg/day; the study establish systemic maternal toxicity at 367 mg/kg/day based on salivation and reduced body weight gain. With regard to teratogenicity and foetal toxicity, NOAELs is established at 365 mg/kg/day based on reduced delivered litter sizes (indicating in utero deaths) and significant incidences of pup mortality in the first four days postpartum;

vi. Key study; Read-across from supporting substance (structural analogue or surrogate); Reliability 2 (reliable without restrictions); GLP; 1992; according to OECD TG 421; conducted in rats via the oral gavage using dehydrolinalool; Doses tested equivalent to 0, 50, 200, and 750 mg/kg/day; the study reports a NOAEL for maternal toxicity at 200 mg/kg/day based on hypersalivation and sedation/ataxia. With regard to teratogenicity and foetotoxicity, the NOAELs for the offspring are also established at 200 mg/kg/day based on reduced pup live birth index and pup viability index; and an increased incidence of abnormalities in the urinary system and of renal and testicular development in the offspring.

ECHA analysis of the grouping and read-across approach in light of the requirements of Annex XI, Section 1.5.

With regard to the proposed predictions ECHA has the following observations:

(i) Explanation on why and how the structural similarities allow predictions

In order to meet the provisions in Annex XI, Section 1.5. to predict human health effects from data for a reference substance within the group by interpolation to other substances in the group, ECHA considers that structural similarity alone is not sufficient. It has to be justified why such prediction is possible in view of the identified structural differences and the provided evidence has to support such explanation. In particular, the structural similarities must be linked to a scientific explanation of how and why a prediction is possible.

ECHA notes the target and source substances share a common structural feature, *i.e.* all substances are tertiary alcohols. However, the target substance and the proposed source substances also display significant structural differences *i.e.* the target substance is saturated, whereas the proposed source substances are unsaturated with either two double-bonds or a double- and a triple- bond as additional functional groups. In addition, all substances have more than one isomer. You claim that the structural differences do not have any toxicological impact. There is no mechanistic explanation offered why the parent compounds with different functional groups (*i.e.* carbon chain with triple-bond *vs.* double-bonds *vs.* saturated carbon chain) and different isomers are expected to have the same toxicity profile.

ECHA concludes that you have not addressed the obvious structural differences between the source substances and the target substance and did not sufficiently explain why those differences would not lead to differences in the toxicity profile of target and source substances. Your approach is not considered as valid to establish a scientific credible link between the structural similarity and the prediction.

(ii) Reliability and adequacy of the source studies

Annex XI, Section 1.5 provides with regard to the reliability and adequacy of the source studies that in all cases the results of the read-across should:

- *be adequate for the purpose of classification and labelling and/or risk assessment,*
- *have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3),*
- *cover an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3) if exposure duration is a relevant parameter, and*
- *adequate and reliable documentation of the applied method shall be provided.*

With regard to the source studies ECHA notes the following:

Sub-chronic toxicity (90 days) study

For the standard information requirement "sub-chronic toxicity study" (90-days; Annex IX, Section 8.6.2.) you have provided study records for "Repeated dose 28-day oral toxicity studies" conducted with both of the proposed source substances (see supporting infromation above, points i and ii). However, these studies provide information required by Annex VIII, section 8.6.1., as it is also stated in your justification document. They do not provide the information required by Annex IX, Section 8.6.2., because the exposure duration is less than 90 days and the number of animals per dose group is significantly lower thus the sensitivity to detect adverse effects is lower than that of a sub-chronic toxicity study (90 days). Therefore, these source studies are not regarded as adequate to cover the information requirement Annex IX, Section 8.6.2.

In addition, you have provided a sub-chronic toxicity study (90 days; see supporting infromation above, point iii) conducted in 1980 with dermal application of the source substance linalool. You claim that this study was conducted according to GLP and with a guideline similar to OECD 411. However, ECHA notes that the study was conducted before introduction of GLP. Concequently, the study can not have been conducted in a certified laboratory as required by GLP. With regard to the OECD 411 test guideline which was adopted in 1981, you have not explained which deviations the study conducted in 1980 shows in comparison to the current OECD 411 guideline and how these deviations may impact the study results.
Furthermore, with regard to the provided study ECHA observes that due to poor reporting ECHA is unable to determine how the provided study compares to the current OECD 411 test guideline; therefore ECHA can not veryfy its relevance.
In line with the information provided on toxicokinetics of linalool the substance has a high systemic availability when administered orally. For topical applications you state in the justification document (section 4.1) that there is limited absorption. Although the poor reporting of the study results does not allow clear conclusions with regard to toxicity via the dermal route and the role of skin irritation for this route, ECHA considers the dermal sub-cronic toxicity study as not informative with regard to assessing potential for systemic toxicity.

In conclusion, due to the poor reporting, the uncertain coverage of parameters of a modern guideline study and the stated limited systemic availability for topical applications this source study is not regarded as adequate to cover the information requirement Annex IX, Section 8.6.2. Therefore, ECHA considers the sub-cronic toxicity study with dermal application as not informative with regard to systemic toxicity. In conclusion, due to the poor reporting, the doubtful coverage of all parameters of a modern guideline study and the limited systemic availability this source study is not regarded as adequate to cover the information requirement Annex IX, Section 8.6.2.

Pre-natal developmental toxicity studies in first and second species

For the standard information reqirement "pre-natal developmental toxicity study in a first species" (Annex IX, Section 8.7.2.) you have provided a valid source study according to OECD TG 414 conducted with linalool, one of the proposed source substances (see supporting infromation above, point iv).

For the standard information requirement "pre-natal developmental toxicity study" in a second species (Annex X, Section 8.7.2.) you have provided no valid source study or adaptation.

Extended one-generation reproductive toxicity study

For the standard information requirement "extended one-generation reproductive toxicity study" (Annex X, Section 8.7.3.) you have provided study records for "reproductive toxicity screening tests" (test method: OECD TG 421) conducted with both of the proposed source substances (see supporting infromation above, point v and vi).

None of the source studies are equivalent to the extended one-generation reproductive toxicity study (test method: OECD TG 443) which is required to meet the standard information requirements of Annex X, Section 8.7.3.; because they do not cover key elements of an extended one-generation reproductive toxicity study. In the appendix 1, Section 4, a detailed assessment is provided.

Conclusion with regard to the source studies provided

ECHA concludes that the source studies discussed above do not provide the information required by Annex IX, Section 8.6.2.; Annex X, Section 8.7.2.; and Annex X, Section 8.7.3, respectively. Concequently, the proposed adaptation does not meet the requirements of Annex XI, Section 1.5.

(iii) Support of a similar or regular pattern as a result of structural similarity

Annex XI, Section 1.5. provides that "*substances whose physicochemical, toxicological and eco-toxicological properties are likely to be similar or follow a regular pattern as result of structural similarity may be considered as a group or 'category' of substances."* One prerequisite for a prediction based on read-across therefore is that the substances involved are structural similar and are likely to have similar properties. One important aspect in this regard is the analysis of the data matrix to compare the properties of source and target substances and to establish whether indeed they are similar or follow a regular pattern.

ECHA observations:

You argue that the source and target substances have similar physico-chemical properties. Indeed, the substances have similar properties. However, physico-chemical similarity is a prerequisite for applying the grouping and read-across approach, but ECHA does not accept in general or in this specific case that physico-chemical similarity *per se* is sufficient to enable the prediction of properties of a substance.

You argue that the source and target substances have comparable results with regard to acute toxicity, skin and eye irritation and genetic toxicity. ECHA notes the substances have similar properties with regard to these properties. Similar results with regard to acute toxicity, skin and eye irritation and genetic toxicity indicate for these properties that the proposed source and target substances are likely to be similar or follow a regular pattern. However, a similar conclusion is not possible for the properties repeated dose toxicity, pre-natal developmental toxicity and reproductive toxicity.

No information is available with regard to these properties on the target substance. As a result ECHA cannot verify a similar pattern of toxicity for source and target substances based on a side-by-side comparison of the effects. ECHA concludes that the information provided does not support the claim that source and target substances are likely to be similar or follow a regular pattern with regard to the properties under consideration.

You assume that source and target substances affect the same biological targets. If this was the case one would expect that the same toxicological effects are observed for all three substances. ECHA notes that the repeated dose toxicity profiles for the source substances appear to differ. Dehydrolinalool causes hypersalivation and sedation/ataxia. In contrast, linalool causes stomach and liver effects. Both source substances also cause kidney effects in male rats. These kidney effects are claimed to be due to alpha-2u-globulin nephropathy; however, no immunohistochemical confirmation was performed in any of the studies. Therefore it is unclear whether indeed alpha-2u-globulin induced nephropathy is the mechanism repsonsible for the kidney effects observed in the studies with the source substances.

In addition, the substances appear to differ with regard to developmental and reproductive toxicity. Dehydrolinalool causes abnormalities in the urinary system and of renal and testicular development in the offspring in the screening test for reproductive toxicity. In contrast, no teratogenicity was observed in the pre-natal developmental toxicity study conducted with linalool.

You argue that the OECD QSAR toolbox confirm the read-across approach. ECHA acknowledges that you report similar results from the endpoint profiler. However, such results cover a limited number of all possible interactions of chemical structures with biological targets investigated in a repeated dose toxicity study, pre-natal developmental toxicity study or a study on reproductive toxicity. Therefore, the results cannot be used to verify a prediction made for the properties under consideration. Moreover, as pointed out above, the source substances also appear to differ with regard to repeated dose toxixity and pre-natal developmental toxicity, which is in apparent contrast to the results of the profiling tool.

ECHA concludes that the presented evidence does not support a similar or regular pattern of toxicity as a result of structural similarity. Therefore it cannot be verified that the proposed group/analogue substance(s) can be used to predict properties of the registered substance.

(iv) Toxicokinetics

One important aspect in establishing that substances have similar effects or follow a regular pattern is the comparison of absorption, distribution, metabolism and elimination of source and target substances. This allows assessing the qualitative and quantitative internal systemic exposure of the test organism when exposed to source and target substances.

You claim that "*The substances are rapidly and completely absorbed after oral or dermal exposure and will be systemically available and metabolised.*" Furthermore you conclude that "*metabolism products/intermediate compounds are not considered to have any toxicological impact*" and "*no reaction products with potential impact on the toxicity or behaviour under physiological conditions are expected and need to to be addressed.*"

To support these claims there is toxicokinetic information presented for the source substance linalool showing that the substance is metabolised and excreted via urine (60% of administered radioactivity), faeces (15% of administered radioactivity), expired air (23% of administered radioactivity). Enterohepatic circulation is mentioned to occur. ECHA notes that there is no toxicokinetic information available for the target substance and the proposed source substance dehydrolinalool. Furthermore, there are some general expectations provided how the substances are metabolised, but no data are presented on the type of metabolites or on their kinetics.

ECHA concludes that it is not clear to which substances the test organisms are exposed when the parent substances are adminstered. Metabolites may be formed at different positions of the carbon chains with different formation kinetics. The formation of reactive intermediate metabolites such as aldehydes cannot be excluded. There is no information provided supporting the claim that these differences do not have an impact on the toxicities of the substances. In particular the comparison of the toxic effects observed for the individual substances (see section (iii), above) appear to indicate that the effects differ between the two source substances whereas it is not possible to verify this for the target substance due to a lack of information on repeated dose toxicity, pre-natal developmental toxicity or reproductive toxicity.

ECHA concludes that you have not explained which metabolites are formed from each of the substances nor how these metabolites influence the toxicity profiles of the substances. Consequently, it is not possible to conclude whether there are differences in the toxicokinetic behaviour, in particular in metabolic fate / (bio)transformation of the substances and how these differences may influence the toxicity profile of the target and source substances. Therefore, it is not possible to verify the substances which are likely to govern the toxicity profiles of source and target substances. In the absence of such information there is not an adequate basis for predicting the properties of the registered substance from the data obtained with the source substances.

In your comments to the draft decision, you have largely re-iterated the arguments presented in your dossier to support your read-across approach, *i.e.* structural similarity between the source substances and the target substance; similarities in their toxicological and physico-chemical properties; and refer to their read-across hypothesis according to which the source and the target substances have the same type of toxicological effects based on common underlying mechanisms. According to this information, you consider that adequate and reliable scientific information has been provided to reliably predict the toxicological properties of the target substance on the basis of this hypothesis.
Further, in response to ECHA's statement in the draft decision indicating that the obvious structural differences between the source and the target substances have not been addressed and that no explanation was provided on why these structural differences would not lead to differences in the toxicity profiles of these substances, you have indicated in your comments that "*Assuming that substances with unsaturated C=C or C≡C bonds show a more pronounced toxicity based on their higher reactivity, the source substances linalool and dehydrolinalool represent a worst case approach*".

As indicated above, ECHA points out that the arguments presented in your comments which were also included in the dossier constituted the basis for ECHA's assessment. However, the argument of a worst-case approach constitutes a new element in the justification of this read-across approach. Whilst this assumption may theoretically be valid, ECHA stresses that no information on the target substance other than QSAR profiling is currently available for the endpoints under consideration in this decision. No experimental data of comparable nature to that existing for the source substances is available for the target substance. In particular, there is currently no study with repeated dosing on the target substance. Therefore there is no evidence to validate the claim of a more pronounced toxicity of the source substances as a result of the presence of either unsaturated C=C or C≡C bonds in the structures of these substances. Therefore, no definitive conclusion on the comparison of the toxicological properties of source and target substances can be made on the basis of the information currently available. ECHA acknowledges that some of the information on the properties of the registered substance requested in this draft decision may constitute valuable information to establish similarities in the toxicological profiles of the source and target substances and potentially strengthen the read-across approach for the endpoints under consideration in this decision. However, since this information is not yet available, the assumption of a more pronounced toxicity of the source substances is not established. Therefore, ECHA concludes that the read-across approach as currently documented in the registration dossier and in the comments to this draft does not constitute an adequate basis for predicting the toxicological properties of the registered substance.

As indicated above, the testing requested may be adapted according to the specific rules of Annexes VI to X and/or according to the general rules contained in Annex XI of the REACH Regulation. The deadline set in the decision to provide the information allows for sequential testing. It is at your discretion to establish the order for conducting the requested testing, with the exception, in respect of the human health testing, of the sub-chronic toxicity study which is to be conducted first, as it may facilitate an adaptation of a request in the draft decision. However, the requested information whether obtained through new testing or by means of an adaptation must be provided in a dossier update by the deadline set in the decision.

You also indicated in your comments that you consider that the "*read-across approach is suitable to address the study requirements according REACH Annex VIII*". ECHA outlines that the draft decision issued to the Registrant does not challenge the read-across approaches applied to Annex VIII information requirements.

Conclusion on the read-across approach

The adaptation of the standard information requirements for the endpoints: Sub-chronic toxicity study (90-day; Annex IX, Section 8.6.2.); Pre-natal developmental toxicity study in a first species (Annex IX, Section 8.7.2.); Pre-natal developmental toxicity study in a second species (Annex X, Section 8.7.2.); and Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.) in the technical dossier is based on the proposed read-across approach examined above. ECHA does not consider the read-across justification to be a reliable basis to predict the properties of the registered substance for the reasons set out above.

Thus, the adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. Therefore, ECHA rejects all adaptations in the technical dossier that are based on Annex XI, Section 1.5.

1. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.)

A "sub-chronic toxicity study (90 day)" is a standard information requirement as laid down in Annex IX, Section 8.6.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.
You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing study records for a repeated dose 28-day oral toxicity studies (OECD TG 407) with the analogue substances 3,7-dimethyloct-6-en-1-yn-3-ol, CAS No 29171-20-8 (EC No 249-482-6); and 3,7-dimethylocta-1,6-dien-3-ol, CAS No 78-70-6 (EC No 201-134-4). However, as explained above in this Appendix, your adaptation of the information requirement is rejected.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA has evaluated the most appropriate route of administration for the study. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA considers that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 5.0, December 2016) Chapter R.7a, section R.7.5.4.3 - is the most appropriate route of administration. More specifically, the substance is a liquid of low vapour pressure (11 Pa). Uses with professional and consumer spray application are reported in the chemical safety report. However, the reported concentrations are low (<[redacted]%). Hence, the test shall be performed by the oral route using the test method EU B.26./OECD TG 408.

According to the test method EU B.26./OECD TG 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

ECHA understands from your comments to the draft decision requesting an extension of the timeframe set to provide the results from this study that you agree to conduct the requested study. Your comments relating to the extension of the deadline to provide this information have been addressed in the indicated deadline above and under section "*Deadline to submit the requested information in this decision*" below.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Repeated dose 90-day oral toxicity study (test method: EU B.26./OECD TG 408) in rats.

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species

A "pre-natal developmental toxicity study" (test method EU B.31./OECD TG 414) for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study recordfor a Prenatal developmental toxicity study in rats (OECD TG 414) with the analogue substance 3,7-dimethylocta-1,6-dien-3-ol, CAS No 78-70-6 (EC No 201-134-4). However, as explained above in this Appendix, your adaptation of the information requirement is rejected.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

According to the test method EU B.31./OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default assumption ECHA considers testing should be performed with rats or rabbits as a first species.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 5.0, December 2016) R.7a, chapter R.7.6.4.2.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

In your comments to the draft decision, you have reported that you consider that no additional information on the pre-natal developmental toxicity of the registered substance in the rat is needed as a pre-natal developmental toxicity study in the rabbit and an extended one-generation reproductive toxicity study will be conducted with this substance as a result of this decision. You also referred to available information from a pre-natal developmental toxicity study conducted in rats with the analogue substance linalool. You have formulated a read-across hypothesis according to which the source and the target substances have the same type of toxicological effects based on common underlying mechanisms. In order to support this hypothesis, you have referred to the structural similarities between the source and the target substance and the similarities in their toxicological and physicochemical profiles. Furthermore, you indicated in your comments that a decision on whether or not a pre-natal developmental toxicity study should be conducted in the rat with the registered substance should be delayed and made only so that the results from the other experimental studies requested in the decision are available, in order to ensure that testing on vertebrate animals is undertaken only as a last resort.

For the reasons presented above in Appendix 1 section Grouping of substances and read-across approach, ECHA considers that the read-across approach between the source substance linalool and the target substance, as currently documented in the registration dossier and in your comments to this draft decision, does not constitute an adequate basis for predicting the properties of the registered substance from the data under consideration.

As already indicated, the testing requested may be adapted according to the specific rules of Annexes VI to X and/or according to the general rules contained in Annex XI of the REACH Regulation. The deadline set in the decision to provide the information allows for sequential testing. In this context, ECHA stresses that the draft decision indicates that in order to comply with the information requirement of Annex IX, 8.7.2 for a pre-natal developmental toxicity species, testing should be conducted with the registered substance either in the rat or in the rabbit. It is at your discretion to decide on which species is the most appropriate for conducting this first pre-natal developmental toxicity study with the registered substance and to assess whether a particular sequence for conducting the requested testing, with the exception in respect of the human health testing, of the sub-chronic toxicity study which is to be conducted first, as it may facilitate an adaptation of other request(s) in the draft decision. However, the requested information whether obtained through new testing or by means of an adaptation must be provided in a dossier update by the deadline set in the decision.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a first species (rat or rabbit) by the oral route.

3. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.) in a second species

Pre-natal developmental toxicity studies (test method EU B.31./OECD TG 414) on two species are part of the standard information requirements for a substance registered for 1000 tonnes or more per year (Annex IX, Section 8.7.2., column 1, Annex X, Section 8.7.2., column 1, and sentence 2 of introductory paragraph 2 of Annex X of the REACH Regulation).

You have sought to adapt the information requirement for the first species according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for a Prenatal developmental toxicity study in rats (OECD TG 414) with the analogue substance 3,7-dimethylocta-1,6-dien-3-ol, CAS No 78-70-6 (EC No 201-134-4). However, as explained above in this Appendix, your adaptation of the information requirement is rejected.

There is no information provided for a pre-natal developmental toxicity study in a second species; and the technical dossier does not contain an adaptation in accordance with column 2 of Annex X, Section 8.7.2. or with the general rules of Annex XI for this standard information requirement.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

According to the test method EU B.31./OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default consideration, ECHA considers testing should be performed with rabbits or rats as a second species, depending on the species tested in the first pre-natal developmental toxicity study.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 5.0, December 2016) R.7a, chapter R.7.6.4.2.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

In your comments to the draft decision you agreed to conduct the requested study, by stating "*The Registrants agree to perform a Pre-natal developmental toxicity study (test method: EUB.31./OECD TG 414) in a second species (rabbit), oral route with the registered substance*".

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a second species (rabbit or rat) by the oral route.

Notes for your consideration

You are reminded that before performing a pre-natal developmental toxicity study in a second species you must consider the specific adaptation possibilities of Annex X, Section 8.7., column 2 and general adaptation possibilities of Annex XI. If the results of the test in the first species enable such adaptation, testing in the second species should be omitted and the registration dossier should be updated containing the corresponding adaptation statement.

4. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)

The basic test design of an extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443 with Cohorts 1A and 1B, without extension of Cohort 1B to include a F2 generation, and without Cohorts 2A, 2B and 3) is a standard information requirement as laid down in column 1 of 8.7.3., Annex X. If the conditions described in column 2 of Annex X are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. Further detailed guidance on study design and triggers is provided in the ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 5.0, December 2016).

Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation. However, as explained above in this Appendix, your adaptation of the information requirement is rejected.

In addition to your adaptation according to Annex XI Section 1.5, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex XI, Section 1.2., weight of evidence. Hence, ECHA has evaluated your adaptation also with respect to this adaptation, although the read-across approach for the source studies is rejected.

a) The information provided

You have provided the following statement "*No reproductive toxicity study is available for tetrahydrolinalool. However, several repeated dose toxicity studies (according to OECD 407, GLP) and reproductive screening studies (according to OECD 421, GLP) on structurally related test substances; i.e linalool nad dehydrolinalool, provide sufficient evidence for the absence of adverse effects on fertility for this substance class. Therefore, further testing of tetrahydrolinalool in a 2-generation study is not considered).*"

To support your weight of evidence adaptation you have provided repeated dose toxicity studies and *reproductive screening studies* (conducted with proposed source substance; see supporting above, points i, ii, v and vi).

b) ECHA's evaluation and conclusion of the provided weight of evidence adaptation

Criteria applied

An adaptation pursuant to Annex XI, Section 1.2. requires sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous (hazardous) property with respect to the information requirement in question.

Your adaptation based on Annex XI, Section 1.2. needs to address the properties of the registered substance by covering the relevant elements investigated in an extended one-generation reproductive toxicity study (EU B.56./OECD TG 443) as requested in this decision. This study type provides relevant information on two aspects, namely on sexual function and fertility in parental (P) and filial (F1) generations (further referred to as "sexual function and fertility") and on developmental toxicity as may be observed peri- and postnatally in the F1 generation (further referred to as "post-natal developmental toxicity").

More explicitly, the relevant elements for sexual function and fertility are, in particular, functional fertility in the parental generation after 10 weeks pre-mating exposure to cover the spermatogenesis and folliculogenesis before mating, sperm parameter analysis, oestrus cyclicity and histopathological examinations of reproductive organs in both P and F1 generations, and ability to support intrauterine and postnatal development of offspring until weaning.

Furthermore, the relevant elements for post-natal developmental toxicity are, in particular, peri- and post-natal investigations of the F1 generation up to adulthood (such as growth, survival/mortality, external malformations, sexual maturation and certain investigations related to hormonal modes of action like anogenital distance, nipple retention, and thyroid hormone measurements).

Sexual function and fertility

With respect to the aspect of sexual function and fertility of P and F1 generations, you have provided information on histopathological changes in major reproductive organs (OECD TG 421 screening study, conducted with proposed source substances). You have also provided information on male and female reproductive performance such as gonadal function, mating behaviour, conception, development of the conceptus and parturition (OECD TG 421 screening study conducted with proposed source substances). However, ECHA notes that the statistical power of OECD TG 421 study is lower than that of the extended one-generation reproductive toxicity study, and certain investigations are not included, such as functional fertility after 10 weeks premating exposure to cover spermatogenesis and folliculogenesis before mating, histopathology of the reproductive organs in F1 animals in adulthood, sexual maturation, oestrous cycle measurements in F1 animals, and investigations related to hormonal modes of action.
Furthermore, you did not provide information on sperm parameters in P and F1 generations. You claim that the available information from the repeated dose toxicity studies in the rat with the proposed source substances provide sufficient evidence for the absence of adverse effects on fertility after repeated exposure to the registered substance. However, the studies provided only investigate adverse effects on reproductive tissues under the conditions of the provided repeated dose toxicity studies. Functional fertility in the parental generation after 10 weeks pre-mating exposure to cover the spermatogenesis and folliculogenesis before mating, sperm parameter analysis, oestrus cyclicity and histopathological examinations of reproductive organs in both P and F1 generations, and the ability to support intrauterine and postnatal development of offspring until weaning are not investigated.

Thus, the information you provided does not support your conclusion that the substance does not have a dangerous property with respect to sexual function and fertility.

Post-natal developmental toxicity

Your adaptation justification does not address the post-natal develop-mental toxicity. The provided information does also not cover the key elements which need to be investigated in this regard. The OECD TG 421 screening study investigates developmental toxicity only until postnatal day 4. The studies according to OECD TG 414 (conducted with a proposed source substance) in the rat provide information only on pre-natal developmental toxicity.

These data do not cover peri-and postnatal developmental toxicity of the registered substance. Thus, the information you provided does not support the conclusion that the substance does not have a hazardous property with respect to postnatal developmental toxicity.

Conclusion

Hence, from the information you provided to support your adaptation when considered individually or together, it cannot be assumed or concluded that the substance does not have a particular dangerous (hazardous) property with respect to the information requirement for Annex X, Section 8.7.3.

Therefore, the general rules for adaptation laid down in Annex XI, Section 1.2 of the REACH Regulation are not met and your adaptation of the information requirement is rejected.

Hence, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently, there is an information gap and it is necessary to provide information for this endpoint. Thus, an extended one-generation reproductive toxicity study according Annex X, Section 8.7.3. is required. The following refers to the specifications of this required study.

c) The specifications for the study design

Information from studies to be conducted before the extended one-generation reproductive toxicity study

The sub-chronic toxicity study shall be conducted before the extended one-generation reproductive toxicity study and the results from that study shall be used, among other relevant information, to decide on the study design of the extended one-generation reproductive toxicity study following ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 5, December 2016).The sub-chronic toxicity study may provide information on effects that is relevant for triggers (e.g. weight changes and histopathological observations of organs as indication(s) of one or more modes of action related to endocrine disruption which may meet the toxicity-trigger for extension of Cohort 1B or as evidence of specific mechanism/modes of action and/or neurotoxicity and/or immunotoxicity which may meet the particular concern criteria for developmental neurotoxicity and/or developmental immunotoxicity cohorts).

Premating exposure duration and dose-level setting

To ensure that the study design adequately addresses the fertility endpoint, the duration of the premating exposure period and the selection of the highest dose level are key aspects to be considered. According to ECHA Guidance, the starting point for deciding on the length of premating exposure period should be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

Ten weeks premating exposure duration is required if there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 5.0, Deember 2016). In this specific case a ten weeks exposure duration is supported by the lipophilicity of the substance to ensure that the steady state in parental animals has been reached before mating.

The highest dose level shall aim to induce some toxicity to allow comparison of effect levels and effects of reproductive toxicity with those of systemic toxicity. The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels.

If there is no existing relevant data to be used for dose level setting, it is recommended that results from a conducted range-finding study (or range finding studies) are reported with the main study. This will support the justifications of the dose level selections and interpretation of the results.

Species and route selection

According to the test method EU B.56./ OECD TG 443, the rat is the preferred species. On the basis of this default assumption, ECHA considers that testing should be performed in rats.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 5.0, December 2016) R.7a, chapter R.7.6.4.2.3. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

In your comments to the draft decision you agreed to conduct the requested study, by stating "*The Registrants agree to perform the requested extended one-generation reproduction toxicity study (OECD TG 443) according to the following study design specifications:*

- *Ten weeks premating exposure duration for the parental (P0) generation;*
- *Dose level setting shall aim to induce some toxicity at the highest dose level;*
- *Cohort 1A (Reproductive toxicity);*
- *Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation".*

d) Outcome

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443), in rats, oral route, according to the following study-design specifications:

- Ten weeks premating exposure duration for the parental (P0) generation;
- Dose level setting shall aim to induce some toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity); and
- Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation.

Currently, the extension of Cohort 1B and the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) are not requested. However, the sub-chronic toxicity study (90-day) requested in this decision (infromation request 1) and/or any other relevant information may trigger changes in the study design. Therefore, the sub-chronic toxicity study (90-day) is to be conducted first and the study results submitted to ECHA in a dossier update **8 August 2019**. If, on the basis of this update and/or other relevant information, a need for changes to the study design is identified, ECHA will inform you by **8 November 2019** (i.e. within three months after expiry of the 24-month deadline to provide the sub-chronic toxicity study (90-day) or within three months of the date of submission of the study summary of the sub-chronic toxicity study) of its intention to initiate a new decision making procedure under Articles 41, 50 and 51 of the REACH Regulation to address the design of the extended one-generation reproductive toxicity study. If you do not receive a communication from ECHA by **8 November 2019**, the request of the present decision for the extended one-generation reproductive toxicity study remains effective and you may commence the conduct of the study and the results will need to be submitted by the deadline given in this decision.

As stated in the decision (information request 4), no triggers for the extension of Cohort 1B and the inclusion of Cohort 3 (developmental immunotoxicity) have been identified based on the available information. However, the sub-chronic toxicity study (90-day) requested in this decision (infromation request 1) and any other relevant available information may provide information that could trigger these changes in study design. Therefore the 90-day study is to be conducted first and the study results submitted to ECHA in a dossier update by the given deadline. If ECHA identifies a need for the above mentioned changes in study design, it will initiate by **8 November 2019** (i.e. within three months after expiry of the 24-month deadline to provide the 90-day study), or within three months of the date of submission of the study summary of the sub-chronic toxicity study a new decision making procedure changing this request and setting a new deadline for the expanded request.

If ECHA does not identify a need for additional changes in study design the request for an extended one-generation reproductive toxicity study of the present decision remains effective including the time by when the requested information has to be provided as specified above.

Notes for your consideration

When submitting the study results of the sub-chronic toxicity study (90-day) you are invited to also include in the registration update your considerations whether changes in the study design are needed (see also *ECHA Guidance on information requirements and chemical safety assessment R.7a, chapter R.7.6 (version 5.0, December 2016)*).

Furthermore, after having commenced the extended one-generation reproduction toxicity study in accordance with the ECHA decision, you may also expand this study to address a concern identified during the conduct of it and also due to other scientific reasons in order to avoid conduct of a new study.

The justification for the changes in the study design must be documented. The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/ triggers must be documented.

ECOTOXICOLOGICAL INFORMATION

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

5. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)

"Long-term toxicity testing on aquatic invertebrates" is a standard information requirement as laid down in Annex IX, Section 9.1.5. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have not provided any study record of a long-term toxicity on aquatic invertebrates in the dossier that would meet the information requirement of Annex IX, Section 9.1.5.

While you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex IX, Section 9.1.5., column 2 . You provided the following justification for the adaptation: "*Tetrahydrolinalool has been identified as a class 1 type compound (neutral organic) according to Verhaar (1992). Thus the mode of action is assumed as nonspecific narcotic. For these MoA class an a/c-ratio (90-percentile) of 11.5 is reported by ECETOC (Technical report No. 91). Taking this into account it can be concluded, that - considering an a/c-ratio <100 - it is unlikely that a chronic daphnia study would decrease the PNEC (relative to the PNEC from acute studies with an AF of 1000) and thus not significantly change the risk assessment. Furthermore the substance is readily biodegradable. In conclusion, a chronic daphnia study therefore is deemed not to be necessary*"
However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 9.1.5., column 2 because of the following. You claim that a chronic invertebrate study would not decrease the aquatic PNEC and there would be no change for the risk assessment. However, you have not provided an exposure assessment (EA) and risk characterisation (RC) for the environment in your Chemical Safety Report. On this basis it is not possible for ECHA to verify whether your claim of no impact on risk assessment is valid.

Therefore, your adaptation of the information requirement cannot be accepted.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

In your comments to the draft decision you indicate that you wish to first complete the chemical safety assessment (CSA) for environment, according to Annex 1 of the REACH Regulation, and depending on the outcome of the CSA to proceed with aquatic testing if needed. ECHA outlines that it is your responsibility to determine the order and the scheduling of the generation of information. The timeline given in this decision allows for sequential testing. ECHA notes, that you may first carry out the environmental exposure assessment (EA) and risk characterisation (RC) (as per request number 7.) and if risks are indicated to proceed with long-term aquatic testing.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) *Daphnia magna* reproduction test (test method EU C.20. / OECD TG 211) is the preferred test to cover the standard information requirement of Annex IX, Section 9.1.5.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Daphnia magna reproduction test (test method: EU C.20./OECD TG 211).

Notes for your consideration

According to ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b (Section R.7.8.5., including Figure R.7.8-4) if based on acute aquatic toxicity data neither fish nor invertebrates are shown to be substantially more sensitive, long-term studies may be required on both. In such case, according to the integrated testing strategy, the *Daphnia* study is to be conducted first. If based on the results of the long-term *Daphnia* study and the application of a relevant assessment factor, no risks are observed (PEC/PNEC<1), no long-term fish testing may need to be conducted. However, if a risk is indicated, the long-term fish study needs to be conducted.

6. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.)

"Long-term toxicity testing on fish" is a standard information requirement as laid down in Annex IX, Section 9.1.6. of the REACH Regulation. Adequate information on Fish, early-life stage (FELS) toxicity test (Annex IX, 9.1.6.1.), or Fish, short-term toxicity test on embryo and sac-fry stages (Annex IX, 9.1.6.2.), or Fish, juvenile growth test (Annex IX, 9.1.6.3.) needs to be present in the technical dossier for the registered substance to meet this information requirement.

While you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex IX, Section 9.1.6., column 2.You provided the same justification as for long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.) under point 5 above.

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 9.1.6., column 2 because of the following. You claim that a chronic fish study would not decrease the aquatic PNEC and there would be no change for the risk assessment. However, you have not provided an exposure assessment (EA) and risk characterisation (RC) for the environment in your Chemical Safety Report. On this basis it is not possible for ECHA to verify whether your claim of no impact on risk assessment is valid.

Therefore, your adaptation of the information requirement cannot be accepted.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

As already discussed above in section 5., in your comments to the draft decision you indicate your wish to first complete the CSA for environment. ECHA agrees that you may first carry out the environmental EA and RC (as per request number 7.) and if risks are indicated to proceed with long-term aquatic testing. ECHA acknowledges your agreement to follow the aquatic ITS given in ECHA Guidance (version 4.0, June 2017), Chapter R7b (Section R.7.8.5., including Figure R.7.8-4) and further specified in the *Notes for your consideration* below. ECHA notes that if following the long-term invertebrate study, a risk is indicated, the long-term fish study is also to be conducted. The timeline given in this decision allows for such stepwise approach.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) fish early-life stage (FELS) toxicity test (test method OECD TG 210), fish short-term toxicity test on embryo and sac-fry stages (test method EU C.15. / OECD TG 212) and fish juvenile growth test (test method EU C.14. / OECD TG 215) are the preferred tests to cover the standard information requirement of Annex IX, Section 9.1.6.

However, the FELS toxicity test according to OECD TG 210 is more sensitive than the fish, short-term toxicity test on embryo and sac-fry stages (test method EU C.15 / OECD TG 212), or the fish, juvenile growth test (test method EU C.14. / OECD TG 215), as it covers several life stages of the fish from the newly fertilized egg, through hatch to early stages of growth (see ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), *Chapter R7b, Figure R.7.8-4)*.

Moreover, the FELS toxicity test is preferable for examining the potential toxic effects of substances which are expected to cause effects over a longer exposure period, or which require a longer exposure period of time to reach steady state (ECHA *Guidance Chapter R7b,* version 4.0, June 2017).

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Fish, early-life stage (FELS) toxicity test (test method: OECD TG 210).

Notes for your consideration

Before conducting any of the tests mentioned above in points 5 and 6 you shall consult the ECHA *Guidance on information requirements and chemical safety assessment (*version 4.0, June 2017*)*, Chapter R7b, Section R.7.8.5 to determine the sequence in which the aquatic long-term toxicity tests are to be conducted and the necessity to conduct long-term toxicity testing on fish.

According to ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b (Section R.7.8.5., including Figure R.7.8-4), if based on acute aquatic toxicity data neither fish nor invertebrates are shown to be substantially more sensitive, long-term studies may be required on both. In such case, according to the integrated testing strategy, the *Daphnia* study is to be conducted first. If based on the results of the long-term *Daphnia* study and the application of a relevant assessment factor, no risks are observed (PEC/PNEC<1), no long-term fish testing may need to be conducted. However, if a risk is indicated, the long-term fish study needs to be conducted.

ENVIRONMENTAL HAZARD ASSESSMENT

7. Exposure assessment and risk characterisation (Annex I, Sections 5. and 6.) for environment

Pursuant to Articles 10(b) and 14(1) of the REACH Regulation, the registration shall contain a chemical safety report (CSR) which shall document the chemical safety assessment (CSA) conducted in accordance with Article 14(2) to (7) and with Annex I of the REACH Regulation.

Pursuant to Article 14(4), if the substance fulfils the criteria for any of the hazard classes listed in that provision or is assessed to be a PBT (persistent, bioaccumulative and toxic) or vPvB (very persistent and very bioaccumulative), the CSA shall include exposure assessment and risk characterisation.

Annex I, Section 5 of the REACH Regulation requires the Registrant to generate exposure scenarios and exposure estimations for the registered substance. The exposure assessment shall consider all stages of the life-cycle of the substance resulting from the manufacture and identified uses and shall cover any exposures that may relate to the identified hazards.

Annex I, Section 6 of the REACH Regulation requires you to characterise the risk for each exposure scenario and to consider the human population (exposed as workers, consumer or indirectly via the environment and if relevant a combination thereof) and the environmental spheres for which exposure to the substance is known or reasonable foreseeable, under the assumption that the risk management measures described under exposure scenario in Section 5 of the same Annex have been implemented. In addition, the overall environmental risk caused by the substance shall be reviewed by integrating the results for the overall releases, emissions and losses from all sources to all environmental compartments.

ECHA's Guidance on information requirements and chemical safety assessment, Part B: Hazard Assessment, Section B.8.4. (pages 47 to 48) (version 2.1, December 2011) states that "*if no adverse effects have been observed in studies at the highest recommended concentration/doses tested, this would normally indicate that no hazard has been identified and no DNEL or PNEC can be derived and hence exposure assessment for that route of exposure, type of effect or protection target would not be needed*".

In the CSR you provided, the exposure assessment for the environment is missing. You claimed that no exposure assessment is necessary for the environment by stating that "*As no environmental hazard was identified no environmental-related exposure assessment and risk characterization was performed.*"

ECHA notes that you have classified the substance as Skin Irrit. 2 (H315) and Eye Irrit. 2 (H 319) thus, fulfilling the criteria set out in Article 14(4) of the REACH Regulation to require an exposure assessment and a risk characterisation in the chemical safety assessment.

With regard to the scope of the required exposure assessment, as stated above and in accordance with Annex I, section 5.0., it has to cover all hazards that have been identified according to sections 1 to 4 of Annex I of REACH Regulation.

ECHA notes that adverse effects were observed in some environmental toxicity studies. In particular, in the short-term toxicity studies to aquatic invertebrates an EC50 of 14.2 mg/L was obtained and an LC50 of 8.9 mg/L was obtained in the short-term toxicity study on fish. You have used the short-term fish result for the derivation of the aquatic PNEC. Therefore, exposure assessment and risk characterisation for environment are needed to address the hazards identified for the environment. As further outlined in Guidance *on information requirements and chemical safety assessment*, Part B: Hazard Assessment, Section B.8.1. (version 2.1, December 2011), such identified hazards (among others) necessitating exposure assessment are the *"hazards for which there are classification criteria and there is information on these properties of the substance showing that it does have these properties, but the severity of the effects is lower than the criteria for classification and so the substance is not classified".* Moreover, the above mentioned guidance specifies further (in Section 8.4.2.2.) that *"If there are ecotoxicity data showing effects in aquatic organisms, but the substance is not classified as dangerous for the aquatic environment, an aquatic PNEC can nevertheless be derived thus indicating a hazard to the aquatic environment.(...) Hence. quantitative exposure assessment, i.e. derivation of PECs, is mandatory for the water, sediment and soil environmental compartments."*

ECHA acknowledges that in your comments to the draft decision you agreed to fulfil this request by stating that you "agree *to provide a chemical safety assessment according to Annex I covering environmental aspects as well*".

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to generate an environmental exposure assessment for all relevant exposure scenarios and subsequently perform the risk characterisation for each exposure scenario to demonstrate the safe use of the substance, and update the dossier accordingly.

Deadline to submit the requested information in this decision

In the draft decision communicated to you, the time indicated to provide the requested information was 48 months except for the information requested under point 1 for a sub-chronic toxicity study (90-day) which shall be submitted in an updated registration dossier by 24 months from the date of the decision. In your comments on the draft decision, you requested an extension of the timeline to provide the information from the sub-chronic toxicity study within 24 months and to adjust accordingly the timeline to provide the other requested information to 60 months. You sought to justify this request by first, stating that the formulation and stability investigations required to account for the difficult physical-chemical properties of the registered substance and the need to conduct a 14-day palatability testing and a 28-day dose range-finding study in the absence of toxicological data after oral repeated administration; and secondly by stating that extra time is needed due to laboratory capacity concerns. On the basis of this justification, ECHA has granted the request and set the deadlines to provide the results from the sub-chronic toxicity study (90-day) to 24 months from the date of the decision and to 60 months from the date of the decision for the remainder of the information requested in the decision.

Appendix 2: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 24 November 2016.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

ECHA notified you of the draft decision and invited you to provide comments.

ECHA took into account your comments and did not amend the request(s), however, the deadline was amended.

ECHA notified the draft decision to the competent authorities of the Member States for proposal(s) for amendment.

As no amendments were proposed, ECHA took the decision according to Article 51(3) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. This compliance check decision does not prevent ECHA from initiating further compliance checks on the present registration at a later stage.

2. Failure to comply with the request(s) in this decision, or to fulfil otherwise the information requirement(s) with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

3. In relation to the information required by the present decision, the sample of the substance used for the new test(s) must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants. It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new test(s) is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported by each registrant. If the registration of the substance by any registrant covers different grades, the sample used for the new test(s) must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the test(s) to be assessed.